

Australian and New Zealand College  
of Anaesthetists and Faculty of Pain Medicine

# ACUTE PAIN MANAGEMENT: SCIENTIFIC EVIDENCE

Third Edition 2010

Edited by:  
Pamela E Macintyre  
David A Scott  
Stephan A Schug  
Eric J Visser  
Suellen M Walker

# Acute Pain Management: Scientific Evidence

Australian and New Zealand  
College of Anaesthetists  
and Faculty of Pain Medicine



## Endorsed by:

Faculty of Pain Medicine, Royal College of Anaesthetists, United Kingdom	Faculty of Pain Medicine, College of Anaesthetists of Ireland
Royal College of Anaesthetists, United Kingdom	Hong Kong College of Anaesthesiologists
Australian Pain Society	Hong Kong Pain Society
Australasian Faculty of Rehabilitation Medicine	Malaysian Association for the Study of Pain
College of Anaesthesiologists, Academy of Medicine, Malaysia	New Zealand Pain Society
College of Anaesthesiologists, Academy of Medicine, Singapore	Pain Association of Singapore
College of Intensive Care Medicine of Australia and New Zealand	Royal Australian and New Zealand College of Psychiatrists
	Royal Australasian College of Physicians
	Royal Australasian College of Surgeons

## Recommended to members:

American Academy of Pain Medicine

## Also endorsed by:

International Association for the Study of Pain



Approved by the NHMRC on 4 February 2010

© Australian and New Zealand College of Anaesthetists 2010

ISBN Print: 978-0-977517-4-4-2 Online: 978-0-9775174-5-9

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from ANZCA. Requests and enquiries concerning reproduction and rights should be addressed to the Chief Executive Officer, Australian and New Zealand College of Anaesthetists, 630 St Kilda Road, Melbourne, Victoria 3004, Australia. Website: [www.anzca.edu.au](http://www.anzca.edu.au) Email: [ceoanzca@anzca.edu.au](mailto:ceoanzca@anzca.edu.au)

This document should be cited as:

Macintyre PE, Schug SA, Scott DA, Visser EJ, Walker SM; APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2010), *Acute Pain Management: Scientific Evidence* (3rd edition), ANZCA & FPM, Melbourne.

### **Copyright information for Tables 11.1 and 11.2**

The material presented in Table 11.1 and Table 11.2 of this document has been reproduced by permission but does not purport to be the official or authorised version. The Commonwealth does not warrant that the information is accurate, comprehensive or up-to-date and you should make independent inquiries, and obtain appropriate advice, before relying on the information in any important matter. Enquiries on the content of the material should be directed to the Therapeutic Goods Administration ([www.tga.gov.au](http://www.tga.gov.au)).

### **Acknowledgements**

The production of a document such as this requires a considerable amount of time over a long period. Although institutional support in terms of time and resources came from a number of centres, in particular the editors would like to thank the Department of Anaesthesia, Hyperbaric Medicine and Pain Medicine at the Royal Adelaide Hospital for its generous support and assistance during the development of this edition. They also wish to acknowledge the support of the Department of Anaesthesia and Pain Medicine at the Royal Perth Hospital, the Department of Anaesthesia, St Vincent's Hospital, Melbourne and The Portex Unit: Pain Research UCL Institute of Child Health and Great Ormond St Hospital, London. Special thanks are also extended to Professor Paul Myles for his assistance in relation to assessment of the meta-analyses that could have been affected by retracted articles (see Introduction and Appendix B for details), to Dr Dan Carr for his guidance in this matter, to Dr Rowan Thomas for his significant contribution to the web site development which underpinned the review process, and to Professor Michael Cousins for his advice and assistance throughout the development process.

### **NHMRC approval**

These guidelines were approved by the NHMRC on 4 February 2010, under section 14A of the *National Health and Medical Research Council Act 1992*. Approval for the guidelines by NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every five years. Readers should check with the Australian and New Zealand College of Anaesthetists for any reviews or updates of these guidelines.

### **Disclaimer**

This document aims to combine a review of the best available evidence for acute pain management with current clinical and expert practice, rather than to formulate specific clinical practice recommendations. It is designed to provide information based on the best evidence available at the time of publication to assist in decision-making. The information provided is not intended to over-ride the clinical expertise of health care professionals and its use is subject to the clinician's judgement and the patient's preference in each individual case. There is no substitute for the skilled assessment of each individual patient's health status, circumstances and perspectives, which health care practitioners will then use to select the treatments that are relevant and appropriate to that person.

This document can be downloaded from the ANZCA website:

<http://www.anzca.edu.au/resources/books-and-publications/>. Copies of the document can be ordered through the Australian and New Zealand College of Anaesthetists on +61 3 9150 6299.

# FOREWORD

---

Less than a generation ago the prevalent attitude towards acute pain was widespread acceptance as inevitable, and frequent indifference to its suboptimal management. Now, proper pain management is understood to be a fundamental human right and integral to the ethical, patient-centred and cost-effective practice of modern medicine. This progress is the result of dedicated efforts by health care professionals worldwide, including many in Australia and New Zealand who have contributed to past and present editions of *Acute Pain: Scientific Evidence*. The consistently high standards of *Acute Pain: Scientific Evidence* have established it as the foremost English-language resource of its type worldwide. Changes between successive editions reflect not simply accumulation of clinical evidence in this dynamic field, but also advancing sophistication in methods of evidence synthesis and decision support. Chaired by Associate Professor Pam Macintyre, assisted by many contributors and a distinguished editorial subgroup of Professor Stephan Schug, Associate Professor David Scott, Dr Eric Visser and Dr Suellen Walker, the working party responsible for the Third Edition of *Acute Pain: Scientific Evidence* have continued to aggregate new clinical evidence and to expand the range of topics. Even more, they have synthesised and presented the consolidated evidence in a clear, user-friendly fashion and highlighted instances where prior editions' conclusions have been altered by new findings.

The use of objective clinical evidence to provide a rational basis for practice is an old concept. In the Old Testament, the Book of Daniel clearly recounts a prospective case-controlled trial. Socrates advocated clinical outcomes assessment as the basis for annual reappointment of state physicians. Yet, aware that an evidence-informed approach to patient care has recently at times inappropriately been used as a rationale for restricting the range of therapeutic options available to patients, the authors of the third edition counsel that 'while knowledge of current best evidence is important, it plays only a part in the management of acute pain for any individual patient and more than evidence is needed if such treatment is to be effective.' Personalised medicine and individualised care — in part necessitated by genetic differences in drug metabolism and action, as discussed in the third edition — require such a balanced approach. Cochrane himself voiced disdain for 'the considerable pressure...to provide physicians with a simple rule to tell them what it all meant' [Cochrane AL: *Effectiveness and Efficiency: Random Reflections on Health Services*. Cambridge (UK): Cambridge University Press, 1989, p. 41].

The first edition of *Acute Pain: Scientific Evidence* (led by MJC) and its counterpart US federal guideline over a decade ago (led by DBC) noted the clinical impression that undertreated acute pain may have damaging long-term consequences. Subsequent epidemiologic evidence now affirms this clinical insight and indicates that for some patients debilitating persistent pain can be averted by minimisation of acute pain after surgery or trauma. Even if it is not possible to prevent the transition from acute to chronic pain in every case, early recognition and treatment of incipient chronic pain by a vigilant healthcare system is necessary for cost-effective intervention. The National Pain Strategy document that underpins the 2010 Australian Pain Summit summarises the emerging literature on social, human and economic costs of undertreated acute and chronic pain — establishing pain as a major disease burden ([www.painsummit.org.au](http://www.painsummit.org.au)) and proposing an integrated new framework for management of acute, chronic and cancer pain. This historic summit also reiterated that apart from considerations of reduced cost and increased efficiency, ethical medical practice mandates prevention of unnecessary pain and suffering. Further the Summit Strategy draws heavily

upon the scientific evidence and clinical practice of acute pain management that is the subject of this volume. The dedicated efforts of Dr Macintyre and colleagues to summarise the scientific evidence on acute pain management play an important role in shaping pain-related practice and policy worldwide. All those who care for patients or family members in pain, or who may one day suffer pain themselves, are in their debt.

**Michael J Cousins AM**

MB BS MD DSc FRCA FANZCA FFPMANZCA FChPM (RACP)  
Professor and Director  
Pain Management Research Institute  
University of Sydney and Royal North Shore Hospital  
Sydney, Australia

**Daniel B Carr**

MD DABPM FFPMANZCA (Hon)  
Saltonstall Professor of Pain Research  
Department of Anesthesia  
Tufts Medical Center  
Boston, USA

# INTRODUCTION

---

This is the third edition of the document *Acute Pain Management: Scientific Evidence*. The first edition was written by a multidisciplinary committee headed by Professor Michael Cousins and published by the National Health and Medical Research Council (NHMRC) of Australia in 1999. The second edition was written by multiple contributors and a working party chaired by Assoc Prof Pam Macintyre. It was approved by the NHMRC and published by the Australian and New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPM) in 2005. It was also endorsed by a number of major organisations — the International Association for the Study of Pain (IASP), the Royal College of Anaesthetists (United Kingdom), the Australasian Faculty of Rehabilitation Medicine, the Royal Australasian College of Physicians, the Royal Australasian College of Surgeons, the Royal Australian and New Zealand College of Psychiatrists and the Australian Pain Society — and recommended to its members by the American Academy of Pain Medicine.

After publication, a companion document for consumers — *Managing Acute Pain: a Guide for Patients* — was prepared and approved by the NHMRC (ANZCA & FPM 2005).

In accord with NHMRC requirements that documents such as these be revised as further evidence accumulates, and as there had been an ongoing and substantial increase in the quantity and quality of information available about acute pain management, it was seen as timely to reassess the available evidence. ANZCA and the FPM therefore again took responsibility for revising and updating the document — this third edition. As with the second edition, this third edition has been endorsed by a number of key professional organisations (see list on the title page). It was also approved by the NHMRC on 4th February 2010, under section 14A of the *National Health and Medical Research Council Act 1992*.

A working party was convened to coordinate and oversee the development process. An editorial subgroup of the working party (Assoc Prof Pam Macintyre, Prof Stephan Schug, Assoc Prof David Scott, Dr Eric Visser and Dr Suellen Walker) coordinated the development process and edited and/or wrote the sections. The working party also included Dr Douglas Justins, Dean of the Faculty of Pain Medicine, Royal College of Anaesthetists in the United Kingdom, and Prof Karen Grimmer-Somers from the University of South Australia, who was the NHMRC-appointed Guidelines Assessment Register representative for the second edition and provided expert advice on the use of evidence-based findings and the application of NHMRC criteria for this edition.

A large panel of contributors was appointed to draft sections of the document and a multidisciplinary consultative committee was chosen to review the early drafts of the document and contribute more broadly as required. To ensure general applicability and inclusiveness, there was a very wide range of experts on the contributor and multidisciplinary committee, including medical, nursing, allied health and complementary medicine clinicians and a consumer. Comments on the document were also invited during a public consultation period. Details of the processes involved are outline in Appendix B, *Process Report*.

*Acute Pain Management: Scientific Evidence* covers a wide range of clinical topics. The purpose of the document is, as with the first two editions, to combine a review of the best available evidence for acute pain management with current clinical and expert practice, rather than to formulate specific clinical practice recommendations. Accordingly, the document aims to summarise the substantial amount of evidence currently available for the management of acute pain in a concise and easily readable form to assist the practising clinician. New and

updated content has been incorporated with the content of the previous version of the document.

It is recognised that while knowledge of current best evidence is important, it plays only a part in the management of acute pain for any individual patient and more than evidence is needed if such treatment is to be effective.

Evidence-based medicine has been defined as ‘the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients’ and that it must ‘integrate research evidence, clinical expertise and patient values’ (Sackett et al, 1996). Therefore evidence, clinical expertise and, importantly, patient participation (ie including the patient as part of the treating and decision-making team, taking into account their values, concerns and expectations) are required if each patient is to get the best treatment. The information provided in this document is not intended to over-ride the clinical expertise of healthcare professionals. There is no substitute for the skilled assessment of each individual patient’s health status, circumstances and perspectives, which healthcare professionals will then use to help select the treatments that are relevant and appropriate to that patient.

## Review of the evidence

This document is a revision of the second edition of *Acute Pain Management: Scientific Evidence*, published in 2005. Therefore, most of the new evidence included in the third edition has been published from January 2005 onwards. Evidence-based guidelines have been published in the areas of acute back and musculoskeletal pain, and recommendations relevant to the management of the acute phase of these conditions were drawn directly from these.

For more details on the review of the evidence see Appendix B, *Process Report*.

## Levels of evidence

Levels of evidence were documented according to the NHMRC designation (NHMRC, 1999).

### Levels of evidence

- I Evidence obtained from a systematic review of all relevant randomised controlled trials
- II Evidence obtained from at least one properly designed randomised controlled trial
- III-1 Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
- III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-controlled studies or interrupted time series with a control group
- III-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
- IV Evidence obtained from case series, either post-test or pre-test and post-test

### Clinical practice points

- Recommended best practice based on clinical experience and expert opinion

## Key messages

Key messages for each topic are given with the highest level of evidence available to support them, or with a symbol indicating that they are based on clinical experience or expert opinion. In the key messages, Level I evidence from the Cochrane Database is identified. Levels of evidence were documented according to the NHMRC designation and, as for the second edition of this document, clinical practice points have been added.

It was felt that there should be an indication of how the key messages in this third edition related to those in the second edition. The system used by Johnston et al (Johnston et al, 2003) to reflect the implications of new evidence on clinical recommendations was therefore



reviewed and adapted. Where the new evidence led to reversal of a conclusion and key message, this was noted in the text.

---

**Review and revision of key messages**

---

<b>New</b>	New evidence leads to new key message(s).
<b>Unchanged</b>	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged.
<b>Strengthened</b>	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged or expanded. The level of evidence and/or content of the key message in the original report has been strengthened to reflect this additional evidence.
<b>Weakened</b>	The new evidence is inconsistent with the data used to inform the original key message(s). However, the new evidence does not alter the key message but weakens the level of evidence.
<b>Qualified</b>	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged but applicability may be limited to specific patient groups/ circumstances.
<b>Reversed</b>	The new evidence is inconsistent with the data used to inform the original key message(s). The strength of the new evidence alters the conclusions of the original document.
<b>NB</b>	Clinical and scientific judgment informed the choices made by the Working Party members; there was no mandatory threshold of new evidence (eg number of studies, types of studies, magnitude of statistical findings) that had to be met before classification to categories occurred.  The first letter of each of the words ( <b>N</b> ew, <b>U</b> nchanged etc) was used to denote the changes (if any) from the last edition of this document.

---

### **Management of retracted publications**

In May 2009, two editorials (Shafer et al, 2009; White et al, 2009) were published in *Anesthesia and Analgesia* giving details of 21 publications that had been retracted by a number of journals because of allegations of scientific fraud. The editorial by Shafer (Shafer et al, 2009) contains a list of the retracted articles. This list can also be found at <http://www.aeditor.org/HWP/Retraction.Notice.pdf>.

The position of the journal was that unretracted articles ‘remain part of the unimpeached literature, at least for now’. In a companion editorial White et al (White et al, 2009) reviewed both the retracted and unimpeached literature, ‘distinguishing our understandings that remain fully supported from those that are no longer supported by the unimpeached literature.’ Also in May 2009, Eisenach (Eisenach, 2009), the editor of *Anesthesiology*, presented a graph of numbers of citations of retracted and unretracted articles affected by this issue and called for research re-examining the conclusions of the retracted articles.

A July 2009 editorial by Neal (Neal, 2009) described contact with ‘the lead or high ranking authors’ of six original articles and one review article in that editor’s journal and which had not been retracted. These articles are listed in this editorial. He concluded that ‘Based on the attestations of the involved coauthors and the investigations of the Chief Academic Officer of Baystate Medical Center, the Editorial Board of *Regional Anesthesia and Pain Medicine* is comfortable recommending that practitioners continue to make clinical decisions based on the information contained within the seven below cited articles.’



Of the references listed in the May 2009 retraction notice (Shafer, 2009), four were included in the second edition of *Acute Pain Management: Scientific Evidence* along with a further two publications that were not included in this list of retractions.

There are no precedents for how best to manage a problem such as this. However, the editors responsible for the development of this third edition of *Acute Pain Management: Scientific Evidence* decided against including any publications by the individuals affected by these retractions when listed as first author on the papers. An assessment was made of each of the meta-analyses that cited affected articles. This was based upon the other papers included in these meta-analyses, other supporting evidence and independent consideration by an expert in biostatistics. In some cases, although cited, the affected references were not actually included in the meta-analysis performed. In other cases, assessment indicated that the strength of the evidence may be reduced because of the inclusion of affected publications.

Following the consensus that appeared to rapidly emerge among editors of the leading peer-reviewed journals in anaesthesiology and pain medicine despite initial concerns about meta-analyses that included this work (White et al, 2009), the editors of the third edition of *Acute Pain Management: Scientific Evidence* felt that indiscriminately omitting all meta-analyses purely on the basis of inclusion of one or two of those papers would be to deny inclusion of some important credible information in the document. Indeed, the purpose of meta-analysis is to aggregate results from the literature as a whole, thereby diluting the impact of any one specific study.

Just prior to finalisation of this third edition of *Acute Pain Management: Scientific Evidence*, an article was published in *Anesthesiology* in December 2009 (Marret et al, 2009) which examined in detail the effect that excluding data obtained from the retracted articles would have on the results of 14 systematic reviews (six quantitative and eight qualitative) in which they were cited. Marret et al (2009) reanalysed the data after excluding results from affected articles and concluded that withdrawal of these articles did not alter the conclusions of five out of the six quantitative reviews (meta-analyses): the sixth meta-analysis has not been included in *Acute Pain Management: Scientific Evidence*. Thus there was agreement with the assessments that had already made about the validity of these meta-analyses which included the retracted articles. Marret et al (2009) concluded that meta-analyses were ‘vulnerable’ if data from retracted studies made up more than 30% of the total.

A footnote has been added to the relevant sections indicating the systematic reviews (quantitative and qualitative) that included affected articles along with a summary of the effect, if any, on the results obtained. Also, specific note has been made in the text of the third edition of *Acute Pain Management: Scientific Evidence* where retraction of the affected papers involved key messages that were published in the second edition. Should additional information become available it will be added as needed before publication of this document. Information that comes to light after publication will be posted as appropriate on the *Acute Pain Management: Scientific Evidence* website.

## **INN drug names**

This document uses the generic names of drugs that apply in Australia and New Zealand. Where this differs from the International Nonproprietary Name (INN), the INN is given in brackets on first use within each of the major sections.

### **Pam Macintyre**

On behalf of the Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine

## References

- Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2005) *Managing Acute Pain: a Guide for Patients*. <http://www.anzca.edu.au/resources/books-and-publications/ManagingAcutePain.pdf>.
- Eisenach JC (2009) Data fabrication and article retraction: how not to get lost in the woods. *Anesthesiology* **110**(5): 955–6.
- Johnston M, Brouwers M & Browman G (2003) Keeping cancer guidelines current: results of a comprehensive prospective literature monitoring strategy for twenty clinical practice guidelines. *Int J Technol Assess Health Care* **19**: 646–55.
- Marret E, Elia N, Dahl JB et al (2009) Susceptibility to fraud in systematic reviews. *Anesthesiology* **111**: 1279–89.
- Neal JM (2009) Retraction. *Reg Anesth Pain Med* **34**(4): 385.
- NHMRC (1999) *A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines*. National Health and Medical Research Council, Canberra. <http://www.nhmrc.gov.au/publications/synopses/cp30syn.htm>
- Sackett DL, Rosenberg WM, Gray JA et al (1996) Evidence based-medicine: what it is and what it isn't. *BMJ* **312**: 71–2.
- Shafer SL (2009) Tattered threads. *Anesth Analg* **108**:1361–3.
- White PF, Kehlet H & Liu S (2009) Perioperative analgesia: what do we still know? *Anesth Analg* **108**: 1364–7.

## Contents

<b>FOREWORD</b> .....	<b>iv</b>
<b>INTRODUCTION</b> .....	<b>vi</b>
<b>SUMMARY OF KEY MESSAGES</b> .....	<b>xix</b>
<b>1. PHYSIOLOGY AND PSYCHOLOGY OF ACUTE PAIN</b> .....	<b>1</b>
<b>1.1 Applied physiology of pain</b> .....	<b>1</b>
1.1.1 Definition of acute pain .....	1
1.1.2 Pain perception and nociceptive pathways.....	1
1.1.3 Neuropathic pain.....	6
<b>1.2 Psychological aspects of acute pain</b> .....	<b>6</b>
1.2.1 Psychological factors .....	7
1.2.2 Acute pain settings .....	8
<b>1.3 Progression of acute to chronic pain</b> .....	<b>9</b>
1.3.1 Predictive factors for chronic postsurgical pain .....	11
1.3.2 Mechanisms for the progression from acute to chronic pain .....	12
<b>1.4 Pre-emptive and preventive analgesia</b> .....	<b>12</b>
<b>1.5 Adverse physiological and psychological effects of acute pain</b> .....	<b>15</b>
1.5.1 Acute pain and the injury response.....	15
1.5.2 Adverse physiological effects .....	16
1.5.3 Pain and analgesia: effects on injury-induced organ dysfunction.....	19
1.5.4 Acute rehabilitation and ‘fast-track’ surgery.....	20
1.5.5 Adverse psychological effects .....	21
<b>1.6 Pharmacogenomics and acute pain</b> .....	<b>21</b>
1.6.1 Loss of pain sensation .....	22
1.6.2 Reduced sensitivity to pain .....	22
1.6.3 Drug metabolism .....	23
<b>References</b> .....	<b>25</b>
<b>2. ASSESSMENT AND MEASUREMENT OF PAIN AND ITS TREATMENT</b> .....	<b>34</b>
<b>2.1 Assessment</b> .....	<b>34</b>
<b>2.2 Measurement</b> .....	<b>35</b>
2.2.1 Unidimensional measures of pain .....	36
2.2.2 Functional impact of acute pain .....	38
2.2.3 Multidimensional measures of pain .....	38
2.2.4 Patients with special needs .....	39
<b>2.3 Outcome measures in acute pain management</b> .....	<b>40</b>
2.3.1 Outcome measures .....	40
<b>References</b> .....	<b>42</b>

<b>3. PROVISION OF SAFE AND EFFECTIVE ACUTE PAIN MANAGEMENT .....</b>	<b>45</b>
<b>3.1 Education .....</b>	<b>45</b>
3.1.1 Patients .....	45
3.1.2 Staff .....	46
<b>3.2 Organisational requirements.....</b>	<b>47</b>
3.2.1 General requirements .....	48
3.2.2 Acute pain services.....	48
<b>References .....</b>	<b>50</b>
<b>4. SYSTEMICALLY ADMINISTERED ANALGESIC DRUGS.....</b>	<b>55</b>
<b>4.1 Opioids .....</b>	<b>55</b>
4.1.1 Choice of opioid.....	55
4.1.2 Specific opioids.....	55
4.1.3 Determinants of opioid dose.....	61
4.1.4 Adverse effects of opioids .....	62
<b>4.2 Paracetamol, non-selective non-steroidal anti-inflammatory drugs and coxibs .....</b>	<b>71</b>
4.2.1 Paracetamol .....	71
4.2.2 Non-selective non-steroidal anti-inflammatory drugs .....	73
4.2.3 Cyclo-oxygenase-2 selective inhibitors (coxibs) .....	75
<b>4.3 Adjuvant drugs.....</b>	<b>79</b>
4.3.1 Inhalational agents .....	79
4.3.2 NMDA-receptor antagonists .....	83
4.3.3 Antidepressant drugs .....	87
4.3.4 Anticonvulsant drugs.....	89
4.3.5 Membrane stabilisers.....	91
4.3.6 Alpha-2 agonists .....	92
4.3.7 Salmon calcitonin and bisphosphonates .....	92
4.3.8 Cannabinoids.....	93
4.3.9 Glucocorticoids.....	94
4.3.10 Complementary and alternative medicines .....	96
<b>References .....</b>	<b>97</b>
<b>5. REGIONALLY AND LOCALLY ADMINISTERED ANALGESIC DRUGS.....</b>	<b>121</b>
<b>5.1 Local anaesthetics .....</b>	<b>121</b>
5.1.1 Short-duration local anaesthetics .....	121
5.1.2 Long-duration local anaesthetics .....	121
5.1.3 Local anaesthetic toxicity .....	124
<b>5.2 Opioids .....</b>	<b>126</b>
5.2.1 Neuraxial opioids.....	126
5.2.2 Peripheral opioids .....	129

<b>5.3 Adjuvant Drugs</b> .....	<b>131</b>
5.3.1 Alpha-2 agonists .....	131
5.3.2 Adrenaline .....	132
5.3.3 Ketamine .....	133
5.3.4 Midazolam.....	134
5.3.5 Neostigmine .....	134
5.3.6 Magnesium.....	135
5.3.7 Botulinum toxin A.....	135
<b>5.4 Anti-inflammatory drugs</b> .....	<b>136</b>
5.4.1 Corticosteroids .....	136
5.4.2 Non-steroidal anti-inflammatory drugs.....	137
<b>References</b> .....	<b>138</b>
<b>6. ADMINISTRATION OF SYSTEMIC ANALGESIC DRUGS</b> .....	<b>150</b>
<b>6.1 Oral route</b> .....	<b>150</b>
6.1.1 Opioids and tramadol.....	153
6.1.2 Non-selective non-steroidal anti-inflammatory drugs and coxibs .....	154
6.1.3 Paracetamol .....	155
<b>6.2 Intravenous route</b> .....	<b>155</b>
6.2.1 Opioids and tramadol.....	155
6.2.2 Non-selective non-steroidal anti-inflammatory drugs and coxibs .....	156
6.2.3 Paracetamol .....	156
<b>6.3 Intramuscular and subcutaneous routes</b> .....	<b>157</b>
6.3.1 Opioids and tramadol.....	157
6.3.2 Non-selective non-steroidal anti-inflammatory drugs and coxibs .....	158
<b>6.4 Rectal route</b> .....	<b>158</b>
6.4.1 Opioids .....	158
6.4.2 Non-selective non-steroidal anti-inflammatory drugs .....	158
6.4.3 Paracetamol .....	159
<b>6.5 Transdermal route</b> .....	<b>159</b>
6.5.1 Opioids .....	159
6.5.2 Other drugs .....	160
<b>6.6 Transmucosal routes</b> .....	<b>160</b>
6.6.1 Intranasal route .....	160
6.6.2 Sublingual and buccal routes.....	162
6.6.3 Inhaled.....	163
<b>References</b> .....	<b>164</b>

<b>7. PCA, REGIONAL AND OTHER LOCAL ANALGESIA TECHNIQUES.....</b>	<b>171</b>
<b>7.1 Patient-controlled analgesia.....</b>	<b>171</b>
7.1.1 Efficacy of intravenous PCA.....	171
7.1.2 Drugs used for parenteral PCA.....	172
7.1.3 Program parameters for intravenous PCA.....	175
7.1.4 Efficacy of PCA using other systemic routes of administration.....	176
7.1.5 Complications related to PCA.....	177
7.1.6 Equipment.....	178
7.1.7 Patient and staff factors.....	179
7.1.8 PCA in specific patient groups.....	180
<b>7.2 Epidural analgesia.....</b>	<b>182</b>
7.2.1 Efficacy.....	182
7.2.2 Drug used for epidural analgesia.....	184
7.2.3 Patient-controlled epidural analgesia.....	185
7.2.4 Adverse effects.....	186
<b>7.3 Intrathecal analgesia.....</b>	<b>190</b>
7.3.1 Drugs used for intrathecal analgesia.....	190
7.3.2 Combined spinal-epidural versus epidural analgesia in labour.....	192
<b>7.4 Regional analgesia and concurrent anticoagulant medications.....</b>	<b>193</b>
7.4.1 Neuraxial blockade.....	193
7.4.2 Plexus and other peripheral regional blockade.....	195
<b>7.5 Other regional and local analgesic techniques.....</b>	<b>195</b>
7.5.1 Continuous peripheral nerve blockade.....	195
7.5.2 Intra-articular analgesia.....	199
7.5.3 Wound infiltration including wound catheters.....	200
7.5.4 Topical application of local anaesthetics.....	200
7.5.5 Safety.....	201
<b>References.....</b>	<b>204</b>
<b>8. NON-PHARMACOLOGICAL TECHNIQUES.....</b>	<b>221</b>
<b>8.1 Psychological interventions.....</b>	<b>221</b>
8.1.1 Provision of information.....	221
8.1.2 Stress and tension reduction.....	222
8.1.3 Attentional techniques.....	223
8.1.4 Cognitive-behavioural interventions.....	224
<b>8.2 Transcutaneous electrical nerve stimulation.....</b>	<b>226</b>
<b>8.3 Acupuncture.....</b>	<b>227</b>
<b>8.4 Other physical therapies.....</b>	<b>228</b>
8.4.1 Manual and massage therapies.....	228
8.4.2 Heat and cold.....	228
8.4.3 Other therapies.....	228
<b>References.....</b>	<b>229</b>

<b>9. SPECIFIC CLINICAL SITUATIONS .....</b>	<b>233</b>
<b>9.1 Postoperative pain .....</b>	<b>233</b>
9.1.1 Risks of acute postoperative neuropathic pain .....	233
9.1.2 Acute postamputation pain syndromes .....	234
9.1.3 Other postoperative pain syndromes .....	236
9.1.4 Day-stay or short-stay surgery .....	238
9.1.5 Cranial neurosurgery .....	241
<b>9.2 Acute pain following spinal cord injury.....</b>	<b>243</b>
<b>9.3 Acute burn injury pain.....</b>	<b>245</b>
9.3.1 Management of procedural pain .....	246
9.3.2 Non-pharmacological pain management .....	247
<b>9.4 Acute back pain.....</b>	<b>248</b>
<b>9.5 Acute musculoskeletal pain.....</b>	<b>249</b>
<b>9.6 Acute medical pain.....</b>	<b>250</b>
9.6.1 Acute abdominal pain .....	250
9.6.2 Herpes zoster-associated pain .....	253
9.6.3 Acute cardiac pain .....	255
9.6.4 Acute pain associated with haematological disorders .....	256
9.6.5 Acute headache.....	260
9.6.6 Acute pain associated with neurological disorders .....	272
9.6.7 Orofacial pain .....	273
9.6.8 Acute pain in patients with HIV infection.....	278
<b>9.7 Acute cancer pain.....</b>	<b>280</b>
9.7.1 The scope of acute cancer pain .....	280
9.7.2 Principles of management of acute cancer pain .....	281
9.7.3 Breakthrough pain.....	281
9.7.4 Postoperative and procedural pain .....	282
9.7.5 Acute cancer pain due to bone involvement .....	283
9.7.6 Other acute cancer pain syndromes .....	284
9.7.7 Interventional therapies for acute cancer pain .....	285
<b>9.8 Acute pain management in intensive care .....</b>	<b>286</b>
9.8.1 Pain assessment in the intensive care unit .....	287
9.8.2 Non-pharmacological measures.....	287
9.8.3 Pharmacological treatment.....	287
9.8.4 Guillain-Barre syndrome .....	288
9.8.5 Procedure-related pain .....	289
<b>9.9 Acute pain management in emergency departments .....</b>	<b>290</b>
9.9.1 Systemic analgesics .....	290
9.9.2 Analgesia in specific conditions.....	291
9.9.3 Non-pharmacological management of pain.....	293



<b>9.10 Prehospital analgesia</b> .....	<b>294</b>
9.10.1 Assessment of pain in the prehospital environment .....	295
9.10.2 Systemic analgesics .....	295
9.10.2 Anxiolytics .....	297
9.10.3 Regional analgesia .....	297
9.10.4 Non-pharmacological management of pain .....	297
9.10.5 Analgesia in specific conditions .....	298
<b>References</b> .....	<b>299</b>
<b>10. THE PAEDIATRIC PATIENT</b> .....	<b>335</b>
<b>10.1 Developmental neurobiology of pain</b> .....	<b>335</b>
<b>10.2 Long-term consequences of early pain and injury</b> .....	<b>336</b>
<b>10.3 Paediatric pain assessment</b> .....	<b>336</b>
10.3.1 Pain assessment in neonates .....	337
10.3.2 Observational and behavioural measures in infants and children .....	338
10.3.3 Self-report in children and adolescents .....	338
10.3.4 Children with cognitive impairment .....	339
<b>10.4 Management of procedural pain</b> .....	<b>342</b>
10.4.1 Procedural pain in the neonate .....	343
10.4.2 Procedural pain in infants and older children .....	343
10.4.3 Immunisation pain in infants and children .....	345
10.4.4 Procedural pain management in the emergency department .....	345
<b>10.5 Analgesic agents</b> .....	<b>347</b>
10.5.1 Paracetamol .....	347
10.5.2 Non-selective non-steroidal anti-inflammatory drugs .....	348
10.5.3 Coxibs .....	349
10.5.4 Opioids and tramadol .....	350
10.5.5 Corticosteroids .....	352
10.5.6 Other pharmacological therapies .....	352
<b>10.6 Opioid infusions and PCA</b> .....	<b>353</b>
10.6.1 Opioid infusions .....	353
10.6.2 Patient-controlled analgesia .....	354
10.6.3 Nurse-controlled analgesia .....	354
<b>10.7 Regional analgesia</b> .....	<b>355</b>
10.7.1 Peripheral nerve blocks .....	355
10.7.2 Central neural blockade .....	357
<b>10.8 Acute pain in children with cancer</b> .....	<b>361</b>
10.8.1 Cancer-related pain .....	361
10.8.2 Procedure-related pain .....	361
10.8.3 Treatment-related pain .....	362
<b>References</b> .....	<b>363</b>

<b>11. OTHER SPECIFIC PATIENT GROUPS .....</b>	<b>381</b>
<b>11.1 The pregnant patient .....</b>	<b>381</b>
11.1.1 Management of acute pain during pregnancy .....	381
11.1.2 Management of pain during delivery .....	386
11.1.3 Pain management during lactation .....	390
11.1.4 Pain management in the puerperium .....	394
<b>11.2 The older patient .....</b>	<b>396</b>
11.2.1 Pharmacokinetic and pharmacodynamic changes .....	397
11.2.2 Physiology and perception of pain .....	398
11.2.3 Assessment of pain .....	400
11.2.4 Drugs used in the management of acute pain in older people .....	402
11.2.5 Patient-controlled analgesia .....	405
11.2.6 Epidural analgesia .....	405
11.2.7 Intrathecal opioid analgesia .....	406
11.2.8 Other regional analgesia .....	406
<b>11.3 Aboriginal and Torres Strait Islander peoples .....</b>	<b>408</b>
<b>11.4 Different ethnic and cultural groups .....</b>	<b>409</b>
<b>11.5 The patient with obstructive sleep apnoea .....</b>	<b>411</b>
<b>11.6 The patient with concurrent hepatic or renal disease .....</b>	<b>414</b>
11.6.1 Patients with renal disease .....	414
11.6.2 Patients with hepatic disease .....	415
<b>11.7 The opioid-tolerant patient .....</b>	<b>422</b>
11.7.1 Definitions and clinical implications .....	422
11.7.2 Patient groups .....	423
11.7.3 Management of acute pain .....	423
<b>11.8 The patient with an addiction disorder .....</b>	<b>427</b>
11.8.1 Management of acute pain in pregnant patients with an addiction disorder ..	429
11.8.2 CNS depressant drugs .....	430
11.8.3 CNS stimulant drugs .....	431
11.8.4 Drugs used in the treatment of addiction disorders .....	431
11.8.5 Recovering patients .....	433
<b>References .....</b>	<b>433</b>
<b>APPENDIX A .....</b>	<b>452</b>
<b>The working party, contributors and members of the multidisciplinary consultative committee .....</b>	<b>452</b>
<b>APPENDIX B .....</b>	<b>462</b>
<b>Process report .....</b>	<b>462</b>
<b>ABBREVIATIONS AND ACRONYMS .....</b>	<b>473</b>
<b>INDEX .....</b>	<b>478</b>

## List of tables and figures

### Tables

1.1	Examples of primary afferent and dorsal horn receptors and ligands .....	2
1.2	Incidence of chronic pain after surgery .....	11
1.3	Risk factors for chronic postsurgical pain .....	11
1.4	Definitions of pre-emptive and preventive analgesia .....	13
1.5	Summary of studies according to target agent administered .....	14
1.6	Metabolic and endocrine responses to injury .....	17
2.1	Fundamentals of a pain history .....	35
3.1	Possible benefits of an Acute Pain Service .....	49
4.1	Antidepressants for the treatment of neuropathic pain .....	87
6.1	The 2007 Oxford league table of analgesic efficacy .....	151
9.1	Taxonomy of acute pain associated with spinal cord injury .....	244
9.2	Simple analgesics for the treatment of migraine .....	262
9.3	Table of triptans .....	263
9.4	Pooled effectiveness data from emergency department studies of the treatment of migraine .....	292
10.1	Acute pain intensity measurement tools — neonates .....	340
10.2	Composite scales for infants and children .....	341
10.3	Self-report tools for children .....	342
11.1	ADEC drug categorisation according to fetal risk .....	383
11.2	Categorisation of drugs used in pain management .....	384
11.3	The breastfeeding patient and drugs used in pain management .....	392
11.4	Direction and approximate magnitude of physiological changes apparent in an older population (> 70 years) and the effects of individual changes on pharmacokinetic variables .....	397
11.5	Analgesic drugs in patients with renal impairment .....	415
11.6	Analgesic drugs in patients with hepatic impairment .....	419
11.7	Definitions for tolerance, physical dependence and addiction .....	422

### Figures

1.1	The main ascending and descending spinal pain pathways .....	5
1.2	The injury response .....	16
1.3	Proposed pathways of glucose-induced cellular toxicity .....	18
1.4	Acute pain management and rehabilitation .....	20
10.1	Faces Pain Scale — Revised .....	340

# SUMMARY OF KEY MESSAGES

---

A description of the levels of evidence and associated symbols can be found in the Introduction (see pages vii to viii).

## 1. PHYSIOLOGY AND PSYCHOLOGY OF ACUTE PAIN

### *Psychological aspects of acute pain*

1. Preoperative anxiety, catastrophising, neuroticism and depression are associated with higher postoperative pain intensity **(U) (Level IV)**.
2. Preoperative anxiety and depression are associated with an increased number of PCA demands and dissatisfaction with PCA **(U) (Level IV)**.
- Pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope **(U)**.

### *Progression of acute to chronic pain*

1. Some specific early anaesthetic and/or analgesic interventions reduce the incidence of chronic pain after surgery **(S) (Level II)**.
2. Chronic postsurgical pain is common and may lead to significant disability **(U) (Level IV)**.
3. Risk factors that predispose to the development of chronic postsurgical pain include the severity of pre- and postoperative pain, intraoperative nerve injury and psychosocial factors **(U) (Level IV)**.
4. All patients with chronic postherniorrhaphy pain had features of neuropathic pain **(N) (Level IV)**.
5. Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean section **(N) (Level IV)**.

### *Pre-emptive and preventive analgesia*

1. The timing of a single analgesic intervention (preincisional rather than postincisional), defined as pre-emptive analgesia, has a significant effect on postoperative pain relief with epidural analgesia **(R) (Level I)**.
2. There is evidence that some analgesic interventions have an effect on postoperative pain and/or analgesic consumption that exceeds the expected duration of action of the drug, defined as preventive analgesia **(U) (Level I)**.
3. NMDA receptor antagonist drugs in particular show preventive analgesic effects **(U) (Level I)**.
4. Perioperative epidural analgesia combined with ketamine intravenously decreases hyperalgesia and long-term pain up to 1 year after colonic surgery compared with intravenous analgesia alone **(N) (Level II)**.

### ***Adverse physiological and psychological effects of acute pain***

1. Recognition of the importance of postoperative rehabilitation including pharmacological, physical, psychological and nutritional components has led to enhanced recovery (**N**) (**Level II**).
- Acute pain and injury of various types are inevitably interrelated and if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (**U**).

### ***Pharmacogenomics and acute pain***

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine and tramadol (**N**) (**Level II**).
- Genetic polymorphisms explain the wide inter-individual variability in plasma concentrations of a given dose of methadone (**N**).

## **2. ASSESSMENT AND MEASUREMENT OF PAIN AND ITS TREATMENT**

### ***Measurement***

1. Regular assessment of pain leads to improved acute pain management (**U**) (**Level III-3**).
2. There is good correlation between the visual analogue and numerical rating scales (**U**) (**Level III-2**).
- Self-reporting of pain should be used whenever appropriate as pain is by definition a subjective experience (**U**).
- The pain measurement tool chosen should be appropriate to the individual patient; developmental, cognitive, emotional, language and cultural factors should be considered (**U**).
- Scoring should incorporate different components of pain including the functional capacity of the patient. In the postoperative patient this should include static (rest) and dynamic (eg pain on sitting, coughing) pain (**U**).
- Uncontrolled or unexpected pain requires a reassessment of the diagnosis and consideration of alternative causes for the pain (eg new surgical/ medical diagnosis, neuropathic pain) (**U**).

### ***Outcome measures in acute pain management***

- Multiple outcome measures are required to adequately capture the complexity of the pain experience and how it may be modified by pain management interventions (**U**).

## **3. PROVISION OF SAFE AND EFFECTIVE ACUTE PAIN MANAGEMENT**

### ***Education***

1. Preoperative education improves patient or carer knowledge of pain and encourages a more positive attitude towards pain relief (**U**) (**Level II**).
2. Video education of patients with a whiplash injury reduces the incidence of persistent pain (**N**) (**Level II**).
3. Written information given to patients prior to seeing an anaesthetist is better than verbal information given at the time of the interview (**N**) (**Level III-2**).

4. While evidence for the benefit of patient education in terms of better pain relief is inconsistent, structured preoperative education may be better than routine information, and information presented in video format may be better still (**N**) (**Level III-2**).
5. Implementation of an acute pain service may improve pain relief and reduce the incidence of side effects (**U**) (**Level III-3**).
6. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices (**U**) (**Level III-3**).
7. Even 'simple' techniques of pain relief can be more effective if attention is given to education, documentation, patient assessment and provision of appropriate guidelines and policies (**U**) (**Level III-3**).
- Successful management of acute pain requires close liaison with all personnel involved in the care of the patient (**U**).
- More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves (**U**).

#### 4. SYSTEMICALLY ADMINISTERED ANALGESIC DRUGS

##### *Opioids*

1. Dextropropoxyphene has low analgesic efficacy (**U**) (**Level I** [Cochrane Review]).
2. Tramadol is an effective treatment for neuropathic pain (**U**) (**Level I** [Cochrane Review]).
3. Gabapentin, non-steroidal NSAIDs and ketamine are opioid-sparing medications and reduce opioid-related side effects (**N**) (**Level I**).
4. In appropriate doses, droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron are effective in the prevention of postoperative nausea and vomiting (**N**) (**Level I** [Cochrane Review]).
5. Alvimopan and methylnaltrexone are effective in reversing opioid-induced slowing of gastrointestinal transit time and constipation (**N**) (**Level I** [Cochrane Review]).
6. Droperidol, dexamethasone and ondansetron are equally effective in the prevention of postoperative nausea and vomiting (**U**) (**Level I**).
7. Paired combinations of 5HT3 antagonist, droperidol or dexamethasone provide superior prophylaxis of postoperative nausea and vomiting than either compound alone (**N**) (**Level I**).
8. Naloxone, naltrexone, nalbuphine, droperidol and 5HT3 antagonists are effective treatments for opioid-induced pruritus (**N**) (**Level I**).
9. Opioids in high doses can induce hyperalgesia (**N**) (**Level I**).
10. Tramadol has a lower risk of respiratory depression and impairs gastrointestinal motor function less than other opioids at equianalgesic doses (**U**) (**Level II**).
11. Pethidine is not superior to morphine in treatment of pain of renal or biliary colic (**U**) (**Level II**).
12. Morphine-6-glucuronide is an effective analgesic (**N**) (**Level II**).
13. In the management of acute pain, one opioid is not superior over others but some opioids are better in some patients (**U**) (**Level II**).

14. The incidence of clinically meaningful adverse effects of opioids is dose-related (**U**) (**Level II**).
  15. High doses of methadone can lead to prolonged QT interval (**N**) (**Level II**).
  16. Haloperidol is effective in the prevention of postoperative nausea and vomiting (**N**) (**Level II**).
  17. Opioid antagonists are effective treatments for opioid-induced urinary retention (**N**) (**Level II**).
  18. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**N**) (**Level III-2**).
  19. Assessment of sedation is a more reliable way of detecting early opioid-induced respiratory depression than a decreased respiratory rate (**S**) (**Level III-3**).
  20. The evidence for risk of cardiac arrhythmias following low-dose droperidol is poor (**N**) (**Level III-3**).
  21. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).
  22. Impaired renal function and the oral route of administration result in higher levels of the morphine metabolites morphine-3-glucuronide and morphine-6-glucuronide with increased risk of sedation and respiratory depression (**S**) (**Level IV**).
- The use of pethidine (**U**) and dextropropoxyphene (**N**) should be discouraged in favour of other opioids.

#### ***Paracetamol, non-selective non-steroidal anti-inflammatory drugs and coxibs***

1. Paracetamol is an effective analgesic for acute pain; the incidence of adverse effects comparable to placebo (**S**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs are effective in the treatment of acute postoperative and low back pain, renal colic and primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
3. Coxibs are effective in the treatment of acute postoperative pain (**N**) (**Level I** [Cochrane Review]).
4. With careful patient selection and monitoring, the incidence of nsNSAID-induced perioperative renal impairment is low (**U**) (**Level I** [Cochrane Review]).
5. Non-selective NSAIDs do not increase the risk of reoperation for bleeding after tonsillectomy in paediatric patients (**Q**) (**Level I** [Cochrane Review]).
6. Coxibs do not appear to produce bronchospasm in individuals known to have aspirin-exacerbated respiratory disease (**U**) (**Level I**).
7. In general, aspirin increases bleeding after tonsillectomy (**N**) (**Level I**).
8. Non-selective NSAIDs given in addition to paracetamol improve analgesia compared with paracetamol alone (**U**) (**Level I**).
9. Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related side effects (**N**) (**Level I**).
10. Non-selective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea, vomiting and sedation (**N**) (**Level I**).



11. Non-selective NSAIDs and coxibs are effective analgesics of similar efficacy for acute pain **(U) (Level I)**.
  12. Preoperative coxibs reduce postoperative pain and opioid consumption, and increase patient satisfaction **(N) (Level I)**.
  13. Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related side effects **(N) (Level I)**.
  14. Coxibs and non-selective NSAIDs have similar adverse effects on renal function **(U) (Level I)**.
  15. Non-selective NSAIDs do not significantly increase blood loss after tonsillectomy but do increase the need for reoperation due to bleeding **(N) (Level I)**.
  16. Parecoxib and/or valdecoxib compared with placebo do not increase the risk of cardiovascular adverse events after non-cardiac surgery **(N) (Level I)**.
  17. Coxibs and non-selective NSAIDs are associated with similar rates of adverse cardiovascular effects, in particular myocardial infarction; naproxen may be associated with a lower risk than other non-selective NSAIDs and celecoxib may be associated with a lower risk than other coxibs and non-selective NSAIDs overall **(N) (Level I)**.
  18. Perioperative non-selective NSAIDs increase the risk of severe bleeding after a variety of other operations compared with placebo **(N) (Level II)**.
  19. Coxibs do not impair platelet function; this leads to reduced perioperative blood loss in comparison with non-selective NSAIDs **(S) (Level II)**.
  20. Short-term use of coxibs results in gastric ulceration rates similar to placebo **(U) (Level II)**.
  21. Use of parecoxib followed by valdecoxib after coronary artery bypass surgery increases the incidence of cardiovascular events and is therefore contraindicated **(S) (Level II)**.
- Adverse effects of NSAIDs are significant and may limit their use **(U)**.
  - The risk of adverse renal effects of non-selective NSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension, use of other nephrotoxic agents and ACE inhibitors **(U)**.

### **Adjuvant drugs**

#### **Inhalational agents**

1. Nitrous oxide has some analgesic efficacy and is safe during labour **(U) (Level I)**.
  2. Nitrous oxide is an effective analgesic agent in a variety of other acute pain situations **(U) (Level II)**.
  3. Methoxyflurane, in low concentrations, may be an effective analgesia in the hospital and prehospital setting **(N) (Level IV)**.
- Neuropathy and bone marrow suppression are rare but potentially serious complications of nitrous oxide use, particularly in at-risk patients **(U)**.

- ☑ The information about the complications of nitrous oxide is from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to nitrous oxide in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to nitrous oxide. The suggestions for the use of nitrous oxide are extrapolations only from the information above. Consideration should be given to duration of exposure and supplementation with vitamin B12, methionine, and folic or folinic acid (**U**).
- ☑ If nitrous oxide is used with other sedative or analgesic agents, appropriate clinical monitoring should be used (**U**).

### **NMDA-receptor antagonists**

1. Perioperative low-dose ketamine used in conjunction with patient-controlled analgesia morphine is opioid-sparing and reduces the incidence of nausea and vomiting (**N**) (**Level I** [Cochrane Review]).
  2. In general, a perioperative low-dose ketamine infusion is opioid-sparing, but does not produce a clinically significant reduction in pain scores or opioid-related adverse effects (**S**) (**Level I**).
  3. Ketamine is a safe and effective analgesic for painful procedures in children (**N**) (**Level I**).
  4. Ketamine and dextromethorphan have preventive (**U**) but not pre-emptive analgesic effects (**N**) (**Level I**).
  5. Magnesium does not reduce postoperative pain scores or opioid consumption and has no preventive analgesic effect (**N**) (**Level I**).
  6. Ketamine may improve analgesia in patients with severe acute pain that is poorly responsive to opioids, although evidence is conflicting (**W**) (**Level II**).
  7. Ketamine reduces postoperative pain in opioid-tolerant patients (**N**) (**Level II**).
- ☑ The primary role of low dose ketamine is as an ‘antihyperalgesic’, ‘antiallodynic’, ‘tolerance-protective’ and preventive analgesic, rather than as an analgesic *per se* (**N**).

### **Antidepressant drugs**

1. In neuropathic pain, tricyclic antidepressants are more effective than selective serotonergic re-uptake inhibitors (**S**) (**Level I** [Cochrane Review]).
2. Duloxetine is effective in painful diabetic neuropathy and fibromyalgia (**N**) (**Level I** [Cochrane Review]).
3. There is no good evidence that antidepressants are effective in the treatment of chronic low back pain (**R**) (**Level I** [Cochrane Review]).
4. Tricyclic antidepressants are effective in the treatment of chronic headaches (**U**) and fibromyalgia (**N**) (**Level I**).
5. Antidepressants reduce the incidence of chronic neuropathic pain after herpes zoster (**U**) (**Level II**).

#### **Note: withdrawal of previous key message:**

*Antidepressants reduce the incidence of chronic neuropathic pain after breast surgery*

This has been deleted as the information and evidence supporting it has been withdrawn.

- ☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use tricyclic antidepressants and selective serotonin re-uptake inhibitors in the management of acute neuropathic pain (**S**).
- ☑ To minimise adverse effects, particularly in elderly people, it is advisable to initiate treatment with low doses (**U**).

### Anticonvulsant drugs

1. Gabapentin is effective in the treatment of chronic neuropathic pain (**Q**); lamotrigine is most likely ineffective (**N**) (**Level I** [Cochrane Review]).
  2. Carbamazepine is effective in the treatment of trigeminal neuralgia (**N**) (**Level I** [Cochrane Review]).
  3. Pregabalin is effective in the treatment of chronic neuropathic pain related to diabetic neuropathy (**N**) (**Level I**).
  4. Perioperative gabapentinoids (gabapentin/ pregabalin) reduce postoperative pain and opioid requirements (**U**) and reduce the incidence of vomiting, pruritus and urinary retention, but increase the risk of sedation (**N**) (**Level I**).
- ☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use anticonvulsants in the management of acute neuropathic pain (**U**).

### Membrane stabilisers

1. Both lignocaine (lidocaine) and mexiletine are effective in the treatment of chronic neuropathic pain (**S**); there is no difference in efficacy or adverse effects compared with carbamazepine, amantadine, or morphine (**N**) (**Level I** [Cochrane Review]).
  2. Perioperative intravenous lignocaine reduces pain and opioid requirements following abdominal surgery (**S**) as well as nausea, vomiting, duration of ileus and length of hospital stay (**N**) (**Level I**).
- ☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use membrane stabilisers in the management of acute neuropathic pain (**U**).
  - ☑ Lignocaine (intravenous or subcutaneous) may be a useful agent to treat acute neuropathic pain (**U**).

### Alpha-2 agonists

1. The use of systemic alpha-2-agonists consistently improves perioperative opioid analgesia but the frequency and severity of side effects may limit their clinical usefulness (**U**) (**Level II**).

### Salmon calcitonin and bisphosphonates

1. Bisphosphonates reduce bone pain associated with metastatic cancer and multiple myeloma (**N**) (**Level I** [Cochrane Review]).
2. Salmon calcitonin reduces pain and improves mobilisation after osteoporosis-related vertebral fractures (**S**) (**Level I**).
3. Salmon calcitonin reduces acute but not chronic phantom limb pain (**N**) (**Level II**).
4. Pamidronate reduces pain associated with acute osteoporotic vertebral fractures (**N**) (**Level II**).

## Cannabinoids

1. Current evidence does not support the use of cannabinoids in acute pain management (**S**) but these drugs appear to be mildly effective when used in the treatment of chronic neuropathic pain, including multiple sclerosis-related pain (**N**) (**Level I**).

## Glucocorticoids

1. Dexamethasone, compared with placebo, reduces postoperative pain, nausea and vomiting, and fatigue (**Level II**).

## Complementary and alternative medicines

- There is some evidence that some complementary and alternative medicines may be effective in some acute pain states. Adverse effects and interactions with medications have been described with complementary and alternative medicines and must be considered before their use (**N**).

## 5. REGIONALLY AND LOCALLY ADMINISTERED ANALGESIC DRUGS

### Local anaesthetics

1. Lignocaine is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**N**) (**Level I** [Cochrane Review]).
  2. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level 1**).
  3. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blockade (**N**) (**Level I**).
  4. Continuous perineural infusions of lignocaine (lidocaine) result in less effective analgesia and more motor block than long-acting local anaesthetic agents (**U**) (**Level II**).
  5. There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine when given in low doses for regional analgesia (epidural and peripheral nerve blockade) in terms of quality of analgesia or motor blockade (**U**) (**Level II**).
  6. Cardiovascular and central nervous system toxicity of the stereospecific isomers ropivacaine and levobupivacaine is less severe than with racemic bupivacaine (**U**) (**Level II**).
  7. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity, however uncertainties relating to dosage, efficacy and side effects still remain and therefore it is appropriate to administer lipid emulsion once advanced cardiac life support has begun and convulsions are controlled (**N**) (**Level IV**).
- Case reports following accidental overdose with ropivacaine and bupivacaine suggest that resuscitation is likely to be more successful with ropivacaine (**U**).

### Opioids

1. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl after Caesarean section (**U**) (**Level I**).
2. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**N**) (**Level I**).
3. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo when administered after surgery (**R**) (**Level I**).

4. Evidence for a clinically relevant peripheral opioid effect at non-articular sites, including perineural, is inconclusive **(U) (Level I)**.
5. Epidural pethidine produces better pain relief and less sedation than IV pethidine after Caesarean section **(U) (Level II)**.
6. Extended release epidural morphine provides analgesia for up to 48 hours, however central depressant effects, including respiratory depression, may also be increased and prolonged **(N) (Level II)**.
- No neurotoxicity has been shown at normal clinical intrathecal doses of morphine, fentanyl and sufentanil **(U)**.
- Neuraxial administration of bolus doses of hydrophilic opioids carries an increased risk of delayed sedation and respiratory depression compared with lipophilic opioids **(U)**.

### **Adjuvant Drugs**

1. Intrathecal clonidine improves duration of analgesia and anaesthesia when used as an adjunct to intrathecal local anaesthetics **(N) (Level I)**.
2. Clonidine improves duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for peribulbar, peripheral nerve and plexus blocks **(N) (Level I)**.
3. Intrathecal neostigmine marginally improves perioperative and peripartum analgesia in combination with other spinal medications but is associated with significant side effects **(S) (Level I)**.
4. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia **(U) (Level I)**.
5. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing side effects **(U) (Level I)**.
6. Intrathecal midazolam combined with a local anaesthetic prolongs the time to first analgesia and reduces postoperative nausea and vomiting **(N) (Level I)**.
7. Following Caesarean section, intrathecal morphine provides improved analgesia compared with placebo **(N) (Level I)** and more prolonged analgesia compared with more lipophilic opioids **(N) (Level II)**.
8. Intrathecal clonidine added to intrathecal morphine improves and prolongs analgesia **(N) (Level II)**.
9. Epidural clonidine reduces postoperative systemic opioid requirements **(N) (Level II)**.
10. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia **(U) (Level II)**.
11. In obstetrics, epidural neostigmine improves postoperative analgesia without increasing the incidence of adverse events **(N) (Level II)**.
12. Addition of either clonidine or dexmedetomidine to intrathecal bupivacaine increases the speed of onset and duration of motor and sensory block without additional side effects **(N) (Level II)**.

## **Anti-inflammatory drugs**

### **Corticosteroids**

1. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**N**) (**Level I**).
2. Lumbar epidural steroid administration is effective for short-term relief of acute radicular pain (**N**) (**Level I**).
3. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**N**) (**Level II**).
4. Intravenous regional anaesthesia combining dexamethasone with lignocaine improves analgesia for up to 24 hours (**N**) (**Level II**).
5. There is a risk of septic arthritis with intra-articular steroids (**N**) (**Level IV**).

### **Non-steroidal anti-inflammatory drugs**

1. Topical NSAIDs are of limited efficacy in lateral elbow pain and provide short-term functional improvement; they result in fewer gastrointestinal side effects compared with oral NSAIDs (**N**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs added to local anaesthetic solutions for IVRA improve postoperative analgesia (**N**) (**Level I**).
3. Topical NSAIDs are effective in treating acute strains, sprains or sports injuries for up to 1 week with ketoprofen being significantly better than all other topical NSAIDs, and indomethacin similar to placebo (**N**) (**Level I**).
4. Topical diclofenac significantly reduces pain and inflammation in a range of sports, traumatic and inflammatory conditions and in acute musculoskeletal injuries is at least comparable to oral naproxen (**N**) (**Level I**).
5. Topical NSAIDs are effective analgesics for traumatic corneal abrasions (**N**) (**Level I**).

## **6. ADMINISTRATION OF SYSTEMIC ANALGESIC DRUGS**

1. Paracetamol combined with codeine is more effective than either drug alone and shows a dose-response effect (**N**) (**Level I** [Cochrane Review]).
2. NSAIDs (both nsNSAIDs and coxibs) given parenterally or rectally are not more effective and do not result in fewer side effects than the same drug given orally (**U**) (**Level I** [Cochrane Review]).
3. Paracetamol combined with tramadol is more effective than either drug alone and shows a dose-response effect (**N**) (**Level I**).
4. Early postoperative oral administration of paracetamol results in highly variable plasma concentrations that may remain subtherapeutic in some patients (**N**) (**Level II**).
5. Rectal administration of single doses of paracetamol results in highly variable plasma concentrations that often remain subtherapeutic (**N**) (**Level II**).
6. Intermittent subcutaneous morphine injections are as effective as intramuscular injections and have better patient acceptance (**U**) (**Level II**).
7. Intranasal opioids, in particular the more lipid-soluble drugs such as fentanyl, are effective for the management of acute pain (**N**) (**Level II**).

8. Continuous intravenous infusion of opioids in the general ward setting is associated with an increased risk of respiratory depression compared with other methods of parenteral opioid administration (**U**) (**Level IV**).
9. Transdermal fentanyl should not be used in the management of acute pain because of safety concerns and difficulties in short-term dose adjustments needed for titration; furthermore, in most countries, it lacks regulatory approval for use in other than opioid-tolerant patients (**S**) (**Level IV**).
- Other than in the treatment of severe acute pain, and providing there are no contraindications to its use, the oral route is the route of choice for the administration of most analgesic drugs (**U**).
- Titration of opioids for severe acute pain is best achieved using intermittent intravenous bolus doses as it allows more rapid titration of effect and avoids the uncertainty of drug absorption by other routes (**U**).
- Controlled-release opioid preparations should only be given at set time intervals (**U**).
- Immediate-release opioids should be used for breakthrough pain and for titration of controlled-release opioids (**U**).
- The use of controlled-release opioid preparations as the sole agents for the early management of acute pain is discouraged because of difficulties in short-term dose adjustments needed for titration (**U**).
- Neither oral transmucosal fentanyl citrate nor fentanyl buccal tablets should be used in the management of acute pain because of safety concerns and, in most countries, lack of regulatory approval for use in other than opioid-tolerant patients (**N**).

## 7. PCA, REGIONAL AND OTHER LOCAL ANALGESIA TECHNIQUES

### ***Patient-controlled analgesia***

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**S**) (**Level I** [Cochrane review]).
2. Opioid administration by intravenous PCA leads to higher opioid consumption (**R**), a higher incidence of pruritus (**R**), and no difference in other opioid-related adverse effects (**S**) or hospital stay (**S**) compared with traditional methods of intermittent parenteral opioid administration (**Level I** [Cochrane review]).
3. In settings where there are high nurse-patient ratios there may be no difference in effectiveness of PCA and conventional parenteral opioid regimens (**N**) (**Level I**).
4. Patient preference for intravenous PCA is higher when compared with conventional regimens (**U**) (**Level I**).
5. The addition of ketamine to PCA morphine does not improve analgesia or reduce the incidence of opioid-related side effects (**U**) (**Level I**).
6. Iontophoretic fentanyl PCA may not be as effective as intravenous morphine PCA, with more patients withdrawing from studies because of inadequate pain relief (**Level I**).
7. There is little evidence that one opioid via PCA is superior to another with regards to analgesic or adverse effects in general; although on an individual patient basis, one opioid may be better tolerated than another (**U**) (**Level II**).



8. There is no analgesic benefit in adding naloxone to the PCA morphine solution; however in ultra-low doses the incidence of nausea and pruritus may be decreased (**U**) (**Level II**).
  9. The addition of a background infusion to intravenous PCA does not improve pain relief or sleep, or reduce the number of PCA demands (**U**) (**Level II**).
  10. Subcutaneous PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
  11. Intranasal PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
  12. The risk of respiratory depression with PCA is increased when a background infusion is used (**U**) (**Level IV**).
- Adequate analgesia needs to be obtained prior to commencement of PCA. Initial orders for bolus doses should take into account individual patient factors such as a history of prior opioid use and patient age. Individual PCA prescriptions may need to be adjusted (**U**).
  - The routine addition of antiemetics to PCA opioids is not encouraged, as it is of no benefit compared with selective administration (**U**).
  - PCA infusion systems must incorporate antisiphon valves and in non-dedicated lines, antireflux valves (**U**).
  - Drug concentrations should be standardised within institutions to reduce the chance of programming errors (**U**).
  - Operator error remains a common safety problem (**N**).

### ***Epidural analgesia***

1. Thoracic epidural analgesia for open abdominal aortic surgery reduces the duration of tracheal intubation and mechanical ventilation, as well as the incidence of myocardial infarction, acute respiratory failure, gastrointestinal complications and renal insufficiency (**N**) (**Level I** [Cochrane]).
2. For all types of surgery, epidural analgesia provides better postoperative pain relief compared with parenteral (including PCA) opioid administration (**S**) (**Level I** [Cochrane review]); except epidural analgesia using a hydrophilic opioid only (**N**) (**Level I**).
3. High thoracic epidural analgesia used for coronary artery bypass graft surgery reduces postoperative pain, risk of dysrhythmias, pulmonary complications and time to extubation when compared with IV opioid analgesia (**N**) (**Level I**).
4. Epidural local anaesthetics improve oxygenation and reduce pulmonary infections and other pulmonary complications compared with parenteral opioids (**S**) (**Level I**).
5. Thoracic epidural analgesia improves bowel recovery after abdominal surgery (including colorectal surgery) (**S**) (**Level I**).
6. Thoracic epidural analgesia extended for more than 24 hours reduces the incidence of postoperative myocardial infarction (**U**) (**Level I**).
7. Epidural analgesia is not associated with increased risk of anastomotic leakage after bowel surgery (**U**) (**Level I**).
8. Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo- or povidone-iodine-impregnated dressings reduce the incidence of catheter colonisation (**N**) (**Level I**).

9. The use of continuous background epidural infusion combined with PCEA results in improved maternal analgesia and reduced unscheduled clinician interventions (**N**) (**Level I**).
  10. Thoracic epidural analgesia reduces need for ventilation in patients with multiple rib fractures (**S**) (**Level I**) and reduces incidence of pneumonia (**U**) (**Level II**).
  11. The combination of thoracic epidural analgesia with local anaesthetics and nutritional support leads to preservation of total body protein after upper abdominal surgery (**U**) (**Level II**).
  12. The risk of permanent neurological damage in association with epidural analgesia is very low; the incidence is higher where there have been delays in diagnosing an epidural haematoma or abscess (**S**) (**Level IV**).
  13. Immediate decompression (within 8 hours of the onset of neurological signs) increases the likelihood of partial or good neurological recovery (**U**) (**Level IV**).
- The provision of epidural analgesia by continuous infusion or patient-controlled administration of local anaesthetic-opioid mixtures is safe on general hospital wards, as long as supervised by an anaesthesia-based pain service with 24-hour medical staff cover and monitored by well-trained nursing staff (**U**).
  - Magnetic resonance imaging investigation may be warranted if patients who have had an epidural catheter inserted develop a fever and infection at the catheter insertion site; urgent investigation is especially indicated if other signs are present that could indicate an abscess, such as back pain or neurological change (**N**).

### ***Intrathecal analgesia***

1. Intrathecal morphine offers improved analgesia and opioid-sparing for up to 24 hours especially following abdominal surgery (**S**) (**Level I**).
  2. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**N**) (**Level I**).
  3. After major surgery, the incidence of respiratory depression and pruritus is higher with intrathecal morphine compared with IV PCA opioids, but there is no difference in the incidence of nausea and vomiting (**N**) (**Level I**).
- Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (**U**).
  - The absence of consistent dose-responsiveness to the efficacy of intrathecal opioids or the adverse event rate, suggests that the lowest effective dose should be used in all circumstances (**N**).

### ***Regional analgesia and concurrent anticoagulant medications***

1. Anticoagulation is the most important risk factor for the development of epidural haematoma after neuraxial blockade (**U**) (**Level IV**).
- Consensus statements of experts guide the timing and choice of regional anaesthesia and analgesia in the context of anticoagulation, but do not represent a standard of care and will not substitute the risk/benefit assessment of the individual patient by the individual anaesthetist (**U**).

### ***Other regional and local analgesic techniques***

1. Topical EMLA® cream (eutectic mixture of lignocaine [lidocaine] and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (**U**) (**Level I** [Cochrane Review]).
2. Compared with opioid analgesia, continuous peripheral nerve blockade (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as nausea, vomiting, pruritus and sedation (**N**) (**Level I**).
3. Femoral nerve block provides better analgesia compared with parenteral opioid-based techniques after total knee arthroplasty (**S**) (**Level I**).
4. Compared with thoracic epidural analgesia, continuous thoracic paravertebral analgesia results in comparable analgesia but has a better side effect profile (less urinary retention, hypotension, nausea, and vomiting) than epidural analgesia and leads to a lower incidence of postoperative pulmonary complications (**N**) (**Level I**).
5. Blocks performed using ultrasound guidance are more likely to be successful, faster to perform, with faster onset and longer duration compared with localisation using a peripheral nerve stimulator (**N**) (**Level I**).
6. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo (**R**) (**Level I**).
7. Intra-articular local anaesthetics reduce postoperative pain to a limited extent only (**U**) (**Level I**).
8. Continuous local anaesthetic wound infusions lead to reductions in pain scores (at rest and with activity), opioid consumption, postoperative nausea and vomiting, and length of hospital stay; patient satisfaction is higher and there is no difference in the incidence of wound infections (**S**) (**Level I**).
9. Intraperitoneal local anaesthetic after laparoscopic cholecystectomy improves early postoperative pain relief (**N**) (**Level I**).
10. Intraurethral instillation of lignocaine gel provides analgesia during flexible cystoscopy (**N**) (**Level I**).
11. Continuous interscalene analgesia provides better analgesia, reduced opioid-related side effects and improved patient satisfaction compared with IV PCA after open shoulder surgery (**U**) (**Level II**).
12. Continuous femoral nerve blockade provides postoperative analgesia that is as effective as epidural analgesia but with fewer side effects following total knee joint replacement surgery (**U**) (**Level II**).
13. Continuous posterior lumbar plexus analgesia is as effective as continuous femoral analgesia following total knee joint replacement surgery (**U**) (**Level II**).
14. Intra-articular bupivacaine infusions have been associated with chondrolysis and their use has been cautioned against (**N**) (**Level IV**).

## 8. NON-PHARMACOLOGICAL TECHNIQUES

### *Psychological interventions*

1. Listening to music produces a small reduction in postoperative pain and opioid requirement (**N**) (**Level I** [Cochrane Review]).
2. The evidence that information is effective in reducing procedure-related pain is tentatively supportive and not sufficient to make recommendations (**Q**) (**Level I**).
3. Distraction is effective in procedure-related pain in children (**N**) (**Level I**).
4. Training in coping methods or behavioural instruction prior to surgery reduces pain, negative affect and analgesic use (**U**) (**Level I**).
5. Evidence of benefit of hypnosis in the management of acute pain is inconsistent (**W**) (**Level I**).
6. Immersive virtual reality distraction is effective in reducing pain in some clinical situations (**N**) (**Level III-2**).
7. Evidence for any benefit of relaxation techniques in the treatment of acute pain is weak and inconsistent (**N**) (**Level IV**).

### *Transcutaneous electrical nerve stimulation*

1. Overall, there is no evidence that TENS is effective for the treatment of pain during labour (**N**) (**Level I** [Cochrane Review]).
2. Certain stimulation patterns of TENS are effective in some acute pain settings (**S**) (**Level I**).

### *Acupuncture*

1. Acupuncture reduces postoperative pain as well as opioid-related adverse effects (**N**) (**Level I**).
2. Acupuncture may be effective in some other acute pain settings (**U**) (**Level I**).

## 9. SPECIFIC CLINICAL SITUATIONS

### *Postoperative pain*

#### **Risks of acute postoperative neuropathic pain**

1. Acute neuropathic pain occurs after trauma and surgery (**U**) (**Level IV**).
- Diagnosis and subsequent appropriate treatment of acute neuropathic pain might prevent development of chronic pain (**U**).

#### **Acute postamputation pain syndromes**

1. Continuous regional blockade via nerve sheath catheters provides effective postoperative analgesia after amputation, but has no preventive effect on phantom limb pain (**U**) (**Level II**).
2. Calcitonin, morphine, ketamine, gabapentin, amitriptyline and tramadol reduce phantom limb pain (**S**) (**Level II**).
3. Sensory discrimination training and motor imagery reduce chronic phantom limb pain (**S**) (**Level II**).

4. Ketamine, lignocaine (lidocaine), tramadol and amitriptyline reduce stump pain (**S**) (**Level II**).
  5. Perioperative epidural analgesia reduces the incidence of severe phantom limb pain (**U**) (**Level III-2**).
- Perioperative ketamine may prevent severe phantom limb pain (**U**).

#### Other postoperative pain syndromes

1. Perioperative epidural analgesia reduces the incidence of post-thoracotomy pain syndrome (**N**) (**Level II**).
2. Cryoanalgesia for thoracotomy relieves postoperative pain but increases the risk of post-thoracotomy pain syndrome (**N**) (**Level II**).
3. Preincisional paravertebral block and perioperative use of gabapentin, mexiletine and/or eutectic mixture of local anaesthetic reduce the incidence of postmastectomy pain (**N**) (**Level II**).
4. Post-thoracotomy, postmastectomy, postherniotomy and posthysterectomy pain syndromes occur frequently (**N**) (**Level IV**).

#### Day-stay or short-stay surgery

1. Infiltration of the wound with local anaesthetic agents provides good and long-lasting analgesia after ambulatory surgery (**U**) (**Level II**).
2. Peripheral nerve blocks with long-acting local anaesthetic agents provide long-lasting postoperative analgesia after ambulatory surgery (**U**) (**Level II**).
3. Single shot infraclavicular blocks provide effective analgesia and less nausea following hand and wrist surgery and earlier ambulation and hospital discharge compared with general anaesthesia (**N**) (**Level II**).
4. Continuous peripheral nerve blocks provide extended analgesia after ambulatory surgery (**U**) (**Level II**), leading to reduced opioid requirements, less sleep disturbance, earlier achievement of discharge criteria and improved rehabilitation (**N**) (**Level II**).
5. Continuous peripheral nerve blocks have been shown to be safe at home, if adequate resources and patient education are provided (**U**) (**Level IV**).
6. Pain relief after ambulatory surgery remains poor (**N**) (**Level IV**) and is a common cause of unplanned readmissions (**N**) (**Level III-3**).

#### Cranial neurosurgery

1. Morphine is more effective than codeine and tramadol for pain relief after craniotomy (**N**) (**Level II**).
2. Local anaesthetic infiltration of the scalp provides early analgesia after craniotomy and reduces incidence of subsequent chronic pain (**N**) (**Level II**).
3. Craniotomy leads to significant pain in the early postoperative period (**N**) (**Level IV**), which is however not as severe as pain from other surgical interventions (**N**) (**Level III-2**).
4. Craniotomy can lead to significant chronic headache (**N**) (**Level IV**).

### **Acute pain following spinal cord injury**

1. Gabapentinoids (gabapentin/pregabalin) (**S**), intravenous opioids, ketamine or lignocaine (lidocaine) (**U**) tramadol, self-hypnosis and electromyograph biofeedback (**N**) are effective in the treatment of neuropathic pain following spinal cord injury (**Level II**).
- ☑ Treatment of acute spinal cord pain is largely based on evidence from studies of other neuropathic and nociceptive pain syndromes (**U**).

### **Acute burn injury pain**

1. The use of biosynthetic dressings is associated with a decrease in time to healing and a reduction in pain during burn dressings changes (**N**) (**Level I** [Cochrane Review]).
2. Opioids, particularly via PCA, are effective in burn pain, including procedural pain (**S**) (**Level II**).
3. Augmented reality techniques (**N**) (**Level II**), virtual reality or distraction techniques (**N**) (**Level III-3**) reduce pain during burn dressings.
4. Gabapentin reduces pain and opioid consumption following acute burn injury (**N**) (**Level III-3**).
5. PCA with ketamine and midazolam mixture provides effective analgesia and sedation for burn dressings (**N**) (**Level IV**).
- ☑ Acute pain following burn injury can be nociceptive and/or neuropathic in nature and may be constant (background pain), intermittent or procedure-related.
- ☑ Acute pain following burn injury requires aggressive multimodal and multidisciplinary treatment.

### **Acute back pain**

1. Acute low back pain is non-specific in about 95% of cases and serious causes are rare; common examination and investigation findings also occur in asymptomatic controls and may not be the cause of pain (**U**) (**Level I**).
2. Advice to stay active, 'activity-focused' printed and verbal information, and behavioural therapy interventions are beneficial in acute low back pain (**U**) (**Level I**).
3. Advice to stay active, exercises, multimodal therapy and pulsed electromagnetic therapy (in the short term) are effective in acute neck pain (**U**) (**Level I**).
4. Soft collars are not effective for acute neck pain (**U**) (**Level I**).
5. Appropriate investigations are indicated in cases of acute low back pain when alerting features ('red flags') of serious conditions are present (**U**) (**Level III-2**).
6. Psychosocial and occupational factors ('yellow flags') appear to be associated with progression from acute to chronic back pain; such factors should be assessed early to facilitate intervention (**U**) (**Level III-2**).

### **Acute musculoskeletal pain**

1. Topical and oral NSAIDs improve acute shoulder pain (**U**) (**Level I**).
2. Subacromial corticosteroid injection relieves acute shoulder pain in the early stages (**U**) (**Level I**).
3. Exercises improve acute shoulder pain in patients with rotator cuff disease (**U**) (**Level I**).

4. Therapeutic ultrasound may improve acute shoulder pain in calcific tendonitis (**U**) (**Level I**).
  5. Advice to stay active, exercises, injection therapy and foot orthoses are effective in acute patellofemoral pain (**U**) (**Level I**).
  6. Low-level laser therapy is ineffective in the management of patellofemoral pain (**U**) (**Level I**).
- A management plan for acute musculoskeletal pain should comprise the elements of assessment (history and physical examination, but ancillary investigations are not generally indicated), management (information, assurance, advice to resume normal activity, pain management) and review to reassess pain and revise management plan (**U**).
  - Information should be provided to patients in correct but neutral terms with the avoidance of alarming diagnostic labels to overcome inappropriate expectations, fears or mistaken beliefs (**U**).
  - Regular paracetamol, then if ineffective, NSAIDs, may be used for acute musculoskeletal pain (**U**).
  - Oral opioids, preferably short-acting agents at regular intervals, may be necessary to relieve severe acute musculoskeletal pain; ongoing need for such treatment requires reassessment (**U**).
  - Adjuvant agents such as anticonvulsants, antidepressants and muscle relaxants are not recommended for the routine treatment of acute musculoskeletal pain (**U**).

### ***Acute medical pain***

#### **Acute abdominal pain**

1. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain (**S**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs, opioids and intravenous metamizole (dipyrone) provide effective analgesia for renal colic (**N**) (**Level I** [Cochrane Review]).
3. Non-selective NSAIDs given for renal colic reduce requirements for rescue analgesia and produce less vomiting compared with opioids, particularly pethidine (meperidine) (**U**) (**Level I** [Cochrane Review]).
4. High frequency TENS is effective in primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
5. The onset of analgesia is faster when non-selective NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
6. Antispasmodics and peppermint oil are effective for the treatment of acute pain in irritable bowel syndrome (**U**) and gastrointestinal spasm (**N**) (**Level I**).
7. Non-selective NSAIDs and vitamin B1 are effective in the treatment of primary dysmenorrhoea (**U**) (**Level I**).
8. There is no difference between pethidine and morphine in the treatment of renal colic (**U**) (**Level II**).
9. Parenteral non-selective NSAIDs are as effective as parenteral opioids in the treatment of biliary colic (**U**) (**Level II**).

### Herpes zoster-associated pain

1. Antiviral agents started within 72 hours of onset of the herpes zoster rash accelerate the resolution of acute pain (**U**) (**Level I**), but do not reduce the incidence of postherpetic neuralgia (**R**) (**Level I**) [Cochrane Review]).
  2. Immunisation of persons aged 60 years or older with varicella-zoster virus vaccine reduces the incidence of herpes zoster and postherpetic neuralgia (**N**) (**Level II**).
  3. Amitriptyline (used in low doses for 90 days from onset of the herpes zoster rash) reduces the incidence of postherpetic neuralgia (**U**) (**Level II**).
  4. Topical aspirin, topical lignocaine patch or oxycodone controlled release, provide analgesia in herpes zoster (**N**) (**Level II**).
- Provision of early and appropriate analgesia is an important component of the management of herpes zoster and may have benefits in reducing the incidence of postherpetic neuralgia.

### Acute cardiac pain

1. Morphine is an effective and appropriate analgesic for acute cardiac pain (**U**) (**Level II**).
  2. Nitroglycerine is an effective and appropriate agent in the treatment of acute ischaemic chest pain (**U**) (**Level IV**).
- The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, including the use of supplemental oxygen, nitroglycerine, beta blockers and strategies to improve coronary vascular perfusion (**U**).

### Acute pain associated with haematological disorders

1. Parenteral corticosteroids appear to reduce the duration of analgesia requirements and length of hospital stay, without major side effects, during sickle cell crises (**S**) (**Level I** [Cochrane Review]).
  2. There is insufficient evidence to suggest that fluid replacement therapy reduces pain associated with sickle cell crises (**N**) (**Level I** [Cochrane Review]).
  3. Hydroxyurea is effective in decreasing the frequency of acute crises, life-threatening complications and transfusion requirements in sickle cell disease (**U**) (**Level I**).
  4. Intravenous opioid loading optimises analgesia in the early stages of an acute sickle cell crisis. Effective analgesia may be continued with intravenous opioid therapy, optimally as PCA (**U**) (**Level II**).
  5. Oxygen supplementation does not decrease pain during a sickle cell crisis (**U**) (**Level II**).
- Pethidine should be avoided for the treatment of acute pain in sickle cell disease or acute porphyria, with increased seizure risk being a potential problem (**U**).



## Acute headache

### *Tension-type headache*

1. Acupuncture is effective in the treatment of tension-type headache (**N**) (**Level I** [Cochrane Review]).
2. The addition of caffeine to aspirin or paracetamol improves analgesia in the treatment of episodic tension-type headache (**U**) (**Level I**).
3. Simple analgesics such as aspirin, paracetamol or NSAIDs, either alone or in combination, are effective in the treatment of episodic tension-type headache (**U**) (**Level II**).

### *Migraine*

4. Triptans are effective in the treatment of severe migraine (**U**) (**Level I**).
5. Aspirin-metoclopramide is effective in the treatment of mild-to-moderate migraine (**U**) (**Level I**).
6. Parenteral metoclopramide is effective in the treatment of migraine (**U**) (**Level I**).
7. Over-the-counter medications, including combined paracetamol-aspirin-caffeine preparations, are effective in the treatment of migraine with mild-to-moderate symptoms and disability (**N**) (**Level I**).
8. Effervescent aspirin, ibuprofen or dipyrone are effective in the treatment of migraine (**N**) (**Level I**).
9. In children or adolescents with migraine, ibuprofen or intranasal sumatriptan (over 12 years of age) are effective treatments (**N**) (**Level I**).
10. Pethidine is less effective than most other migraine treatments and should not be used (**N**) (**Level I**).
11. Parenteral prochlorperazine, chlorpromazine or droperidol are effective in the treatment of migraine, especially in the emergency department (**N**) (**Level II**).
12. Paracetamol is effective in the treatment of mild-to-moderate migraine (**U**) (**Level II**).
13. A 'stratified care strategy' is effective in treating migraine (**U**) (**Level II**).

### *Cluster headache*

14. Parenteral triptans (sumatriptan or zolmitriptan) (**S**) or oxygen therapy (**U**), are effective treatments for cluster headache attacks (**Level II**).

### *Postdural puncture headache*

15. There is no evidence that bed rest is beneficial in the treatment and prevention of postdural puncture headache (**U**) (**Level I** [Cochrane Review]).
  16. The incidence of postdural puncture headache is reduced by using small-gauge spinal needles and/or a non-cutting bevel (**U**) (**Level I**).
  17. Further high quality trials are required to determine the efficacy of epidural blood patch administration in the treatment of postdural puncture headache (**U**) (**Level I**), however benefit is likely (**N**) (**Level II**).
- Opioids should be used with extreme caution in the treatment of headache (**U**).
  - Frequent use of analgesics, triptans and ergot derivatives in the treatment of recurrent acute headache may lead to medication overuse headache (**U**).

## Acute pain associated with neurological disorders

- ☑ Treatment of acute pain associated with neurological disorders is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain states.

## Orofacial pain

### *Dental extraction*

1. Paracetamol 1000 mg provides safe and effective analgesia with minimal adverse effects, following dental extraction (**N**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs, coxibs, paracetamol, opioids or tramadol provide effective analgesia after dental extraction (**U**) (**Level I**).
3. Non-selective NSAIDs or coxibs provide better analgesia with fewer adverse effects, than paracetamol, paracetamol/opioid, paracetamol/tramadol, tramadol or weaker opioids, following dental extraction (**U**) (**Level I**).
4. Perioperative steroid administration reduces swelling (**S**) but not pain (**R**) (**Level I**) and reduces postoperative nausea (**U**) (**Level II**), following third molar extraction.
5. The combination of paracetamol with a non-selective NSAID provides analgesia that is superior to each drug given alone following third molar extraction (**N**) (**Level II**).

### *Tonsillectomy*

6. Aspirin and some NSAIDs increase the risk of perioperative bleeding after tonsillectomy (**U**) except in children (**N**) (**Level I** [Cochrane Review]).
7. Peritonsillar infiltration or topical application of local anaesthetics produces a modest reduction in acute post-tonsillectomy pain (**R**) with topical application and infiltration being equally effective (**N**) (**Level I**).
8. Intraoperative dexamethasone administration reduces acute pain (**S**) (**Level I**), nausea and vomiting (**U**) (**Level I**) post-tonsillectomy, although there may be an increased bleeding risk (**N**) (**Level II**).
9. Peritonsillar infiltration with tramadol or ketamine may reduce post-tonsillectomy pain and analgesia requirements, but was no more effective than equivalent doses administered parenterally (**N**) (**Level II**).

### *Mucositis*

10. Opioids, via PCA or a continuous infusion, provide effective analgesia in mucositis, however PCA is associated with reduced opioid requirements and pain duration (**U**) (**Level I** [Cochrane Review]).
11. Topical treatments, including oral cooling or povidone-iodine solution, provide effective analgesia in mucositis (**N**) (**Level I**).
12. Oral laser light therapy reduces mucositis pain and progression (**N**) (**Level II**).

### *Pharyngitis*

13. Steroids improve analgesia in sore throat, in particular in severe and exudative conditions (**N**) (**Level I**).
14. Paracetamol, nsNSAIDs or coxibs and opioids, administered as monotherapy or in combination, are effective analgesics in acute pharyngitis (**N**) (**Level I**).

15. Steroids may reduce acute pain associated with severe pharyngitis or peritonsillar abscess (following drainage and antibiotics) **(N) (Level II)**.
- Recurrent or persistent orofacial pain requires biopsychosocial assessment and appropriate multidisciplinary approaches. Neuropathic orofacial pain (atypical odontalgia, phantom pain) may be exacerbated by repeated dental procedures, incorrect drug therapy or psychological factors **(U)**.

### **Acute pain in patients with HIV infection**

1. High concentration capsaicin patches, smoking cannabis and lamotrigine are effective in treating neuropathic pain in patients with HIV/AIDS **(N) (Level II)**.
  2. Nucleoside reverse transcriptase inhibitor (NRTIs)-induced neuropathic pain in HIV/AIDS patients is treatable with acetyl-L-carnitine (ALCAR) **(N) (Level II)**.
  3. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use, but also more intense pain **(N) (Level III-2)**.
- Neuropathic pain is common in patients with HIV/AIDS **(U)**.
- In the absence of specific evidence, the treatment of pain in patients with HIV/AIDS should be based on similar principles to those for the management of cancer and chronic pain **(U)**.
- Interaction between antiretroviral and antibiotic medications and opioids should be considered in this population **(U)**.

### **Acute cancer pain**

1. Oral transmucosal fentanyl is effective in treating acute breakthrough pain in cancer patients **(S) (Level I [Cochrane Review])**.
  2. Radiotherapy and bisphosphonates are effective treatments of acute cancer pain due to bone metastases **(N) (Level I [Cochrane Review])**.
  3. Opioid doses for individual patients with cancer pain should be titrated to achieve maximum analgesic benefit with minimal adverse effects **(S) (Level II)**.
  4. Analgesic medications prescribed for cancer pain should be adjusted to alterations of pain intensity **(U) (Level III)**.
- Acute pain in patients with cancer often signals disease progression; sudden severe pain in patients with cancer should be recognised as a medical emergency and immediately assessed and treated **(U)**.
- Cancer patients receiving controlled-release opioids need access to immediate-release opioids for breakthrough pain; if the response is insufficient after 30 to 60 minutes, administration should be repeated **(U)**.
- Breakthrough analgesia should be one-sixth of the total regular daily opioid dose in patients with cancer pain (except when methadone is used, because of its long and variable half life) **(U)**.
- If nausea and vomiting accompany acute cancer pain, parenteral opioids are needed **(U)**.

### ***Acute pain management in intensive care***

1. Daily interruptions of sedative infusions reduce duration of ventilation and ICU stay without causing adverse psychological outcomes (**U**) (**Level II**) or increasing the risk of myocardial ischaemia (**N**) (**Level III-1**).
  2. Gabapentin is more effective than carbamazepine in reducing the pain associated with Guillain-Barre syndrome (**S**) (**Level II**).
  3. Remifentanyl or remifentanyl with morphine provides better analgesia than morphine alone in ventilated intensive care unit patients (**N**) (**Level II**).
  4. The use of formal pain and agitation assessment and subsequent treatment in ventilated intensive care unit patients decreases the incidence of pain and duration of ventilation (**N**) (**Level III-1**).
- Observation of behavioural and physiological responses permits assessment of pain in unconscious patients (**U**).
  - Patients should be provided with appropriate sedation and analgesia during potentially painful procedures (**U**).

### ***Acute pain management in emergency departments***

#### *Migraine*

1. Triptans or phenothiazines (prochlorperazine, chlorpromazine) are effective in at least 75% of patients presenting to the emergency department with migraine (**U**) (**Level II**).

#### *Local anaesthesia*

2. Topical local anaesthetic agents (including those in liposomal formulations) (**N**) (**Level I**) or topical local anaesthetic-adrenaline agents (**N**) (**Level II**) provide effective analgesia for wound care in the emergency department.
  3. Femoral nerve blocks in combination with intravenous opioids are superior to intravenous opioids alone in the treatment of pain from a fractured neck of femur (**S**) (**Level II**).
- To ensure optimal management of acute pain, emergency departments should adopt systems to ensure adequate assessment of pain, provision of timely and appropriate analgesia, frequent monitoring and reassessment of pain (**U**).

### ***Prehospital analgesia***

1. Intravenous morphine, fentanyl and tramadol are equally effective in the prehospital setting (**N**) (**Level II**).
2. Nitrous oxide is an effective analgesic agent in prehospital situations (**N**) (**Level IV**).
3. Methoxyflurane, in low concentrations, may be an effective analgesia in the hospital and prehospital setting (**N**) (**Level IV**).
4. Ketamine provides effective analgesia in the prehospital setting (**N**) (**Level IV**).
5. Moderate to severe pain is common in both adult and paediatric patients in the prehospital setting (**N**) (**Level IV**).

- ☑ The ideal prehospital analgesic agent should be simple to use, safe, effective, not lead to delays in transport and have a rapid onset and short duration of action so that it can be repeated as often as necessary and titrated to effect for each patient. Consideration should be given to both choice of analgesic drug and route of administration (N).
- ☑ Non-pharmacological measures are effective in providing pain relief and should always be considered and used if practical (N).

## 10. THE PAEDIATRIC PATIENT

### *Long-term consequences of early pain and injury*

- ☑ Following birth, even the most premature neonate responds to nociceptive stimuli (U).
- ☑ In early development more generalised reflex nociceptive responses occur in response to lower intensity stimuli (U).
- ☑ Due to the increased plasticity of the developing nervous system, pain and injury in early life may have adverse long-term consequences (U).

### *Paediatric pain assessment*

- ☑ Pain assessment and measurement are important components of paediatric pain management (U).
- ☑ Pain measurement tools are available for children of all ages (U).
- ☑ Pain measurement tools must be matched to the age and development of the child, be appropriate for the clinical context and be explained and used consistently (U).

### *Management of procedural pain*

1. Sucrose reduces the behavioural response to heel-stick blood sampling in neonates (U) (Level I [Cochrane Review]).
  2. Breastfeeding or breast milk reduces measures of distress in neonates undergoing a single painful procedure compared to positioning or no intervention (U) (Level I [Cochrane Review]).
  3. Distraction, hypnosis, and combined cognitive-behavioural interventions reduce pain and distress associated with needle-related procedures in children and adolescents (S) (Level I [Cochrane Review]).
  4. EMLA® is an effective topical anaesthetic for children, but amethocaine is superior for reducing needle insertion pain (N) (Level I [Cochrane Review]).
  5. Topical local anaesthetic application, inhalation of nitrous oxide (50%) or the combination of both provides effective and safe analgesia for minor procedures (U) (Level I).
  6. Combinations of hypnotic and analgesic agents are effective for procedures of moderate severity (U) (Level II).
- ☑ Inadequate monitoring of the child, lack of adequate resuscitation skills and equipment, and the use of multiple drug combinations has been associated with major adverse outcomes during procedural analgesia and sedation (U).

### **Analgesic agents**

1. Non-selective NSAIDs do not increase the risk of reoperation for bleeding after tonsillectomy in paediatric patients (**R**) (**Level I** [Cochrane Review]).
  2. Dexamethasone reduces post-tonsillectomy pain and postoperative nausea and vomiting (**N**) (**Level I**) but high doses may increase the risk of bleeding (**N**) (**Level II**).
  3. Paracetamol and non-selective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major surgery (**U**) (**Level II**).
  4. The efficacy of oral codeine in children is variable, individual differences in the ability to generate active metabolites may reduce efficacy (**U**) (**Level II**) or increase side effects (**N**) (**Level IV**).
- Safe dosing of paracetamol requires consideration of the age and body weight of the child, and the duration of therapy (**U**).
  - Aspirin should be avoided in children, but serious adverse events after non-selective NSAIDs are rare in children over 6 months of age (**U**).

### **Opioid infusions and PCA**

1. Routine morphine infusion does not improve neurological outcome in ventilated preterm neonates (**N**) (**Level I** [Cochrane Review]).
  2. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**N**) (**Level II**).
  3. Effective PCA prescription in children incorporates a bolus that is adequate for control of movement-related pain, and may include a low dose background infusion (**U**) (**Level II**).
  4. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).
- Intravenous opioids can be used safely and effectively in children of all ages (**U**).
  - Initial doses of opioid should be based on the age, weight and clinical status of the child and then titrated against the individual's response (**U**).

### **Regional analgesia**

1. Topical local anaesthetic does not adequately control pain associated with circumcision in awake neonates (**U**) (**Level I** [Cochrane Review]).
2. Caudal local anaesthetic and dorsal penile nerve block provide perioperative analgesia for circumcision (**U**) (**Level I** [Cochrane Review]).
3. Clonidine prolongs analgesia when added to caudal local anaesthetic blocks (**U**) (**Level I**) and improves analgesia when added to epidural local anaesthetic infusions (**U**) (**Level II**).
4. Wound infiltration, peripheral nerve blocks, and caudal local anaesthetic provide effective analgesia after day-case inguinal surgery (**U**) (**Level II**).
5. Epidural infusions of local anaesthetic and systemic opioids provide similar levels of analgesia (**U**) (**Level II**).
6. Epidural opioids alone are less effective than local anaesthetic or combinations of local anaesthetic and opioid (**U**) (**Level II**).
7. Intrathecal opioids provide prolonged analgesia after surgery (**N**) (**Level II**) and reduce blood loss during spinal fusion (**N**) (**Level II**).

- ☑ Caudal local anaesthetic blocks provide effective analgesia for lower abdominal, perineal and lower limb surgery and have a low incidence of serious complications (**U**).
- ☑ Continuous epidural infusions provide effective postoperative analgesia in children of all ages and are safe if appropriate doses and equipment are used by experienced practitioners, with adequate monitoring and management of complications (**U**).

### ***Acute pain in children with cancer***

1. PCA and continuous opioid infusions are equally effective in the treatment of pain in mucositis, but opioid consumption is less with PCA (**U**) (**Level I**).
2. PCA morphine and hydromorphone are equally effective for the control of pain associated with oral mucositis (**U**) (**Level II**).

## **11. OTHER SPECIFIC PATIENT GROUPS**

### ***The pregnant patient***

#### **Management of acute pain during pregnancy**

1. Exercises reduce back and pelvic pain during pregnancy. There is weak evidence for improvements with acupuncture and chiropractic care (**N**) (**Level I**).
2. Use of NSAIDs during pregnancy is associated with an increased risk of miscarriage (**U**) (**Level III-2**).
- ☑ For pain management in pregnancy non-pharmacological treatment options should be considered where possible before analgesic medications are used (**U**).
- ☑ Use of medications for pain in pregnancy should be guided by published recommendations; ongoing analgesic use requires close liaison between the obstetrician and the medical practitioner managing the pain (**U**).
- ☑ NSAIDs should be used with caution in the last trimester of pregnancy and should be avoided after the 32<sup>nd</sup> week (**U**).

#### **Management of pain during delivery**

1. Epidural and combined spinal-epidural analgesia provide superior pain relief for labour and delivery compared with systemic analgesics (**S**) (**Level I** [Cochrane Review]).
2. Combined spinal-epidural in comparison with epidural analgesia reduces time to effective analgesia and increases the incidence of pruritus (**U**), does not increase maternal satisfaction (**R**), but increases the risk of urinary retention (**N**) (**Level I** [Cochrane Review]).
3. Epidural analgesia does not increase the incidence of Caesarean section or long-term backache (**S**) (**Level I** [Cochrane Review]).
4. Epidural analgesia is associated with increased duration of labour and increased rate of instrumental vaginal delivery (**S**) (**Level I** [Cochrane Review]).
5. Hypnosis used in labour reduces analgesic requirements (**S**) and improves satisfaction (**N**) (**Level I** [Cochrane Review]).
6. Acupuncture reduces analgesic requirements in labour (**U**) (**Level I** [Cochrane Review]).
7. TENS may reduce severe pain in labour but does not reliably reduce pain scores (**U**) or analgesic requirements (**N**) (**Level I** [Cochrane Review]).

8. Local anaesthetic wound infiltration and abdominal nerve blocks reduce opioid consumption following Caesarean section (**N**) (**Level I** [Cochrane Review]).
9. Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, operative delivery and dissatisfaction (**U**) (**Level I**).
10. There is no significant difference in any outcome between use of bupivacaine and ropivacaine for epidural labour analgesia (**U**) (**Level I**).
11. Patient-controlled epidural analgesia provides effective analgesia but optimal settings are not clear (**N**) (**Level I**).
12. Single-injection intrathecal opioids provide comparable early labour analgesia to epidural local anaesthetics with increased pruritus (**U**) (**Level I**).
13. Systemic opioids in labour increase the need for neonatal resuscitation and worsen acid-base status compared with regional analgesia (**U**) (**Level I**).
14. Nitrous oxide has some analgesic efficacy and is safe during labour (**U**) (**Level I**).

#### **Pain management during lactation**

- Prescribing medications during lactation requires consideration of possible transfer into breast milk, uptake by the baby and potential adverse effects for the baby; it should follow available prescribing guidelines (**U**).
- Local anaesthetics, paracetamol and several non-selective NSAIDs, in particular ibuprofen, are considered to be safe in the lactating patient (**U**).
- Morphine and fentanyl are considered safe in the lactating patient and are preferred over pethidine (**U**).

#### **Pain management in the puerperium**

1. Routine episiotomy does not reduce perineal pain (**U**) (**Level I**).
  2. Paracetamol and non-selective NSAIDs are effective in treating perineal pain after childbirth (**U**) (**Level I**).
  3. Paracetamol and non-selective NSAIDs are equally but only modestly effective in treating uterine pain (**U**) (**Level II**).
  4. Topical agents may improve nipple pain, but no one treatment is superior (**N**) (**Level I**).
  5. There is only limited evidence to support the effectiveness of local cooling treatments in treatment of perineal pain after childbirth (**Q**) (**Level I**).
  6. Topical local anaesthetic preparations are not effective for perineal pain after childbirth (**N**) (**Level I**).
- Pain after childbirth requires appropriate treatment as it coincides with new emotional, physical and learning demands and may trigger postnatal depression (**U**).
  - Management of breast and nipple pain should target the cause (**U**).

#### **The older patient**

1. Experimental pain thresholds to a variety of noxious stimuli are altered in older people; there is also a reduction in tolerance to pain (**Q**) (**Level I**).
2. PCA and epidural analgesia are more effective in older people than conventional opioid regimens (**U**) (**Level II**).



3. Reported frequency and intensity of acute pain in clinical situations may be reduced in the older person (**U**) (**Level III-2**).
4. Common unidimensional self-report measures of pain can be used in the older patient in the acute pain setting; in the clinical setting, the verbal descriptor and numerical rating scales may be preferred (**S**) (**Level III-2**).
5. Undertreatment of acute pain is more likely to occur in cognitively impaired patients (**N**) (**Level III-2**).
6. There is an age-related decrease in opioid requirements; significant interpatient variability persists (**U**) (**Level IV**).
7. The use of nsNSAIDs and coxibs in older people requires extreme caution; paracetamol is the preferred non-opioid analgesic (**U**) (**Level IV**).
- The assessment of pain and evaluation of pain relief therapies in the older patient may present problems arising from differences in reporting, cognitive impairment and difficulties in measurement (**U**).
- Measures of present pain may be more reliable than past pain, especially in patients with some cognitive impairment (**U**).
- The physiological changes associated with ageing are progressive. While the rate of change can vary markedly between individuals, these changes may decrease the dose (maintenance and/or bolus) of drug required for pain relief and may lead to increased accumulation of active metabolites (**U**).
- The age-related decrease in opioid requirements is related more to the changes in pharmacodynamics that accompany aging than to the changes in pharmacokinetics (**N**).

### ***Aboriginal and Torres Strait Islander peoples***

1. The verbal descriptor scale may be a better choice of pain measurement tool than verbal numerical rating scales (**U**) (**Level III-3**).
2. Medical comorbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander peoples and New Zealand Maoris, and may influence the choice of analgesic agent (**U**) (**Level IV**).
3. Clinicians should be aware that pain may be under-reported by this group of patients (**U**) (**Level IV**).
- Communication may be hindered by social, language and cultural factors (**U**).
- Provision of quality analgesia requires sensitivity to cultural practices and beliefs, and behavioural expressions of pain (**N**).

### ***Different ethnic and cultural groups***

1. Disparities in assessment and effective treatment of pain exist across ethnic groups (**N**) (**Level III-3**).
- Ethnic and cultural background can significantly affect the ability to assess and treat acute pain (**U**).
- Multilingual printed information and pain measurement scales are useful in managing patients from different cultural or ethnic backgrounds (**U**).

- ☑ Differences between different ethnic and cultural groups should not be used to stereotype patients and lead to assumptions about responses to pain or pain therapies; pain assessment and management should be done on an individual patient basis (**N**).

### ***The patient with obstructive sleep apnoea***

1. Patients with obstructive sleep apnoea may be at higher risk of complications after some types of surgery (**Q**).
  2. Patients with obstructive sleep apnoea have an including an increased risk of obstructive episodes and desaturations (**N**) (**Level III-2**).
  3. Morbidly obese patients undergoing bariatric surgery may be at increased risk of postoperative hypoxaemia independent of a diagnosis of obstructive sleep apnoea (**N**) (**Level III-2**).
  4. Continuous positive airway pressure does not increase the risk of anastomotic leak after upper gastrointestinal surgery (**U**) (**Level III-2**).
- ☑ Management strategies that may increase the efficacy and safety of pain relief in patients with obstructive sleep apnoea include the provision of appropriate multimodal opioid-sparing analgesia, continuous positive airway pressure, monitoring and supervision (in a high-dependency area if necessary) and supplemental oxygen (**U**).

### ***The patient with concurrent hepatic or renal disease***

- ☑ Consideration should be given to choice and dose regimen of analgesic agents in patients with hepatic and particularly renal impairment (**U**).

### ***The opioid-tolerant patient***

1. Opioid-tolerant patients report higher pain scores and have a lower incidence of opioid-induced nausea and vomiting (**U**) (**Level III-2**).
  2. Ketamine improves pain relief after surgery in opioid-tolerant patients (**N**) (**Level II**).
  3. Opioid-tolerant patients may have significantly higher opioid requirements than opioid-naive patients and interpatient variation in the doses needed may be even greater (**N**) (**Level III-2**).
  4. Ketamine may reduce opioid requirements in opioid-tolerant patients (**U**) (**Level IV**).
- ☑ Usual preadmission opioid regimens should be maintained where possible or appropriate substitutions made (**U**).
  - ☑ Opioid-tolerant patients are at risk of opioid withdrawal if non-opioid analgesic regimens or tramadol alone are used (**U**).
  - ☑ PCA settings may need to include a background infusion to replace the usual opioid dose and a higher bolus dose (**U**).
  - ☑ Neuraxial opioids can be used effectively in opioid-tolerant patients although higher doses may be required and these doses may be inadequate to prevent withdrawal (**U**).
  - ☑ Liaison with all health care professionals involved in the treatment of the opioid-tolerant patient is important (**U**).
  - ☑ In patients with escalating opioid requirements the possibility of the development of both tolerance and opioid-induced hyperalgesia should be considered (**N**).

### ***The patient with an addiction disorder***

- ☑ Naltrexone should be stopped at least 24 hours prior to elective surgery (**U**).
- ☑ Patients who have completed naltrexone therapy should be regarded as opioid naive; in the immediate post-treatment phase they may be opioid-sensitive (**U**).
- ☑ Maintenance methadone regimens should be continued where possible (**U**).
- ☑ Buprenorphine maintenance may be continued; if buprenorphine is ceased prior to surgery conversion to an alternative opioid is required (**U**).
- ☑ There is no cross-tolerance between central nervous system stimulants and opioids (**U**).

# 1. PHYSIOLOGY AND PSYCHOLOGY OF ACUTE PAIN

---

## 1.1 APPLIED PHYSIOLOGY OF PAIN

### 1.1.1 Definition of acute pain

Pain is defined by the International Association for the Study of Pain (IASP) as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ (Merskey & Bogduk, 1994). However, the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of suitable pain-relieving treatment. This emphasises the need for appropriate assessment and management of pain when caring for unconscious patients, preverbal or developmentally delayed children, and individuals with impaired communication skills due to disease or language barriers, as well as those who do not possess a command of the caregiver’s language (Craig, 2006). Even individuals with native command of language and cultural skills can face difficulty in communicating the complexities of the pain experience (Craig, 2009).

Acute pain is defined as ‘pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease’. Chronic pain ‘commonly persists beyond the time of healing of an injury and frequently there may not be any clearly identifiable cause’ (Ready & Edwards, 1992).

It is increasingly recognised that acute and chronic pain may represent a continuum rather than distinct entities. Increased understanding of the mechanisms of acute pain has led to improvements in clinical management and in the future it may be possible to more directly target the pathophysiological processes associated with specific pain syndromes.

Section 1.1 focuses on the physiology and pathophysiology of the transmission and modulation of painful stimuli (ie nociception). Psychological factors that impact on the experience of pain are outlined in Section 1.2. However, in individual patients, biological, psychological and environmental or social factors will all interact. An integrated biopsychosocial approach to management that also considers patient preferences and prior experiences is encouraged.

### 1.1.2 Pain perception and nociceptive pathways

The ability of the somatosensory system to detect noxious and potentially tissue-damaging stimuli is an important protective mechanism that involves multiple interacting peripheral and central mechanisms. The neural processes underlying the encoding and processing of noxious stimuli are defined as ‘nociception’ (Loeser & Treede, 2008). In addition to these sensory effects, the perception and subjective experience of ‘pain’ is multifactorial and will be influenced by psychological and environmental factors in every individual.

#### ***Peripheral nociceptors***

The detection of noxious stimuli requires activation of peripheral sensory organs (nociceptors) and transduction into action potentials for conduction to the central nervous system. Nociceptive afferents are widely distributed throughout the body (skin, muscle, joints, viscera, meninges) and comprise both medium-diameter lightly myelinated A-delta fibres and small-diameter, slow-conducting unmyelinated C-fibres. The most numerous subclass of nociceptor

is the C-fibre polymodal nociceptor, which responds to a broad range of physical (heat, cold, pressure) and chemical stimuli. Thermal sensation is detected by a range of transient receptor potential (TRP) channels (Patapoutian et al, 2009). A number of receptors have been postulated to signal noxious mechanical stimuli, including acid-sensing ion channels (ASICs), TRPs and potassium channels (Woolf & Ma, 2007).

Tissue damage, such as that associated with infection, inflammation or ischaemia, produces disruption of cells, degranulation of mast cells, secretion by inflammatory cells, and induction of enzymes such as cyclo-oxygenase-2 (COX-2). Ranges of chemical mediators act either directly via ligand-gated ion channels or via metabotropic receptors to activate and/or sensitise nociceptors (see Table 1.1). Endogenous modulators of nociception, including proteinases (Russell & McDougall, 2009), pro-inflammatory cytokines (eg  $\text{TNF}\alpha$ , IL-1 $\beta$ , IL-6) (Schafers & Sorokin, 2008), anti-inflammatory cytokines (eg IL-10) (Sloane et al, 2009) and chemokines (eg CCL3, CCL2, CX3CL1) (Woolf & Ma, 2007; White & Wilson, 2008), can also act as signalling molecules in pain pathways. Following activation, intracellular kinase cascades result in phosphorylation of channels (such as voltage-gated sodium and TRP channels), alterations in channel kinetics and threshold, and sensitisation of the nociceptor. Neuropeptides (substance P and calcitonin gene-related peptide) released from the peripheral terminals also contribute to the recruitment of serum factors and inflammatory cells at the site of injury (neurogenic oedema). This increase in sensitivity within the area of injury due to peripheral mechanisms is termed peripheral sensitisation, and is manifest as primary hyperalgesia (Woolf & Ma, 2007). Non-steroidal anti-inflammatory drugs (NSAIDs) modulate peripheral pain by reducing prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) synthesis by locally induced COX-2. Inflammation also induces changes in protein synthesis in the cell body in the dorsal root ganglion and alters the expression and transport of ion channels and receptors, such as TRPV<sub>1</sub> and opioid receptors respectively, to the periphery (Woolf & Ma, 2007). The latter underlies the peripheral action of opioid agonists in inflamed tissue (Stein et al, 2009).

**Table 1.1** Examples of primary afferent and dorsal horn receptors and ligands

<b>Ionotropic receptor</b>	<b>Subtype/subunits</b>	<b>Ligand</b>
TRP	TRPV <sub>1</sub>	heat (>42°C), capsaicin, H <sup>+</sup>
	TRPV <sub>2</sub>	heat (>53°C)
	TRPV <sub>3</sub> , TRPV <sub>4</sub>	warm (>32°C)
	TRPM <sub>8</sub>	cool
	TRPA <sub>1</sub>	noxious cold (<17°C)
acid sensing	DRASIC, ASIC	H <sup>+</sup>
purine	P <sub>2</sub> X <sub>3</sub>	ATP
serotonin	5HT <sub>3</sub>	5HT
NMDA	NR1, NR2A-D, NR3	glutamate
AMPA	iGluR1/iGluR2 and iGluR3/iGluR4	glutamate
kainate	iGluR5	glutamate
<b>Metabotropic receptor</b>	<b>Subtype</b>	<b>Ligand</b>
metabotropic glutamate	mGluR <sub>1,2/3,5</sub>	glutamate
prostanoids	EP1-4	PGE <sub>2</sub>
	IP	PGI <sub>2</sub>

Metabotropic receptor	Subtype	Ligand
histamine	H <sub>1</sub>	HA
serotonin	5HT <sub>1A</sub> , 5HT <sub>4</sub> , 5HT <sub>2A</sub>	5HT
bradykinin	B <sub>1</sub> , B <sub>2</sub>	BK
cannabinoid	CB <sub>1</sub> , CB <sub>2</sub>	anandamide
tachykinin	neurokinin-1 (NK <sub>1</sub> )	substance P, neurokinin A
proteinase	PAR <sub>1-4</sub>	protease
opioid	mu, delta, kappa	enkephalin, dynorphin, beta-endorphin

Notes: 5HT: serotonin; ASIC: acid sensing ion channel; ATP: adenosine triphosphate; BK: bradykinin; DRASIC: subtype of acid sensing ion channel; iGluR: ionotropic glutamate receptor; mGluP: metabotropic glutamate receptor; NK1: neurokinin-1; P2X3: purinergic receptor subtype; PAR: proteinase-activated receptor; PGE<sub>2</sub>: prostaglandin E2; PGI<sub>2</sub>: prostacyclin; TRP: transient receptor potential. Others (eg H1, EP1-4, TRPV<sub>2</sub>) are designated subtypes of receptors rather than abbreviations.

Sodium channels are important modulators of neuronal excitability, signalling and conduction of neuronal action potentials to the central nervous system (CNS) (Cummins et al, 2007; Momin & Wood, 2008; Dib-Hajj et al, 2009). A rapidly inactivating fast sodium current that is blocked by tetrodotoxin is present in all sensory neurons. This is the principal site of action for local anaesthetics, but as the channel is present in all nerve fibres, conduction in sympathetic and motor neurons may also be blocked. Subtypes of slowly activating and inactivating tetrodotoxin-resistant sodium currents are selectively present on nociceptive fibres. Following injury, changes in sodium channel kinetics contribute to hyperexcitability, and specific alterations in the expression of sodium channels (upregulation or downregulation) occur in different pain states. The importance of sodium channels in pain sensitivity is reflected by the impact of mutations in the SCN9A gene encoding the Na(v)1.7 channel: loss-of-function results in insensitivity to pain whereas gain-of-function mutations produce erythromelalgia and severe pain (Dib-Hajj et al, 2008). However, subtype-selective drugs are not yet available (Momin & Wood, 2008).

The cell bodies of nociceptive afferents that innervate the trunk, limbs and viscera are found in the dorsal root ganglia (DRG), while those innervating the head, oral cavity and neck are in the trigeminal ganglia and project to the brainstem trigeminal nucleus. The central terminals of C and A-delta fibres convey information to nociceptive-specific neurons within laminae I and II of the superficial dorsal horn and also to wide dynamic range neurons in lamina V, which encode both innocuous and noxious information. By contrast, large myelinated A-beta fibres transmit light touch or innocuous mechanical stimuli to deep laminae III and IV.

### ***Pain transmission in the spinal cord***

Primary afferent terminals contain excitatory amino acids (eg glutamate, aspartate), peptides (eg substance P, calcitonin gene-related peptide [CGRP]) and neurotrophic factors (eg brain-derived neurotrophic factor [BDNF]), which act as neurotransmitters and are released by different intensity stimuli (Sandkuhler, 2009). Depolarisation of the primary afferent terminal results in glutamate release, which activates postsynaptic ionotropic alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors and rapidly signals information relating to the location and intensity of noxious stimuli. In this 'normal mode' a high intensity stimulus elicits brief localised pain, and the stimulus-response relationship between afferent input and dorsal horn neuron output is predictable and reproducible (Woolf & Salter, 2000).

Summation of repeated C-fibre inputs results in a progressively more depolarised postsynaptic membrane and removal of the magnesium block from the N-methyl-D-aspartate (NMDA)

receptor. This is mediated by glutamate acting on ionotropic NMDA receptors and metabotropic glutamate receptors (mGluR), and by substance P acting on neurokinin-1 (NK<sub>1</sub>) receptors. A progressive increase in action potential output from the dorsal horn cell is seen with each stimulus, and this rapid increase in responsiveness during the course of a train of inputs has been termed 'wind-up'. Long-term potentiation (LTP) is induced by higher frequency stimuli, but the enhanced response outlasts the conditioning stimulus, and this mechanism has been implicated in learning and memory in the hippocampus and pain sensitisation in the spinal cord (Sandkuhler, 2009). Behavioural correlates of these electrophysiological phenomena have been seen in human volunteers, as repeated stimuli elicit progressive increases in reported pain (Hansen et al, 2007).

Intense and ongoing stimuli further increase the excitability of dorsal horn neurons. Electrophysiological studies have identified two patterns of increased postsynaptic response: 'windup' is evoked by low frequency C-fibre (but not A-beta fibre) stimuli and is manifest as an enhanced postsynaptic response during a train of stimuli; and 'LTP' is generated by higher frequency stimuli and outlasts the conditioning stimulus. Increases in intracellular calcium due to influx through the NMDA receptor and release from intracellular stores activate a number of intracellular kinase cascades. Subsequent alterations in ion channel and/or receptor activity and trafficking of additional receptors to the membrane increase the efficacy of synaptic transmission. Centrally mediated changes in dorsal horn sensitivity and/or functional connectivity of A-beta mechanosensitive fibres and increased descending facilitation contribute to 'secondary hyperalgesia' (ie sensitivity is increased beyond the area of tissue injury). Windup, LTP and secondary hyperalgesia may share some of the same intracellular mechanisms but are independent phenomena. All may contribute to 'central sensitisation', which encompasses the increased sensitivity to both C and A-beta fibre inputs resulting in hyperalgesia (increased response following noxious inputs) and allodynia (pain in response to low intensity previously non-painful stimuli) (Sandkuhler, 2009).

The intracellular changes associated with sensitisation may also activate a number of transcription factors both in DRG and dorsal horn neurons, with resultant changes in gene and protein expression (Ji et al, 2009). Unique patterns of either upregulation or downregulation of neuropeptides, G-protein coupled receptors, growth factors and their receptors, and many other messenger molecules occur in the spinal cord and DRG in inflammatory, neuropathic and cancer pain. Further elucidation of changes specific to different pain states may allow more accurate targeting of therapy in the future.

In addition to the excitatory processes outlined above, inhibitory modulation also occurs within the dorsal horn and can be mediated by non-nociceptive peripheral inputs, local inhibitory GABAergic and glycinergic interneurons, descending bulbospinal projections, and higher order brain function (eg distraction, cognitive input). These inhibitory mechanisms are activated endogenously to reduce the excitatory responses to persistent C-fibre activity through neurotransmitters such as endorphins, enkephalins, noradrenaline (norepinephrine) and serotonin, and are also targets for many exogenous analgesic agents.

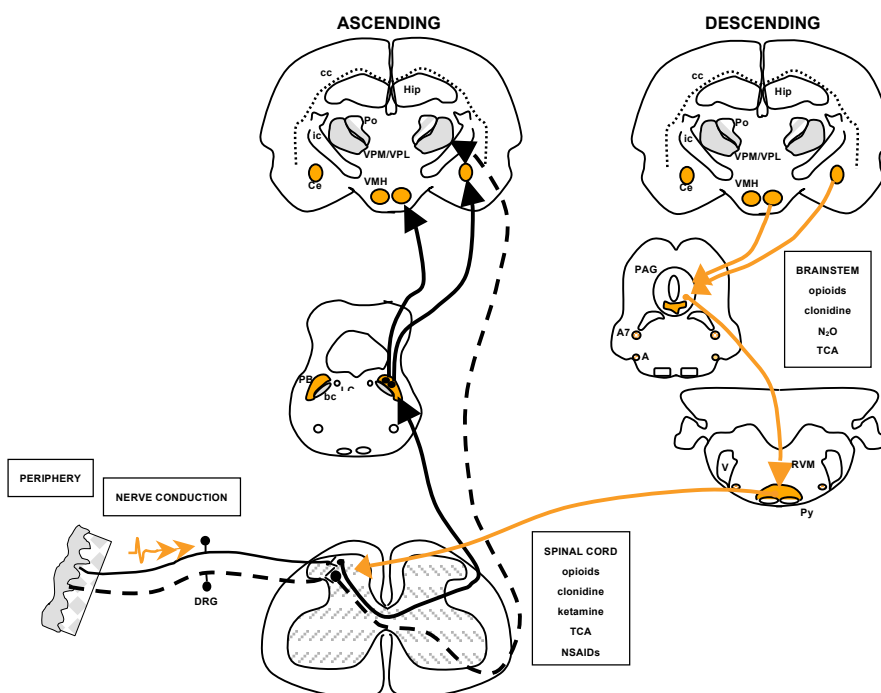
Thus, analgesia may be achieved by either enhancing inhibition (eg opioids, clonidine, antidepressants) or by reducing excitatory transmission (eg local anaesthetics, ketamine).

### **Central projections of pain pathways**

Different qualities of the overall pain experience are subserved by projections of multiple parallel ascending pathways from the spinal cord to the midbrain, forebrain and cortex. The spinothalamic pathway ascends from primary afferent terminals in laminae I and II, via connections in lamina V of the dorsal horn, to the thalamus and then to the somatosensory cortex. This pathway provides information on the sensory-discriminative aspects of pain

(ie the site and type of painful stimulus). The spinoreticular (spinoparabrachial) and spinomesencephalic tracts project to the medulla and brainstem and are important for integrating nociceptive information with arousal, homeostatic and autonomic responses as well as projecting to central areas mediating the emotional or affective component of pain. The spinoparabrachial pathway originates from superficial dorsal horn lamina I neurons that express the NK<sub>1</sub> receptor and projects to the ventromedial hypothalamus and central nucleus of the amygdala. Multiple further connections include those with cortical areas involved in the affective and motivational components of pain (eg anterior cingulate cortex, insular and prefrontal cortex), projections back to the periaqueductal grey (PAG) region of the midbrain and rostroventromedial medulla (RVM), which are crucial for fight or flight responses and stress-induced analgesia, and projections to the reticular formation, which are important for the regulation of descending pathways to the spinal cord (see Figure 1.1) (Hunt & Mantyh, 2001; Tracey & Mantyh, 2007; Tracey, 2008).

**Figure 1.1** The main ascending and descending spinal pain pathways



- Notes: (a) There are 2 primary ascending nociceptive pathways. The spinoparabrachial pathway (red) originates from the superficial dorsal horn and feeds areas of the brain concerned with affect. The spinothalamic pathway (blue) originates from deeper in the dorsal horn (lamina V) after receiving input from the superficial dorsal horn and predominantly distributes nociceptive information to areas of the cortex concerned with discrimination.
- (b) The descending pathway highlighted originates from the amygdala and hypothalamus and terminates in the PAG. Neurons project from here to the lower brainstem and control many of the antinociceptive and autonomic responses that follow noxious stimulation.
- Other less prominent pathways are not illustrated.
- The site of action of some commonly utilised analgesics are included.

**Legend** A: adrenergic nucleus; bc: brachium conjunctivum; cc: corpus colosum; Ce: central nucleus of the amygdala; DRG: dorsal root ganglion; Hip: hippocampus; ic: internal capsule; LC: locus coeruleus; PAG: periaqueductal grey; PB: parabrachial area; Po: posterior group of thalamic nuclei; Py: pyramidal tract; RVM: rostroventromedial medulla; V: ventricle; VMH: ventral medial nucleus of the hypothalamus; VPL: ventral posterolateral nucleus of the thalamus; VPM: ventral posteromedial nucleus of the thalamus

Source: Modified from Hunt (Hunt & Mantyh, 2001).



## **Descending modulatory pain pathways**

Descending pathways contribute to the modulation of pain transmission in the spinal cord via presynaptic actions on primary afferent fibres, postsynaptic actions on projection neurons, or via effects on intrinsic interneurons within the dorsal horn. Sources include direct corticofugal and indirect (via modulatory structures such as the PAG) pathways from the cortex, and the hypothalamus, which is important for coordinating autonomic and sensory information. The RVM receives afferent input from brainstem regions (PAG, parabrachial nucleus and nucleus tractus solitarius) as well as direct ascending afferent input from the superficial dorsal horn, and is an important site for integration of descending input to the spinal cord (Millan, 2002). The relative balance between descending inhibition and facilitation varies with the type and intensity of the stimulus and also with time following injury (Vanegas & Schaible, 2004; Heinricher et al, 2009; Tracey & Mantyh, 2007). Serotonergic and noradrenergic pathways in the dorsolateral funiculus (DLF) contribute to descending inhibitory effects (Millan, 2002) and serotonergic pathways have been implicated in facilitatory effects (Suzuki et al, 2004).

### **1.1.3 Neuropathic pain**

Neuropathic pain has been defined as ‘pain initiated or caused by a primary lesion or dysfunction in the nervous system’ (Merskey & Bogduk, 1994; Loeser & Treede, 2008). Although commonly a cause of chronic symptoms, neuropathic pain can also present acutely following trauma and surgery. The incidence has been conservatively estimated as 3% of acute pain service patients and often it produces persistent symptoms (Hayes et al, 2002). Similarly, acute medical conditions may present with neuropathic pain (Gray, 2008) as discussed further in Section 9.

Nerve injury and associated alterations in afferent input can induce structural and functional changes at multiple points in nociceptive pathways. Damage to peripheral axons results in loss of target-derived growth factors and marked transcriptional changes in DRG of injured neurons (including downregulation of TRP and sodium channels) and a differing pattern in non-injured neighbouring neurons that contributes to spontaneous pain (Woolf & Ma, 2007). In the spinal cord, activation of the same signal transduction pathways as seen following inflammation can result in central sensitisation, with additional effects due to loss of inhibition (Sandkuhler, 2009). Central neurons in the RVM were sensitised after peripheral nerve injury (Carlson et al, 2007) and structural reorganisation in the cortex after spinal cord injury (Wrigley et al, 2009), and changes in cerebral activation have been noted in imaging studies of patients with neuropathic pain (Tracey & Mantyh, 2007).

## **1.2 PSYCHOLOGICAL ASPECTS OF ACUTE PAIN**

Pain is an individual, multifactorial experience influenced, among other things, by culture, previous pain experience, belief, mood and ability to cope. Pain may be an indicator of tissue damage but may also be experienced in the absence of an identifiable cause. The degree of disability experienced in relation to the experience of pain varies; similarly there is individual variation in response to methods to alleviate pain (Eccleston, 2001).

The IASP’s definition of pain (Merskey & Bogduk, 1994) emphasises that pain is not a directly observable or measurable phenomenon, but rather a subjective experience that bears a variable relationship with tissue damage. The task of researchers and clinicians is to identify any factors that might contribute to the individual’s pain experience. These could include somatic (physical) and psychological factors, as well as contextual factors, such as situational

and cultural considerations. Pain expression, which may include facial expressions, body posture, language, vocalizations, and avoidance behaviour, partially represents the complexity of the psychological experience, but is not equivalent to it (Crombez & Eccleston, 2002; Kunz et al, 2004; Vervoot et al, 2009). Engel's enunciation (Engel, 1977) of a biopsychosocial model of illness has provided a framework for considering pain phenomena. A dynamic engagement between the clinician and the patient was recommended in order to explore possible relevant biological, psychological, and socio-cultural contributions to the clinical problem at hand.

The biopsychosocial model of pain (Turk & Monarch, 1995) proposed that biological factors can influence physiological changes and that psychological factors are reflected in the appraisal and perception of internal physiological phenomena. These appraisals and behavioural responses are, in turn, influenced by social or environmental factors, such as reinforcement contingencies (eg Flor et al, 2002). At the same time, the model also proposes that psychological and social factors can influence biological factors, such as hormone production, activity in the autonomic nervous system and physical deconditioning. Experimental evidence supports these propositions (Flor & Hermann, 2004). Other concepts and models of pain which challenge traditional reductionist, mind-body or biomedical paradigms have also been promulgated (Quintner et al, 2008).

### 1.2.1 Psychological factors

Psychological factors that influence the experience of pain include the processes of attention, other cognitive processes (eg memory/learning, thought processing, beliefs, mood), behavioural responses, and interactions with the person's environment.

#### **Attention**

In relation to pain, attention is viewed as an active process and the primary mechanism by which nociception accesses awareness and disrupts current activity (Eccleston & Crombez, 1999).

The degree to which pain may interrupt attention depends on factors such as intensity, novelty, unpredictability, degree of awareness of bodily information, threat value of pain, catastrophic thinking, presence of emotional arousal, environmental demands (such as task difficulty), and emotional significance. Evidence from experimental studies has demonstrated that anxiety sensitivity (Keogh & Cochrane, 2002 **Level III-2**) and pain catastrophising (Vancleef & Peters, 2006 **Level III-2**) may also influence the interruptive qualities of pain on attention.

#### **Learning and memory**

The role of learning or memory has primarily been studied in laboratory settings with experimentally induced pain. A number of studies using healthy subjects have demonstrated that reports of pain (eg pain severity ratings) can be operantly conditioned by their consequences and this effect can be reflected in measures of associated skin conductance responses, facial activity and cortical responses (Flor et al, 2002; Jolliffe & Nicholas, 2004). Taken together, these studies provide support for the thesis that the experience of pain is not solely due to noxious input, but that environmental contingencies can also contribute.

Learning processes may also be involved in the development and maintenance of chronic pain (Birbaumer et al, 1995). Evidence of both classical and instrumental (operant) learning responses were reflected in stereotypy, or repetitive movements, of certain muscle groups to personally relevant stressful situations, as well as conditioning of muscle and pain responses to previously neutral tones and images.

#### **Beliefs, thought processes**

Empirical evidence supports a role for fear of pain contributing to the development of avoidance responses following pain and injury, which ultimately lead to disability in many

people with persisting pain (Leeuw et al, 2007). Negative appraisals of internal and external stimuli (eg catastrophising), negative affectivity and anxiety sensitivity could contribute to the development of pain-related fear and, in turn, lead to escape and avoidance behaviours, as well as hypervigilance to internal and external illness information, muscular reactivity, and physical disuse and behavioural changes.

### 1.2.2 Acute pain settings

The contribution of psychosocial factors to the pain experience is important in acute and chronic pain settings as well as in the transition from acute to chronic pain (Linton, 2000 **Level IV**; Pincus et al, 2002 **Level IV**).

Preoperative anxiety has been shown to be associated with higher pain intensities in the first hour after a variety of different operations (Kalkman et al, 2003 **Level IV**), including abdominal (Caumo et al, 2002 **Level IV**; Granot & Ferber, 2005 **Level IV**), coronary artery bypass (Nelson et al, 1998 **Level IV**), gynaecological (Hsu et al, 2005 **Level IV**; Carr et al, 2006 **Level IV**) and varicose vein (Terry et al, 2007 **Level IV**) surgery, and after laparoscopic tubal ligation (Rudin et al, 2008 **Level IV**). Preoperative anxiety was also associated with increased pain and reduced function 1 year after total knee replacement (Brander et al, 2003 **Level IV**), but not 5 years after the surgery (Brander et al, 2007 **Level IV**). Similarly, preoperative psychological distress was shown to predict pain up to 2 years after knee arthroplasty (Lingard & Riddle, 2007 **Level IV**). Pain from 2 to 30 days after breast surgery was also predicted by preoperative anxiety (Katz et al, 2005 **Level IV**). After elective Caesarean section, preoperative anxiety did not predict analgesic use, but was negatively associated with maternal satisfaction and speed of recovery (Hobson et al, 2006 **Level IV**).

In patients who underwent repair of their anterior cruciate ligament, those with high Pain Catastrophising Scale (PCS) scores, assessed prior to surgery, reported more pain immediately after surgery and when walking at 24 hours compared with those with low scores, but there was no difference in analgesic consumption (Pavlin et al, 2005 **Level IV**). After breast surgery, catastrophising was associated with increased pain intensity and analgesic use (Jacobsen & Butler, 1996 **Level IV**) and with higher pain scores after abdominal surgery (Granot & Ferber, 2005 **Level IV**) and Caesarean section (Strulov et al, 2007 **Level IV**). Preoperative PCS scores also predicted pain after knee arthroplasty on the second postoperative day (Roth et al, 2007 **Level IV**) and at 6 weeks (Sullivan et al, 2009 **Level IV**) and 2 years after surgery (Forsythe et al, 2008 **Level IV**).

Preoperative depression (Caumo et al, 2002 **Level IV**; Kudoh et al, 2002 **Level III-2**; Katz et al, 2005 **Level IV**; Rudin et al, 2008 **Level IV**) and neuroticism (Bisgaard et al, 2001 **Level IV**) were predictors of postoperative pain early after surgery; preoperative depression was also associated with pain 1 year after total knee replacement (Brander et al, 2003 **Level IV**) and reduced function at both 1 year (Brander et al, 2003 **Level IV**) and 5 years later (Brander et al, 2007 **Level IV**). Strong information-seeking behaviour was associated with a reduction in the incidence of severe pain (Kalkman et al, 2003 **Level IV**).

Preoperative anxiety and moderate to severe postoperative pain are, in turn, predictors of postoperative anxiety (Caumo et al, 2001 **Level IV**; Carr et al, 2006 **Level IV**).

In opioid-tolerant patients, the anxiety and autonomic arousal associated with withdrawal (Tetrault & O'Connor, 2008) may also impact on acute pain experience and report (see Section 11.7 for further details). Behavioural problems were more common in methadone-maintained patients who required inpatient acute pain management (Hines et al, 2008 **Level III-2**).

## Patient-controlled analgesia

A number of studies have looked specifically at the relationship between pain relief and psychological factors in patients using patient-controlled analgesia (PCA) in the postoperative period.

In general, anxiety seems to be the most important psychological variable that affects PCA use. Preoperative anxiety correlated with increased postoperative pain intensity, the number of PCA demands made by the patient (often 'unsuccessful', that is, during the lockout interval), degree of dissatisfaction with PCA and lower self-reports of quality of analgesia (Jamison et al, 1993 **Level IV**; Perry et al, 1994 **Level IV**; Thomas et al, 1995 **Level III-1**; Brandner et al, 2002 **Level IV**; Ozalp et al, 2003 **Level IV**; Hsu et al, 2005 **Level IV**; De Cosmo et al, 2008 **Level IV**). Another study designed to look at predictors of PCA demands made during the lockout interval also found that anxiety and negative affect positively predicted PCA lockout interval demands and postoperative pain, as did preoperative intrusive thoughts and avoidant behaviours about the impending surgery (Katz et al, 2008 **Level IV**).

Evidence regarding PCA opioid consumption is contradictory; both no change (Gil et al, 1990 **Level IV**; Gil et al, 1992 **Level IV**; Jamison et al, 1993 **Level IV**) and an increase (Ozalp et al, 2003 **Level IV**; De Cosmo et al, 2008 **Level IV**; Katz et al, 2008 **Level IV**) have been reported.

In a study looking at the effect of a number of psychological factors on both pain and PCA morphine use in the immediate postoperative period and on pain 4 weeks after surgery, preoperative self-distraction coping positively predicted postoperative pain levels and morphine consumption; emotional support and religious-based coping positively predicted PCA morphine consumption; and preoperative distress, behavioural disengagement, emotional support, and religious-based coping also positively predicted pain levels 4 weeks after surgery (Cohen et al, 2005 **Level IV**).

There was no relationship between locus of control and postoperative pain intensity, satisfaction with PCA or PCA dose-demand ratio (Brandner et al, 2002 **Level IV**). However, preoperative depression was associated with increased pain intensity, opioid requirements, PCA demands and degree of dissatisfaction (Ozalp et al, 2003 **Level IV**; De Cosmo et al, 2008 **Level IV**).

### Key messages

1. Preoperative anxiety, catastrophising, neuroticism and depression are associated with higher postoperative pain intensity (**U**) (**Level IV**).
2. Preoperative anxiety and depression are associated with an increased number of PCA demands and dissatisfaction with PCA (**U**) (**Level IV**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope (**U**).

## 1.3 PROGRESSION OF ACUTE TO CHRONIC PAIN

The importance of addressing the link between acute and chronic pain has been emphasised by recent studies. To highlight this link, chronic pain is increasingly referred to as persistent pain. A survey of the incidence of chronic pain-related disability in the community concluded

that patients often relate the onset of their pain to an acute injury, drawing attention to the need to prevent the progression from acute to chronic pain (Blyth et al, 2003 **Level IV**).

The association between acute and chronic pain is well-defined, but few randomised controlled studies have addressed the aetiology, time course, prevention or therapy of the transition between the two pain states. Acute pain states that may progress to chronic pain include postoperative and post-traumatic pain (see below and Section 9.1), acute back pain (see Section 9.4) and herpes zoster (see Section 9.6.2).

Chronic pain is common after surgery (see Table 1.2) (Kehlet et al, 2006; Macrae, 2008) and represents a significant source of ongoing disability, often with considerable economic consequences. Such pain frequently has a neuropathic element. For example, all patients with chronic postherniorrhaphy pain had features of neuropathic pain (Aasvang et al, 2008 **Level IV**). Neuropathic pain may be seen early in the postoperative period (see Section 9.1.1).

There is some evidence that specific early analgesic interventions may reduce the incidence of chronic pain after surgery. Epidural analgesia initiated prior to thoracotomy and continued into the postoperative period resulted in significantly fewer patients reporting pain 6 months later compared with patients who had received intravenous (IV) PCA opioids for postoperative analgesia (45% vs 78% respectively) (Senturk et al, 2002 **Level II**). There was no statistically significant difference in the incidence of chronic pain between patients given pre-emptive epidural analgesia (initiated prior to surgery) and patients in whom epidural analgesia was commenced after surgery – 39.6% vs 48.6% (Bong et al, 2005 **Level I**). In patients undergoing colonic resection, continuous perioperative epidural analgesia led to a lower risk of developing persistent pain up to 1 year after surgery compared with IV analgesia (Lavand'homme et al, 2005 **Level II**).

Spinal anaesthesia in comparison to general anaesthesia reduced the risk of chronic postsurgical pain after Caesarean section (Nikolajsen et al, 2004 **Level IV**) and hysterectomy (OR: 0.42; CI 0.21 to 0.85) (Brandsborg et al, 2007 **Level IV**). The latter study found no difference in risk between abdominal and vaginal hysterectomy.

An infusion of ropivacaine into the site of iliac crest bone graft harvest resulted in significantly less pain in the iliac crest during movement at 3 months (Blumenthal et al, 2005 **Level II**).

Local anaesthetic wound infiltration reduced the proportion of patients with persistent pain and neuropathic pain 2 months following intracranial tumour resection (Batoz et al, 2009 **Level II**).

Preincisional paravertebral block reduced prevalence and intensity of pain 12 months after breast surgery (Kairaluoma et al, 2006 **Level II**). Perioperative use of gabapentin or mexiletine after mastectomy reduced the incidence of neuropathic pain at 6 months postoperatively, from 25% in the placebo to 5% in both treatment groups (Fassoulaki et al, 2002 **Level II**). Similar protective results were achieved by the same group by the use of a eutectic mixture of local anaesthetics alone (Fassoulaki et al, 2000 **Level II**) or in combination with gabapentin (Fassoulaki et al, 2005 **Level II**).

Deliberate neurectomy (of the ilioinguinal nerve) for inguinal hernia repair reduced the incidence of chronic postsurgical pain (from 21% to 6%) (Malekpour et al, 2008 **Level II**), although this was not seen in an earlier study (Picchio et al, 2004 **Level II**).

See Section 1.5 below for more examples of the use of pre-emptive and preventive analgesic interventions in attempts to reduce the risk of persistent pain after surgery, and Sections 9.1.2 to 9.1.3 for more details on prevention of phantom pain after limb amputation and other postoperative pain syndromes.

**Table 1.2 Incidence of chronic pain after surgery**

Type of operation	Incidence of chronic pain (%)	Estimated incidence of chronic severe pain [>5 out of 10/10] (%)
Amputation	30–85	5–10
Thoracotomy	5–65	10
Mastectomy	11–57	5–10
Inguinal hernia	5–63	2–4
Coronary bypass	30–50	5–10
Caesarean section	6–55	4
Cholecystectomy	3–50	Not estimated
Vasectomy	0–37	Not estimated
Dental surgery	5–13	Not estimated

Sources: Adapted from Kehlet et al (Kehlet et al, 2006) and Macrae (Macrae, 2008)

### 1.3.1 Predictive factors for chronic postsurgical pain

A number of risk factors for the development of chronic postsurgical pain have been identified (Kehlet et al, 2006; Macrae, 2008). A systematic review of psychosocial factors identified depression, psychological vulnerability, stress and late return to work as having a correlation to chronic postsurgical pain (Hinrichs-Rocker et al, 2009 **Level III-3**). Very young age may be a protective factor as hernia repair in children under 3 months age did not lead to chronic pain in adulthood (Aasvang & Kehlet, 2007 **Level IV**).

**Table 1.3 Risk factors for chronic postsurgical pain**

<b>Preoperative factors</b>	Pain, moderate to severe, lasting more than 1 month Repeat surgery Psychologic vulnerability (eg catastrophising) Preoperative anxiety Female gender Younger age (adults) Workers' compensation Genetic predisposition Inefficient diffuse noxious inhibitory control (DNIC)
<b>Intraoperative factors</b>	Surgical approach with risk of nerve damage
<b>Postoperative factors</b>	Pain (acute, moderate to severe) Radiation therapy to area Neurotoxic chemotherapy Depression Psychological vulnerability Neuroticism Anxiety

Sources: Adapted from Kehlet et al (Kehlet et al, 2006) and Macrae (Macrae, 2008)

### 1.3.2 Mechanisms for the progression from acute to chronic pain

The pathophysiological processes that occur after tissue or nerve injury mean that acute pain may become persistent (Cousins et al, 2000). Such processes include inflammation at the site of tissue damage with a barrage of afferent nociceptor activity that produces changes in the peripheral nerves, spinal cord, higher central pain pathways and the sympathetic nervous system (see Section 1.1).

After limb amputation, reorganisation or remapping of the somatosensory cortex and other cortical structures may be a contributory mechanism in the development of phantom limb pain (Flor et al, 1995; Grusser et al, 2004). There is preclinical and clinical evidence of a genetic predisposition for chronic pain (Mogil, 1999), although one study found that an inherited component did not feature in the development of phantom pain in members of the same family who all had a limb amputation (Schott, 1986).

Descending pathways of pain control may be another relevant factor as patients with efficient diffuse noxious inhibitory control (DNIC) had a reduced risk of developing chronic postsurgical pain (Yarnitsky et al, 2008 **Level III-2**).

#### Key messages

1. Some specific early anaesthetic and/or analgesic interventions reduce the incidence of chronic pain after surgery (**S**) (**Level II**).
2. Chronic postsurgical pain is common and may lead to significant disability (**U**) (**Level IV**).
3. Risk factors that predispose to the development of chronic postsurgical pain include the severity of pre- and postoperative pain, intraoperative nerve injury and psychosocial factors (**U**) (**Level IV**).
4. All patients with chronic postherniorrhaphy pain had features of neuropathic pain (**N**) (**Level IV**).
5. Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean section (**N**) (**Level IV**).

## 1.4 PRE-EMPTIVE AND PREVENTIVE ANALGESIA

In laboratory studies, administration of an analgesic prior to an acute pain stimulus more effectively minimises dorsal horn changes associated with central sensitisation than the same analgesic given after the pain state is established (see Section 1.1) (Woolf, 1983). This led to the hypothesis that pain relief prior to surgery may enhance postoperative pain management – that is, ‘pre-emptive preoperative analgesia’ (Wall, 1988). However, individual clinical studies have reported conflicting outcomes when comparing ‘preincisional’ with ‘postincisional’ interventions. In part this relates to variability in definitions, deficiencies in clinical trial design and differences in the outcomes available to laboratory and clinical investigators (Kissin, 1994; Katz & McCartney, 2002).

As the process of central sensitisation relates not only to skin incision but also to the extent of intraoperative tissue injury and postoperative inflammation, the focus has shifted from the timing of a single intervention to the concept of ‘protective’ and therefore ‘preventive’ analgesia (Kissin, 1994) (see Table 1.4). The differences in these terms relates to the outcomes being described, because all rely on minimising sensitisation. *Pre-emptive* analgesia has been described above and is measured in terms of pain intensity or related outcomes. *Protective* analgesia describes a technique that reduces measures of sensitisation such as hyperalgesia.



*Preventive analgesia* is the persistence of analgesic treatment efficacy beyond its expected duration. In clinical practice, preventive analgesia appears to be the most relevant and holds the most hope for minimising chronic pain after surgery or trauma, possibly because it decreases central sensitisation and ‘windup’. An important consideration to maximise the benefit of any preventive strategy is that the active intervention should be continued for as long as the sensitising stimulus persists, that is well into the postoperative period (Dahl & Moiniche, 2004; Pogatzki-Zahn & Zahn, 2006).

**Table 1.4 Definitions of pre-emptive and preventive analgesia**

<b>Pre-emptive analgesia</b>	Preoperative treatment is more effective than the identical treatment administered after incision or surgery. The only difference is the timing of administration.
<b>Preventive analgesia</b>	Postoperative pain and/or analgesic consumption is reduced relative to another treatment, a placebo treatment, or no treatment as long as the effect is observed at a point in time that exceeds the expected duration of action of the intervention. The intervention may or may not be initiated before surgery.

Sources: Moiniche et al (Moiniche et al, 2002) and Katz & McCartney (Katz & McCartney, 2002).

The benefits of pre-emptive analgesia have been questioned by two systematic reviews (Dahl & Moiniche, 2004; Moiniche et al, 2002). However a more recent meta-analysis provided support for pre-emptive epidural analgesia (Ong et al, 2005 **Level I**<sup>1</sup>). The efficacy of different pre-emptive analgesic interventions (epidural analgesia, local anaesthetic wound infiltration, systemic NMDA antagonists, systemic opioids, and systemic NSAIDs) was analysed in relation to different analgesic outcomes (pain intensity scores, supplemental analgesic consumption, time to first analgesic). The effect size was most marked for epidural analgesia (0.38; CI 0.28 to 0.47) and improvements were found in all outcomes. Pre-emptive effects of local anaesthetic wound infiltration and NSAID administration were also found, but results were equivocal for systemic NMDA antagonists and there was no clear evidence for a pre-emptive effect of opioids.

**Note: reversal of conclusions**

This reverses the Level 1 conclusion in the previous edition of this document as pre-emptive effects have been shown with epidural analgesia; earlier meta-analyses using more simple outcomes had reported no pre-emptive effects.

Pre-emptive thoracic epidural analgesia (local anaesthetic +/- opioid) reduced the severity of acute pain only on coughing following thoracotomy. There was a marginal effect on pain at rest and, although acute pain was a predictor of chronic pain at 6 months in two studies, there was no statistically significant difference in the incidence of chronic pain in the pre-emptive (epidural analgesia initiated prior to surgery) versus control (epidural analgesia initiated after surgery) — 39.6% vs 48.6% (Bong et al, 2005 **Level I**).

<sup>1</sup> This meta-analysis includes studies that have since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. After excluding results obtained from the retracted publications, Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data relating to possible pre-emptive effects of local anaesthetic wound infiltration and NSAID administration. They concluded that removal of this information did not significantly alter the results of the meta-analysis.



A systematic review (Katz & Clarke, 2008 **Level 1**<sup>2</sup>) reported preventive effects following the use of a number of different drugs, but equivocal or no benefit from pre-emptive treatment (Table 1.5). The methodology was unable to identify specific therapeutic techniques that may be of benefit.

**Table 1.5 Summary of studies according to target agent administered**

Agent(s)	No. of studies	Pre-emptive effects		Preventive effects		Opposite effects	Total no. effects
		Positive	Negative	Positive	Negative		
Gabapentin	6	0 (0)	1 (16.7)	4 (66.6)	1 (16.7)	0 (0)	<b>6 (100)</b>
Local anaesthetics	13	3 (20)	3 (20)	6 (40)	1 (6.7)	2 (13.3)	15 (100)
Opioids	5 [-1]	3 (60) [-1]	1 (20)	0 (0)	1 (20)	0 (0)	<b>5 (100)</b> [-1]
NSAIDs	14 [-2]	7 (43.8) [-1]	3 (18.8)	4 (25) [-1]	2 (12.4)	0 (0)	<b>16 (100)</b> [-2]
NMDA antagonists	14	2 (11.8)	1 (5.9)	9 (53)	4 (23.4)	1 (5.9)	<b>17 (100)</b>
Multimodal	5	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	0 (0)	<b>6 (100)</b>
Other	4 [-1]	1 (25)	0 (0)	3 (75) [-1]	0 (0)	0 (0)	<b>4 (100)</b> [-1]
<b>Total<sup>a</sup></b>	<b>61</b>	<b>17<sup>b</sup></b> <b>(24.6)</b>	<b>10</b> <b>(14.5)</b>	<b>28<sup>c</sup></b> <b>(40.6)</b>	<b>11</b> <b>(15.9)</b>	<b>3</b> <b>(4.4)</b>	<b>69</b> <b>(100)</b>

Notes: Table shows the total number of studies and number (%) with positive and negative pre-emptive and preventive effects. Also shown is the number (%) of studies reporting effects opposite to those predicted and the total number of effects (positive, negative and opposite). The total number of effects exceeds the number of studies because some studies were designed to evaluate both pre-emptive and preventive effects. See text for definition of pre-emptive and preventive effects.

- a  $p = 0.02$  for z-test comparison of proportion of total positive pre-emptive plus preventive effects (0.64) versus proportion of total negative pre-emptive plus preventive effects (0.31).
- b  $p = 0.36$  for z-test comparison of proportion of total positive pre-emptive effects (17/27 = 0.63) versus proportion of total negative pre-emptive effects (10/27 = 0.37)
- c  $p = 0.03$  for z-test comparison of proportion of total positive preventive effects (28/39 = 0.72) versus proportion of total negative preventive effects (11/39 = 0.28)

Legend: NSAIDs: non-steroidal anti-inflammatory drugs; NMDA: N-methyl-D-aspartate

Source: Reproduced with kind permission from Katz and Clark, Preventive analgesia and beyond: current status, evidence, and future directions, Table 9.4 p 165 *Clinical Pain Management: Acute Pain 2e*, Hodder Arnold.

<sup>2</sup> This meta-analysis includes studies that have since been withdrawn from publication and which are shown as subtractions in Table 1.5. These were four positive reports: pre-emptive effects of opioids, pre-emptive effects of venlafaxine (listed under 'Other'), and both pre-emptive and preventive effects of NSAIDs. Reanalysis of the data would be required to determine the overall strength of the evidence. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles.

As activation of the NMDA receptor plays an important role in central sensitisation, many studies have focussed on the ability of NMDA receptor antagonists to produce pre-emptive or preventive analgesic effects. A qualitative systematic review of NMDA receptor antagonists showed that ketamine and dextromethorphan produced a significant preventive analgesic benefit; in all positive preventive studies, a direct analgesic benefit of the drug also occurred in the early postoperative period; no positive effect was seen in four studies using magnesium (McCartney et al, 2004 **Level I**). The addition of low-dose IV ketamine to thoracic epidural analgesia reduced the severity and need for treatment of post-thoracotomy pain at 1 and 3 months postoperatively (Suzuki et al, 2006 **Level II**). However, in a later study of thoracic surgery patients, when single dose intrapleural ropivacaine and intravenous analgesia was combined with either perioperative ketamine or saline, no difference in chronic pain up to 4 months was noted (Duale et al, 2009 **Level II**).

In a study of multimodal analgesia (local anaesthetic, opioid, ketamine and clonidine) in four groups of patients having colonic resection, a clear preventive effect on the development of residual pain up to 1 year after surgery was demonstrated with continuous perioperative epidural analgesia; residual pain at 1 year was lowest in patients who received intraoperative versus postoperative epidural analgesia (Lavand'homme et al, 2005 **Level II**).

### Key messages

1. The timing of a single analgesic intervention (preincisional rather than postincisional), defined as pre-emptive analgesia, has a significant effect on postoperative pain relief with epidural analgesia (**R**) (**Level I**).
2. There is evidence that some analgesic interventions have an effect on postoperative pain and/or analgesic consumption that exceeds the expected duration of action of the drug, defined as preventive analgesia (**U**) (**Level I**).
3. NMDA receptor antagonist drugs in particular show preventive analgesic effects (**U**) (**Level I**).
4. Perioperative epidural analgesia combined with ketamine intravenously decreases hyperalgesia and long-term pain up to 1 year after colonic surgery compared with intravenous analgesia alone (**N**) (**Level II**).

## 1.5 ADVERSE PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF ACUTE PAIN

### 1.5.1 Acute pain and the injury response

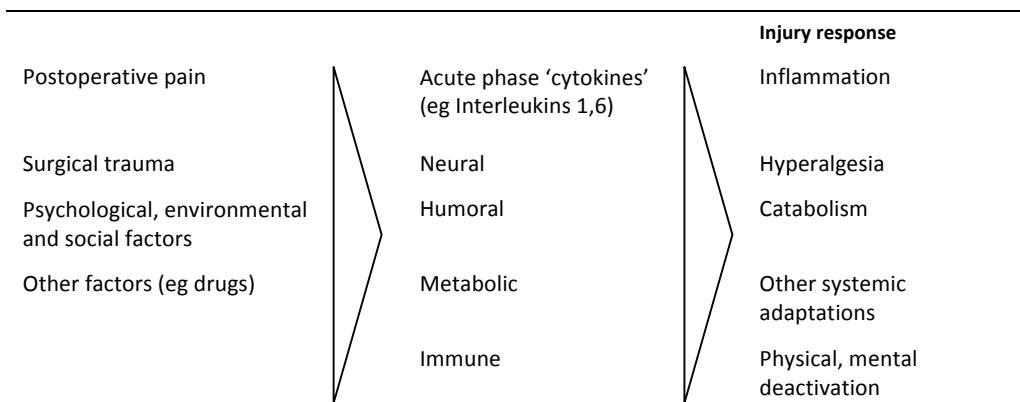
Acute pain is one of the activators of the complex neurohumoral and immune response to injury (Figure 1.2), and both peripheral and central injury responses have a major influence on acute pain mechanisms. Thus acute pain and injury of various types are inevitably interrelated and if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (Kehlet & Dahl, 2003; Chapman et al, 2008).

Although published data relate to the *combination* of surgery or trauma and the associated acute pain, some data have been obtained with experimental pain in the absence of injury. Electrical stimulation of the abdominal wall results in a painful experience (visual analogue scale [VAS] 8/10) and an associated hormonal/metabolic response, which includes increased cortisol, catecholamines and glucagon, and a decrease in insulin sensitivity (Greisen et al, 2001). Although acute pain is only one of the important triggers of the 'injury response' (Figure 1.2),

as the magnitude and duration of the response is related to the magnitude and duration of the stimulus, effective pain relief can have a significant impact on the injury response (Liu & Wu, 2008; Carli & Schricker, 2009).

Release of proinflammatory cytokines may contribute to postoperative ileus, but the impact of modulating this response on overall patient outcome requires further evaluation. Intravenous lignocaine infusion attenuated postoperative increases in pro-inflammatory cytokines, such as IL-6 (interleukin-6), IL-8 and IL-1RA (a competitive inhibitor of IL-1 $\beta$ ) and was associated with more rapid return of bowel function following abdominal surgery (Kuo et al, 2006 **Level II**; Herroeder et al, 2007 **Level II**). Reductions in pain scores and opioid consumption were found in only one study (Kuo et al, 2006 **Level II**). Benefits of lignocaine were more marked when administered via the thoracic epidural route than by intravenous infusion (Kuo et al, 2006 **Level II**).

**Figure 1.2 The injury response**



**Note:** Pain is only one of the factors, including psychological and environmental factors, that trigger complex intermediates (neural, humoral etc) leading to the 'injury response'. Thus acute pain and the injury response are inevitably inter-related. The end result is physical and mental deactivation.

**Source:** *Acute Pain Management: the Scientific Evidence* (NHMRC 1999); © Commonwealth of Australia, reproduced with permission.

### 1.5.2 Adverse physiological effects

Clinically significant injury responses can be broadly classified as inflammation, hyperalgesia, hyperglycaemia, protein catabolism, increased free fatty acid levels (lipolysis) and changes in water and electrolyte flux (Liu & Wu, 2008; Carli & Schricker, 2009) (Figure 1.3). In addition, there are cardiovascular effects of increased sympathetic activity and diverse effects on respiration, coagulation and immune function (Liu & Wu, 2008).

**Table 1.6 Metabolic and endocrine responses to injury**

<b>Endocrine</b>	↑ Catabolic hormones	↑ ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons, IL-1, TNF, IL-6
	↓ Anabolic hormones	↓ Insulin, testosterone
<b>Metabolic</b>		
<i>carbohydrate</i>	Hyperglycaemia, glucose intolerance, insulin resistance	↑ Glycogenolysis, gluconeogenesis (cortisol, glucagon, growth hormone, adrenaline, free fatty acids) ↓ Insulin secretion/activation
<i>protein</i>	Muscle protein catabolism, ↑ synthesis of acute phase proteins	↑ Cortisol, adrenaline, glucagons, IL-1, IL-6, TNF
<i>lipid</i>	↑ Lipolysis and oxidation	↑ Catecholamines, cortisol, glucagon, growth hormone
<b>Water and electrolyte flux</b>	Retention of water and sodium, ↑ excretion of potassium and ↓ functional ECF with shifts to ICF	↑ Catecholamine, aldosterone, ADH, cortisol, angiotensin II, prostaglandins and other factors

Note: ACTH: adrenocorticotrophic hormone; ADH: antidiuretic hormone; ECF: extracellular fluid; ICF: intracellular fluid; IL: interleukin; TNF: tumour necrosis factor.

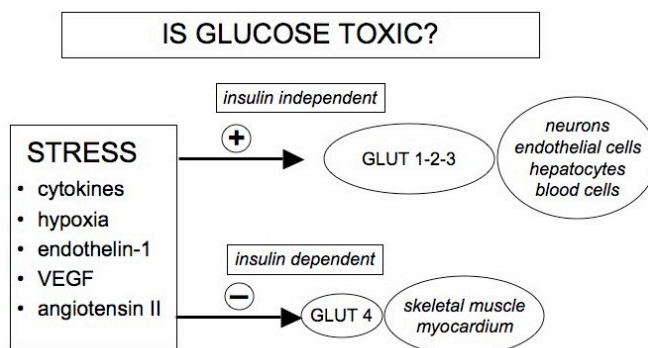
Source: *Acute Pain Management: the Scientific Evidence* (NHMRC 1999); copyright Commonwealth of Australia, reproduced with permission.

## Hyperglycaemia

Hyperglycaemia is broadly proportional to the extent of the injury response. Injury response mediators stimulate insulin-independent membrane glucose transporters *glut-1*, *2* and *3*, which are located diversely in brain, vascular endothelium, liver and some blood cells. Circulating glucose enters cells that do not require insulin for uptake, resulting in cellular glucose overload and diverse toxic effects. Excess intracellular glucose non-enzymatically glycosylates proteins such as immunoglobulins, rendering them dysfunctional. Alternatively, excess glucose enters glycolysis and oxidative phosphorylation pathways, leading to excess superoxide molecules that bind to nitric oxide (NO), with formation of peroxynitrate, ultimately resulting in mitochondrial dysfunction and death of cells served by *glut-1*, *2* and *3*. Myocardium and skeletal muscle are protected from this toxicity because these two tissues are served by *glut-4*, the expression of which is inhibited by injury response mediators (Figure 1.3) (Carli & Schricker, 2009).

Even modest increases in blood glucose can be associated with poor outcome particularly in metabolically challenged patients such as people with diabetes (Lugli et al, 2008 **Level II**). Fasting glucose levels over 7 mmol/L or random levels of greater than 11.1 mmol/L were associated with increased inhospital mortality, a longer length of stay and higher risk of infection in intensive care patients (Van den Berghe, 2004). Tight glycaemic control has been associated with improved outcomes following coronary artery bypass graft (CABG) in patients with diabetes (Lazar et al, 2004 **Level II**), but the risks and benefits of tight glycaemic control in intensive care patients (Wiener et al, 2008 **Level I**) continues to be debated (Fahy et al, 2009 **Level IV**).

**Figure 1.3 Proposed pathways of glucose-induced cellular toxicity**



Source: Reproduced with kind permission from Carli and Schricker, Modification of Metabolic Response to Surgery by Neural Blockade, Figure 6.3 page 134 *Neural Blockade in Clinical Anesthesia and Pain Medicine 4th Ed*, Wolters Kluwer, Lippincott Williams & Wilkins.

### Lipotoxicity

Free fatty acid (FFA) levels are increased due to several factors associated with the injury response and its treatment (see Table 1.6) and can have detrimental effects on cardiac function. High levels of FFA can depress myocardial contractility (Korvald et al, 2000), increase myocardial oxygen consumption (without increased work) (Oliver & Opie, 1994; Liu et al, 2002), and impair calcium homeostasis and increase free radical production leading to electrical instability and ventricular arrhythmias (Oliver & Opie, 1994).

### Protein catabolism

The injury response is associated with an accelerated protein breakdown and amino acid oxidation, in the face of insufficient increase in protein synthesis. Following abdominal surgery, amino acid oxidation and release from muscle increased by 90% and 30% respectively, while whole body protein synthesis increased only 10% (Harrison et al, 1989 **Level IV**). After cholecystectomy 50 g of nitrogen may be lost (1 g nitrogen = 30 g lean tissue) which is equivalent to 1500 g of lean tissue. Importantly, the length of time for return of normal physical function after hospital discharge has been related to the total loss of lean tissue during hospital stay (Chandra, 1983).

Protein represents both structural and functional body components, thus loss of lean tissue may lead to delayed wound healing (Windsor & Hill, 1988 **Level III-3**), reduced immune function (Chandra, 1983) and diminished muscle strength (Watters et al, 1993 **Level III-3**) — all of which may contribute to prolonged recovery and increased morbidity (Watters et al, 1993; Christensen et al, 1982).

An overall reduced ability to carry out activities of daily living (ADLs) results from muscle fatigue and muscle weakness. Impaired nutritional intake, inflammatory–metabolic responses, immobilisation, and a subjective feeling of fatigue may all contribute to muscle weakness (Christensen et al, 1990). Such effects are broadly proportional to the extent of injury but there are major variations across populations, with durations also varying up to 3 to 4 weeks.

### 1.5.3 Pain and analgesia: effects on injury-induced organ dysfunction

Pain from injury sites can activate sympathetic efferent nerves and increase heart rate, inotropy, and blood pressure. As sympathetic activation increases myocardial oxygen demand and reduces myocardial oxygen supply, the risk of cardiac ischaemia, particularly in patients with pre-existing cardiac disease, is increased. Enhanced sympathetic activity can also reduce gastrointestinal (GI) motility and contribute to ileus. Severe pain after upper abdominal and thoracic surgery contributes to an inability to cough and a reduction in functional residual capacity, resulting in atelectasis and ventilation-perfusion abnormalities, hypoxaemia and an increased incidence of pulmonary complications. The injury response also contributes to a suppression of cellular and humoral immune function and a hypercoagulable state following surgery, both of which can contribute to postoperative complications. Patients at greatest risk of adverse outcomes from unrelieved acute pain include very young or elderly patients, those with concurrent medical illnesses and those undergoing major surgery (Liu & Wu, 2008).

All relevant studies address the combination of injury and pain. The majority involve use of epidural neural blockade, which in addition to effects on pain *per se* can influence the injury response (eg via reduced sympathetic activity). As a result, the site of epidural placement and extent of block can influence results. The impact of analgesic technique on outcome is more fully discussed in Section 7. Epidural analgesia has been reported to improve pain and decrease arrhythmias following cardiac surgery (Liu et al, 2004 **Level I**), but early reports of reduced postoperative myocardial infarction (Beattie et al, 2001 **Level I**) and impact on mortality have not been replicated (Rigg et al, 2002 **Level II**; Liu et al, 2004 **Level I**). Regional versus systemic analgesia decreased postoperative pulmonary complications (Rodgers et al, 2000 **Level I**; Ballantyne et al, 1998 **Level I**; Jorgensen et al, 2000 **Level I**) but the impact was greater following abdominal (Nishimori et al, 2006 **Level I**) than hip or knee surgery (Choi et al, 2003 **Level I**). Intraoperative epidural analgesia/anaesthesia (versus general anaesthesia) decreased the odds ratio for deep vein thrombosis (DVT) and postoperative confusion, but did not reduce mortality following hip fracture (Parker et al, 2004 **Level I**). Epidural local anaesthetic, when compared to epidural or systemic opioid, enhanced return of GI function (Jorgensen et al, 2000 **Level I**). Compared with systemic opioid administration, intraoperative thoracic epidural anaesthesia also led to lower plasma concentrations of adrenaline (epinephrine) and cortisol, and prevented perioperative impairment of proinflammatory lymphocyte function (Ahlers et al, 2008 **Level II**). The advantages of epidural analgesia were greatest when used as part of a multimodal, accelerated rehabilitation care pathway, since other factors may influence GI recovery (Joshi, 2005).

There is also some evidence that regional anaesthetic and analgesic techniques might have a beneficial effect on rates of cancer recurrence after tumour resection. Paravertebral anaesthesia/analgesia reduced the risk of recurrence or metastases following mastectomy from 23% to 6% compared with general anaesthesia and systemic morphine analgesia (Exadaktylos et al, 2006 **Level IV**). Similarly, after prostatectomy under general anaesthesia, epidural analgesia compared with systemic morphine reduced the risk of recurrence by 57% (Biki et al, 2008 **Level IV**).

## 1.5.4 Acute rehabilitation and ‘fast-track’ surgery

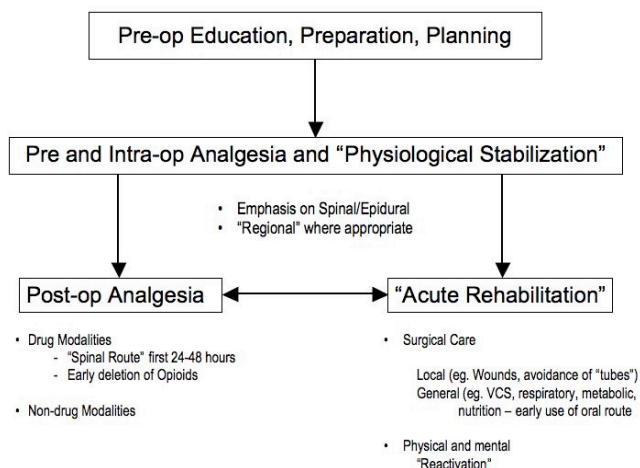
In view of the numerous triggers of the injury response, including acute nociception and pain, it is not surprising that early attempts to modify the catabolism of the injury response, with *pain relief alone*, were not successful. Following abdominal surgery, epidural analgesia without nutritional support had no effect on protein catabolism and related outcomes (Hjortso et al, 1985 **Level II**). Minimising the impact of perioperative fasting with IV amino acid infusions decreased postoperative protein catabolism following colorectal surgery (Schricker et al, 2008 **Level III-2**; Donatelli et al, 2006 **Level III-2**).

Epidural analgesia, aimed at the operative area spinal segments and comprising low doses of local anaesthetic and opioid, facilitated mobilisation and accelerated food intake. Such a program permitted a more rapid postoperative return of normal cardiopulmonary response to treadmill exercise and facilitated return of overall exercise capacity 6 weeks after surgery (Basse et al, 2002 **Level III-2**; Carli et al, 2002 **Level II**).

It can be seen from the foregoing that a multi-interventional and rehabilitation strategy is required, including very effective pain relief, if optimal outcomes are to be achieved, as outlined in procedure-specific recommendations from the PROSPECT group (Kehlet et al, 2007). Postoperative rehabilitation should include pharmacological, physical, psychological and nutritional components (Figure 1.4).

Recognition of the importance of the above factors has led to the concept of ‘fast-track’ surgery (Wilmore & Kehlet, 2001; White et al, 2007). This has provided enhanced recovery leading to decreased hospital stay with an apparent reduction in medical morbidity (Kehlet & Wilmore, 2008). For example, ‘fast-track’ colorectal programs have led to a reduction in length of hospital stay (Delaney et al, 2003 **Level II**; Jakobsen et al, 2006 **Level III-2**; Wind et al, 2006 **Level III-1**; Khoo et al, 2007 **Level II**); readmission rates may (Khoo et al, 2007 **Level II**; Jakobsen et al, 2006 **Level III-2**) or may not (Wind et al, 2006 **Level III-1**) be higher. A fast-track system also enabled early discharge (less than 3 days) after total hip and knee arthroplasty, although after total knee arthroplasty, pain at 10 days after discharge was still significant (52% of patients with moderate pain and 16% with severe pain) indicating a need for improved postdischarge analgesia (Andersen et al, 2009 **Level III-3**).

**Figure 1.4 Acute pain management and rehabilitation**



Source: Reproduced with kind permission from Carli and Schricker, Modification of Metabolic Response to Surgery by Neural Blockade, Figure 6.12 page 134 *Neural Blockade in Clinical Anesthesia and Pain Medicine, 4th Ed*, Wolters Kluwer, Lippincott Williams & Wilkins .

### 1.5.5 Adverse psychological effects

Psychological changes associated with acute pain have received less attention than those associated with chronic pain, however they are no less important. Sustained acute nociceptive input, as occurs after surgery, trauma or burns, can also have a major influence on psychological function, which may in turn alter pain perception. Failure to relieve acute pain may result in increasing anxiety, inability to sleep, demoralisation, a feeling of helplessness, loss of control, inability to think and interact with others — in the most extreme situations, where patients can no longer communicate, effectively they have lost their autonomy (Cousins et al, 2004). In some forms of acute pain (eg low back pain), psychological and environmental responses in the acute phase may be major determinants of progression to a persistent phase (Young Casey et al, 2008).

In acute pain, attention has been focussed on postoperative cognitive dysfunction (POCD). Although the aetiology of POCD is unknown, factors probably include dysregulation of cerebral neurotransmitters, patient factors (age, comorbidities, preoperative cognitive function and general health) (Newman et al, 2007; Monk et al, 2008), surgical procedures (eg coronary artery bypass) and perioperative drug therapy (Flacker & Lipsitz, 1999). Elderly patients have an increased incidence of POCD and are more likely to have prolonged symptoms (see Section 11.2.3). Neurotransmitters involved may include acetylcholine and serotonin and inflammatory mediators (eg cytokines) may also contribute, especially in the elderly (Caza et al, 2008). POCD after cardiac surgery may also be due in part to cerebral microembolism, global cerebral hypoperfusion, cerebral temperature perturbations, cerebral oedema, and possible blood-brain barrier dysfunction (Flacker & Lipsitz, 1999; Gao et al, 2005).

#### Key messages

1. Recognition of the importance of postoperative rehabilitation including pharmacological, physical, psychological and nutritional components has led to enhanced recovery (**N**) (**Level II**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Acute pain and injury of various types are inevitably interrelated and if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (**U**).

## 1.6 PHARMACOGENOMICS AND ACUTE PAIN

An increasing number of genetic variants modulating nociception, susceptibility to pain conditions, as well as response to pharmacotherapy have been discovered.

Pharmacogenomics deals with the influence of genetic variation on drug response in patients. By correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity, the aim is to develop rational means to optimise drug therapy with respect to the patient's genotype and ensure maximum efficacy with minimal adverse effects. For example, genetic factors regulating opioid pharmacokinetics (metabolising enzymes, transporters) and pharmacodynamics (receptors and signal transduction elements) contribute to the large inter-patient variability in postoperative opioid requirements (Anderson & Palmer, 2006). Information from genotyping may help in selecting the analgesic drug and the dosing regimen for an individual patient (Lotsch & Geisslinger, 2006). Although there is currently limited information, often from small numbers of subjects, for translation into clinical practice (Stamer & Stuber,



2007; Anderson & Palmer, 2006), some preliminary estimates for dose adaptations are possible (Lotsch & Geisslinger, 2006). However, genetic factors must be considered within the context of the multiple interacting physiological, psychological and environmental factors that influence responses to pain and analgesia (Kim et al, 2009; Searle & Hopkins, 2009).

### 1.6.1 Loss of pain sensation

Recognised hereditary syndromes associated with loss of pain sensation include the 'channelopathy-associated insensitivity to pain' caused by variants in the SCN9A gene, which codes for the alpha-subunit of the voltage-gated sodium channel Na(v)1.7. Na(v)1.7 is located in peripheral neurons and plays an important role in action potential production in these cells. Mutations result in loss of Na(v)1.7 function and affected individuals are unable to feel physical pain (Drenth & Waxman, 2007).

Hereditary sensory and autonomic neuropathy (HSAN) I-V syndromes are associated with a range of genetic abnormalities and produce varying patterns of sensory and autonomic dysfunction and peripheral neuropathy (Oertel & Lotsch, 2008). Hereditary sensory neuropathy type I (HSN-I) is a dominantly transmitted sensorimotor axonal neuropathy accompanied by painless injuries. Hereditary sensory neuropathy type II (HSN-2) variants result in loss of sensitivity to touch, pain and temperature (Drenth & Waxman, 2007). Familial dysautonomia is a congenital sensory and autonomic neuropathy (HSN-3) that affects the development and survival of sensory, sympathetic, and some parasympathetic neurons and results in an indifference to pain and temperature. Hereditary sensory and autonomic neuropathy type IV (HSAN-4) is a severe autosomal recessive disorder characterised by childhood onset of insensitivity to pain and anhidrosis. HSAN-4 is caused by mutations in the NTRK1 gene coding for the tyrosine kinase receptor A (Wieczorek et al, 2008). HSAN type V is a very rare disorder. It is characterised by the absence of thermal and mechanical pain perception caused by a decreased number of small diameter neurons in peripheral nerves (de Andrade et al, 2008).

### 1.6.2 Reduced sensitivity to pain

Reduced pain sensitivity has been associated with variants in genes encoding the mu-opioid receptor (OPRM1), catechol-O-methyltransferase (COMT), guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia (GCH1), transient receptor potential (TRPV<sub>1</sub>), and the melanocortin-1 receptor (MC1R) (Lotsch et al, 2006).

The mu-opioid receptor variant N40D which is coded by the single nucleotide polymorphism (SNP) 118A > G of the OPRM1 gene has been associated with reduced acute pain responsiveness (Fillingim et al, 2005 **Level III-3**; Lotsch et al, 2006 **Level IV**) but increased exogenous opioid analgesic requirements (Klepstad et al, 2004 **Level III-3**). Intrathecal fentanyl requirements in labour were reduced in women with the 304G allele but increased in those with the 304A allele of OPRM1 (Landau et al, 2008 **Level III-3**). For additional detail related to individual opioids see Section 4.1.2.

COMT metabolises noradrenaline, adrenaline, and dopamine, and has recently been implicated in the modulation of pain. COMT inhibition may lead to increased pain sensitivity via beta-adrenergic receptor dependent mechanisms (Nackley et al, 2007). Haplotypes with high COMT activity are associated with low pain sensitivity to mechanical and thermal stimuli (Diatchenko et al, 2005). The Val158Met polymorphism influences the activity of the COMT enzyme. In cancer pain, carriers of COMT Val/Val and Val/Met genotypes had higher morphine requirements than carriers of the Met/Met genotype (Reyes-Gibby et al, 2007 **Level III-3**).

GCH1 is the rate-limiting enzyme for tetrahydrobiopterin (BH<sub>4</sub>) synthesis, an essential cofactor in the biosynthesis of biogenic amines and nitric oxide. It is a key modulator of peripheral

neuropathic and inflammatory pain (Montagna, 2007). A haplotype of the GCH1 gene present in 15.4% of humans has been associated with reduced sensitivity to pain following discectomy (Tegeer et al, 2006 **Level III-2**) and homozygotes have reduced sensitivity to experimental pain (Tegeer et al, 2008 **Level III-2**).

Point mutations affecting TRPV<sub>1</sub> were found in a person with total insensitivity to capsaicin (Park et al, 2007). Polymorphisms in the human TRPV<sub>1</sub> gene have been identified, but there has been no systematic investigation of their functional consequences (Xu et al, 2007).

Kappa-opioid agonists such as nalbuphine and pentazocine have greater analgesic efficacy in women than in men (Gear et al, 1996 **Level III-3**; Gear et al, 1999 **Level II**). Subjects carrying loss-of-function melanocortin-1 receptor gene (MC1R) variants possess a red-hair fair-skin phenotype (Oertel & Lotsch, 2008). There was a significantly greater analgesic effect from a kappa-opioid agonist in female subjects with two variant (non-functional) alleles of the MC1R gene compared with those with zero or one allele (Mogil et al, 2003 **Level III-3**). Subject with non-functional alleles also had reduced sensitivity to noxious stimuli and an increased analgesic response to morphine-6-glucuronide (Mogil et al, 2005 **Level III-3**).

### 1.6.3 Drug metabolism

Drug-metabolising enzymes represent a major target for identifying associations between an individual's genetic profile and drug response (pharmacogenetics) (Stamer & Stuber, 2007). The polymorphic cytochrome P450 enzymes metabolise numerous drugs and show inter-individual variability in their catalytic activity. The CYP2D6 gene is highly polymorphic (Stamer & Stuber, 2007) and is of clinical interest as it influences the metabolism of codeine, dihydrocodeine, oxycodone and tramadol to the more potent hydroxyl metabolites, which have a higher affinity for the mu-opioid receptor (Anderson & Palmer, 2006; Mikus & Weiss, 2005).

Over 100 allelic variants of CYP2D6 have been identified, resulting in wide variability in function. Individuals carrying two wild type alleles display normal enzyme activity and are known as extensive metabolisers; intermediate metabolisers are heterozygotes with two variant alleles known to decrease enzymatic capacity; and poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Stamer et al, 2007; Stamer & Stuber, 2007). In Caucasian populations, 8% to 10% of people are poor metabolisers; however 3% to 5% are ultrarapid metabolisers (Stamer & Stuber, 2007).

For additional detail related to individual opioids see Section 4.1.2.

#### Codeine

In children and adults receiving codeine for postoperative pain, very low or undetectable levels of plasma morphine have been noted in those with poor metaboliser or intermediate metaboliser genotypes, but with variable impact on analgesia (Williams et al, 2002 **Level II**; Poulsen et al, 1998 **Level IV**; Persson et al, 1995 **Level IV**).

CYP2D6 genotypes predicting ultrarapid metabolism (CYP2D6 gene duplication) resulted in about 50% higher plasma concentrations of morphine and its glucuronides following oral codeine compared with the extensive metabolisers (Kirchheiner et al, 2007 **Level IV**). Both the impaired renal clearance of metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in reports of respiratory depression due to codeine (Stamer & Stuber, 2007 **Level IV**). Morphine toxicity and death has been reported in a breastfed neonate whose mother was an ultrarapid metaboliser of codeine (Madadi et al, 2007). CYP2D6 genotyping predicts subjects with reduced metabolism to morphine, but must be combined with additional phenotyping to accurately predict patients at risk of morphine toxicity (Lotsch et al, 2009 **Level III-2**).

## Tramadol

O-demethylation of tramadol by CYP2D6 produces the active metabolite (+)-*O*-desmethytramadol or M1, which has an affinity for mu-opioid receptors that is approximately 200 times more than the parent drug (Shipton, 2000). Poor metabolisers have significantly lower plasma concentrations of M1 compared with both homozygous and heterozygous extensive metabolisers (Stamer et al, 2003 **Level III-3**; Fliegert et al, 2005 **Level II**) and experience less analgesia (Poulsen et al, 1998 **Level IV**; Stamer et al, 2003 **Level III-3**). The selective serotonin reuptake inhibitor (SSRI) paroxetine (a CYP2D6 inhibitor) significantly inhibited (+) and (–) tramadol metabolism by about a third (Laugesen et al, 2005 **Level II**). As with codeine, impaired renal clearance of metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in cases of respiratory depression after tramadol (Desmeules et al, 1996 **Level II**).

## Methadone

Genetic polymorphisms in genes coding for methadone-metabolising enzymes, transporter proteins (p-glycoprotein), and mu-opioid receptors may explain part of the observed inter-individual variation in the pharmacokinetics and pharmacodynamics of methadone; blood concentrations may vary up to 20-fold for a given dose (Li et al, 2008).

Cytochrome P450 (CYP) 2B6 and 3A4 have been identified as the main CYP isoforms involved in methadone metabolism, but CYP2D6 has also been reported to have an effect (Li et al, 2008). Differing effects for isomers of methadone have also been reported. Genetic variability in CYP2B6 influenced (S)-, and to a lesser extent, plasma (R)-methadone concentrations; fluoxetine (CYP2D6 inhibitor) only increased (R)-methadone (Kharasch et al, 2004 **Level III-1**); and paroxetine (CYP2D6 inhibitor) increased steady-state (R)-, (S)-, and (R, S)-methadone in extensive metabolisers, but only increased (S)-methadone in poor metaboliser genotypes (Anderson & Palmer, 2006).

## NSAIDs

Wide variability in gene expression and functional polymorphisms in the COX-2 gene (PTGS2) may explain part of the inter-individual variations in acute pain and the analgesic efficacy of non-selective NSAIDs (nsNSAIDs) and coxibs; this may be useful to predict patient risk and benefit to drugs based on individual genetic variations (Somogyi et al, 2007; Lee et al, 2006 **Level III-2**).

NsNSAIDs like ibuprofen, naproxen and piroxicam are metabolised by CYP2C9 (Rollason et al, 2008). Between 1% and 3% of Caucasians are poor metabolisers. Homozygous carriers of the CYP2D9\* 3 allele may accumulate celecoxib and ibuprofen in blood and tissues and be at risk of increased adverse effects (Kirchheiner et al, 2003 **Level III-3**; Kirchheiner et al, 2002 **Level IV**; Stamer & Stuber, 2007).

### Key messages

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine and tramadol (**N**) (**Level II**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Genetic polymorphisms explain the wide inter-individual variability in plasma concentrations of a given dose of methadone (**N**).

## REFERENCES

- Aasvang EK & Kehlet H (2007) Chronic pain after childhood groin hernia repair. *J Pediatr Surg* **42**(8): 1403–8.
- Aasvang EK, Brandsborg B, Christensen B et al (2008) Neurophysiological characterization of postherniotomy pain. *Pain* **137**(1): 173–81.
- Ahlers O, Nachtigall I, Lenze J et al (2008) Intraoperative thoracic epidural anaesthesia attenuates stress-induced immunosuppression in patients undergoing major abdominal surgery. *Br J Anaesth* **101**(6): 781–7.
- Andersen LO, Gaarn-Larsen L, Kristensen BB et al (2009) Subacute pain and function after fast-track hip and knee arthroplasty. *Anaesthesia* **64**(5): 508–13.
- Anderson BJ & Palmer GM (2006) Recent pharmacological advances in paediatric analgesics. *Biomed Pharmacother* **60**(7): 303–9.
- Ballantyne JC, Carr DB, deFerranti S et al (1998) The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. *Anesth Analg* **86**(3): 598–612.
- Basse L, Raskov HH, Hjort Jakobsen D et al (2002) Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *Br J Surg* **89**(4): 446–53.
- Batoz H, Verdonck O, Pellerin C et al (2009) The analgesic properties of scalp infiltrations with ropivacaine after intracranial tumoral resection. *Anesth Analg* **109**(1): 240–4.
- Beattie WS, Badner NH & Choi P (2001) Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesth Analg* **93**(4): 853–8.
- Biki B, Mascha E, Moriarty DC et al (2008) Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology* **109**(2): 180–7.
- Birbaumer N, Flor H & Lutzenberger W (1995) The corticalization of chronic pain. In: *Pain and the Brain: From Nociception to Cognition. Advances in Pain Research and Therapy* edn. Burkhart B and Desmedt JE (eds). New York, Raven Press.
- Bisgaard T, Klarskov B, Rosenberg J et al (2001) Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain* **90**(3): 261–9.
- Blumenthal S, Dullenkopf A, Rentsch K et al (2005) Continuous infusion of ropivacaine for pain relief after iliac crest bone grafting for shoulder surgery. *Anesthesiology* **102**(2): 392–7.
- Blyth FM, March LM & Cousins MJ (2003) Chronic pain-related disability and use of analgesia and health services in a Sydney community. *Med J Aust* **179**(2): 84–7.
- Bong CL, Samuel M, Ng JM et al (2005) Effects of preemptive epidural analgesia on post-thoracotomy pain. *J Cardiothorac Vasc Anesth* **19**(6): 786–93.
- Brander V, Gondek S, Martin E et al (2007) Pain and depression influence outcome 5 years after knee replacement surgery. *Clin Orthop Relat Res* **464**: 21–6.
- Brander VA, Stulberg SD, Adams AD et al (2003) Predicting total knee replacement pain: a prospective, observational study. *Clin Orthop Relat Res* **416**: 27–36.
- Brandner B, Bromley L & Blagrove M (2002) Influence of psychological factors in the use of patient controlled analgesia. *Acute Pain* **4**: 53–56.
- Brandsborg B, Nikolajsen L, Hansen CT et al (2007) Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. *Anesthesiology* **106**(5): 1003–12.
- Carli F, Mayo N, Klubien K et al (2002) Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. *Anesthesiology* **97**(3): 540–9.
- Carli F & Schricker T (2009) Modification of Metabolic Response to Surgery by Neural Blockade. In: *Neural Blockade in Clinical Anesthesia and Pain Medicine* 4th edn. Cousins MJ, Bridenbaugh PO, Carr D and Horlocker T (eds). Philadelphia, Lippincott, Wolters Kluwer, Lippincott Williams & Wilkins.
- Carlson JD, Maire JJ, Martenson ME et al (2007) Sensitization of pain-modulating neurons in the rostral ventromedial medulla after peripheral nerve injury. *J Neurosci* **27**(48): 13222–31.
- Carr E, Brockbank K, Allen S et al (2006) Patterns and frequency of anxiety in women undergoing gynaecological surgery. *J Clin Nurs* **15**(3): 341–52.

- Caumo W, Schmidt AP, Schneider CN et al (2001) Risk factors for postoperative anxiety in adults. *Anaesthesia* **56**(8): 720–8.
- Caumo W, Schmidt AP, Schneider CN et al (2002) Preoperative predictors of moderate to intense acute postoperative pain in patients undergoing abdominal surgery. *Acta Anaesthesiol Scand* **46**(10): 1265–71.
- Caza N, Taha R, Qi Y et al (2008) The effects of surgery and anesthesia on memory and cognition. *Prog Brain Res* **169**: 409–22.
- Chandra RK (1983) Nutrition, immunity, and infection: present knowledge and future directions. *Lancet* **1**(8326 Pt 1): 688–91.
- Chapman CR, Tuckett RP & Song CW (2008) Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. *J Pain* **9**(2): 122–45.
- Choi PT, Bhandari M, Scott J et al (2003) Epidural analgesia for pain relief following hip or knee replacement. *Cochrane Database Syst Rev*(3): CD003071.
- Christensen T, Bendix T & Kehlet H (1982) Fatigue and cardiorespiratory function following abdominal surgery. *Br J Surg* **69**(7): 417–9.
- Christensen T, Nygaard E, Stage JG et al (1990) Skeletal muscle enzyme activities and metabolic substrates during exercise in patients with postoperative fatigue. *Br J Surg* **77**(3): 312–5.
- Cohen L, Fouladi RT & Katz J (2005) Preoperative coping strategies and distress predict postoperative pain and morphine consumption in women undergoing abdominal gynecologic surgery. *J Psychosom Res* **58**(2): 201–9.
- Cousins MJ, Power I & Smith G (2000) 1996 Labat lecture: pain—a persistent problem. *Reg Anesth Pain Med* **25**(1): 6–21.
- Cousins MJ, Brennan F & Carr DB (2004) Pain relief: a universal human right. *Pain* **112**(1-2): 1–4.
- Craig KD (2006) The construct and definition of pain in developmental disability. In: *Pain in individuals with developmental disabilities*. Symons FJ and Oberlander, TF (eds). Brookes, Baltimore.
- Craig KD (2009) The social communication model of pain. *Canadian Psychology* **50**(1): 22–32.
- Crombez G, Eccleston C (2002) To express or suppress may be a function of others' distress. *Behavioral and Brain Sciences* **25**: 457.
- Cummins TR, Sheets PL & Waxman SG (2007) The roles of sodium channels in nociception: Implications for mechanisms of pain. *Pain* **131**(3): 243–57.
- Dahl JB & Moiniche S (2004) Pre-emptive analgesia. *Br Med Bull* **71**: 13–27.
- de Andrade DC, Baudic S, Attal N et al (2008) Beyond neuropathy in hereditary sensory and autonomic neuropathy type V: cognitive evaluation. *Eur J Neurol* **15**(7): 712–9.
- De Cosmo G, Congedo E, Lai C et al (2008) Preoperative psychologic and demographic predictors of pain perception and tramadol consumption using intravenous patient-controlled analgesia. *Clin J Pain* **24**(5): 399–405.
- Delaney CP, Zutshi M, Senagore AJ et al (2003) Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum* **46**(7): 851–9.
- Desmeules JA, Piguët V, Collart L et al (1996) Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol* **41**(1): 7–12.
- Diatchenko L, Slade GD, Nackley AG et al (2005) Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* **14**(1): 135–43.
- Dib-Hajj SD, Yang Y & Waxman SG (2008) Genetics and molecular pathophysiology of Na(v)1.7-related pain syndromes. *Adv Genet* **63**: 85–110.
- Dib-Hajj SD, Binstok AM, Cummins TR et al (2009) Voltage-gated sodium channels in pain states: Role in pathophysiology and targets for treatment. *Brain Res Rev* **60**(1): 65–83.
- Donatelli F, Schrickler T, Mistraretti G et al (2006) Postoperative infusion of amino acids induces a positive protein balance independently of the type of analgesia used. *Anesthesiology* **105**(2): 253–9.
- Drenth JP & Waxman SG (2007) Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. *J Clin Invest* **117**(12): 3603–9.

- Duale C, Sibaud F, Guastella V et al (2009) Perioperative ketamine does not prevent chronic pain after thoracotomy. *Eur J Pain* **13**(5): 497–505.
- Eccleston C (2001) Role of psychology in pain management. *Br J Anaesth* **87**(1): 144–52.
- Eccleston C & Crombez G (1999) Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull* **125**(3): 356–66.
- Engel GL (1977) The need for a new medical model: a challenge for biomedical science. *Science* **196**: 129–36.
- Exadaktylos AK, Buggy DJ, Moriarty DC et al (2006) Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* **105**(4): 660–4.
- Fahy BG, Sheehy AM & Coursin DB (2009) Glucose control in the intensive care unit. *Crit Care Med* **37**(5): 1769–76.
- Fassoulaki A, Sarantopoulos C, Melemini A et al (2000) EMLA reduces acute and chronic pain after breast surgery for cancer. *Reg Anesth Pain Med* **25**(4): 350–5.
- Fassoulaki A, Patris K, Sarantopoulos C et al (2002) The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* **95**(4): 985–91.
- Fassoulaki A, Triga A, Melemini A et al (2005) Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. *Anesth Analg* **101**(5): 1427–32.
- Fillingham RB, Kaplan L, Staud R et al (2005) The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. *J Pain* **6**(3): 159–67.
- Flacker JM & Lipsitz LA (1999) Neural mechanisms of delirium: current hypotheses and evolving concepts. *J Gerontol A Biol Sci Med Sci* **54**(6): B239–46.
- Fliegert F, Kurth B & Gohler K (2005) The effects of tramadol on static and dynamic pupillometry in healthy subjects—the relationship between pharmacodynamics, pharmacokinetics and CYP2D6 metaboliser status. *Eur J Clin Pharmacol* **61**(4): 257–66.
- Flor H, Elbert T, Knecht S et al (1995) Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* **375**(6531): 482–4.
- Flor H, Knost B & Birbaumer N (2002) The role of operant conditioning in chronic pain: an experimental investigation. *Pain* **95**(1-2): 111–8.
- Flor H & Hermann C (2004) Biopsychosocial models of pain. In: *Psychosocial Aspects of Pain: a Handbook for Health Care Providers. Progress in Pain Research and Management* edn. Dworkin RH and Breitbart WS (eds). Seattle, IASP Press.
- Forsythe ME, Dunbar MJ, Hennigar AW et al (2008) Prospective relation between catastrophizing and residual pain following knee arthroplasty: two-year follow-up. *Pain Res Manag* **13**(4): 335–41.
- Gao L, Taha R, Gauvin D et al (2005) Postoperative cognitive dysfunction after cardiac surgery. *Chest* **128**(5): 3664–70.
- Gear RW, Gordon NC, Heller PH et al (1996) Gender difference in analgesic response to the kappa-opioid pentazocine. *Neurosci Lett* **205**(3): 207–9.
- Gear RW, Miaskowski C, Gordon NC et al (1999) The kappa opioid nalbuphine produces gender- and dose-dependent analgesia and antianalgesia in patients with postoperative pain. *Pain* **83**(2): 339–45.
- Gil KM, Ginsberg B, Muir M et al (1990) Patient-controlled analgesia in postoperative pain: the relation of psychological factors to pain and analgesic use. *Clin J Pain* **6**(2): 137–42.
- Gil KM, Ginsberg B, Muir M et al (1992) Patient controlled analgesia: the relation of psychological factors to pain and analgesic use in adolescents with postoperative pain. *Clin J Pain* **8**(3): 215–21.
- Granot M & Ferber SG (2005) The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. *Clin J Pain* **21**(5): 439–45.
- Gray P (2008) Acute neuropathic pain: diagnosis and treatment. *Curr Opin Anaesthesiol* **21**(5): 590–5.
- Greisen J, Juhl CB, Grofte T et al (2001) Acute pain induces insulin resistance in humans. *Anesthesiology* **95**(3): 578–84.
- Grusser SM, Muhlneckel W, Schaefer M et al (2004) Remote activation of referred phantom sensation and cortical reorganization in human upper extremity amputees. *Exp Brain Res* **154**(1): 97–102.



- Hansen N, Klein T, Magerl W et al (2007) Psychophysical evidence for long-term potentiation of C-fiber and A-delta fiber pathways in humans by analysis of pain descriptors. *J Neurophysiol* **97**(3): 2559–63.
- Harrison RA, Lewin MR, Halliday D et al (1989) Leucine kinetics in surgical patients. I: A study of the effect of surgical 'stress'. *Br J Surg* **76**(5): 505–8.
- Hayes C, Browne S, Lantry G et al (2002) Neuropathic pain in the acute pain service: a prospective study. *Acute Pain* **4**: 45–48.
- Heinricher MM, Tavares I, Leith JL et al (2009) Descending control of nociception: Specificity, recruitment and plasticity. *Brain Res Rev* **60**(1): 214–25.
- Herroeder S, Pecher S, Schönherr ME et al (2007) Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg* **246**(2): 192–200.
- Hines S, Theodorou S, Williamson A et al (2008) Management of acute pain in methadone maintenance therapy in-patients. *Drug Alcohol Rev* **27**(5): 519–23.
- Hinrichs-Rocker A, Schulz K, Järvinen I et al (2009) Psychosocial predictors and correlates for chronic post-surgical pain (CSPS) – A systematic review. *Eur J Pain* **13**: 719–30
- Hjortso NC, Neumann P, Frosig F et al (1985) A controlled study on the effect of epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. *Acta Anaesthesiol Scand* **29**(8): 790–6.
- Hobson JA, Slade P, Wrench IJ et al (2006) Preoperative anxiety and postoperative satisfaction in women undergoing elective caesarean section. *Int J Obstet Anesth* **15**(1): 18–23.
- Hsu YW, Somma J, Hung YC et al (2005) Predicting postoperative pain by preoperative pressure pain assessment. *Anesthesiology* **103**(3): 613–8.
- Hunt SP & Mantyh PW (2001) The molecular dynamics of pain control. *Nat Rev Neurosci* **2**(2): 83–91.
- Jacobsen PB & Butler RW (1996) Relation of cognitive coping and catastrophizing to acute pain and analgesic use following breast cancer surgery. *J Behav Med* **19**(1): 17–29.
- Jakobsen DH, Sonne E, Andreasen J et al (2006) Convalescence after colonic surgery with fast-track vs conventional care. *Colorectal Dis* **8**(8): 683–7.
- Jamison RN, Taft K, O'Hara JP et al (1993) Psychosocial and pharmacologic predictors of satisfaction with intravenous patient-controlled analgesia. *Anesth Analg* **77**(1): 121–5.
- Ji RR, Gereau RWt, Malcangio M et al (2009) MAP kinase and pain. *Brain Res Rev* **60**(1): 135–48.
- Jolliffe CD & Nicholas MK (2004) Verbally reinforcing pain reports: an experimental test of the operant model of chronic pain. *Pain* **107**(1-2): 167–75.
- Jorgensen H, Wetterslev J, Moinicke S et al (2000) Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev*(4): CD001893.
- Joshi GP (2005) Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. *Anesth Analg* **101**(2): 601–5.
- Kairaluoma PM, Bachmann MS, Rosenberg PH et al (2006) Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery. *Anesth Analg* **103**(3): 703–8.
- Kalkman CJ, Visser K, Moen J et al (2003) Preoperative prediction of severe postoperative pain. *Pain* **105**(3): 415–23.
- Katz J & McCartney CJ (2002) Current status of preemptive analgesia. *Curr Opin Anaesthesiol* **15**(4): 435–41.
- Katz J, Poleshuck EL, Andrus CH et al (2005) Risk factors for acute pain and its persistence following breast cancer surgery. *Pain* **119**(1-3): 16–25.
- Katz J & Clarke H (2008) Preventive analgesia and beyond: current status, evidence, and future directions. In: *Clinical Pain Management: Acute Pain* 2nd edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
- Katz J, Buis T & Cohen L (2008) Locked out and still knocking: predictors of excessive demands for postoperative intravenous patient-controlled analgesia. *Can J Anaesth* **55**(2): 88–99.
- Kehlet H & Dahl JB (2003) Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* **362**(9399): 1921–8.

- Kehlet H, Jensen TS & Woolf CJ (2006) Persistent postsurgical pain: risk factors and prevention. *Lancet* **367**(9522): 1618–25.
- Kehlet H, Wilkinson RC, Fischer HB et al (2007) PROSPECT: evidence-based, procedure-specific postoperative pain management. *Best Pract Res Clin Anaesthesiol* **21**(1): 149–59.
- Kehlet H & Wilmore DW (2008) Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* **248**(2): 189–98.
- Keogh E & Cochrane M (2002) Anxiety sensitivity, cognitive biases, and the experience of pain. *J Pain* **3**(4): 320–9.
- Kharasch ED, Hoffer C, Whittington D et al (2004) Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. *Clin Pharmacol Ther* **76**(3): 250–69.
- Khoo CK, Vickery CJ, Forsyth N et al (2007) A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. *Ann Surg* **245**(6): 867–72.
- Kim H, Clark D & Dionne RA (2009) Genetic contributions to clinical pain and analgesia: avoiding pitfalls in genetic research. *J Pain* **10**(7): 663–93.
- Kirchheiner J, Meineke I, Freytag G et al (2002) Enantiospecific effects of cytochrome P450 2C9 amino acid variants on ibuprofen pharmacokinetics and on the inhibition of cyclooxygenases 1 and 2. *Clin Pharmacol Ther* **72**(1): 62–75.
- Kirchheiner J, Stormer E, Meisel C et al (2003) Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics* **13**(8): 473–80.
- Kirchheiner J, Schmidt H, Tzvetkov M et al (2007) Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* **7**(4): 257–65.
- Kissin I (1994) Preemptive analgesia: terminology and clinical relevance. *Anesth Analg* **79**(4): 809–10.
- Klepstad P, Rakvag TT, Kaasa S et al (2004) The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. *Acta Anaesthesiol Scand* **48**(10): 1232–9.
- Korvald C, Elvenes OP & Myrmet T (2000) Myocardial substrate metabolism influences left ventricular energetics in vivo. *Am J Physiol Heart Circ Physiol* **278**(4): H1345–51.
- Kudoh A, Katagai H & Takazawa T (2002) Increased postoperative pain scores in chronic depression patients who take antidepressants. *J Clin Anesth* **14**(6): 421–5.
- Kunz M, Mylius V, Schepelmann K, Lautenbacher S (2004) On the relationship between self-report and facial expression of pain. *Journal of Pain* **5**: 367–376.
- Kuo CP, Jao SW, Chen KM et al (2006) Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth.* **97**(5): 640–6.
- Landau R, Kern C, Columb MO et al (2008) Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women. *Pain* **139**(1): 5–14.
- Laugesen S, Enggaard TP, Pedersen RS et al (2005) Paroxetine, a cytochrome P450 2D6 inhibitor, diminishes the stereoselective O-demethylation and reduces the hypoalgesic effect of tramadol. *Clin Pharmacol Ther* **77**(4): 312–23.
- Lavand'homme P, De Kock M & Waterloos H (2005) Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. *Anesthesiology* **103**(4): 813–20.
- Lazar HL, Chipkin SR, Fitzgerald CA et al (2004) Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. *Circulation* **109**(12): 1497–502.
- Lee YS, Kim H, Wu TX et al (2006) Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. *Clin Pharmacol Ther* **79**(5): 407–18.
- Leeuw M, Goossens ME, Linton SJ et al (2007) The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med* **30**(1): 77–94.



- Li Y, Kantelip JP, Gerritsen-van Schieveen P et al (2008) Interindividual variability of methadone response: impact of genetic polymorphism. *Mol Diagn Ther* **12**(2): 109–24.
- Lingard EA & Riddle DL (2007) Impact of psychological distress on pain and function following knee arthroplasty. *J Bone Joint Surg Am* **89**(6): 1161–9.
- Linton SJ (2000) A review of psychological risk factors in back and neck pain. *Spine* **25**(9): 1148–56.
- Liu Q, Docherty JC, Rendell JC et al (2002) High levels of fatty acids delay the recovery of intracellular pH and cardiac efficiency in post-ischemic hearts by inhibiting glucose oxidation. *J Am Coll Cardiol* **39**(4): 718–25.
- Liu SS, Block BM & Wu CL (2004) Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. *Anesthesiology* **101**(1): 153–61.
- Liu SS & Wu CL (2008) Neural blockade: impact on outcome. In: *Neural Blockade in Clinical Anesthesia and Pain Medicine* 4th edn. Cousins MJ, Bridenbaugh PO, Carr D and Horlocker T (eds). Philadelphia, Wolters Kluwer, Lippincott, Williams & Wilkins.
- Loeser JD & Treede RD (2008) The Kyoto protocol of IASP Basic Pain Terminology. *Pain* **137**(3): 473–7.
- Lotsch J & Geisslinger G (2006) Current evidence for a genetic modulation of the response to analgesics. *Pain* **121**(1-2): 1–5.
- Lotsch J, Rohrbacher M, Schmidt H et al (2009) Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? *Pain* **144**(1-2): 119–24.
- Lotsch J, Stuck B & Hummel T (2006) The human mu-opioid receptor gene polymorphism 118A > G decreases cortical activation in response to specific nociceptive stimulation. *Behav Neurosci* **120**(6): 1218–24.
- Lugli AK, Donatelli F, Schricker T et al (2008) Epidural analgesia enhances the postoperative anabolic effect of amino acids in diabetes mellitus type 2 patients undergoing colon surgery. *Anesthesiology* **108**(6): 1093–9.
- Macrae WA (2008) Chronic post-surgical pain: 10 years on. *Br J Anaesth* **101**(1): 77–86.
- Madadi P, Koren G, Cairns J et al (2007) Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician* **53**(1): 33–5.
- Malekpour F, Mirhashemi SH, Hajinasrolah E et al (2008) Ilioinguinal nerve excision in open mesh repair of inguinal hernia—results of a randomized clinical trial: simple solution for a difficult problem? *Am J Surg* **195**(6): 735–40.
- McCartney CJ, Sinha A & Katz J (2004) A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. *Anesth Analg* **98**(5): 1385–400.
- Merskey H & Bogduk N (1994) *Classification of Chronic Pain, IASP Task Force on Taxonomy*. Seattle, IASP Press.
- Mikus G & Weiss J (2005) Influence of CYP2D6 genetics on opioid kinetics, metabolism and response. *Curr Pharmacogenom* **3**: 43–52.
- Millan MJ (2002) Descending control of pain. *Prog Neurobiol* **66**(6): 355–474.
- Mogil JS (1999) The genetic mediation of individual differences in sensitivity to pain and its inhibition. *Proc Natl Acad Sci U S A* **96**(14): 7744–51.
- Mogil JS, Wilson SG, Chesler EJ et al (2003) The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. *Proc Natl Acad Sci U S A* **100**(8): 4867–72.
- Mogil JS, Ritchie J, Smith SB et al (2005) Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. *J Med Genet* **42**(7): 583–7.
- Moiniche S, Kehlet H & Dahl JB (2002) A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology* **96**(3): 725–41.
- Momin A & Wood JN (2008) Sensory neuron voltage-gated sodium channels as analgesic drug targets. *Curr Opin Neurobiol* **18**(4): 383–8.
- Monk TG, Weldon BC, Garvan CW et al (2008) Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* **108**(1): 18–30.
- Montagna P (2007) Recent advances in the pharmacogenomics of pain and headache. *Neuro Sci* **28**(Suppl 2): S208–12.

- Nackley AG, Tan KS, Fecho K et al (2007) Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors. *Pain* **128**(3): 199–208.
- Nelson FV, Zimmerman L, Barnason S et al (1998) The relationship and influence of anxiety on postoperative pain in the coronary artery bypass graft patient. *J Pain Symptom Manage* **15**(2): 102–9.
- Newman S, Stygall J, Hirani S et al (2007) Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology* **106**(3): 572–90.
- Nikolajsen L, Sorensen HC, Jensen TS et al (2004) Chronic pain following Caesarean section. *Acta Anaesthesiol Scand* **48**(1): 111–6.
- Nishimori M, Ballantyne JC & Low JH (2006) Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. *Cochrane Database Syst Rev* **3**: CD005059.
- Oertel B & Lotsch J (2008) Genetic mutations that prevent pain: implications for future pain medication. *Pharmacogenomics* **9**(2): 179–94.
- Oliver MF & Opie LH (1994) Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. *Lancet* **343**(8890): 155–8.
- Ong CK, Lirk P, Seymour RA et al (2005) The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg* **100**(3): 757–73.
- Ozalp G, Sarioglu R, Tuncel G et al (2003) Preoperative emotional states in patients with breast cancer and postoperative pain. *Acta Anaesthesiol Scand* **47**(1): 26–9.
- Park JJ, Lee J, Kim MA et al (2007) Induction of total insensitivity to capsaicin and hypersensitivity to garlic extract in human by decreased expression of TRPV1. *Neurosci Lett* **411**(2): 87–91.
- Parker MJ, Handoll HH & Griffiths R (2004) Anaesthesia for hip fracture surgery in adults. *Cochrane Database Syst Rev*(4): CD000521.
- Patapoutian A, Tate S & Woolf CJ (2009) Transient receptor potential channels: targeting pain at the source. *Nat Rev Drug Discov* **8**(1): 55–68.
- Pavlin DJ, Sullivan MJ, Freund PR et al (2005) Catastrophizing: a risk factor for postsurgical pain. *Clin J Pain* **21**(1): 83–90.
- Perry F, Parker RK, White PF et al (1994) Role of psychological factors in postoperative pain control and recovery with patient-controlled analgesia. *Clinical Journal of Pain* **10**(1): 57–63.
- Persson K, Sjostrom S, Sigurdardottir I et al (1995) Patient-controlled analgesia (PCA) with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. *Br J Clin Pharmacol* **39**(2): 182–6.
- Picchio M, Palimento D, Attanasio U et al (2004) Randomized controlled trial of preservation or elective division of ilioinguinal nerve on open inguinal hernia repair with polypropylene mesh. *Arch Surg* **139**(7): 755–8.
- Pincus T, Vlaeyen JW, Kendall NA et al (2002) Cognitive-behavioral therapy and psychosocial factors in low back pain: directions for the future. *Spine* **27**(5): E133–8.
- Pogatzki-Zahn EM & Zahn PK (2006) From preemptive to preventive analgesia. *Curr Opin Anaesthesiol* **19**(5): 551–5.
- Poulsen L, Riishede L, Brosen K et al (1998) Codeine in post-operative pain. Study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide. *Eur J Clin Pharmacol* **54**(6): 451–4.
- Quintner JL, Cohen ML, Buchanan D, Katz JD, Williamson OD (2008). Pain medicine and its models: helping or hindering? *Pain Med* **9**:824–34.
- Ready LB & Edwards WT (1992) *Management of Acute Pain: a Practical Guide. Taskforce on Acute Pain*. Seattle, IASP Publications.
- Reyes-Gibby CC, Shete S, Ravvag T et al (2007) Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. *Pain* **130**(1-2): 25–30.
- Rigg JR, Jamrozik K, Myles PS et al (2002) Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* **359**(9314): 1276–82.
- Rodgers A, Walker N, Schug S et al (2000) Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* **321**(7275): 1493.

- Rollason V, Samer C, Piguet V et al (2008) Pharmacogenetics of analgesics: toward the individualization of prescription. *Pharmacogenomics* **9**(7): 905–33.
- Roth ML, Tripp DA, Harrison MH et al (2007) Demographic and psychosocial predictors of acute perioperative pain for total knee arthroplasty. *Pain Res Manag* **12**(3): 185–94.
- Rudin A, Wolner-Hanssen P, Hellbom M et al (2008) Prediction of post-operative pain after a laparoscopic tubal ligation procedure. *Acta Anaesthesiol Scand* **52**(7): 938–45.
- Russell FA & McDougall JJ (2009) Proteinase activated receptor (PAR) involvement in mediating arthritis pain and inflammation. *Inflamm Res* **58**(3): 119–26.
- Sandkuhler J (2009) Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev* **89**(2): 707–58.
- Schafers M & Sorkin L (2008) Effect of cytokines on neuronal excitability. *Neurosci Lett* **437**(3): 188–93.
- Schott GD (1986) Pain and its absence in an unfortunate family of amputees. *Pain* **25**(2): 229–31.
- Schricker T, Meterissian S, Lattermann R et al (2008) Anticatabolic effects of avoiding preoperative fasting by intravenous hypocaloric nutrition: a randomized clinical trial. *Ann Surg* **248**(6): 1051–9.
- Searle R & Hopkins PM (2009) Pharmacogenomic variability and anaesthesia. *Br J Anaesth* **103**(1): 14–25.
- Senturk M, Ozcan PE, Talu GK et al (2002) The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* **94**(1): 11–5.
- Shipton EA (2000) Tramadol—present and future. *Anaesth Intensive Care* **28**(4): 363–74.
- Sloane EM, Soderquist RG, Maier SF et al (2009) Long-term control of neuropathic pain in a non-viral gene therapy paradigm. *Gene Ther* **16**(4): 470–5.
- Somogyi AA, Barratt DT & Collier JK (2007) Pharmacogenetics of opioids. *Clin Pharmacol Ther* **81**(3): 429–44.
- Stamer UM, Lehnen K, Hothker F et al (2003) Impact of CYP2D6 genotype on postoperative tramadol analgesia. *Pain* **105**(1-2): 231–8.
- Stamer UM & Stuber F (2007) Genetic factors in pain and its treatment. *Curr Opin Anaesthesiol* **20**(5): 478–84.
- Stamer UM, Musshoff F, Kobilay M et al (2007) Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clin Pharmacol Ther* **82**(1): 41–7.
- Stein C, Clark JD, Oh U et al (2009) Peripheral mechanisms of pain and analgesia. *Brain Res Rev* **60**(1): 90–113.
- Strulov L, Zimmer EZ, Granot M et al (2007) Pain catastrophizing, response to experimental heat stimuli, and post-caesarean section pain. *J Pain* **8**(3): 273–9.
- Sullivan M, Tanzer M, Stanish W et al (2009) Psychological determinants of problematic outcomes following Total Knee Arthroplasty. *Pain* **143**(1-2): 123–9.
- Suzuki R, Rygh LJ & Dickenson AH (2004) Bad news from the brain: descending 5-HT pathways that control spinal pain processing. *Trends Pharmacol Sci* **25**(12): 613–7.
- Suzuki M, Haraguti S, Sugimoto K et al (2006) Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* **105**(1): 111–9.
- Tegeder I, Costigan M, Griffin RS et al (2006) GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med* **12**(11): 1269–77.
- Tegeder I, Adolph J, Schmidt H et al (2008) Reduced hyperalgesia in homozygous carriers of a GTP cyclohydrolase 1 haplotype. *Eur J Pain* **12**(8): 1069–77.
- Terry R, Niven C, Brodie E et al (2007) An exploration of the relationship between anxiety, expectations and memory for postoperative pain. *Acute Pain* **9**: 135–43.
- Tetrault JM & O'Connor PG (2008) Substance abuse and withdrawal in the critical care setting. *Crit Care Clin* **24**(4): 767–88.
- Thomas V, Heath M, Rose D et al (1995) Psychological characteristics and the effectiveness of patient-controlled analgesia. *Br J Anaesth* **74**(3): 271–6.
- Tracey I & Mantyh PW (2007) The cerebral signature for pain perception and its modulation. *Neuron* **55**(3): 377–91.
- Tracey I (2008) Imaging pain. *Br J Anaesth* **101**(1): 32–9.

- Turk DC & Monarch ES (1995) Biopsychosocial perspective on chronic pain. In: *Psychological Approaches to Pain Management* 2nd edn. Turk DC and Gatchel RJ (eds). New York, Guildford Press.
- Van den Berghe G (2004) How does blood glucose control with insulin save lives in intensive care? *J Clin Invest* **114**(9): 1187–95.
- Vancleef LM & Peters ML (2006) Pain catastrophizing, but not injury/illness sensitivity or anxiety sensitivity, enhances attentional interference by pain. *J Pain* **7**(1): 23–30.
- Vanegas H & Schaible HG (2004) Descending control of persistent pain: inhibitory or facilitatory? *Brain Res Brain Res Rev* **46**(3): 295–309.
- Vervoot T, Goubert L, Crombez G (2009) The relationship between high catastrophizing children's facial display of pain and parental judgment of their child's pain. *Pain* **142**: 142–148.
- Wall PD (1988) The prevention of postoperative pain. *Pain* **33**(3): 289–90.
- Watters JM, Clancey SM, Moulton SB et al (1993) Impaired recovery of strength in older patients after major abdominal surgery. *Ann Surg* **218**(3): 380–90.
- White PF, Kehlet H, Liu S (2009) Perioperative analgesia: what do we still know? *Anesth Analg* **108**: 1364–7.
- White PF, Kehlet H, Neal JM et al; Fast-Track Surgery Study Group (2007). The role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. *Anesth Analg* **104**(6): 1380–96.
- White FA & Wilson NM (2008) Chemokines as pain mediators and modulators. *Curr Opin Anaesthesiol* **21**(5): 580–5.
- Wieczorek S, Bergstrom J, Saaf M et al (2008) Expanded HSAN4 phenotype associated with two novel mutations in NTRK1. *Neuromuscul Disord* **18**(8): 681–4.
- Wiener RS, Wiener DC & Larson RJ (2008) Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* **300**(8): 933–44.
- Williams DG, Patel A & Howard RF (2002) Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* **89**(6): 839–45.
- Wilmore DW & Kehlet H (2001) Management of patients in fast track surgery. *BMJ* **322**(7284): 473–6.
- Wind J, Polle SW, Fung Kon Jin PH et al (2006) Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* **93**(7): 800–9.
- Windsor JA & Hill GL (1988) Weight loss with physiologic impairment. A basic indicator of surgical risk. *Ann Surg* **207**(3): 290–6.
- Woolf CJ (1983) Evidence for a central component of post-injury pain hypersensitivity. *Nature* **306**(5944): 686–8.
- Woolf CJ & Salter MW (2000) Neuronal plasticity: increasing the gain in pain. *Science* **288**(5472): 1765–9.
- Woolf CJ & Ma Q (2007) Nociceptors—noxious stimulus detectors. *Neuron* **55**(3): 353–64.
- Wrigley PJ, Press SR, Gustin SM et al (2009) Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. *Pain* **141**(1-2): 52–9.
- Xu H, Tian W, Fu Y et al (2007) Functional effects of nonsynonymous polymorphisms in the human TRPV1 gene. *Am J Physiol Renal Physiol* **293**(6): F1865–76.
- Yarnitsky D, Crispel Y, Eisenberg E et al (2008) Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain* **138**(1): 22–8.
- Young Casey C, Greenberg MA, Nicassio PM et al (2008) Transition from acute to chronic pain and disability: a model including cognitive, affective, and trauma factors. *Pain* **134**(1-2): 69–79.

## 2. ASSESSMENT AND MEASUREMENT OF PAIN AND ITS TREATMENT

---

### 2.1 ASSESSMENT

Reliable and accurate assessment of acute pain is necessary to ensure patients experience safe, effective and individualised pain management. The assessment and measurement of pain are fundamental to the process of assisting in the diagnosis of the cause of a patient's pain, selecting an appropriate analgesic therapy and evaluating then modifying that therapy according to a patient's response. Pain should be assessed within a biopsychosocial model that recognises that physiological, psychological and environmental factors influence the overall pain experience.

The assessment of acute pain should include a thorough general medical history and physical examination, a specific 'pain history' (see Table 2.1) and an evaluation of associated functional impairment (see Section 2.3). In acute pain management, assessment must be undertaken at appropriately frequent intervals. At these times, evaluation of pain intensity, functional impact, and side effects of treatment must be undertaken and recorded using tools and scales that are consistent, valid and reliable (Scott & McDonald, 2008). In addition, pain assessment must lead to changes in management and re-evaluation of the patient to ensure improvements in the quality of care (Gordon et al, 2005).

Although not always possible in an acute setting, a complete pain history provides important diagnostic information that may help distinguish different underlying pain states such as nociceptive (somatic and visceral) or neuropathic pain (Victor et al, 2008). Somatic pain may be described as sharp, hot or stinging, is generally well localised, and is associated with local and surrounding tenderness. By contrast, visceral pain may be described as dull, cramping, or colicky, is often poorly localised and may be associated with tenderness locally or in the area of referred pain, or with symptoms such as nausea, sweating and cardiovascular changes (Scott & McDonald, 2008).

While nociceptive pain typically predominates in the acute pain setting, patients may also experience neuropathic pain (see Section 1.3). Features in the pain history that may suggest a diagnosis of neuropathic pain include (Gray, 2008; Dworkin et al, 2007):

- clinical circumstances associated with a high risk of nerve injury eg thoracic or chest wall procedures, amputations or hernia repairs;
- pain descriptors such as burning, shooting and stabbing;
- the paroxysmal or spontaneous nature of the pain, which may have no clear precipitating factors;
- the presence of dysaesthesias (spontaneous or evoked unpleasant abnormal sensations), hyperalgesia (increased response to a normally painful stimulus), allodynia (pain due to a stimulus that does not normally evoke pain such as light touch) or areas of hypoaesthesia; and
- regional autonomic features (changes in colour, temperature and sweating) and phantom phenomena.

It is useful to draw the distinction between the different types of pain because the likely duration of the pain and the response to analgesic strategies may vary. The concept of 'mechanism-based pain diagnosis' has been promoted (Woolf & Max, 2001) and although the

correlation between symptoms, mechanisms and response to therapy is not fully defined, specific therapy targeted at, for example, neuropathic pain, may be of benefit (Gray, 2008).

**Table 2.1 Fundamentals of a pain history**

- 
- 1 Site of pain**
    - a primary location: description ± body map diagram
    - b radiation
  - 2 Circumstances associated with pain onset**

including details of trauma or surgical procedures
  - 3 Character of pain**
    - a sensory descriptors eg sharp, throbbing, aching (Victor et al, 2008)
    - b McGill Pain Questionnaire: includes sensory and affective descriptors (Melzack, 1987)
    - c neuropathic pain characteristics (eg Neuropathic Pain Questionnaire) (Backonja & Krause, 2003)
  - 4 Intensity of pain**
    - a at rest
    - b on movement
    - c temporal factors
      - i duration
      - ii current pain, during last week, highest level
      - iii continuous or intermittent
    - d aggravating or relieving factors
  - 5 Associated symptoms (eg nausea)**
  - 6 Effect of pain on activities and sleep**
  - 7 Treatment**
    - a current and previous medications — dose, frequency of use, efficacy, side effects
    - b other treatment eg transcutaneous electrical nerve stimulation
    - c health professionals consulted
  - 8 Relevant medical history**
    - a prior or coexisting pain conditions and treatment outcomes
    - b prior or coexisting medical conditions
  - 9 Factors influencing the patient's symptomatic treatment**
    - a belief concerning the causes of pain
    - b knowledge, expectations and preferences for pain management
    - c expectations of outcome of pain treatment
    - d reduction in pain required for patient satisfaction or to resume 'reasonable activities'
    - e typical coping response for stress or pain, including presence of anxiety or psychiatric disorders (eg depression or psychosis)
    - f family expectations and beliefs about pain, stress and postoperative course
- 

## 2.2 MEASUREMENT

The definition of pain underlies the complexity of its measurement. Pain is an individual and subjective experience modulated by physiological, psychological and environmental factors such as previous events, culture, prognosis, coping strategies, fear and anxiety. Therefore, most measures of pain are based on self-report. These measures lead to sensitive and

consistent results if done properly (Moore et al, 2003). Self-report measures may be influenced by mood, sleep disturbance and medications (Scott & McDonald, 2008).

In some instances it may not be possible to obtain reliable self-reports of pain (eg patients with impaired consciousness or cognitive impairment, young children (see Section 10.3), elderly patients (see Section 11.2.3), or where there are failures of communication due to language difficulties, inability to understand the measures, unwillingness to cooperate or severe anxiety). In these circumstances other methods of pain assessment will be needed.

There are no objective measures of 'pain' but associated factors such as hyperalgesia (eg mechanical withdrawal threshold), the stress response (eg plasma cortisol concentrations), behavioural responses (eg facial expression), functional impairment (eg coughing, ambulation) or physiological responses (eg changes in heart rate) may provide additional information.

Analgesic requirements (eg patient-controlled opioid doses delivered) are commonly used as *post hoc* measures of pain experienced (Moore et al, 2003).

Recording pain intensity as 'the fifth vital sign' aims to increase awareness and utilisation of pain assessment (JCAHO & NPC, 2001) and may lead to improved acute pain management (Gould et al, 1992 **Level III-3**). Regular and repeated measurements of pain should be made to assess ongoing adequacy of analgesic therapy. An appropriate frequency of reassessment will be determined by the duration and severity of the pain, patient needs and response, and the type of drug or intervention (Gordon et al, 2005). Such measurements should incorporate different components of pain. For example, in the postoperative patient this should include assessments of static (rest) and dynamic (on sitting, coughing or moving the affected part) pain. Whereas static measures may relate to the patient's ability to sleep, dynamic measures can provide a simple test for mechanical hyperalgesia and determine whether analgesia is adequate for recovery of function (Breivik et al, 2008).

Uncontrolled pain should always trigger a reassessment of the diagnosis and consideration of alternatives such as developing surgical or other complications, or the presence of neuropathic pain. Review by an acute pain service or other specialist group should be considered.

### 2.2.1 Unidimensional measures of pain

A number of scales are available that measure either pain intensity, or the degree of pain relief following an intervention. Pain *relief* scales, although less commonly used, have some advantage when comparing the response to different treatments, as all patients start with the same baseline relief score (zero), whereas they may have differing levels of baseline pain intensity (Moore et al, 2003; Breivik et al, 2008).

#### **Categorical scales**

Categorical scales use words to describe the magnitude of pain or the degree of pain relief (Moore et al, 2003). The verbal descriptor scale (VDS) is the most common example (eg using terms such as none, mild, moderate, severe and excruciating or agonising) typically using four or five graded descriptors.

These terms can then be converted to numeric scores (eg 0, 2, 5, 8, 10) for charting and easy comparison over time. There is a good correlation between descriptive verbal categories and visual analogue scales (Banos et al, 1989 **Level III-2**), but the VDS is a less sensitive measure of pain treatment outcome than the VAS (Jensen et al, 2002 **Level IV**). Pain *relief* may also be graded as none, mild, moderate or complete using a VDS.

Categorical scales have the advantage of being quick and simple and may be useful in the elderly or visually impaired patient and in some children. However, the limited number of choices in categorical compared with numerical scales may make it more difficult to detect



differences between treatments (Breivik et al, 2000 **Level II**). Other limitations include personal, cultural or linguistic differences in interpretation of the specific words chosen as descriptors both between patients and also between patients and their clinicians.

### **Numerical rating scales**

Numerical rating scales (NRS) have both written and verbal forms. Patients rate their pain intensity on the scale of 0 to 10 where 0 represents 'no pain' and 10 represents 'worst pain imaginable'. The Verbal NRS (VNRS) is typically administered using a phrase such as: 'On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain you could imagine, where would you rate the pain you are experiencing right now?'. It is important that scales are consistent, and it is recommended that the 'no pain' point be represented as zero (0) rather than 1 (Scott & McDonald, 2008). Pain *relief* may be measured in the reverse direction with 0 representing 'no relief' to 10 representing 'complete relief'. A visual form of the 11-point NRS with tick marks on a line or boxes with numbers may also be used (Breivik et al, 2008). This is widely used, but some patients have difficulty representing their pain in numerical terms and are better suited to a categorical scale. A value of 4 or more is often used as a threshold to guide clinical intervention (Hartrick et al, 2003).

*Visual analogue scales* (VAS) consist of a 100 mm horizontal line with verbal anchors at both ends and no tick marks. The patient is asked to mark the line and the 'score' is the distance in millimetres from the left side of the scale to the mark. VAS are the most commonly used scales for rating pain intensity in research, with the words 'no pain' at the left end and 'worst pain imaginable' at the right. Pictorial versions also exist. VAS can also be used to measure other aspects of the pain experience (eg affective components, patient satisfaction, side effects).

Assessment of pain immediately after surgery can be more difficult and lead to greater interpatient variability in pain scores because of transient anaesthetic-related cognitive impairment and decreases in visual acuity. A 'pain meter' (PAULA) which used five coloured emoticon faces on the front of a ruler and corresponding VAS scores on the back, and allowed patients to move a slider to mark the pain they were experiencing, resulted in less variance than pain scores obtained from a standard VAS (Machata et al, 2009 **Level III-2**).

VAS ratings of greater than 70 mm are indicative of 'severe pain' (Aubrun et al, 2003 **Level IV**; Jensen et al, 2003 **Level IV**) and 0 to 5 mm 'no pain', 5 to 44 mm 'mild pain' and 45 to 74 'moderate pain' (Aubrun et al, 2003 **Level IV**). A reduction in pain intensity by 30% to 35% has been rated as clinically meaningful by patients with postoperative pain (Cepeda et al, 2003 **Level IV**; Jensen et al, 2003 **Level IV**), acute pain in the emergency department (Lee et al, 2003 **Level IV**), breakthrough cancer pain (Farrar et al, 2000 **Level IV**) and chronic pain (Farrar et al, 2001 **Level IV**).

These scales have the advantage of being simple and quick to use, allow for a wide choice of ratings and avoid imprecise descriptive terms (Scott & McDonald, 2008). However, the scales require more concentration and coordination, need physical devices, are unsuitable for children under 5 years and may also be unsuitable in up to 26% of adult patients (Cook et al, 1999).

The VAS has been shown to be a linear scale for patients with postoperative pain of mild–moderate intensity (Myles et al, 1999 **Level IV**) and severe pain (Myles & Urquhart, 2005 **Level IV**). Therefore, results are equally distributed across the scale, such that the difference in pain between each successive increment is equal.

*Verbal numerical rating scales* (VNRS) are often preferred because they are simpler to administer, give consistent results and correlate well with the VAS (Murphy et al, 1988 **Level IV**; DeLoach et al, 1998 **Level IV**; Breivik et al, 2000 **Level IV**). Recall of pain intensity using the VNRS



over the previous 24 hours was a reasonable indicator of average pain experienced by the patient during that time (Jensen et al, 2008 **Level III-2**).

Patients asked to rate their pain using a VNRS prior to and after morphine administration were also asked to rate their pain relief on a 5-point standard Likert scale as 0 = no pain relief, 1 = a little pain relief, 2 = moderate pain relief, 3 = a lot of pain relief and 4 = complete pain relief. The VNRS reductions associated with these pain relief ratings were 9.0, 7.5, 3.9, 2.1 and -0.1 respectively (Bernstein et al, 2006 **Level III-2**).

## 2.2.2 Functional impact of acute pain

Analgesia should be titrated to achieve both decreased pain intensity and the ability to undertake appropriate functional activity (Breivik et al, 2008). This will enable analgesia to optimise recovery. Most tools for measuring the functional impact of pain are based on chronic pain assessment, and therefore are not routinely applicable to the acute pain environment.

Measurement of pain intensity scores on movement or with coughing is a useful guide, however this reflects the subjective pain experience and not the capacity to undertake the specific activity. The Functional Activity Scale score (FAS score) is a simple three-level ranked categorical score designed to be applied at the point of care (Scott & McDonald, 2008). Its fundamental purpose is to assess whether the patient can undertake appropriate activity at their current level of pain control and to act as a trigger for intervention should this not be the case. The patient is asked to perform the activity, or is taken through the activity in the case of structured physiotherapy (joint mobilisation) or nurse-assisted care (eg ambulation, turned in bed). The ability to complete the activity is then assessed using the FAS as:

- |                            |   |
|----------------------------|---|
| A — no limitation          | the patient is able to undertake the activity without limitation due to pain (pain intensity score is typically 0 to 3);                  |
| B — mild limitation        | the patient is able to undertake the activity but experiences moderate to severe pain (pain intensity score is typically 4 to 10); and    |
| C — significant limitation | the patient is unable to complete the activity due to pain, or pain treatment-related side effects, independent of pain intensity scores. |

This score is then used to track effectiveness of analgesia on function and trigger interventions if required. Disadvantages of the FAS score are that it has not been independently validated and clinical staff need to be educated in its application.

## 2.2.3 Multidimensional measures of pain

Rather than assessing only pain intensity, multidimensional tools provide further information about the characteristics of the pain and its impact on the individual. Examples include the Brief Pain Inventory, which assesses pain intensity and associated disability (Daut et al, 1983) and the McGill Pain Questionnaire, which assesses the sensory, affective and evaluative dimensions of pain (Melzack, 1987).

Unidimensional tools such as the VAS are inadequate when it comes to quantifying neuropathic pain. Specific scales have been developed that identify (and/or quantify) descriptive factors specific for neuropathic pain (Bouhassira et al, 2004 **Level IV**; Cruccu et al, 2004 **Level IV**; Bouhassira et al, 2005 **Level IV**; Dworkin et al, 2007 **Level III-2**) and that may also include

sensory examination (Crucchi et al, 2004; Bouhassira et al, 2005) and allow evaluation of response to treatment (Bouhassira et al, 2004).

Global scales are designed to measure the effectiveness of overall treatment (see Section 2.3.1). They are more suited to outcome evaluation at the end of treatment than to modifying treatment in the acute stage (Moore et al, 2003). Questions such as ‘How effective do you think the treatment was?’ recognise that unimodal measures of pain intensity cannot adequately represent all aspects of pain perception.

Satisfaction is often used as a global indicator of outcome, however patients may report high levels of satisfaction even if they have moderate to severe acute pain (Svensson et al, 2001 **Level IV**). Satisfaction may also be influenced by preoperative expectations of pain, effectiveness of pain relief, the patient–provider relationship (eg communication by medical and nursing staff), interference with function due to pain and number of opioid-related side effects (Svensson et al, 2001 **Level IV**; Carlson et al, 2003 **Level IV**; Jensen et al, 2004 **Level IV**). Although complete absence of pain is not required for patients to report high levels of satisfaction, moderate pain (VAS greater than 50, scale 0 to 100) has been associated with dissatisfaction (Jensen et al, 2005 **Level III-2**).

## 2.2.4 Patients with special needs

Validated tools are available for measuring pain in neonates, infants and children, but must be both age and developmentally appropriate (see Section 10.3). These include behavioural assessments, pictorial scales (eg faces) and response to treatment. Adult patients who have difficulty communicating their pain (eg patients with cognitive impairment or who are critically unwell in the emergency department or intensive care) require special attention as do patients whose language or cultural background differs significantly from that of their health care team (see Sections 9.8, 9.9, 11.2.3, 11.3 and 11.4). Communication aids and behavioural scales such as the modified Faces, Legs, Activity, Cry and Consolability (FLACC) scale (Erdek & Pronovost, 2004) can be particularly useful in these situations (see Section 11.2.3).

### Key messages

1. Regular assessment of pain leads to improved acute pain management (**U**) (**Level III-3**).
2. There is good correlation between the visual analogue and numerical rating scales (**U**) (**Level III-2**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Self-reporting of pain should be used whenever appropriate as pain is by definition a subjective experience (**U**).
- The pain measurement tool chosen should be appropriate to the individual patient; developmental, cognitive, emotional, language and cultural factors should be considered (**U**).
- Scoring should incorporate different components of pain including the functional capacity of the patient. In the postoperative patient this should include static (rest) and dynamic (eg pain on sitting, coughing) pain (**U**).
- Uncontrolled or unexpected pain requires a reassessment of the diagnosis and consideration of alternative causes for the pain (eg new surgical/ medical diagnosis, neuropathic pain) (**U**).

## 2.3 OUTCOME MEASURES IN ACUTE PAIN MANAGEMENT

What follows is a brief guide to some of the outcome measures used particularly in the acute pain literature. A comprehensive review is beyond the scope of this document and more detail may be found elsewhere (Breivik et al, 2008).

### 2.3.1 Outcome measures

#### **Pain**

The aim of many clinical trials is to determine whether a drug or intervention provides adequate pain relief for the majority of participants or is equivalent or non-inferior to an existing accepted treatment. This can be achieved by repeated single measures at fixed time points, which may encompass only a proportion of the total illness. When comparison is made with a placebo, a statistically significant result can be achieved with a relatively small number of patients (eg n=40) (Collins et al, 2001). The primary outcome is chosen by the researcher and may not be of direct importance to the individual patient, particularly if it relates to only a proportion of the total time he/she was in pain. It is also important to consider that statistically significant differences in pain scores may not reflect clinically significant differences, although these are harder to define (see above).

Data derived from categorical and visual analogue scales of pain intensity or relief produce a range of summary outcomes that can be used to assess (Moore et al, 2003):

- the degree of analgesic effect:
  - difference between the baseline and postintervention score of pain intensity or pain relief (Summed pain intensity difference [SPID]);
  - the area under the time-analgesic effect curve for a given time (total pain relief [TOTPAR]);
  - dose of rescue analgesic consumption required in a given time period (eg PCA use);
- the time to analgesic effect:
  - the time to onset of analgesic effect;
  - mean time to maximum reduction in pain intensity or to peak relief;
- the duration of effect:
  - time for pain to return to at least 50% of baseline;
  - time for pain intensity to return to baseline or for pain relief to fall to zero;
  - time to re-medication/rescue analgesia.

A widely used method of describing the effectiveness of an analgesic intervention is the number-needed-to-treat (NNT). In this setting it is commonly defined as the number of patients that need to be treated to achieve at least 50% pain relief (eg at least 50% maximum TOTPAR) in one patient compared with a placebo over a 4 to 6 hour treatment period (Moore et al, 2003). Analysis at other cut-off points (30% to 70% max TOTPAR) has shown the same relative efficacy of different treatments (McQuay et al, 2003).

The validity of this approach as a true method of comparison may be questioned as there is no standardisation of the acute pain model or patient and only single doses of the analgesic agents are used. However, it may sometimes be reasonable to extrapolate estimates of analgesic efficacy from one pain model to another (Barden et al, 2004 **Level I**).

The use of supplemental analgesic consumption as an outcome measure has been questioned in situations where pain scores are not similar (McQuay et al, 2008).

### **Physical functioning**

Measures of physical functioning quantify many aspects of a patient's life including their ability to sleep, eat, think, deep breathe, cough, mobilise, perform activities of self-care and daily living, undertake their usual vocation, and to enjoy leisure activities and sport (Williams, 1999). In acute pain this may be measured by pain intensity scores with movement or other functional activity scores (see above).

Global or multidimensional measures of function attempt to combine various abilities or disabilities to derive a summary measure. Scales that employ a large number of items might be comprehensive but risk patient exhaustion or error, while scales with fewer items might be patient-friendly but risk becoming insensitive to state or change (Williams, 1999). These scales have been used in some studies of acute spinal pain and cancer-related pain:

- *disability scales* — generic scales include the Short Form 36 of Medical Outcomes Study (SF-36), the Sickness Impact Profile (SIP), and Roland & Morris Short SIP (Williams, 1999); and
- *Quality of life (QOL) measures* — these measures are not widely used in pain studies other than for cancer-related pain (Higginson, 1997).

Disease-specific measures quantify the impact of a specific pain problem on function and can be used to track changes after an intervention (eg ability to cough after thoracotomy, ability to lift a baby after Caesarean section) (Garratt et al, 2001). Generic measures facilitate comparisons among the functional limitations of different conditions and treatments, and may have advantages for audit of an acute pain service that includes patients with a range of conditions (Patrick & Deyo, 1989).

### **Emotional functioning**

Acute pain is an unpleasant sensory and emotional experience. The unpleasantness of the experience and its meaning for the individual may have short-term (anxiety, depression, irritability) and long-term consequences (lost confidence or self-efficacy or post-traumatic stress disorder) for the individual's emotional functioning.

### **Adverse symptoms and events**

In trials of efficacy, adverse events are usually considered to be of secondary importance and inadequate reporting has been found in as many as half of randomised trials reviewed (Edwards et al, 1999; Ioannidis & Lau, 2001). If adverse events are sufficiently common (eg nausea with opioids) they may be quantifiable in trials of efficacy and specifically measured using dichotomous (present or absent), categorical (none, mild, moderate, severe) or interval (analogue or Likert) scales. Analogous to NNTs, the number-needed-to-harm (NNH) may be used to describe the incidence of adverse effects.

Most efficacy trials will have inadequate power to detect rare adverse events and therefore they are also absent from systematic reviews. Large clinical trials specifically designed to detect adverse events are required (eg the VIGOR study investigated GI toxicity and NSAIDs) (Bombardier et al, 2000). Case reports and postmarketing epidemiological research and surveillance (eg the Australian Adverse Drug Reactions Advisory Committee) remain important for detection of delayed events occurring after the initial trial period. More recently, results from comprehensive large prospective audits and database reviews have provided a sufficiently reliable denominator for incidence and risk factor evaluation in rare but serious adverse outcomes in acute pain management (Cameron et al, 2007 **Level IV**; Wijesundera et al, 2008 **Level IV**; Wijesundera & Feldman, 2008).

Besides the adverse outcomes attributed to acute pain management interventions, another area of interest is whether the adverse outcomes of trauma and surgery might be prevented by effective acute pain management. Outcomes such as mortality, morbidity due to derangements of the cardiovascular, respiratory, GI and coagulation systems and progression to chronic pain have also been reported (see Section 1.3).

### Key message

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Multiple outcome measures are required to adequately capture the complexity of the pain experience and how it may be modified by pain management interventions (**U**).

## REFERENCES

- Aubrun F, Langeron O, Quesnel C et al (2003) Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration. *Anesthesiology* **98**(6): 1415–21.
- Backonja MM & Krause SJ (2003) Neuropathic pain questionnaire—short form. *Clin J Pain* **19**(5): 315–6.
- Banos JE, Bosch F, Canellas M et al (1989) Acceptability of visual analogue scales in the clinical setting: a comparison with verbal rating scales in postoperative pain. *Methods Find Exp Clin Pharmacol* **11**(2): 123–7.
- Barden J, Edwards JE, McQuay HJ et al (2004) Pain and analgesic response after third molar extraction and other postsurgical pain. *Pain* **107**(1-2): 86–90.
- Bernstein SL, Bijur PE & Gallagher EJ (2006) Relationship between intensity and relief in patients with acute severe pain. *Am J Emerg Med* **24**(2): 162–6.
- Bombardier C, Laine L, Reicin A et al (2000) Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* **343**(21): 1520–8.
- Bouhassira D, Attal N, Fermanian J et al (2004) Development and validation of the Neuropathic Pain Symptom Inventory. *Pain* **108**(3): 248–57.
- Bouhassira D, Attal N, Alchaar H et al (2005) Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* **114**(1-2): 29–36.
- Breivik EK, Bjornsson GA & Skovlund E (2000) A comparison of pain rating scales by sampling from clinical trial data. *Clin J Pain* **16**(1): 22–8.
- Breivik H, Borchgrevink PC, Allen SM et al (2008) Assessment of pain. *Br J Anaesth* **101**(1): 17–24.
- Cameron CM, Scott DA, McDonald WM et al (2007) A review of neuraxial epidural morbidity: experience of more than 8,000 cases at a single teaching hospital. *Anesthesiology* **106**(5): 997–1002.
- Carlson J, Youngblood R, Dalton JA et al (2003) Is patient satisfaction a legitimate outcome of pain management? *J Pain Symptom Manage* **25**(3): 264–75.
- Cepeda MS, Africano JM, Polo R et al (2003) What decline in pain intensity is meaningful to patients with acute pain? *Pain* **105**(1-2): 151–7.
- Collins SL, Edwards J, Moore RA et al (2001) Seeking a simple measure of analgesia for mega-trials: is a single global assessment good enough? *Pain* **91**(1-2): 189–94.
- Cook AK, Niven CA & Downs MG (1999) Assessing the pain of people with cognitive impairment. *Int J Geriatr Psychiatry* **14**(6): 421–5.
- Cruccu G, Anand P, Attal N et al (2004) EFNS guidelines on neuropathic pain assessment. *Eur J Neurol* **11**(3): 153–62.
- Daut RL, Cleeland CS & Flanery RC (1983) Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain* **17**(2): 197–210.

- DeLoach LJ, Higgins MS, Caplan AB et al (1998) The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. *Anesth Analg* **86**(1): 102–6.
- Dworkin RH, Jensen MP, Gammaitoni AR et al (2007) Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. *J Pain* **8**(2): 118–26.
- Edwards JE, McQuay HJ, Moore RA et al (1999) Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. *J Pain Symptom Manage* **18**(6): 427–37.
- Erdek MA & Pronovost PJ (2004) Improving assessment and treatment of pain in the critically ill. *Int J Qual Health Care* **16**(1): 59–64.
- Farrar JT, Portenoy RK, Berlin JA et al (2000) Defining the clinically important difference in pain outcome measures. *Pain* **88**(3): 287–94.
- Farrar JT, Young JP, Jr., LaMoreaux L et al (2001) Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* **94**(2): 149–58.
- Garratt AM, Kluber Moffett J & Farrin AJ (2001) Responsiveness of generic and specific measures of health outcome in low back pain. *Spine* **26**(1): 71–7.
- Gordon DB, Dahl JL, Miaskowski C et al (2005) American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. *Arch Intern Med* **165**(14): 1574–80.
- Gould TH, Crosby DL, Harmer M et al (1992) Policy for controlling pain after surgery: effect of sequential changes in management. *BMJ* **305**(6863): 1187–93.
- Gray P (2008) Acute neuropathic pain: diagnosis and treatment. *Curr Opin Anaesthesiol* **21**(5): 590–5.
- Hartrick CT, Kovan JP & Shapiro S (2003) The Numeric Rating Scale for Clinical Pain Measurement: A Ratio Measure? *Pain Practice* **3**(4): 310–16.
- Higginson IJ (1997) Innovations in assessment: epidemiology and assessment of pain in advanced cancer. In: *Proceedings of the 8th World Congress on Pain, Progress in Pain Research and Management* edn. Jensen TS, Turner JA and Weisenfeld-Hallin Z (eds). Seattle, IASP Press. 8: 707–16.
- Ioannidis JP & Lau J (2001) Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA* **285**(4): 437–43.
- JCAHO & NPC (2001) *Pain: Current Understanding of Assessment, Management and Treatments*. [www.jcaho.org/news+room/health+care+issues/pm+monographs.htm](http://www.jcaho.org/news+room/health+care+issues/pm+monographs.htm) Joint Commission on Accreditation of Healthcare Organizations and the National Pharmaceutical Council, Inc.
- Jensen MP, Chen C & Brugger AM (2002) Postsurgical pain outcome assessment. *Pain* **99**(1-2): 101–9.
- Jensen MP, Chen C & Brugger AM (2003) Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *J Pain* **4**(7): 407–14.
- Jensen MP, Mendoza T, Hanna DB et al (2004) The analgesic effects that underlie patient satisfaction with treatment. *Pain* **110**(1-2): 480–7.
- Jensen MP, Martin SA & Cheung R (2005) The meaning of pain relief in a clinical trial. *J Pain* **6**(6): 400–6.
- Jensen MP, Mardekian J, Lakshminarayanan M et al (2008) Validity of 24-h recall ratings of pain severity: biasing effects of "Peak" and "End" pain. *Pain* **137**(2): 422–7.
- Lee JS, Hobden E, Stiell IG et al (2003) Clinically important change in the visual analog scale after adequate pain control. *Acad Emerg Med* **10**(10): 1128–30.
- Machata AM, Kabon B, Willschke H et al (2009) A new instrument for pain assessment in the immediate postoperative period. *Anaesthesia* **64**(4): 392–8.
- McQuay HJ, Barden J & Moore RA (2003) Clinically important changes-what's important and whose change is it anyway? *J Pain Symptom Manage* **25**(5): 395–6.
- McQuay HJ, Poon KH, Derry S et al (2008) Acute pain: combination treatments and how we measure their efficacy. *Br J Anaesth* **101**(1): 69–76.
- Melzack R (1987) The short-form McGill Pain Questionnaire. *Pain* **30**(2): 191–7.
- Moore A, Edwards J, Barden J et al (2003) *Bandolier's Little Book of Pain*. Oxford, Oxford University Press.
- Murphy DF, McDonald A, Power C et al (1988) Measurement of pain: A comparison of the visual analogue with a nonvisual analogue scale. *Clin J Pain* **3**(4): 191–97.

- Myles PS, Troedel S, Boquest M et al (1999) The pain visual analog scale: is it linear or nonlinear? *Anesth Analg* **89**(6): 1517–20.
- Myles PS & Urquhart N (2005) The Linearity of the Visual Analogue Scale in Patients with Severe Acute Pain. *Anaesth Intensive Care* **33**(1): 54–58.
- Patrick DL & Deyo RA (1989) Generic and disease-specific measures in assessing health status and quality of life. *Med Care* **27**(3 Suppl): S217–32.
- Scott DA & McDonald WM (2008) Assessment, Measurement and History. In: *Textbook of Clinical Pain Management* 2E edn. Macintyre PE, Rowbotham D and Walker S (eds). Acute Pain.
- Svensson I, Sjostrom B & Haljamae H (2001) Influence of expectations and actual pain experiences on satisfaction with postoperative pain management. *Eur J Pain* **5**(2): 125–33.
- Victor TW, Jensen MP, Gammaioni AR et al (2008) The dimensions of pain quality: factor analysis of the Pain Quality Assessment Scale. *Clin J Pain* **24**(6): 550–5.
- Wijeysundera DN, Beattie WS, Austin PC et al (2008) Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. *Lancet* **372**(9638): 562–9.
- Wijeysundera DN & Feldman BM (2008) Quality, not just quantity: the role of qualitative methods in anesthesia research. *Can J Anaesth* **55**(10): 670–3.
- Williams AdC (1999) Measures of function and psychology. In: *Textbook of Pain* 4th edn. Wall P and Melzack R (eds). Edinburgh, Churchill Livingstone. 427–44.
- Woolf CJ & Max MB (2001) Mechanism-based pain diagnosis: issues for analgesic drug development. *Anesthesiology* **95**(1): 241–9.

## 3. PROVISION OF SAFE AND EFFECTIVE ACUTE PAIN MANAGEMENT

---

The safe and effective management of acute pain requires the appropriate education of medical, nursing and allied health staff and patients, and attention to the organisational aspects involved in the delivery of pain relief. These include appropriate guidelines for drug prescription, monitoring of patients and recognition and treatment of any adverse effects of pain relief, and in some situations, the provision of an acute pain service (APS). It is recognised that the need for and complexity of these requirements will vary according to the setting in which acute pain relief is delivered (eg hospital, general practice).

Successful acute pain management also requires close liaison with all personnel involved in the care of the patient including anaesthetists, pain specialists, surgeons, physicians, palliative care clinicians, general practitioners, specialists in addiction medicine, nurses, physiotherapists and psychologists.

Equally, if not more importantly, patient participation (ie including the patient as part of the treating and decision-making team, taking into account their values, concerns and expectations) is required if each patient is to get the best treatment. Patients should be provided with accurate and up-to-date information, including risks and likely outcomes of treatment, and be partners in discussions relating to choice of care. They should also have access to other evidence-informed information that explains current treatment recommendations as well as have access to treatment consistent with those recommendations (Duckett, 2009).

### 3.1 EDUCATION

#### 3.1.1 Patients

Patients and their carers who learn about assessment of pain as well as risks and side effects of treatment, and who are made aware that they should communicate both effectiveness (or otherwise) and the onset of any side effects, will have some control over the delivery and success of their pain relief, regardless of the technique used. There should also be information on treatment options, goals, and likely benefits and probability of success (Macintyre & Schug, 2007; Counsell et al, 2008).

Patient or carer education may take a number of forms — the most common methods are the use of booklets or short videos and specialist one-on-one education. A review of the evidence for any benefit from preoperative education or the best educational technique concluded that it is varied and inconsistent (Oshodi, 2007).

Patients may find that preoperative education is helpful (Shuldham, 1999) and it may increase patient or carer knowledge about pain and positive attitudes towards pain relief (Chambers et al, 1997 **Level II**; Greenberg et al, 1999 **Level II**; Watkins, 2001 **Level II**; Cheung et al, 2007 **Level II**). Patient knowledge about pain relief was lower in those given verbal (non-standardised) information at the time of seeing the anaesthetist prior to surgery compared with those given written information before they attended the interview; more patients in the latter group felt that the information was thorough and understandable and helped in discussion about postoperative pain management options (Binhas et al, 2008 **Level III-2**).



Others have suggested that in general, structured preoperative patient education may improve patient outcome including pain relief (Devine, 1992 **Level III-2**; Guruge & Sidani, 2002 **Level III-2**; Giraudet-Le Quintrec et al, 2003 **Level II**). Compared with routine and also structured patient information, education using a video about patient-controlled analgesia (PCA) improved both patient knowledge and pain relief (Chen et al, 2005 **Level III-2**).

Some studies have shown no effect of education on postoperative pain or analgesic requirements (Griffin et al, 1998 **Level II**; Greenberg et al, 1999 **Level II**), including PCA (Chumbley et al, 2004 **Level III-1**), although there may be an increase in patient satisfaction (Knoerl et al, 1999 **Level III-1**; Watkins, 2001 **Level II**; Sjolting et al, 2003 **Level III-2**) and less preoperative anxiety (Sjolting et al, 2003 **Level III-2**).

In studies looking at specific types of surgery, there was no evidence that preoperative patient education has any effect on postoperative pain after:

- hip or knee replacement (McDonald et al, 2004 **Level I**);
- cardiac surgery in adults (Shuldham et al, 2002 **Level II**; Watt-Watson et al, 2004 **Level II**) or children (Huth et al, 2003 **Level II**);
- gynaecological surgery (Lam et al, 2001 **Level II**);
- laparoscopic cholecystectomy (Blay & Donoghue, 2005 **Level II**);
- gastric banding (Horchner & Tuinebreijer, 1999 **Level III-1**); or
- spinal fusion in children and adolescents (Kotzer et al, 1998 **Level III-3**).

A systematic review of studies, looking at the benefits or otherwise of preoperative education for orthopaedic patients, highlighted the difficulties of comparing studies of variable methodological quality; while some individual studies may show benefits of preoperative education, the lack of a consistent pattern with regard to effect was confirmed (Johansson et al, 2005 **Level III-2**).

The effect of patient education has also been studied in patients with non-surgical pain. Antenatal teaching about postnatal nipple pain and trauma resulted in reduced nipple pain and improved breastfeeding (Duffy et al, 1997 **Level II**). After an acute whiplash injury, fewer patients shown an educational video in addition to 'usual care' had persistent pain at 3 and 6 months; opioid use and use of health care resources was also lower (Oliveira et al, 2006 **Level II**). Education and counseling regarding pain management, physical activity, and exercise reduced the number of days off work in patients with acute low back pain (Godges et al, 2008 **Level III-1**). In a study of patients with pain presenting to an emergency department, those shown educational videos or printed brochures had greater decreases in self-reported pain than those given no education (Marco et al, 2006 **Level III-1**). Compared with verbal advice, provision of an information sheet to patients with acute chest pain reduced anxiety and depression and improved mental health and perception of general health, but did not alter patient satisfaction with health care or other outcomes such as lifestyle changes or presentation with further chest pain (Arnold et al, 2009 **Level II**).

### 3.1.2 Staff

Appropriate education of medical and nursing staff is essential if more sophisticated forms of analgesia (eg PCA or epidural analgesia) are to be managed safely and effectively, and if better results are to be gained from conventional methods of pain relief (Macintyre & Schug, 2007). Medical and nursing staff education may take a number of forms — the evidence for any benefit or the best educational technique is varied and inconsistent. Education may also include the provision of guidelines.

Improvements in nursing knowledge and ability to manage epidural analgesia followed the reintroduction of an epidural education program using an audit/ guideline/ problem-based teaching approach, accompanied by practical assessments (Richardson, 2001 **Level III-3**). Pain documentation in surgical wards (Ravaud et al, 2004 **Level III-1**; Karlsten et al, 2005 **Level III-2**) and intensive care units (Arbour, 2003 **Level IV**; Erdek & Pronovost, 2004 **Level III-3**) was also improved by education programs. Implementation of a quality improvement program led to improvements in nurses' knowledge and assessment of pain using pain rating scales; however while the number of patients assessed increased, there was no improvement in pain relief (Hansson et al, 2006 **Level III-2**).

Improvements in postoperative pain relief, assessment of pain, and prescribing practices, can result from staff education as well as the introduction of medical and nursing guidelines (Gould et al, 1992 **Level III-2**; Harmer & Davies, 1998 **Level III-3**). In emergency departments, education of junior medical staff improved patient pain relief (Jones, 1999 **Level III-3**) and implementation of an education program and guidelines for pain management improved analgesia and patient satisfaction (Decosterd et al, 2007 **Level III-2**). Personalised feedback forms given to anaesthetists have been shown to increase the use of PCA, non-steroidal anti-inflammatory drugs (NSAIDs), epidural morphine and nerve blocks (Rose et al, 1997 **Level III-3**).

A number of studies have shown the benefits of education and/or guidelines on improved prescribing patterns both in general terms (Humphries et al, 1997 **Level III-3**; Ury et al, 2002 **Level III-3**) and specifically for NSAIDs (May et al, 1999 **Level III-3**; Figueiras et al, 2001 **Level I**; Ray et al, 2001 **Level II**), paracetamol (acetaminophen) (Ripouteau et al, 2000 **Level III-3**) and pethidine (meperidine) (Gordon et al, 2000 **Level III-3**). Use of an electronic decision-support system significantly improved adherence to guidelines for the prescription of postoperative nausea and vomiting (PONV) prophylaxis for patients at high risk of PONV (Kooij et al, 2008 **Level III-3**).

However, education programs may not always be successful in improving nursing staff knowledge or attitudes (Dahlman et al, 1999 **Level III-3**) or pain relief (Knoblauch & Wilson, 1999 **Level IV**). In rural and remote settings, distance and professional isolation could impact on the ability of health care staff to receive up-to-date education about pain relief. However, similarities between urban and rural nurses' knowledge and knowledge deficits relating to acute pain management have been reported (Kubecka et al, 1996) and a tailored education program in a rural hospital improved the management of acute pain (Jones, 1999 **Level III-3**). An education program delivered to nurses in rural and remote locations and focusing on acute pain, chronic pain and cancer pain, improved understanding of pain management (Linkewich et al, 2007 **Level III-2**).

While the focus of most research has been on the impact of education on efficacy of pain treatments, there remains much work to be done on establishing the role of education in patient monitoring and safety.

## 3.2 ORGANISATIONAL REQUIREMENTS

It is recognised that patients should be able to access best practice care, including appropriate assessment of their pain and effective pain management strategies (ANZCA & FPM, 2008). However, effective acute pain management will, to a large extent, depend not on the drugs and techniques available but on the systems involved in their delivery (Macintyre & Schug, 2007). Even simple methods of pain relief can be more effective if proper attention is given to education (see Section 3.1), analgesic drug orders, documentation, monitoring of patients and the provision of appropriate policies, protocols and guidelines (Gould et al, 1992 **Level III-3**). In

some institutions, the APS will assume responsibility for managing more advanced methods of pain relief such as PCA and epidural analgesia.

### 3.2.1 General requirements

Guidelines that aim to enhance patient outcomes and standardise analgesic techniques (eg drug and drug concentrations, dose, dose intervals), monitoring requirements, equipment used, and responses to inadequate or excessive analgesic doses and other complications, may lead to consistency of practice and potentially improved patient safety and analgesic efficacy, regardless of technique used (Macintyre & Schug, 2007; Counsell et al, 2008; Macintyre & Scott, 2009).

Marked improvements in conventional methods of pain relief have followed the introduction of guidelines for intramuscular (IM) opioid administration (Gould et al, 1992 **Level III-3**; Humphries et al, 1997 **Level III-3**). However, implementation of guidelines and not their development remains the greatest obstacle to their use. Compliance with available guidelines is highly variable and may be better in larger institutions (Carr et al, 1998 **Level IV**). Resource availability, particularly staff with pain management expertise, and the existence of formal quality assurance programs to monitor pain management are positive predictors of compliance with guidelines (Jiang et al, 2001 **Level IV**).

Professional bodies in a number of countries have issued guidelines for the management of acute pain (Carr et al, 1992; ANZCA & FPM, 2003; ASA, 2004; RCA et al, 2004; ANZCA & FPM, 2007).

### 3.2.2 Acute pain services

Many institutions would now say that they have an APS. However, there is a very wide diversity of APS structures, no consensus as to the best model, and no agreed definition of what might constitute such a service (Counsell et al, 2008). Some are 'low-cost' nurse-based (Shapiro et al, 2004; Rawal, 2005), others are anaesthetist-led but rely primarily on APS nurses as there may not be daily clinical participation by an anaesthetist (Harmer, 2001; Nagi, 2004), and some are comprehensive and multidisciplinary services with APS nursing staff, sometimes pharmacists or other staff, and daily clinical input from, and 24-hour cover by, anaesthetists (Ready et al, 1988; Macintyre et al, 1990; Schug & Haridas, 1993).

The degree of medical input varies enormously. In training hospitals in Australia, 91% of hospitals accredited for anaesthetic training had an APS run from the department of anaesthesia with daily input from medical staff, although consultant anaesthetist sessions (one session is a half day) varied from zero in 27%, just one or two a week in a further 22%, four to six per week in 22% and ten per week in 15% (Roberts, 2008). A survey in the United Kingdom reported that while 90% of hospitals reported having an APS, dedicated medical staff sessions did not exist in 37%, were limited to one or two per week in 40% and in only 4% were there five or more sessions (Nagi, 2004).

Some APSs supervise primarily 'high-tech' forms of pain relief while others have input into all forms of acute pain management in an institution and will work towards optimising traditional methods of pain relief so that all patients in that institution benefit (Macintyre & Schug, 2007; Breivik, 2002; Counsell et al, 2008). Increasingly, APSs are also called on to deal with much more complex pain management issues (eg acute-on-chronic pain, acute pain after spinal cord injury and other major trauma, and acute pain resulting from a multitude of medical illnesses) and much more complex patients (eg opioid-tolerant patients, older patients) (Counsell et al, 2008).

Given the enormous heterogeneity of APS models and types of patients and pain treated, as well as variation in the quality of published studies, it is not surprising that it is difficult to come up with a meaningful analysis of the benefits or otherwise of an APS. Individual

publications have reported that the presence of an APS reduced pain scores (Gould et al, 1992 **Level III-3**; Harmer & Davies, 1998 **Level III-3**; Miaskowski et al, 1999 **Level IV**; Sartain & Barry, 1999 **Level III-3**; Salomaki et al, 2000 **Level III-3**; Bardiau et al, 2003 **Level III-3**; Stadler et al, 2004 **Level III-3**) and side effects (Schug & Torrie, 1993 **Level IV**; Stacey et al, 1997 **Level III-3**; Miaskowski et al, 1999 **Level IV**; Sartain & Barry, 1999 **Level III-3**).

A review of publications (primarily audits) looking at the effectiveness of APSs (77% were physician-based, 23% nurse-based) concluded that the implementation of an APS is associated with a significant improvement in postoperative pain and a possible reduction in PONV, but that it was not possible to determine which model was superior (Werner et al, 2002 **Level IV**). The authors comment, however, that it is not possible to assess the contribution of factors such as an increased awareness of the importance of postoperative analgesia, the use of more effective analgesic regimens (eg epidural analgesia), the effects of APS visits and better strategies for antiemetic therapy.

Possible benefits of an APS are summarised in Table 3.1.

Although systematic reviews have been attempted (McDonnell et al, 2003; NICS, 2002), the poor quality of the studies looking at the effectiveness or otherwise of APSs, and the many different types of APSs, means that a proper meta-analysis cannot be performed.

In addition, the above studies looked at outcome in terms of immediate pain and side effects in postoperative patients only. It is possible that an APS may benefit patients in other ways.

Combination of an APS with a physician-based critical care outreach team, which systematically reviewed high-risk postoperative patients for 3 days after their return to a general ward, showed a significant improvement in postoperative outcome; the incidence of serious adverse events decreased from 23 events per 100 patients to 16 events per 100 patients, and the 30-day mortality fell from 9% to 3% (Story et al, 2006 **Level III-2**). Finally, members of an APS may also be more likely to recognise the early onset of neuropathic pain associated with surgery, trauma or medical disease, and institute the appropriate treatment (Counsell et al, 2008).

**Table 3.1 Possible benefits of an Acute Pain Service**

Benefit	References
Better pain relief	Gould et al, 1992; Harmer & Davies, 1998; Miaskowski et al, 1999; Sartain & Barry, 1999; Salomaki et al, 2000; Werner et al, 2002; Bardiau et al, 2003; Stadler et al, 2004
Lower incidence of side effects	Schug & Torrie, 1993; Stacey et al, 1997; Miaskowski et al, 1999; Sartain & Barry, 1999; Werner et al, 2002
Lower postoperative morbidity/ mortality	Story et al, 2006
Management of analgesic techniques that may reduce the incidence of persistent pain after surgery	Obata et al, 1999; Senturk et al, 2002; Gehling & Tryba, 2003

**Key messages**

1. Preoperative education improves patient or carer knowledge of pain and encourages a more positive attitude towards pain relief **(U)** **(Level II)**.
2. Video education of patients with a whiplash injury reduces the incidence of persistent pain **(N)** **(Level II)**.
3. Written information given to patients prior to seeing an anaesthetist is better than verbal information given at the time of the interview **(N)** **(Level III-2)**.
4. While evidence for the benefit of patient education in terms of better pain relief is inconsistent, structured preoperative education may be better than routine information, and information presented in video format may be better still **(N)** **(Level III-2)**.
5. Implementation of an acute pain service may improve pain relief and reduce the incidence of side effects **(U)** **(Level III-3)**.
6. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices **(U)** **(Level III-3)**.
7. Even 'simple' techniques of pain relief can be more effective if attention is given to education, documentation, patient assessment and provision of appropriate guidelines and policies **(U)** **(Level III-3)**.

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Successful management of acute pain requires close liaison with all personnel involved in the care of the patient **(U)**.
- More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves **(U)**.

**REFERENCES**

- ANZCA & FPM (2003) *Guidelines for the management of major regional analgesia*. <http://www.anzca.edu.au/resources/professional-documents/professional-standards/ps3.html> Australasian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Accessed January 2009.
- ANZCA & FPM (2007) *Guidelines on acute pain management*. <http://www.anzca.edu.au/resources/professional-documents/professional-standards/ps41.html> Australian and New Zealand College of Anaesthetists, Faculty of Pain Medicine. Accessed January 2009.
- ANZCA & FPM (2008) *Statement on patients' rights to pain management and associated responsibilities*. <http://www.anzca.edu.au/resources/professional-documents/professional-standards/ps45.html> Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Accessed January 2009.
- Arbour R (2003) A continuous quality improvement approach to improving clinical practice in the areas of sedation, analgesia, and neuromuscular blockade. *J Contin Educ Nurs* **34**(2): 64–71.
- Arnold J, Goodacre S, Bath P et al (2009) Information sheets for patients with acute chest pain: randomised controlled trial. *BMJ* **338**: b541.
- ASA (2004) Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* **100**(6): 1573–81.

- Bardiau FM, Taviaux NF, Albert A et al (2003) An intervention study to enhance postoperative pain management. *Anesth Analg* **96**(1): 179–85.
- Binhas M, Roudot-Thoraval F, Thominet D et al (2008) Impact of written information describing postoperative pain management on patient agreement with proposed treatment. *Eur J Anaesthesiol* **25**(11): 884–90.
- Blay N & Donoghue J (2005) The effect of pre-admission education on domiciliary recovery following laparoscopic cholecystectomy. *Aust J Adv Nurs* **22**(4): 14–9.
- Breivik H (2002) How to implement an acute pain service. *Best Pract Res Clin Anaesthesiol* **16**(4): 527–47.
- Carr DB, Jacox AK, Chapman CR, et al (eds) (1992) *Acute Pain Management: Operative or Medical Procedures and Trauma, Clinical Practice Guideline*. Publication No. AHCPR 92-0032. Agency for Health Care Policy and Research PHS, US Department of Health and Human Services. Rockville.
- Carr DB, Miaskowski C, Dedrick SC et al (1998) Management of perioperative pain in hospitalized patients: a national survey. *J Clin Anesth* **10**(1): 77–85.
- Chambers CT, Reid GJ, McGrath PJ et al (1997) A Randomized Trial of a Pain Education Booklet: Effects on Parents' Attitudes and Postoperative Pain Management. *Children's Health Care* **26**(1): 1–13.
- Chen HH, Yeh ML & Yang HJ (2005) Testing the impact of a multimedia video CD of patient-controlled analgesia on pain knowledge and pain relief in patients receiving surgery. *Int J Med Inform* **74**(6): 437–45.
- Cheung A, Finegan BA, Torok-Both C et al (2007) A patient information booklet about anesthesiology improves preoperative patient education. *Can J Anaesth* **54**(5): 355–60.
- Chumbley GM, Ward L, Hall GM et al (2004) Pre-operative information and patient-controlled analgesia: much ado about nothing. *Anaesthesia* **59**(4): 354–8.
- Counsell D, Macintyre PE & Breivik H (2008) Organisation and role of acute pain services. In: *Clinical Pain Management: practice and procedures* edn. Breivik H, Campbell WI and Nicholas MK (eds). London, Hodder Arnold.
- Dahlman GB, Dykes AK & Elander G (1999) Patients' evaluation of pain and nurses' management of analgesics after surgery. The effect of a study day on the subject of pain for nurses working at the thorax surgery department. *J Adv Nurs* **30**(4): 866–74.
- Decosterd I, Hugli O, Tamches E et al (2007) Oligoanalgesia in the emergency department: short-term beneficial effects of an education program on acute pain. *Ann Emerg Med* **50**(4): 462–71.
- Devine EC (1992) Effects of psychoeducational care for adult surgical patients: a meta-analysis of 191 studies. *Patient Educ Couns* **19**(2): 129–42.
- Duckett SJ (2009) Are we ready for the next big thing? *Med J Aust* **190**(12): 687–8.
- Duffy EP, Percival P & Kershaw E (1997) Positive effects of an antenatal group teaching session on postnatal nipple pain, nipple trauma and breast feeding rates. *Midwifery* **13**(4): 189–96.
- Erdek MA & Pronovost PJ (2004) Improving assessment and treatment of pain in the critically ill. *Int J Qual Health Care* **16**(1): 59–64.
- Figueiras A, Sastre I, Tato F et al (2001) One-to-one versus group sessions to improve prescription in primary care: a pragmatic randomized controlled trial. *Med Care* **39**(2): 158–67.
- Gehling M & Tryba M (2003) [Prophylaxis of phantom pain: is regional analgesia ineffective?]. *Schmerz* **17**(1): 11–9.
- Giraudet-Le Quintrec JS, Coste J, Vastel L et al (2003) Positive effect of patient education for hip surgery: a randomized trial. *Clin Orthop Relat Res*(414): 112–20.
- Godges JJ, Anger MA, Zimmerman G et al (2008) Effects of education on return-to-work status for people with fear-avoidance beliefs and acute low back pain. *Phys Ther* **88**(2): 231–9.
- Gordon DB, Jones HD, Goshman LM et al (2000) A quality improvement approach to reducing use of meperidine. *Jt Comm J Qual Improv* **26**(12): 686–99.
- Gould TH, Crosby DL, Harmer M et al (1992) Policy for controlling pain after surgery: effect of sequential changes in management. *BMJ* **305**(6863): 1187–93.
- Greenberg RS, Billett C, Zahurak M et al (1999) Videotape increases parental knowledge about pediatric pain management. *Anesth Analg* **89**(4): 899–903.

- Griffin MJ, Brennan L & McShane AJ (1998) Preoperative education and outcome of patient controlled analgesia. *Can J Anaesth* **45**(10): 943–8.
- Guruge S & Sidani S (2002) Effects of demographic characteristics on preoperative teaching outcomes: a meta-analysis. *Can J Nurs Res* **34**(4): 25–33.
- Hansson E, Fridlund B & Hallstrom I (2006) Effects of a quality improvement program in acute care evaluated by patients, nurses, and physicians. *Pain Manag Nurs* **7**(3): 93–108.
- Harmer M (2001) When is a standard, not a standard? When it is a recommendation. *Anaesthesia* **56**(7): 611–2.
- Harmer M & Davies KA (1998) The effect of education, assessment and a standardised prescription on postoperative pain management. The value of clinical audit in the establishment of acute pain services. *Anaesthesia* **53**(5): 424–30.
- Horchner R & Tuinebreijer W (1999) Preoperative preparatory program has no effect on morbidly obese patients undergoing a Lap-Band operation. *Obes Surg* **9**(3): 250–7.
- Humphries CA, Counsell DJ, Pediani RC et al (1997) Audit of opioid prescribing: the effect of hospital guidelines. *Anaesthesia* **52**(8): 745–9.
- Huth MM, Broome ME, Mussatto KA et al (2003) A study of the effectiveness of a pain management education booklet for parents of children having cardiac surgery. *Pain Manag Nurs* **4**(1): 31–9.
- Jiang HJ, Lagasse RS, Ciccone K et al (2001) Factors influencing hospital implementation of acute pain management practice guidelines. *J Clin Anesth* **13**(4): 268–76.
- Johansson K, Nuutila L, Virtanen H et al (2005) Preoperative education for orthopaedic patients: systematic review. *J Adv Nurs* **50**(2): 212–23.
- Jones JB (1999) Assessment of pain management skills in emergency medicine residents: the role of a pain education program. *J Emerg Med* **17**(2): 349–54.
- Karlsten R, Strom K & Gunningberg L (2005) Improving assessment of postoperative pain in surgical wards by education and training. *Qual Saf Health Care* **14**(5): 332–5.
- Knoblauch SC & Wilson CJ (1999) Clinical outcomes of educating nurses about pediatric pain management. *Outcomes Manag Nurs Pract* **3**(2): 87–9.
- Knoerl DV, Faut-Callahan M, Paice J et al (1999) Preoperative PCA teaching program to manage postoperative pain. *Medsurg Nurs* **8**(1): 25–33, 36.
- Kooij FO, Klok T, Hollmann MW et al (2008) Decision support increases guideline adherence for prescribing postoperative nausea and vomiting prophylaxis. *Anesth Analg* **106**(3): 893–8.
- Kotzer AM, Coy J & LeClaire AD (1998) The effectiveness of a standardized educational program for children using patient-controlled analgesia. *J Soc Pediatr Nurs* **3**(3): 117–26.
- Kubecka KE, Simon JM & Boettcher JH (1996) Pain management knowledge of hospital-based nurses in a rural Appalachian area. *J Adv Nurs* **23**(5): 861–7.
- Lam KK, Chan MT, Chen PP et al (2001) Structured preoperative patient education for patient-controlled analgesia. *J Clin Anesth* **13**(6): 465–9.
- Linkewich B, Sevean P, Habjan S et al (2007) Educating for tomorrow: enhancing nurses' pain management knowledge. *Can Nurse* **103**(4): 24–8.
- Macintyre PE, Runciman WB & Webb RK (1990) An acute pain service in an Australian teaching hospital: the first year. *The Medical Journal of Australia* **153**: 417–21.
- Macintyre PE & Schug SA (2007) *Acute pain management: a practical guide*. London, Elsevier.
- Macintyre PE & Scott DA (2009) Acute pain management and acute pain services. In: *Neural Blockade in Clinical Anesthesia and Pain Medicine* edn. Cousins MJ, Carr DB, Horlocker TT and Bridenbaugh PO (eds). Philadelphia, Wolters Kluwer, Lippincott, Williams and Wilkins.
- Marco CA, Marco AP, Plewa MC et al (2006) The verbal numeric pain scale: effects of patient education on self-reports of pain. *Acad Emerg Med* **13**(8): 853–9.
- May FW, Rowett DS, Gilbert AL et al (1999) Outcomes of an educational-outreach service for community medical practitioners: non-steroidal anti-inflammatory drugs. *Med J Aust* **170**(10): 471–4.
- McDonald S, Hetrick S & Green S (2004) Pre-operative education for hip or knee replacement. *Cochrane Database Syst Rev*(1): CD003526.



- McDonnell A, Nicholl J & Read SM (2003) Acute pain teams and the management of postoperative pain: a systematic review and meta-analysis. *J Adv Nurs* **41**(3): 261–73.
- Miaskowski C, Crews J, Ready LB et al (1999) Anesthesia-based pain services improve the quality of postoperative pain management. *Pain* **80**(1-2): 23–9.
- Nagi H (2004) Acute pain services in the United Kingdom. *Acute Pain* **5**: 89–107.
- NICS (2002) *Institutional Approaches to Pain Assessment and Management: A Systematic Literature Review*. Melbourne, Prepared by the Health Technology Assessment Unit, Department of Public Health, University of Adelaide. National Institute of Clinical Studies.
- Obata H, Saito S, Fujita N et al (1999) Epidural block with mepivacaine before surgery reduces long-term post-thoracotomy pain. *Can J Anaesth* **46**(12): 1127–32.
- Oliveira A, Gevirtz R & Hubbard D (2006) A psycho-educational video used in the emergency department provides effective treatment for whiplash injuries. *Spine* **31**(15): 1652–7.
- Oshodi TO (2007) The impact of preoperative education on postoperative pain. Part 2. *Br J Nurs* **16**(13): 790–7.
- Ravaud P, Keita H, Porcher R et al (2004) Randomized clinical trial to assess the effect of an educational programme designed to improve nurses' assessment and recording of postoperative pain. *Br J Surg* **91**(6): 692–8.
- Rawal N (2005) Organization, function, and implementation of acute pain service. *Anesthesiol Clin North America* **23**(1): 211–25.
- Ray WA, Stein CM, Byrd V et al (2001) Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: a randomized controlled trial. *Med Care* **39**(5): 425–35.
- RCA, RCN, AAGBI et al (2004) *Good practice in the management of continuous epidural analgesia in the hospital setting: joint recommendations by the Royal College of Anaesthetists, Royal College of Nursing, Association of Anaesthetists of Great Britain and Ireland, and European Society of Regional Anaesthesia*. <http://www.rcoa.ac.uk/docs/Epid-Analg.pdf>. Accessed January 2009.
- Ready LB, Oden R, Chadwick HS et al (1988) Development of an anesthesiology-based postoperative pain management service. *Anesthesiology* **68**(1): 100–6.
- Richardson J (2001) Post-operative epidural analgesia: introducing evidence-based guidelines through an education and assessment process. *J Clin Nurs* **10**(2): 238–45.
- Ripouteau C, Conort O, Lamas JP et al (2000) Effect of multifaceted intervention promoting early switch from intravenous to oral acetaminophen for postoperative pain: controlled, prospective, before and after study. *BMJ* **321**(7274): 1460–3.
- Roberts L (2008) Pain medicine experience and FANZCA training: an audit of hospital accreditation reports. *ANZCA Bulletin* **17**: 32–5.
- Rose DK, Cohen MM & Yee DA (1997) Changing the practice of pain management. *Anesth Analg* **84**(4): 764–72.
- Salomaki TE, Hokajarvi TM, Ranta P et al (2000) Improving the quality of postoperative pain relief. *Eur J Pain* **4**(4): 367–72.
- Sartain JB & Barry JJ (1999) The impact of an acute pain service on postoperative pain management. *Anaesth Intensive Care* **27**(4): 375–80.
- Schug SA & Haridas RP (1993) Development and organizational structure of an acute pain service in a major teaching hospital. *Aust N Z J Surg* **63**(1): 8–13.
- Schug SA & Torrie JJ (1993) Safety assessment of postoperative pain management by an acute pain service. *Pain* **55**(3): 387–91.
- Senturk M, Ozcan PE, Talu GK et al (2002) The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* **94**(1): 11–5.
- Shapiro A, Zohar E, Kantor M et al (2004) Establishing a nurse-based, anesthesiologist-supervised inpatient acute pain service: experience of 4,617 patients. *J Clin Anesth* **16**(6): 415–20.
- Shuldham C (1999) A review of the impact of pre-operative education on recovery from surgery. *Int J Nurs Stud* **36**(2): 171–7.



- Shuldham CM, Fleming S & Goodman H (2002) The impact of pre-operative education on recovery following coronary artery bypass surgery. A randomized controlled clinical trial. *Eur Heart J* **23**(8): 666–74.
- Sjoling M, Nordahl G, Olofsson N et al (2003) The impact of preoperative information on state anxiety, postoperative pain and satisfaction with pain management. *Patient Educ Couns* **51**(2): 169–76.
- Stacey BR, Rudy TE & Nellhaus D (1997) Management of patient-controlled analgesia: a comparison of primary surgeons and a dedicated pain service. *Anesth Analg* **85**: 130–4.
- Stadler M, Schlander M, Braeckman M et al (2004) A cost-utility and cost-effectiveness analysis of an acute pain service. *J Clin Anesth* **16**(3): 159–67.
- Story DA, Shelton AC, Poustie SJ et al (2006) Effect of an anaesthesia department led critical care outreach and acute pain service on postoperative serious adverse events. *Anaesthesia* **61**(1): 24–8.
- Ury WA, Rahn M, Tolentino V et al (2002) Can a pain management and palliative care curriculum improve the opioid prescribing practices of medical residents? *J Gen Intern Med* **17**(8): 625–31.
- Watkins GR (2001) Effect of Pain Education on Postoperative Pain Management (thesis). Chicago, Health Sciences Center, University of Illinois.
- Watt-Watson J, Stevens B, Katz J et al (2004) Impact of preoperative education on pain outcomes after coronary artery bypass graft surgery. *Pain* **109**(1-2): 73–85.
- Werner MU, Soholm L, Rotboll-Nielsen P et al (2002) Does an acute pain service improve postoperative outcome? *Anesth Analg* **95**(5): 1361–72.

## 4. SYSTEMICALLY ADMINISTERED ANALGESIC DRUGS

---

### 4.1 OPIOIDS

Opioids remain the mainstay of systemic analgesia for the treatment of moderate to severe acute pain.

#### 4.1.1 Choice of opioid

All full opioid agonists given in appropriate doses produce the same analgesic effect and therapeutic index (McQuay, 1991), although accurate determination of equianalgesic doses is difficult due to interindividual variabilities in kinetics and dynamics (Gammaitoni et al, 2003). Equianalgesic conversion dose tables are often used to assist in the change from one opioid to another. However, such tables should be used as a guide only as they are based largely on single-dose studies in opioid-naïve subjects and may not be as relevant when conversions are made after repeated doses of an opioid have been given (either in the acute pain or chronic pain setting) and do not take into account incomplete cross-tolerance (Weschules & Bain, 2008). In general there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of side effects between any of the pure agonist opioids, although the results of individual studies are inconsistent. However, for pharmacokinetic and other reasons, some opioids may be better in some patients (Woodhouse et al, 1999 **Level II**). Comparisons of the different opioids are commonly done in patients using patient-controlled analgesia (PCA) (see Section 7.1.2 for these comparisons).

While the data to support the concept of opioid rotation originate from cancer pain (Quigley, 2004 **Level I**), it may be a useful strategy in the management of acute pain in patients with intolerable opioid-related side effects that are unresponsive to treatment, and in opioid-tolerant patients (see Section 11.7).

#### 4.1.2 Specific opioids

The efficacy of various opioids administered by the different routes used in the management of acute pain is discussed in detail in Sections 6 and 7.1. The following section describes other relevant aspects of selected opioid agents including tramadol.

##### **Buprenorphine**

Buprenorphine is a semi-synthetic derivative of thebaine, an alkaloid of opium, and a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist with high receptor affinity and slow dissociation from the mu-receptor (Johnson et al, 2005). Mean terminal half-lives are 24 hours following sublingual administration and 2 to 3 hours after parenteral injection; two-thirds of the drug is excreted unchanged, mainly in faeces, while the remaining one-third is metabolised predominantly in the liver and gut wall via glucuronidation to an inactive metabolite, buprenorphine-3-glucuronide, and via CYP3A4 to norbuprenorphine, which has 40 times less analgesic effect than buprenorphine (Kress, 2009). Maximum onset of effect is slower than for other opioids making acute titration difficult. In a study using experimental pain stimuli, the time to maximal peak effect after administration of an IV bolus dose of buprenorphine was between 70 and 100 minutes (Yassen et al, 2006 **Level III-3**).

In clinically relevant doses, buprenorphine appears to behave like a full mu-opioid receptor agonist, and in animals as well as humans in low doses (ie transdermal buprenorphine), there also appears to be no antagonism of other concurrently administered mu-agonist drugs (Kress, 2009). Contrary to earlier concerns, there was a ceiling effect found for respiratory depression but not for analgesia (Dahan et al, 2005 **Level III-2**; Dahan et al, 2006 **Level III-2**). The risk of respiratory depression is low compared with morphine, methadone, hydromorphone and fentanyl, even in the doses used for the treatment of opioid addiction, as long as concurrent sedative medications are not given (Kress, 2009). Should buprenorphine-induced respiratory depression occur, reversal is possible although higher-than-usual doses and a longer duration infusion of naloxone may be required (van Dorp, Yassen et al, 2006 **Level III-2**).

In animal models of pain, buprenorphine appears to have good efficacy for neuropathic pain (Hans, 2007). In the clinical setting, case reports have suggested that buprenorphine is also effective (Kress, 2009). Using experimental pain stimuli in humans, and unlike pure mu-opioid agonists, buprenorphine has been shown to be antihyperalgesic (ie the area of hyperalgesia was reduced), which may be related in part to its kappa-opioid antagonist activity (Koppert et al, 2005).

Withdrawal symptoms, which may be seen if the drug is ceased after long-term treatment, are milder and more delayed in onset (72 hours or more) than other opioids (Kress, 2009).

## Codeine

Codeine is classified as a weak opioid. However, it is only a very weak mu-receptor agonist and its analgesic action depends on the metabolism of about 10% of the dose given to morphine, via the CYP2D6 cytochrome P450 isoenzyme (Lotsch, 2005).

Over 100 allelic variants of CYP2D6 have been identified, resulting in wide variability in enzyme activity (Somogyi et al, 2007). Individuals carrying two wild type alleles display normal enzyme activity and are known as extensive metabolisers; intermediate metabolisers are heterozygotes with two variant alleles known to decrease enzymatic capacity; and poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Stamer & Stuber, 2007). In Caucasian populations, 8% to 10% of people are poor metabolisers; however 3% to 5% are ultrarapid metabolisers (Stamer & Stuber, 2007; Madadi et al, 2009). Those who are ultrarapid metabolisers (carriers of the CYP2D6 gene duplication) have significantly higher levels of morphine and morphine metabolites after the same dose of codeine (Kirchheiner et al, 2007 **Level IV**).

There are large inter-ethnic differences in the frequencies of the variant alleles. For example, the proportion of ultrarapid metabolisers is higher (up to 29%) in Middle Eastern and Northern African populations, and lower (0.5%) in Asians (Stamer & Stuber, 2007); the proportion of poor metabolisers is lower in Asians and African Americans (Holmquist, 2009).

A case-control study including a case of a newborn dying while breastfed by a mother taking codeine has highlighted that breastfed infants of mothers who are ultrarapid metabolisers are at increased risk of life-threatening CNS depression (Madadi et al, 2009 **Level III-2**). A number of similar cases have been reported and health care workers and mothers of breastfeeding infants should be aware of this risk (Madadi et al, 2008 **Level IV**). CYP2D6 genotyping predicts subjects with reduced metabolism to morphine, but must be combined with additional phenotyping to accurately predict patients at risk of morphine toxicity (Lotsch et al, 2009 **Level III-2**).

The principal metabolite of codeine is codeine-6-glucuronide, which has a similar low potency to the parent drug and is renally excreted.

## **Dextropropoxyphene**

Dextropropoxyphene is often used in combination with paracetamol but this combination does not lead to better pain relief compared with paracetamol alone and increases the incidence of dizziness (Li Wan Po & Zhang, 1997 **Level I**). A later study comparing this combination with paracetamol alone in the treatment of pain after third molar surgery confirmed the lack of analgesic benefit (Sorich et al, 2004 **Level II**).

The use of this compound is discouraged, not only because of its low efficacy, but also because of a number of risks related to its use (Barkin et al, 2006). These include a euphorogenic component with risk of abuse and complex pharmacokinetics (particularly in the elderly), with the risk of accumulation and QT-interval prolongation and possibility of Torsades de Pointes (TdP) and cardiogenic death. For these reasons, it was announced that a phased withdrawal of dextropropoxyphene combination preparations would commence in the United Kingdom from January 2005 (Hawton et al, 2009). A marked decrease in prescribing of this combination was followed by a major reduction in deaths (accidental and suicide) related to its use, and while prescriptions of other analgesics increased significantly during this time, there was no evidence of a corresponding increase in deaths related to use of these other drugs (Hawton et al, 2009).

The major metabolite of dextropropoxyphene is nordextropropoxyphene, which has a mean half-life of 29 hours (compared with 16 hours for the parent drug) and is renally excreted (Brosen et al, 1985); accumulation of nordextropropoxyphene can lead to CNS, respiratory and cardiac depression (Davies et al, 1996).

## **Diamorphine**

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to monoacetylmorphine (MAM) and morphine; diamorphine and MAM are more lipid soluble than morphine and penetrate the CNS more rapidly, although it is MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine (Miyoshi & Lackband, 2001).

There was no difference between parenteral diamorphine and morphine in terms of analgesia and side effects after hip surgery (Robinson et al, 1991 **Level II**). Epidurally administered diamorphine resulted in a longer time to first PCA use and lower total 24-hour morphine requirements compared with the same dose given as an IM injection (Green et al, 2007 **Level II**).

## **Dihydrocodeine**

Dihydrocodeine is a semi-synthetic derivative of codeine and has similar mu-opioid agonist activity. However, unlike codeine, inhibition of CYP2D6 by quinine does not alter its analgesic effect, even though the CYP2D6-dependant active metabolite, dihydromorphine, has a much higher mu-opioid receptor affinity than the parent drug (Lotsch, 2005).

## **Fentanyl**

Fentanyl is a highly potent phenylpiperidine derivative, structurally related to pethidine. It is metabolised almost exclusively in the liver to minimally active metabolites. Less than 10% of unmetabolised fentanyl is renally excreted. Fentanyl is commonly used in the treatment of acute pain, especially when its lack of active metabolites and fast onset of action may be of clinical benefit (Peng & Sandler, 1999).

Mu-opioid receptor A304G polymorphisms can affect pain relief after fentanyl administration. Intrathecal fentanyl requirements in labour were reduced in women with the 304G allele but increased in those with the 304A allele of genes encoding the mu-opioid receptor (Landau et al, 2008 **Level III-3**).

## **Hydromorphone**

Hydromorphone is a derivative of morphine that is approximately five times as potent as morphine. The main metabolite of hydromorphone is hydromorphone-3-glucuronide (H3G), a structural analogue of morphine-3-glucuronide (M3G). Like M3G (see below) H3G is dependent on the kidney for excretion, has no analgesic action and can lead to dose-dependent neurotoxic effects (Smith, 2000; Wright et al, 2001; Murray & Hagen, 2005).

## **Methadone**

Methadone is a synthetic opioid commonly used for the maintenance treatment of patients with an addiction to opioids and in patients with chronic pain. It is commercially available as a racemic mixture of R- and L-enantiomers, but it is the R-enantiomer that is responsible for most, if not all, its mu-opioid receptor mediated analgesic effects (Lugo et al, 2005; Fredheim et al, 2008).

It has good oral bioavailability (70% to 80%), high potency and long duration of action, and a lack of active metabolites, (Lugo et al, 2005). It is also a weak NMDA receptor antagonist and monoamine (5HT and noradrenaline [norepinephrine]) reuptake inhibitor and has a long and unpredictable half-life (mean of 22 hours; range 4 to 190 hours) leading to an increased risk of accumulation (Weschules et al, 2008). Therefore it is of limited use for acute pain treatment. Dose conversion is complex and depends on many factors including absolute doses of other opioids and duration of treatment.

Methadone is metabolised primarily by the cytochrome P450 group of enzymes including CYP2B6, CYP3A4 and, to a lesser extent, CYP2D6 (Weschules et al, 2008). Concurrent administration of other drugs that are cytochrome P450 inducers may increase methadone metabolism and lower methadone blood levels (eg carbamazepine, rifampicin, phenytoin, St John's Wort and some antiretroviral agents). Conversely, drugs that inhibit cytochrome P450 (eg other antiretroviral agents, some selective serotonin reuptake inhibitors, grapefruit juice, and antifungal agents) may lead to raised methadone levels and an increase in adverse effects (Fredheim et al, 2008). See Section 9.6.8 for interactions in patients with human immunodeficiency virus (HIV).

High dose methadone has been associated with prolonged QT intervals (see below).

## **Morphine**

Morphine remains the most widely used opioid for the management of pain and the standard against which other opioids are compared. Morphine-6-glucuronide (M6G) and M3G, the main metabolites of morphine, are formed by morphine glucuronidation, primarily in the liver. M6G is a mu-opioid receptor agonist that crosses the blood-brain barrier more slowly than morphine, contributes to morphine analgesia in patients with both normal and impaired renal function, and has other morphine-like effects including respiratory depression; M3G has very low affinity for opioid receptors, has no analgesic activity, and animal studies have shown that it may be responsible for the neurotoxic symptoms (not mediated via opioid receptors), such as hyperalgesia, allodynia and myoclonus, sometimes associated with high doses of morphine (Lotsch, 2005; van Dorp, Romberg et al, 2006; Dahan, van Dorp et al, 2008).

Clinical trials have investigated M6G as an analgesic agent after a variety of different types of surgery. Two showed that M6G was as effective as morphine (Cann et al, 2002 **Level II**; Hanna et al, 2005 **Level II**). In another two, in higher doses, it was more effective than placebo (Romberg et al, 2007 **Level II**; Smith et al, 2009 **Level II**).

Excellent pain relief was also obtained after intrathecal administration of 100 or 125 mcg M6G in patients after hip replacement surgery, but there was a high incidence (10%) of late respiratory depression (9 to 12 hours after the dose was given) requiring treatment with

naloxone, and a high incidence of nausea (76% to 88%, depending on dose) and vomiting (60% to 64%) (Grace & Fee, 1996 **Level II**).

Although it has been shown that M6G is more potent than morphine in various pain models and that the potency ratios also vary according to route of administration (Lotsch, 2005; van Dorp, Romberg et al, 2006), clinical studies suggest that the same amount of, or more, M6G is required to produce the same analgesic effect as a given dose of morphine (Dahan, van Dorp et al, 2008).

Most of the studies were not designed to look at side effects, but the incidence of nausea and vomiting may be less than with morphine (Cann et al, 2002 **Level II**). In healthy volunteers, morphine 0.15 mg/kg and M6G 0.2 mg/kg resulted in similar reductions in ventilatory response to carbon dioxide (Romberg et al, 2003 **Level III-1**).

Both M6G and M3G are dependent on the kidney for excretion. Impaired renal function, the oral route of administration (first pass metabolism), higher doses and increased patient age are predictors of higher M3G and M6G concentrations (Faura et al, 1998 **Level IV**; Klepstad et al, 2003 **Level IV**) with the potential risk of severe long-lasting sedation and respiratory depression.

Genetic polymorphisms of the mu-opioid receptor may influence the efficacy of morphine. Several single nucleotide polymorphisms have been identified, A118G being the most common. Patients can be genotyped as A118 homozygous (AA), that is homozygous for the wild-type A allele, heterozygous (AG), or homozygous for the variant G allele (GG). Studies from Taiwan (Chou, Wang et al, 2006 **Level III-2**; Chou, Yang et al, 2006 **Level III-2**) and Singapore (Sia, 2008 **Level III-2**) showed that patients who were GG homozygotes had increased PCA morphine requirements in the postoperative period. However, no significant difference in morphine use was seen in two other studies (Coulbault et al, 2006 **Level III-2**; Janicki et al, 2006 **Level III-2**) looking at populations of predominantly white or mixed ethnicity patients respectively. In one of these studies (Coulbault et al, 2006), where a trend to higher morphine requirements was associated with the G allele, a low frequency of the G allelic variant was noted. The frequency of AG and GG variants is higher in Asian than Caucasian populations (Landau, 2006), which could influence results when small numbers of a mixed-ethnicity population are studied.

Other polymorphisms at genes encoding for morphine metabolism (UGT2B7 gene) and transport across the blood-brain barrier by p-glycoprotein (MDR1 gene) may also influence the clinical efficacy of morphine (Klepstad et al, 2005). Other substrates of p-glycoprotein, one of the main efflux transporters, include methadone and fentanyl (Sweeney, 2007). As well as morphine, UGT2B7 also mediates the metabolism and formation of glucuronides from other opioids including buprenorphine, codeine, dihydrocodeine and hydromorphone, but the clinical significance of UGT2B7 gene variants has not yet been well defined (Somogyi et al, 2007; Holmquist, 2009).

## Oxycodone

Oxycodone is a potent opioid agonist derived from the opium alkaloid thebaine. It is metabolised in the liver primarily to noroxycodone and oxymorphone, but these metabolites have clinically negligible analgesic effects (Lalovic et al, 2006; Riley et al, 2008). Oxymorphone, the production of which relies on CYP2D6, is more potent than oxycodone, but plasma concentrations are low; noroxycodone, the major metabolite and the production of which relies on CYP3A4, is only weakly active (Coluzzi & Mattia, 2005; Lalovic et al, 2006; Holmquist, 2009). Unlike codeine, inhibition of CYP2D6 with quinidine does not reduce the analgesic effect of oxycodone (Lalovic et al, 2006). Animal studies have shown that oxycodone is actively taken up into the brain, resulting in a brain concentration that is up to six times those of free plasma levels (Bostrom et al, 2008).

In an experimental pain model comparing oxycodone, morphine and placebo, and involving mechanical, thermal and electrical pain stimuli in skin, muscle and oesophagus, oxycodone was more effective than morphine for pain related to mechanical and thermal stimulation of the oesophagus, suggesting it could be better than morphine for visceral pain (Staahl et al, 2006 **Level II**). One explanation of this difference is that, in animal studies at least, oxycodone is thought to act as a kappa-receptor agonist (Nielsen et al, 2007) and these receptors may play an important role in the mediation of visceral pain (Staahl et al, 2006).

### **Pethidine**

Pethidine (meperidine) is a synthetic opioid still widely used even though it has multiple disadvantages. Despite a common belief that it is the most effective opioid in the treatment of renal colic, it was no better than morphine (O'Connor et al, 2000 **Level II**) or hydromorphone (Jasani et al, 1994 **Level II**). Similarly, pethidine and morphine had similar effects on the sphincter of Oddi and biliary tract and there was no evidence that pethidine was better in the treatment of biliary colic (Latta et al, 2002 **Level IV**).

Pethidine induced more nausea and vomiting than morphine when used parenterally in the emergency department (Silverman et al, 2004 **Level III-3**) and in the first 2 hours after gynaecological surgery (Ezri et al, 2002 **Level II**).

Accumulation of its active metabolite, norpethidine (normeperidine), is associated with neuroexcitatory effects that range from nervousness to tremors, twitches, multifocal myoclonus and seizures (Simopoulos et al, 2002 **Level IV**). As impaired renal function increases the half-life of norpethidine, patients with poor renal function are at increased risk of norpethidine toxicity. Naloxone does not reverse and may increase the problems related to norpethidine toxicity. Overall, the use of pethidine should be discouraged in favour of other opioids (Latta et al, 2002).

### **Tramadol**

Tramadol is commonly referred to as an atypical centrally acting analgesic because of its combined effects as an opioid agonist and a serotonin and noradrenaline reuptake inhibitor (Lotsch, 2005). Although an effective analgesic, it may not provide adequate pain relief if used as the sole agent for the management of moderate to severe acute pain in the currently recommended doses (Thevenin et al, 2008 **Level II**). Tramadol is an effective treatment of neuropathic pain with an NNT of 3.8 (Hollingshead et al, 2006 **Level I**).

Tramadol given with morphine to patients immediately after surgery was shown to be morphine-sparing, but the combination was infra-additive (Marcou et al, 2005 **Level II**).

The (+) enantiomer of tramadol is the stronger inhibitor of serotonin reuptake and the (-) enantiomer the more potent inhibitor of noradrenaline reuptake; tramadol is metabolised by CYP2D6 and the resultant active metabolite, O-desmethyltramadol (or M1), is a more potent mu-opioid receptor agonist than the parent drug (Raffa et al, 1992; Lotsch, 2005). Patients who are poor metabolisers may get less analgesic effect from tramadol (Stamer et al, 2003).

Conversely, carriers of a CYP2D6 gene duplication allele (ultrarapid metabolisers) may be more sensitive to the effects of tramadol (Kirchheiner et al, 2008).

Coadministration with other drugs that inhibit CYP2D6 may also influence the effectiveness of tramadol. For example, pretreatment with paroxetine in healthy extensive metabolisers reduced the hypoalgesic effect of tramadol in an experimental pain model (Laugesen et al, 2005 **Level II**).

Inhibition of 5HT<sub>3</sub> receptors by ondansetron also decreased the analgesic effect of tramadol (Arcioni et al, 2002 **Level II**; De Witte et al, 2001 **Level II**).



Tramadol's adverse effect profile is different from other opioids. The risk of respiratory depression is significantly lower at equianalgesic doses (Tarkkila et al, 1997 **Level II**; Tarkkila et al, 1998 **Level II**; Mildh et al, 1999 **Level II**) and it does not depress the hypoxic ventilatory response (Warren et al, 2000 **Level II**). Significant respiratory depression has only been described in patients with severe renal failure, most likely due to accumulation of the metabolite M1 (Barnung et al, 1997).

In addition, tramadol has less effect on gastrointestinal (GI) motor function than morphine (Wilder-Smith, Hill, Osler et al, 1999 **Level II**; Wilder-Smith, Hill, Wilkins et al, 1999 **Level II**; Lim & Schug, 2001 **Level II**). Nausea and vomiting are the most common adverse effects and occur at rates similar to other opioids (Radbruch et al, 1996 **Level IV**). Tramadol given within recommended dose limits does not increase the incidence of seizures compared with other analgesic agents (Jick et al, 1998 **Level III-2**; Gasse et al, 2000 **Level III-2**).

### 4.1.3 Determinants of opioid dose

Interpatient opioid requirements vary greatly (Macintyre & Jarvis, 1996 **Level IV**) and opioid doses therefore need to be titrated to suit each patient. Reasons for variation include patient age and gender, genetic differences and psychological factors as well as opioid tolerance.

#### **Patient age**

Age, rather than patient weight, appears to be a better determinant of the amount of opioid an adult is likely to require for effective management of acute pain. There is clinical and experimental evidence of a two-fold to four-fold decrease in opioid requirements as patient age increases (Burns et al, 1989 **Level IV**; Macintyre & Jarvis, 1996 **Level IV**; Gagliese et al, 2000 **Level IV**; Coulbault et al, 2006 **Level IV**; Gagliese et al, 2008 **Level IV**). The decrease in opioid requirement is not associated with reports of increased pain (Burns et al, 1989 **Level IV**; Macintyre & Jarvis, 1996 **Level IV**).

This age-related decrease in opioid requirement is due mainly to differences in pharmacodynamics or brain penetration rather than systemic pharmacokinetic factors (Scott & Stanski, 1987; Minto et al, 1997; Macintyre & Upton, 2008) (see Section 11.2).

#### **Gender**

In general it has been found that females report more severe pain than males with similar disease processes or in response to experimental pain stimuli (Hurley & Adams, 2008; Fillingim et al, 2009). Response to opioids may also differ although both the degree and direction of variation depend on many variables (Dahan, Kest et al, 2008). There is no consistent evidence for any difference in mu-opioid agonist requirements (Fillingim et al, 2009). However, kappa-opioid agonists such as nalbuphine and pentazocine have greater analgesic efficacy in women than in men – see Section 1.6.2. These variations as well as other known and unknown factors involved in the very large interpatient differences in opioid requirements seen clinically, mean that gender cannot be used as a basis for opioid dose alteration and confirms the need to titrate doses to effect for each patient.

Acute postsurgical pain shows a tendency towards greater intensity in females, although the evidence is inconsistent, as is the evidence for any difference in opioid requirements (Fillingim et al, 2009). For example, higher pain scores and higher morphine requirements in the immediate postoperative period have been reported for female patients (Cepeda & Carr, 2003 **Level III-2**; Aubrun et al, 2005 **Level III-2**). After knee ligament reconstruction, women reported higher pain scores than men on the first day after surgery but there was no difference in morphine consumption (Taenzer et al, 2000 **Level III-2**). Females also reported more pain after endoscopic inguinal hernia repair (Lau & Patil, 2004 **Level III-2**), laparoscopic cholecystectomy (De



Cosmo et al, 2008 **Level III-2**; Uchiyama et al, 2006 **Level III-2**), and arthroscopic knee surgery (Rosseland & Stubhaug, 2004 **Level III-2**). However, in adolescent patients using PCA morphine in the postoperative period, no difference was seen between male and female patients in average daily pain ratings (Logan & Rose, 2004 **Level III-2**). In a study of Chinese patients, females consumed significantly less morphine than males (Chia et al, 2002 **Level III-2**).

When pain is assessed at a longer time interval after surgery, there appears to be no differences between male and female patients (Fillingim et al, 2009). For example, there was no difference in pain after arthroscopic knee surgery at one year, although disability was greater in females (Rosseland et al, 2008 **Level III-2**), or in pain at 12 to 18 months after hip arthroplasty (Nikolajsen, Brandsborg et al, 2006 **Level III-2**).

## **Genetics**

Genetic variability may also affect a patient's response to opioids (see Section 1.6).

## **Psychological factors**

Evidence of any effect of psychological factors such as anxiety on opioid requirements is contradictory (see Section 1.2).

### **4.1.4 Adverse effects of opioids**

Common adverse effects of opioids are sedation, pruritus, nausea, vomiting, slowing of GI function and urinary retention. Meta-analyses have shown that the risk of side effects from opioids administered by PCA is similar to the risks from traditional methods of systemic opioid administration, with the exception of pruritus, which is increased in patients using PCA (Hudcova et al, 2005 **Level I**).

Results from a review of all trials (including cohort studies, case-controlled studies and audit reports as well as randomised-controlled trials) suggested that there may be differences in the clinical setting (Cashman & Dolin, 2004; Dolin & Cashman, 2005). The following incidences (means) were associated with the use of PCA opioids: respiratory depression 1.2% to 11.5% (using decreased respiratory rate and oxygen desaturation, respectively, as indicators), nausea 32%, vomiting 20.7%, pruritus 13.8% and excessive sedation 5.3%. The incidences reported for IM opioid analgesia were: respiratory depression 0.8% to 37% (using the same indicators), nausea 17%, vomiting 21.9%, pruritus 3.4%, and excessive sedation 5.2% (Cashman & Dolin, 2004 **Level IV**; Dolin & Cashman, 2005 **Level IV**).

Clinically meaningful adverse effects of opioids are dose-related. There was an increased risk of 0.9% for nausea and 0.3% for vomiting for every 1 mg increase in PCA morphine consumption after surgery (Marret et al, 2005 **Level I**<sup>3</sup>). In a later prospective evaluation of the incidence of nausea and vomiting in elderly surgical inpatients requiring a length of stay greater than 2 days and given no postoperative nausea and vomiting (PONV) prophylaxis, there was also a direct correlation between increasing opioid dose and the incidence of both nausea and vomiting (Roberts et al, 2005 **Level IV**). In patients after laparoscopic cholecystectomy performed on an ambulatory basis, once a threshold dose was reached, every 3 to 4 mg increase of morphine-equivalent dose per day was associated with one additional meaningful adverse event or patient-day with such an event (Zhao et al, 2004 **Level II**).

---

<sup>3</sup> This meta-analysis includes a study or studies that have since been withdrawn from publication. Please refer to the Introduction at the beginning of this document for comments regarding the management of retracted articles. Expert advice suggested that withdrawal of the retracted articles would not influence the conclusions but that reanalysis would be required for this to be confirmed. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data included in this meta-analysis after excluding that obtained from the retracted publications. They concluded that removal of this information did not significantly alter the results.

Opioid-related adverse effects in surgical patients were associated with increased length of stay in hospital and total hospital costs; the use of opioid-sparing techniques can be cost-effective (Philip et al, 2002; Oderda et al, 2007 **Level IV**).

### **Respiratory depression**

Respiratory depression (decreased central CO<sub>2</sub> responsiveness resulting in hypoventilation and elevated PaCO<sub>2</sub> levels), the most feared side effect of opioids, can usually be avoided by careful titration of the dose against effect. However, a variety of clinical indicators have been used to indicate respiratory depression, and not all may be appropriate or accurate.

A number of studies investigating hypoxia in the postoperative period, in patients receiving opioids for pain relief, have found that measurement of respiratory rate as an indicator of respiratory depression may be of little value and that hypoxaemic episodes often occur in the absence of a low respiratory rate (Catley et al, 1985 **Level IV**; Jones et al, 1990; Wheatley et al, 1990 **Level IV**; Kluger et al, 1992 **Level IV**). As respiratory depression is almost always preceded by sedation, the best early clinical indicator is increasing sedation (Ready et al, 1988; Vila et al, 2005; Macintyre & Schug, 2007).

Introduction of a numerical pain treatment algorithm in a cancer setting was followed by a review of opioid-related adverse reactions. Use of this algorithm, in which opioids were given to patients in order to achieve satisfactory pain scores, resulted in a two-fold increase in the risk of respiratory depression (Vila et al, 2005 **Level III-3**). Importantly, the authors noted that respiratory depression was usually not accompanied by a decrease in respiratory rate. Of the 29 patients who developed respiratory depression (either before or after the introduction of the algorithm), only 3 had a respiratory rates of <12 breaths/min but 27 (94%) had a documented decrease in their level of consciousness (Vila et al, 2005 **Level III-3**). This study highlights the risk of titrating opioids to achieve a desirable pain score without appropriate patient monitoring.

In a review of PCA, case reports of respiratory depression in patients with obstructive sleep apnoea were examined (Macintyre & Coldrey, 2008). It would appear that the development of respiratory depression may have been missed because of an apparent over-reliance on the use of respiratory rate as an indicator of respiratory depression; the significance of excessive sedation was not recognised (see Section 11.5).

In an audit of 700 acute pain patients who received PCA for postoperative pain relief, respiratory depression was defined as a respiratory rate of <10 breaths/min and/or a sedation score of 2 (defined as 'asleep but easily roused') or more. Of the 13 patients (1.86%) reported with respiratory depression, 11 had sedation scores of at least 2 and, in contrast to the statements above, all had respiratory rates of <10 breaths/min (Shapiro et al, 2005 **Level IV**).

These studies confirm that assessment of sedation is a more reliable way of detecting opioid-induced respiratory depression, although monitoring respiratory rate is still important.

Checking a patient's level of alertness was considered by the American Society of Anesthesiologists (ASA) Task Force on Neuraxial Opioids to be important in the detection of respiratory depression in patients given neuraxial opioids, as well as assessments of adequacy of ventilation and oxygenation (Horlocker et al, 2009). However, it was noted only that 'in cases with other concerning signs, it is acceptable to awaken a sleeping patient to assess level of consciousness'. In this situation it would be possible for increasing sedation and respiratory depression to be missed if no attempt is made to rouse the patient.

A workshop convened by the Anesthesia Patient Safety Foundation to discuss this issue in response to concerns about the safety of IV PCA, recommended 'the use of continuous monitoring of oxygenation (generally pulse oximetry) and ventilation in nonventilated

patients' (Weinger, 2007). This was despite recognising the limitations of currently available monitors, and despite the low sensitivity of continuous pulse oximetry in patients given supplemental oxygen (common in many countries). In contrast, the ASA publication (Horlocker et al, 2009) stated that both the Task Force members and consultants 'disagree that pulse oximetry is more likely to detect respiratory depression than are clinical signs'.

Measuring haemoglobin oxygen saturation levels may not be a reliable method of detecting respiratory depression in the postoperative setting. In addition to the use of supplemental oxygen, there may be reasons other than opioids for hypoxaemia. For example, when measurement of oxygen saturation was used as an indicator of respiratory depression, the incidence was reported to be 11.5% in patients receiving PCA and 37% in those given IM opioids (Cashman & Dolin, 2004 **Level IV**). However, the same authors showed that patients given IM opioids reported significantly more pain (moderate–severe pain in 67.2% and severe pain in 29.1% compared with 35.8% and 10.4% respectively in PCA patients), suggesting that these patients received much lower doses of opioids (Dolin et al, 2002 **Level IV**).

Increases in PCO<sub>2</sub> are the most reliable way of detecting respiratory depression. Continuous monitoring of transcutaneous CO<sub>2</sub> for 24 hours after major abdominal surgery showed that patients given IV PCA morphine had significantly higher CO<sub>2</sub> levels than those receiving epidural local anaesthetic/fentanyl infusions (Kopka et al, 2007 **Level III-2**; McCormack et al, 2008 **Level III-2**).

### **Cardiac effects**

The use of methadone has been linked to the development of prolonged QT interval with a risk of TdP and cardiac arrest (Gupta et al, 2007). Most case reports of TdP in patients taking methadone have identified the presence of at least one other risk factor in addition to methadone (Justo et al, 2006; Fredheim et al, 2008). Risk factors include female sex, heart disease, other drugs with effects on QT interval (eg tricyclic antidepressants, antipsychotics, diuretics) or methadone metabolism, congenital or acquired prolonged QT syndromes, liver impairment and hypokalaemia (Fredheim et al, 2008).

Of patients receiving 60 to 100 mg methadone per day, 23% developed prolonged QT intervals during treatment compared with none of the buprenorphine patients taking 16 to 32 mg three times a week (Wedam et al, 2007 **Level II**). In the methadone group, the QT interval continued to increase over time, even with stable doses.

There is as yet no consensus regarding the benefits or otherwise of obtaining an electrocardiogram (ECG) in patients prior to starting methadone, although it may be that the threshold for doing so should be lower in patients with other concomitant risk factors, including those receiving higher doses of methadone (Cruciani, 2008).

The use of dextropropoxyphene also carries a risk of TdP (Barkin et al, 2006).

## Nausea and vomiting

PONV is common and related to opioid administration in a dose-dependent manner (Marret et al, 2005 **Level I**<sup>4</sup>; Roberts et al, 2005 **Level IV**), although many other risk factors for PONV have also been identified (Gan, 2006). Therefore, drugs used as components of multimodal analgesia and which are opioid-sparing may also reduce PONV. Opioid-sparing and a reduction in PONV has been shown with concurrent administration of gabapentin (Tiippana et al, 2007 **Level I**), non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) (Elia et al, 2005 **Level I**<sup>4</sup>; Marret et al, 2005 **Level I**<sup>4</sup>); and ketamine (Bell et al, 2006 **Level I**). Opioid-sparing with no decrease in PONV was reported for paracetamol and coxibs (Elia et al, 2005 **Level I**<sup>4</sup>; Remy et al, 2005 **Level I**).

The risk of PONV is significantly reduced by the use of droperidol, dexamethasone and ondansetron, which are equally effective (Tramer, 2001 **Level I**; Apfel et al, 2004 **Level II**); propofol and omission of nitrous oxide (N<sub>2</sub>O) are less effective (Apfel et al, 2004 **Level II**).

A Cochrane review identified eight drugs that effectively prevented PONV compared with placebo: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron (Carlisle & Stevenson, 2006 **Level I**<sup>4</sup>). The authors concluded that evidence for differences between the drugs was unreliable due to publication bias. There were few data to compare side effects, but droperidol was more sedative and headache was more common after ondansetron.

Combinations of antiemetics may be more effective than one drug given alone. Prophylaxis with the combination of a 5HT<sub>3</sub>-receptor antagonist and dexamethasone was associated with lower use of rescue antiemetics than 5HT<sub>3</sub>-receptor antagonist or dexamethasone alone (Kovac, 2006 **Level I**). Similarly, the combination of droperidol and ondansetron was additive (Chan et al, 2006 **Level I**). Other combinations that were more effective than either drug given alone were cyclizine and granisetron (Johns et al, 2006 **Level II**), dexamethasone and haloperidol (Rusch et al, 2007 **Level II**; Chu CC et al, 2008 **Level II**), and dexamethasone and dolasetron (Rusch et al, 2007 **Level II**). The addition of metoclopramide to dexamethasone also led to better PONV prophylaxis but, compared with dexamethasone 8 mg alone, only if doses of 25 mg and 50 mg metoclopramide were used and not 10 mg (Wallenborn et al, 2006 **Level II**).

Droperidol, and to a lesser extent, ondansetron, may lead to prolonged QT intervals. Concerns about the potential for serious cardiac arrhythmias secondary to QT prolongation associated with administration of droperidol led to a 'black box' warning by the United States Food and Drug Administration (FDA) in 2001. Following this there has been a significant reduction in the use of this drug, even though the warning was felt by many to be unwarranted (Habib & Gan, 2008a).

In a study in healthy volunteers, QT prolongation with droperidol 1 mg IV was significantly greater than following ondansetron 4 mg IV, but the effect of combining both drugs was no worse than droperidol alone (Charbit et al, 2008 **Level II**). Significant but similar QT prolongation (compared with pretreatment values) was also noted in patients given droperidol 0.75 mg IV or ondansetron 4 mg IV after surgery (Charbit et al, 2005 **Level II**). However, QT interval was already prolonged in 21% of these patients prior to administration of any antiemetic drug. There was also a transient increase in QT interval after administration of ondansetron 4 mg IV, droperidol 1.25 mg IV, or their combination given prior to surgery, but there were also no

<sup>4</sup> This meta-analysis includes a study or studies that have since been withdrawn from publication. Please refer to the Introduction at the beginning of this document for comments regarding the management of retracted articles. Expert advice suggested that withdrawal of the retracted articles would not influence the conclusions but that reanalysis would be required for this to be confirmed. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data included in this meta-analysis after excluding that obtained from the retracted publications. They concluded that removal of this information did not significantly alter the results.

differences between the groups (Chan et al, 2006 **Level II**). Another study showed that QT prolongation occurred after 0.625 and 1.25 mg IV droperidol, but that this was not significantly different from that seen with saline, indicating that other causes of mild QT prolongation occur with anesthesia and surgery (White et al, 2005 **Level II**).

A large review (Nuttall et al, 2007 **Level III-3**) of surgical patients in the periods 3 years before (139 932 patients) and 3 years after (151 256 patients) the FDA 'black box' warning merged anaesthesia database information with information from ECG and other databases as well as patients' case notes, and recorded all patients who had documented prolonged QT intervals, TdP or death within 48 hours of their surgery. Despite a reduction in the use of droperidol from 12% to 0% of patients following the warning, there was no difference in the incidence of QT prolongation, ventricular tachycardia, or death within 48 hours of surgery and no clearly identified case of TdP related to use of droperidol (Nuttall et al, 2007 **Level III-3**). The authors concluded that for low-dose droperidol, the 'black box' warning was 'excessive and unnecessary'. Others have supported use of the warning but suggested it should be made clear that the doses commonly used in the prevention and treatment of PONV are 'off-label' and that the 'FDA has no position on the safety and efficacy of doses below 2.5 mg' (Ludwin & Shafer, 2008).

The authors of recent guidelines for the management of PONV also expressed concerns about the quality and validity of evidence that led to the FDA caution and concluded that without this warning, 'droperidol would have been the panel's overwhelming choice for PONV prophylaxis' (Gan, Meyer et al, 2007).

Haloperidol has also been associated with prolonged QT intervals and TdP (Habib & Gan, 2008b). Using data from studies published up until 1988, a meta-analysis showed that haloperidol was also an effective antiemetic (Buttner et al, 2004 **Level I**). More recent studies have confirmed its effectiveness compared with placebo (Aouad et al, 2007 **Level II**), ondansetron (no differences in efficacy, side effects or QT intervals) (Aouad et al, 2007 **Level II**; Lee Y et al, 2007 **Level II**; Rosow et al, 2008 **Level II**) and droperidol (as effective) (Wang et al, 2008 **Level II**). Combination of haloperidol with ondansetron was more effective than ondansetron alone (Grecu et al, 2008 **Level II**) and haloperidol and dexamethasone also more effective than either drug given alone (Chu CC et al, 2008 **Level II**), again with no difference in side effects or QT intervals. Compared with droperidol, the only advantage of haloperidol may be 'that there is no black box warning' (Ludwin & Shafer, 2008).

Dolasetron (IV and oral formulations) is contraindicated by the Canadian authorities for any therapeutic use in children and adolescents under 18 years of age and the prevention or treatment of PONV in adults because of the risk of QT prolongation (Health Canada, 2006). The age restriction is not limited to Canada, but valid in a number of countries including the United Kingdom; cases of prolonged QT interval have also been reported after overdose (Rochford et al, 2007).

NK1-receptor antagonists may also be effective in the treatment of PONV. Aprepitant was more effective than ondansetron for preventing vomiting at 24 and 48 hours after open abdominal surgery, and in reducing the severity of nausea in the first 48 hours (Diemunsch et al, 2007 **Level II**). In a similar study with a slightly smaller number of patients after open abdominal surgery, aprepitant was also found to be superior to ondansetron for prevention of vomiting in the first 24 and 48 hours, but no difference was seen in the incidence of nausea (Gan, Apfel et al, 2007 **Level II**).

P6 acupoint stimulation in patients with no antiemetic prophylaxis resulted in significant reductions in the risks of nausea, vomiting and the need for rescue antiemetics; compared

with antiemetic prophylaxis, P6 acupoint stimulation seems to reduce the risk of nausea but not vomiting (Lee & Done, 2004 **Level I**).

Supplemental oxygen (inspired oxygen concentration 80%) did not reduce PONV (Orhan-Sungur et al, 2008 **Level I**).

### **Impairment of gastrointestinal motility**

Opioids impair return of bowel function after surgery. The peripheral acting opioid antagonists alvimopan and methylnaltrexone were effective in reversing opioid-induced slowing of GI transit time and constipation, and alvimopan was an effective treatment for postoperative ileus; insufficient evidence exists about the efficacy or safety of naloxone or nalbuphine (McNicol et al, 2008 **Level I**).

A combined formulation of controlled-release (CR) oxycodone and naloxone has been studied. Compared with CR oxycodone alone in patients with chronic non-malignant pain, the combination formulation resulted in similar analgesic efficacy but less bowel dysfunction (Vondrackova et al, 2008 **Level II**).

### **Urinary retention**

Opioids cause urinary retention due to presumed central and peripheral mechanisms. Opioid antagonists reverse this effect; naloxone reversed opioid-induced urinary retention in 100% of patients, while the peripheral opioid antagonist methylnaltrexone was effective in 42% of study participants (Rosow et al, 2007 **Level II**). These data suggest that at least part of the bladder dysfunction caused by opioids is peripherally mediated.

Premedication with gabapentin reduced urinary retention caused by opioids (NNT 7) (Tiippana et al, 2007 **Level I**). This effect is most likely related to the opioid-sparing effect of gabapentin.

### **Pruritus**

The mechanism of opioid-induced pruritus, which is particularly common after neuraxial opioid administration, is not fully understood, but central mu-opioid receptor-mediated mechanisms are thought to be the primary cause (Ganesh & Maxwell, 2007). Naloxone, naltrexone, nalbuphine and droperidol are effective in the treatment of opioid-induced pruritus, although minimum effective doses remain unknown (Kjellberg & Tramer, 2001 **Level I**).

Prophylactic 5HT<sub>3</sub> antagonists reduce the incidence of pruritus after neuraxial opioids (Bonnet et al, 2008 **Level I**); however the authors of this meta-analysis were concerned about possible publication bias.

Premedication with gabapentin (Sheen, Ho, Lee, Tsung & Chang, 2008 **Level II**) and mirtazepine (Sheen, Ho, Lee, Tsung, Chang et al, 2008 **Level II**) also reduced the incidence and severity of pruritus associated with intrathecal opioids. Evidence of any benefit with propofol is mixed (Ganesh & Maxwell, 2007). Promethazine was not effective for the treatment of spinal morphine-induced pruritus but was associated with more sedation; droperidol and, to a lesser extent propofol, were of use (Horta et al, 2006 **Level II**).

### **Cognitive function and confusion**

The risk of delirium and/or changes in cognitive function has been compared in patients receiving different PCA opioids. There was no statistically significant difference in the rates of confusion between morphine and fentanyl but the rates were 4.3% for patients given fentanyl and 14.3% for those receiving morphine; there was less depression of cognitive function with fentanyl (Herrick et al, 1996 **Level II**). Compared with morphine, no differences in cognitive function were reported in patients receiving tramadol (Silvasti et al, 2000 **Level II**; Ng et al, 2006 **Level II**), but cognitive function was poorer in patients given hydromorphone (Rapp et al, 1996 **Level II**). Studies of lower quality reported a significantly greater incidence of delirium with



pethidine compared with morphine (Adunsky et al, 2002 **Level III-3**) and a variety of other opioids (Morrison et al, 2003 **Level III-2**). Pethidine use postoperatively was associated with an increased risk of delirium in the postoperative period; there was no difference between various other opioids (Fong et al, 2006 **Level I**).

### **Tolerance and hyperalgesia**

In the absence of disease progression, a decrease in the effectiveness of opioid analgesia has traditionally been attributed to opioid tolerance. It is now known that administration of opioids can lead to both opioid-tolerance (a desensitisation of antinociceptive pathways to opioids) and, paradoxically, to opioid-induced hyperalgesia (OIH) (a sensitisation of pronociceptive pathways leading to pain hypersensitivity), and that both these phenomena can significantly reduce the analgesic effect of opioids (Angst & Clark, 2006; Chu LF et al, 2008). The mechanisms underlying the development of tolerance and OIH are still not fully understood but, as with neuropathic pain, are thought to include activation of the glutaminergic system via the NMDA receptor, as well as other transmitter and receptor systems (Angst & Clark, 2006; Mao, 2008).

Mao (Chang et al, 2007; Mao, 2008) distinguishes between 'pharmacological tolerance' (ie tolerance, as defined in Section 11.7 — the predictable and physiological decrease in the effect of a drug over time) and 'apparent tolerance', where both tolerance and OIH contribute to a decrease in the effectiveness of opioids. The clinical significance of this mix, and the relevant contribution of pharmacological tolerance and OIH to 'apparent tolerance' in any particular patient, is difficult if not impossible to determine (Angst & Clark, 2006). Inadequate pain relief because of pharmacological tolerance may improve with opioid dose escalation, while improvements in analgesia in the presence of OIH may follow a reduction in opioid dose (Chang et al, 2007; Mao, 2008; Chu LF et al, 2008).

It is probable that the degree of OIH varies between opioids. Morphine, in high doses, may be more likely to result in OIH than other opioids; experimental data and a very limited number of case reports have shown an improvement when morphine doses were reduced or a change to methadone, fentanyl or sufentanil was made (Angst & Clark, 2006). Similarly, it appears that opioids differ in their ability to induce tolerance and, at least in part, this may reflect their varying ability to promote receptor internalisation and recycling. While drugs such as methadone, fentanyl and sufentanil promote receptor internalisation and thereby recycling, activation of opioid receptors by morphine leads to little or no receptor internalisation and an increased risk of development of tolerance (Joo, 2007).

The difference between opioids is one reason why opioid-rotation may be a useful strategy in the clinical setting in attempts to improve pain relief (see Section 11.7.3).

### **Studies using experimental pain stimuli**

Many animal studies have shown that opioid administration can lead to OIH (Angst & Clark, 2006). A number of human studies have also investigated changes in pain sensitivity following long-term opioid use and reported increases in sensitivity to certain pain stimuli.

Patients taking methadone as part of a drug-dependence treatment program have been shown to have an increased sensitivity to cold pressor pain stimuli (Compton et al, 2000 **Level IV**; Doverty et al, 2001 **Level III-2**; Athanasos et al, 2006 **Level III-2**). Similarly, pain sensitivity to cold pressor but not heat stimuli was noted in patients 1 month after starting oral morphine therapy (Chu et al, 2006 **Level III-2**), and to cold pressor but not electrical pain stimuli in patients with chronic non-cancer pain taking either methadone or morphine (Hay et al, 2009 **Level III-2**). In a comparison of methadone-maintained and buprenorphine-maintained patients, pain sensitivity to cold pressor pain stimuli was increased in both groups and overall there was no

difference between the groups; in the few patients not also taking illicit opioids, subjects taking buprenorphine were less hyperalgesic than those taking methadone (Compton et al, 2001 **Level III-2**).

Angst and Clark (Angst & Clark, 2006 **Level I**) summarised studies that investigated the effects of a short-duration remifentanil infusion in volunteer subjects with pre-existing experimentally induced mechanical hyperalgesia; the use of remifentanil was shown to aggravate hyperalgesia, the magnitude of the effect was directly related to the dose given, and coadministration of ketamine abolished the effect of remifentanil. Methadone-maintained subjects were shown to have a significant tolerance to remifentanil given by short-duration infusion, suggesting that opioid-tolerant patients may require significantly higher doses for the treatment of acute pain compared with opioid-naïve patients; dose-dependent increases in cold pressor tolerance were found (Hay et al, 2009 **Level III-2**).

### **Clinical studies**

It may be more difficult to distinguish between pharmacological tolerance and OIH in the clinical setting when subjective pain scores are used to assess adequacy of analgesia (Chang et al, 2007). Many of the studies to date provide only indirect evidence for the development of OIH (Angst & Clark, 2006; Chu LF et al, 2008). A formal diagnosis of hyperalgesia requires quantitative sensory testing (QST), that is, serial assessment of the responses to varying intensities of a nociceptive stimulus in order to determine pain thresholds (Mitra, 2008). QST before and after starting chronic opioid therapy, may assist in the differentiation between OIH and pharmacological tolerance (Chu LF et al, 2008) but this is unlikely to become common practice in the acute pain setting.

There have been a number of studies, summarised in reviews by Angst and Clark (Angst & Clark, 2006 **Level IV**) and Chu et al (Chu LF et al, 2008 **Level IV**), investigating the effects of intraoperative use of a potent opioid (commonly a remifentanil infusion) on pain and postoperative opioid requirements, but the results are conflicting. Some have shown that this leads to increased pain and postoperative opioid requirements, and attributed this to OIH, other studies have not been able to replicate these findings — leading to the suggestion that the outcome may be dose-dependent and more likely to occur when higher opioid doses are administered (Chu LF et al, 2008). For example, morphine requirements and hyperalgesia and allodynia adjacent to the surgical wound were greater following high-dose intraoperative remifentanil infusions compared with low-dose infusions (Joly et al, 2005 **Level II**). A study in volunteers given remifentanil infusions to obtain two different ‘but clinically relevant’ steady-state target concentrations of the drug, found that these were not associated with changes in response to thermal, electrical and cold pressor stimuli (Angst et al, 2009 **Level II**).

Also, it is not yet clear from many of these papers whether this acute ‘apparent tolerance’ is due to pharmacological tolerance or OIH (Angst & Clark, 2006; Mao, 2008). True differentiation between pharmacological tolerance and OIH requires direct assessment of pain sensitivity, as noted above (Mitra, 2008). However, if patients given a remifentanil infusion intraoperatively report higher levels of postoperative pain than matched controls who have not received any opioids, then OIH should be considered (Chang et al, 2007).

Severity of acute pain following a single subcutaneous (SC) injection of lignocaine was compared in patients taking opioids for chronic pain and opioid-naïve controls; pain and unpleasantness scores were higher in those patients taking opioids and correlated with opioid dose and duration of treatment (Cohen et al, 2008 **Level III-2**).

There are case reports of patients with cancer and chronic non-cancer pain and taking high doses of opioid, who developed OIH and whose pain relief improved following reduction of



their opioid dose or after a change was made to another opioid (Angst & Clark, 2006; Chu LF et al, 2008), however there have been no similar reports from an acute pain setting.

### **Clinical implications and possible attenuation of tolerance and OIH**

See Section 11.7.1.

### **Tolerance to adverse effects of opioids**

Tolerance to the side effects of opioids also occurs; tolerance to sedation, cognitive effects, nausea and respiratory depression can occur reasonably rapidly, but there is little if any change in miosis or constipation (Chang et al, 2007).

#### **Key messages**

1. Dextropropoxyphene has low analgesic efficacy (**U**) (**Level I** [Cochrane Review]).
2. Tramadol is an effective treatment for neuropathic pain (**U**) (**Level I** [Cochrane Review]).
3. Gabapentin, non-steroidal NSAIDs and ketamine are opioid-sparing medications and reduce opioid-related side effects (**N**) (**Level I**).
4. In appropriate doses, droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron are effective in the prevention of postoperative nausea and vomiting (**N**) (**Level I** [Cochrane Review]).
5. Alvimopan and methylnaltrexone are effective in reversing opioid-induced slowing of gastrointestinal transit time and constipation (**N**) (**Level I** [Cochrane Review]).
6. Droperidol, dexamethasone and ondansetron are equally effective in the prevention of postoperative nausea and vomiting (**U**) (**Level I**).
7. Paired combinations of 5HT<sub>3</sub> antagonist, droperidol or dexamethasone provide superior prophylaxis of postoperative nausea and vomiting than either compound alone (**N**) (**Level I**).
8. Naloxone, naltrexone, nalbuphine, droperidol and 5HT<sub>3</sub> antagonists are effective treatments for opioid-induced pruritus (**N**) (**Level I**).
9. Opioids in high doses can induce hyperalgesia (**N**) (**Level I**).
10. Tramadol has a lower risk of respiratory depression and impairs gastrointestinal motor function less than other opioids at equianalgesic doses (**U**) (**Level II**).
11. Pethidine is not superior to morphine in treatment of pain of renal or biliary colic (**U**) (**Level II**).
12. Morphine-6-glucuronide is an effective analgesic (**N**) (**Level II**).
13. In the management of acute pain, one opioid is not superior over others but some opioids are better in some patients (**U**) (**Level II**).
14. The incidence of clinically meaningful adverse effects of opioids is dose-related (**U**) (**Level II**).
15. High doses of methadone can lead to prolonged QT interval (**N**) (**Level II**).
16. Haloperidol is effective in the prevention of postoperative nausea and vomiting (**N**) (**Level II**).
17. Opioid antagonists are effective treatments for opioid-induced urinary retention (**N**) (**Level II**).

18. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**N**) (**Level III-2**).
19. Assessment of sedation is a more reliable way of detecting early opioid-induced respiratory depression than a decreased respiratory rate (**S**) (**Level III-3**).
20. The evidence for risk of cardiac arrhythmias following low-dose droperidol is poor (**N**) (**Level III-3**).
21. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).
22. Impaired renal function and the oral route of administration result in higher levels of the morphine metabolites morphine-3-glucuronide and morphine-6-glucuronide with increased risk of sedation and respiratory depression (**S**) (**Level IV**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- The use of pethidine (**U**) and dextropropoxyphene (**N**) should be discouraged in favour of other opioids.

## 4.2 PARACETAMOL, NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND COXIBS

### 4.2.1 Paracetamol

Paracetamol (acetaminophen) is the only remaining para-aminophenol used in clinical practice and is an effective analgesic (see below) and antipyretic. It is absorbed rapidly and well from the small intestine after oral administration with a bioavailability of between 63% and 89% (Oscier & Milner, 2009). It can also be given rectally and intravenously (see below and Section 6).

The mechanism of action of paracetamol remains unclear. In contrast with opioids, paracetamol has no known endogenous binding sites, and unlike NSAIDs, apparently does not inhibit peripheral cyclo-oxygenase activity. There is increasing evidence of a central antinociceptive effect. Although the mechanism of analgesic efficacy of paracetamol remains elusive, it may involve direct and indirect inhibition of central cyclo-oxygenases, but the activation of the endocannabinoid system and spinal serotonergic pathways also appear to be essential (Bertolini et al, 2006; Botting, 2006; Pickering et al, 2006; Mallet et al, 2008; Pickering et al, 2008). Paracetamol has also been shown to prevent prostaglandin production at the cellular transcriptional level, independent of cyclo-oxygenase activity (Mancini et al, 2003).

As one of the mechanisms of action of paracetamol appears to be linked to the serotonergic system, it is possible that other drugs with serotonergic effects could affect pain relief. In volunteers, coadministration of tropisetron or granisetron blocked the analgesic effects of paracetamol (Pickering et al, 2006 **Level II**; Pickering et al, 2008 **Level II**). The significance of this in the clinical setting has not yet been elucidated.

#### **Efficacy**

Single doses of paracetamol are effective in the treatment of postoperative pain. The NNTs for a variety of doses as well as combinations of paracetamol with other analgesic drugs such as codeine are discussed and listed in Section 6 and Table 6.1.

Superiority of an oral dose of 1000 mg over doses below 1000 mg was shown after wisdom tooth extraction (Weil et al, 2007 **Level I**). In a meta-analysis designed to look at dose response,

1000 mg was superior to 500 mg (McQuay & Moore, 2007 **Level I**). However, in a broader meta-analysis, no dose-response was noted between doses of 500 mg, 600 to 650 mg and 975 to 1000 mg; the rate of adverse effects was comparable to placebo (Toms et al, 2008 **Level I**). A comparison of two high-dose regimens of oral paracetamol in young adults undergoing third molar extractions showed no difference between doses of 90 mg/kg and 60 mg/kg (Zacharias et al, 2007 **Level II**). Another comparison of single doses of IV doses of 2 g and 1 g showed better pain relief following third molar surgery with the 2 g dose (Juhl et al, 2006 **Level II**).

Paracetamol is also an effective adjunct to opioid analgesia, opioid requirements being reduced by 20% to 30% when combined with a regular regimen of oral or rectal paracetamol (Romsing et al, 2002 **Level I**). The use of oral paracetamol in higher daily doses (1 g every 4 hours) in addition to PCA morphine lowered pain scores, shortened the duration of PCA use and improved patient satisfaction (Schug et al, 1998 **Level II**). Meta-analyses looking at paracetamol as an adjunct to PCA opioids also showed that PCA morphine requirements were decreased but that there was no improvement in pain relief or decrease in opioid-related adverse effects (Elia et al, 2005 **Level I**; Remy et al, 2005 **Level I**).

In the same doses, orally administered paracetamol was less effective and of slower onset than paracetamol given by IV injection, but more effective and of faster onset than paracetamol administered by the rectal route, when subtherapeutic blood concentrations are common (see Section 6).

IV paracetamol was an effective analgesic after surgery (Sinatra et al, 2005 **Level II**). It was as effective as ketorolac (Varrassi et al, 1999 **Level II**; Zhou et al, 2001 **Level II**), diclofenac (Hynes et al, 2006 **Level II**) and metamizol (Landwehr et al, 2005 **Level II**) and was equivalent to morphine and better tolerated after dental surgery (Van Aken et al, 2004 **Level II**), although there was evidence of a ceiling effect (Hahn et al, 2003 **Level II**). Compared with parecoxib, propacetamol (the IV prodrug of paracetamol) led to the same degree of opioid-sparing after surgery, although patients receiving parecoxib were more likely to rate their pain relief as 'good' or 'excellent' (Beaussier et al, 2005 **Level II**).

The combination of paracetamol and NSAID was clearly more effective than paracetamol alone, but evidence for superiority relative to the NSAID alone was more limited and of uncertain clinical significance (Hyllested et al, 2002 **Level I**; Romsing et al, 2002 **Level I**).

### **Adverse effects**

Paracetamol has fewer side effects than NSAIDs and can be used when the latter are contraindicated (eg patients with a history of asthma or peptic ulcers). It is commonly recommended that paracetamol should be used with caution or in reduced doses in patients with active liver disease, history of heavy alcohol intake and glucose-6-phosphate dehydrogenase deficiency. However, others report that it can be used safely in patients with liver disease and is preferred to NSAIDs, and that therapeutic doses of paracetamol, at least for short-term use, are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol (Benson et al, 2005; Graham et al, 2005; Oscier & Milner, 2009). There is no evidence that patients who have depleted glutathione stores (eg patients who are malnourished, or who have cirrhosis, hepatitis C or human immunodeficiency virus [HIV]) are at increased risk of liver dysfunction when exposed to therapeutic doses of paracetamol (Benson et al, 2005; Graham et al, 2005; Oscier & Milner, 2009).

Paracetamol interacts with warfarin to increase the International Normalised Ratio (INR) (Mahe et al, 2005 **Level II**; Parra et al, 2007 **Level II**).

## 4.2.2 Non-selective non-steroidal anti-inflammatory drugs

The term NSAIDs is used to refer to both nsNSAIDs and coxibs (COX-2 selective inhibitors). NSAIDs have a spectrum of analgesic, anti-inflammatory and antipyretic effects and are effective analgesics in a variety of acute pain states. Many effects of NSAIDs can be explained by inhibition of prostaglandin synthesis in peripheral tissues, nerves, and the CNS (Botting, 2006). However, NSAIDs and aspirin may have other mechanisms of action independent of any effect on prostaglandins, including effects on basic cellular and neuronal processes.

Prostaglandins are produced by the enzyme prostaglandin endoperoxide (PGH) synthase, which has both cyclo-oxygenase and hydroperoxidase sites. Two subtypes of cyclo-oxygenase enzyme have been identified – the ‘constitutive’ COX-1, the ‘inducible’ COX-2; a COX-3 is also being investigated (Simmons et al, 2004; Gajraj & Joshi, 2005; Botting, 2006; Kam & So, 2009).

Prostaglandins have many physiological functions including gastric mucosal protection, renal tubular function and intrarenal vasodilation, bronchodilatation, production of endothelial prostacyclin that leads to vasodilation and prevents platelet adhesion, and platelet thromboxane that results in platelet aggregation and vessel spasm. Such physiological roles are mainly regulated by COX-1 and are the basis for many of the adverse effects associated with nsNSAID use. Tissue damage induces COX-2 production leading to synthesis of prostaglandins that result in pain and inflammation, and COX-2 induction within the spinal cord may play a role in central sensitisation. COX-2 may also be ‘constitutive’ in some tissues, including the kidney, cardiovascular system and brain (Kam & So, 2009). nsNSAIDs are ‘non-selective’ cyclo-oxygenase inhibitors that inhibit both COX-1 and COX-2. Aspirin acetylates and inhibits cyclo-oxygenase irreversibly but nsNSAIDs are reversible inhibitors of the enzymes. The coxibs have been developed to inhibit selectively the inducible form (Simmons et al, 2004; Gajraj & Joshi, 2005; Botting, 2006).

### Efficacy

Single doses of nsNSAIDs are effective in the treatment of pain after surgery (Derry et al, 2009a **Level I**; Derry et al, 2009b **Level I**; Derry et al, 2009c **Level I**), low back pain (Roelofs et al, 2008 **Level I**), renal colic (Holdgate & Pollock, 2004 **Level I**) and primary dysmenorrhoea (Marjoribanks et al, 2003 **Level I**). For a list of NNTs for each drug see Table 6.1.

nsNSAIDs are integral components of multimodal analgesia (Kehlet, 1997; Brodner et al, 2001; Barratt et al, 2002). However, while useful analgesic adjuncts, they are inadequate as the sole analgesic agent in the treatment of severe postoperative pain. When given in combination with opioids after surgery, nsNSAIDs resulted in better analgesia, reduced opioid consumption and a lower incidence of PONV and sedation (Elia et al, 2005 **Level I**<sup>5</sup>; Marret et al, 2005 **Level I**<sup>5</sup>). There was no effect on pruritus, urinary retention and respiratory depression (Marret et al, 2005 **Level I**<sup>5</sup>). Similarly, in patients less than 70 years of age undergoing cardiothoracic surgery, the use of nsNSAIDs reduced pain scores and opioid requirements (Bainbridge et al, 2006 **Level I**) although the use of these drugs in patients following coronary artery bypass surgery is controversial (see below).

<sup>5</sup> This meta-analysis includes a study or studies that have since been withdrawn from publication. Please refer to the Introduction at the beginning of this document for comments regarding the management of retracted articles. Expert advice suggested that withdrawal of the retracted articles would not influence the conclusions but that reanalysis would be required for this to be confirmed. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data included in this meta-analysis after excluding that obtained from the retracted publications. They concluded that removal of this information did not significantly alter the results.

The combination of paracetamol and nsNSAID was clearly more effective than paracetamol alone, but evidence for superiority relative to the nsNSAID alone was more limited and of uncertain clinical significance (Hyllested et al, 2002 **Level I**; Romsing et al, 2002 **Level I**).

### **Adverse effects**

NsNSAID side effects are more common with long-term use — and there are concerns relating to prothrombotic effects. In the perioperative period the main concerns are renal impairment, interference with platelet function, wound and bone healing, and peptic ulceration or bronchospasm in individuals at risk. Certain risks are accentuated in the perioperative period because of haemodynamic disturbances, fluid shifts, activation of the neurohumoral stress response and deficient enteral feeding. In general, the risk and severity of nsNSAID-associated side effects is increased in elderly people (Pilotto et al, 2003; Juhlin et al, 2005).

#### **Renal function**

Renal prostaglandins regulate tubular electrolyte handling, modulate the actions of renal hormones, and maintain renal blood flow and glomerular filtration rate in the presence of circulating vasoconstrictors. The adverse renal effects of chronic nsNSAID use are common and well-recognised. In some clinical conditions, including hypovolaemia, dehydration and major surgery, high circulating concentrations of the vasoconstrictors angiotensin II, noradrenaline and vasopressin increase production of intrarenal vasodilators including prostacyclin — maintenance of renal function may then depend on prostaglandin synthesis and thus can be sensitive to brief nsNSAID administration.

In patients with normal preoperative renal function, nsNSAIDs caused a clinically insignificant and transient decrease in creatinine clearance the first day after surgery, and there were no differences between patients given diclofenac, ketorolac, indomethacin (indometacin) or ketoprofen (Lee A et al, 2007 **Level I**). The risk of adverse renal effects of nsNSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension, use of other nephrotoxic agents and angiotensin-converting enzyme (ACE) inhibitors (RCA, 1998 **Level IV**).

With proper selection and monitoring, the incidence of NSAID-induced perioperative renal impairment is low and NSAIDs need not be withheld in patients with normal preoperative renal function (Lee A et al, 2007 **Level I**).

#### **Platelet function**

NsNSAIDs inhibit platelet function. In meta-analyses of tonsillectomy in both adult and paediatric patients, nsNSAIDs were found to increase the risk of reoperation for bleeding (NNH 29 to 60) (Marret et al, 2003 **Level I**; Moiniche et al, 2003 **Level I**) but surgical blood loss was not significantly increased (Moiniche et al, 2003 **Level I**) (see also Sections 9.6.7 and 10.5). Looking at studies in children only, there was no increase in the risk of reoperation for bleeding after tonsillectomy (Cardwell et al, 2005 **Level I**). Aspirin, which irreversibly inhibits platelet aggregation, increased the risk of post-tonsillectomy haemorrhage (Krishna et al, 2003 **Level I**).

After a variety of different operations, the use of nsNSAIDs showed a significant increase in risk of severe bleeding from 0 to 1.7% compared with placebo (NNH 59) (Elia et al, 2005 **Level I**). This was also found in the large HIPAID study after hip replacement, where the ibuprofen group had a significantly increased risk of major bleeding complications (OR 2.1) (Fransen et al, 2006 **Level II**). After gynaecological or breast surgery, use of diclofenac led to more blood loss than rofecoxib (Hegi et al, 2004 **Level II**). After otorhinolaryngological surgery in an outpatient setting, tenoxicam increased bleeding at the surgical site (Merry et al, 2004 **Level II**).

### **Peptic ulceration**

A large case-controlled study using a general practice database identified 10 892 patients over 4 years with a 'first ever' diagnosis of an upper GI ulcer or bleeding and compared them with matched controls (Hippisley-Cox et al, 2005 **Level III-3**). Where individual drugs were specified in the results, the risks were shown to be significantly increased for patients using naproxen, diclofenac, ibuprofen, aspirin and rofecoxib, but not those taking celecoxib.

Acute gastroduodenal damage and bleeding can also occur with short-term nsNSAID use — the risk is increased with higher doses, a history of peptic ulceration, use for more than 5 days and in elderly people (Strom et al, 1996 **Level IV**). After 5 days of naproxen and ketorolac use in healthy elderly subjects, ulcers were found on gastroscopy in 20% and 31% of cases respectively (Harris et al, 2001 **Level II**; Stoltz et al, 2002 **Level II**; Goldstein et al, 2003 **Level II**).

The gastric and duodenal epithelia have various protective mechanisms against acid and enzyme attack and many of these involve prostaglandin production. Chronic nsNSAID use is associated with peptic ulceration and bleeding and the latter may be exacerbated by the antiplatelet effect. It has been estimated that the relative risk of perforations, ulcers and bleeds associated with nsNSAIDs is 2.7 compared with people not consuming nsNSAIDs (Ofman et al, 2002 **Level III-2**). Use of ketorolac and piroxicam carried the highest risk (Lanas et al, 2003 **Level III-3**). Concurrent use of a proton-pump inhibitor (PPI) significantly reduced the incidence of nsNSAID-related peptic ulcer disease (Targownik et al, 2008 **Level III-2**).

### **Aspirin-exacerbated respiratory disease**

Precipitation of bronchospasm by aspirin is a recognised phenomenon in individuals with asthma, chronic rhinitis and nasal polyps. Aspirin-exacerbated respiratory disease (AERD) affects 10% to 15% of people with asthma, can be severe and there is a cross-sensitivity with nsNSAIDs but not coxibs (Simon & Namazy, 2003 **Level IV**; Szczeklik & Stevenson, 2003 **Level IV**; West & Fernandez, 2003 **Level I**). A history of AERD is a contraindication to nsNSAID use, although there is no reason to avoid nsNSAIDs in other people with asthma.

### **Bone healing**

Evidence for an effect on bone healing is conflicting. In one study of 88 patients, 30 of whom were given ketorolac after spinal fusion, the incidence of incomplete union or non-union was higher in those given ketorolac; the relative risk was approximately six times higher than control group of patients who did not receive an NSAID and smoking was said to have had no effect on the spinal fusion outcome (Park et al, 2005 **Level III-2**). In another study of 405 patients, 228 of whom were given ketorolac after similar surgery, there was no significant difference in the non-union rates between the two groups; in this study there were no patients who smoked (Pradhan et al, 2008 **Level III-3**).

### **Cardiovascular**

Most publications looking at the risk of cardiovascular side effects associated with nsNSAID use also include information relating to risks with coxibs. See discussion under Section 4.2.3 below.

## **4.2.3 Cyclo-oxygenase-2 selective inhibitors (coxibs)**

Coxibs selectively inhibit the inducible cyclo-oxygenase enzyme, COX-2, and spare constitutive COX-1 (see above). The coxibs available at present include celecoxib, etoricoxib and parecoxib, the injectable precursor of valdecoxib. By sparing physiological tissue prostaglandin production while inhibiting inflammatory prostaglandin release, coxibs offer the potential for effective analgesia with fewer side effects than nsNSAIDs.

## Efficacy

Coxibs were as effective as nsNSAIDs in the management of postoperative pain (Romsing & Moiniche, 2004 **Level I**<sup>6</sup>). They were also as effective as nsNSAIDs for the treatment of low back pain (although effect sizes were small) but the incidence of side effects was lower with coxibs (Roelofs et al, 2008 **Level I**). NNTs are comparable with those for nsNSAIDs for the treatment of moderate to severe acute pain. For a list of NNTs for each drug see Table 6.1.

Preoperative coxibs reduced postoperative pain and opioid consumption and increased patient satisfaction (Straube et al, 2005 **Level I**<sup>6</sup>). When given in combination with opioids after surgery, coxibs were opioid-sparing (Hubbard et al, 2003 **Level II**; Malan et al, 2003 **Level II**; Ng et al, 2003 **Level II**; Reynolds et al, 2003 **Level II**; Gan et al, 2004 **Level II**; Celik et al, 2005 **Level II**; Nussmeier et al, 2006 **Level II**; Snabes et al, 2007 **Level II**; White PF et al, 2007 **Level II**), but both a decrease in the incidence of opioid-related side effects (Malan et al, 2003 **Level II**; Gan et al, 2004 **Level II**) and no difference (Hubbard et al, 2003 **Level II**; Ng et al, 2003 **Level II**; Celik et al, 2005 **Level II**; Snabes et al, 2007 **Level II**; White PF et al, 2007 **Level II**) has been reported. A meta-analysis concluded that there was no evidence for a decrease in adverse effects (Romsing et al, 2005 **Level I**) as did a meta-analysis that included trials of coxibs given to patients receiving PCA morphine; it showed reduced opioid consumption but no significant reductions in pain scores or opioid-related adverse effects (Elia et al, 2005 **Level I**<sup>7</sup>).

Timing of administration may not be critical. A comparison of celecoxib, started preoperatively or postoperatively and continued for 3 days after surgery, showed opioid-sparing and improved patient satisfaction in both patient groups compared with placebo, but there was no advantage for administration before surgery (Sun et al, 2008 **Level II**). Similarly, in patients undergoing hip arthroplasty, preoperative administration of parecoxib offered no advantage compared with postoperative use; opioid-sparing was again seen in both groups compared with placebo (Martinez et al, 2007 **Level II**). Pain relief was also no better when parecoxib was given before incision compared with administration at the end of surgery in patients undergoing colorectal surgery (Lee et al, 2008 **Level II**).

## Adverse effects

### Renal function

COX-2 is constitutively expressed in the kidney and is highly regulated in response to alterations in intravascular volume. COX-2 has been implicated in maintenance of renal blood flow, mediation of renin release and regulation of sodium excretion (Cheng & Harris, 2004 **Level IV**; Kramer et al, 2004 **Level IV**).

Coxibs and nsNSAIDs have similar adverse effects on renal function (Curtis et al, 2004 **Level I**). A statistically significant increased risk of renal failure was reported following administration of

---

<sup>6</sup> This systematic review includes a study or studies that have since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. While reanalysis of the data would be required to confirm the conclusions, in this instance, expert advice suggested that withdrawal of the retracted articles would not influence the results. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) re-examined the data included in this review. While unable to reach a unanimous agreement as to whether exclusion of the retracted papers would have altered any of the conclusions, their disagreement did not concern the statement above to which this reference is attached but referred to specific comments about rofecoxib.

<sup>7</sup> This meta-analysis includes a study or studies that have since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. Expert advice suggested that withdrawal of the retracted articles would not influence the conclusions but that reanalysis would be required for this to be confirmed. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data included in this meta-analysis after excluding that obtained from the retracted publications. They concluded that removal of this information did not significantly alter the results.



coxibs in cardiac surgery patients (NNH 73) (Elia et al, 2005 **Level I**). An analysis of the effects of different coxibs on renal function showed that a COX-2 inhibitor class effect was not evident as rofecoxib was associated with an increased risk of renal dysfunction while celecoxib was not (Zhang et al, 2006 **Level I**).

### **Platelet function**

Platelets produce only COX-1, not COX-2, and as a corollary coxibs do not impair platelet function (Munsterhjelm et al, 2006 **Level II**). The use of rofecoxib reduced surgical blood loss in comparison with diclofenac (Hegi et al, 2004 **Level II**).

### **Cardiovascular effects**

Information relating to the cardiovascular (CV) risks associated with the use of nsNSAIDs and coxibs is derived from long-term treatment data and may not reflect the risk of short-term use in the acute pain setting.

In a comparison of drug groups, there was no difference in the incidence of CV complications with nsNSAIDs compared with coxibs (Moore et al, 2007 **Level I**). However, there may be differences between different drugs in each class, although the evidence is conflicting.

One meta-analysis failed to show any difference in the risk of CV events between celecoxib and placebo or between celecoxib and nsNSAIDs (White WB et al, 2007 **Level I**) but another concluded that the risk was less with celecoxib and valdecoxib compared with nsNSAIDs as a group (Moore et al, 2007 **Level I**). Yet another study reported that coxibs were associated with a moderate increase in the risk of CV events, as were high dose regimens of ibuprofen and diclofenac, but not high doses of naproxen (Kearney et al, 2006 **Level I**). The American Heart Association has identified naproxen as the preferred NSAID for long-term use in patients with or at high risk for cardiovascular disease (Antman et al, 2007).

A large case-controlled study using a general practice database identified 9218 patients over 4 years with a 'first ever' diagnosis of myocardial infarction and compared them with matched controls (Hippisley-Cox & Coupland, 2005 **Level III-3**). Where individual drugs were specified in the results, the risks were significantly increased for patients using rofecoxib, diclofenac and ibuprofen but not those taking celecoxib. Systematic reviews of case-control and cohort studies also found that celecoxib in commonly used doses may not increase the CV risk but confirmed an increased risk with diclofenac and rofecoxib (Hernandez-Diaz et al, 2006 **Level I**; McGettigan & Henry, 2006 **Level I**).

An increase in the incidence of cerebrovascular and CV events in patients given parecoxib, then valdecoxib after coronary artery bypass graft (CABG) surgery has also been reported (Nussmeier et al, 2005 **Level II**). Therefore, their use is contraindicated after this type of surgery. However, short-term use of parecoxib and/or valdecoxib after non-cardiac surgery does not increase the risk of CV adverse events (Schug et al, 2009 **Level I**).

The FDA concluded that 'Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately postoperative from coronary artery bypass surgery)' (FDA, 2005).

It is possible that some nsNSAIDs may inhibit the protective effect of aspirin. Ibuprofen but not diclofenac may abolish the benefits of aspirin (MacDonald & Wei, 2003 **Level III-3**; Hudson et al, 2005 **Level III-3**). The FDA issued a caution about the concomitant use of ibuprofen and immediate-release preparations (not enteric coated) of aspirin saying that 'At least 8 hours should elapse after ibuprofen dosing, before giving aspirin, to avoid significant interference'; insufficient data were available to make any recommendations on the use of enteric coated aspirin (FDA, 2006).



## ***Gastrointestinal***

GI complications are less likely with use of coxibs compared with nsNSAIDs; the incidence was lowest with celecoxib and valdecoxib (Moore et al, 2007 **Level I**).

Short-term use of parecoxib as required to treat acute pain results in gastroscopic ulcer rates similar to placebo, even in elderly patients at increased risk, in contrast to increased rates of ulceration with nsNSAIDs in the same setting (Harris et al, 2001 **Level II**; Stoltz et al, 2002 **Level II**; Goldstein et al, 2003 **Level II**).

The best gastroprotective strategy was the combination of a coxib and a PPI (Targownik et al, 2008 **Level III-2**). In high-risk populations, ulcer recurrence can be avoided even in long-term therapy by combining a coxib (celecoxib) with a PPI (Chan et al, 2007 **Level II**).

## ***Aspirin-exacerbated respiratory disease***

Investigation of patients with AERD has provided encouraging evidence that coxibs, administered at analgesic doses, do not produce bronchospasm in these patients (Martin-Garcia et al, 2003 **Level II**; West & Fernandez, 2003 **Level I**).

## ***Bone healing***

At present, data on the effect of coxibs on bone healing are mainly limited to animal models. There is no good evidence of any clinically significant inhibitory effect of coxibs on bone healing (Gerstenfeld & Einhorn, 2004; Bandolier, 2004).

### **Key messages**

1. Paracetamol is an effective analgesic for acute pain; the incidence of adverse effects comparable to placebo (**S**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs are effective in the treatment of acute postoperative and low back pain, renal colic and primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
3. Coxibs are effective in the treatment of acute postoperative pain (**N**) (**Level I** [Cochrane Review]).
4. With careful patient selection and monitoring, the incidence of nsNSAID-induced perioperative renal impairment is low (**U**) (**Level I** [Cochrane Review]).
5. Non-selective NSAIDs do not increase the risk of reoperation for bleeding after tonsillectomy in paediatric patients (**Q**) (**Level I** [Cochrane Review]).
6. Coxibs do not appear to produce bronchospasm in individuals known to have aspirin-exacerbated respiratory disease (**U**) (**Level I**).
7. In general, aspirin increases bleeding after tonsillectomy (**N**) (**Level I**).
8. Non-selective NSAIDs given in addition to paracetamol improve analgesia compared with paracetamol alone (**U**) (**Level I**).
9. Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related side effects (**N**) (**Level I**).
10. Non-selective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea, vomiting and sedation (**N**) (**Level I**).
11. Non-selective NSAIDs and coxibs are effective analgesics of similar efficacy for acute pain (**U**) (**Level I**).
12. Preoperative coxibs reduce postoperative pain and opioid consumption, and increase patient satisfaction (**N**) (**Level I**).

13. Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related side effects (**N**) (**Level I**).
14. Coxibs and non-selective NSAIDs have similar adverse effects on renal function (**U**) (**Level I**).
15. Non-selective NSAIDs do not significantly increase blood loss after tonsillectomy but do increase the need for reoperation due to bleeding (**N**) (**Level I**).
16. Parecoxib and/or valdecoxib compared with placebo do not increase the risk of cardiovascular adverse events after non-cardiac surgery (**N**) (**Level I**).
17. Coxibs and non-selective NSAIDs are associated with similar rates of adverse cardiovascular effects, in particular myocardial infarction; naproxen may be associated with a lower risk than other non-selective NSAIDs and celecoxib may be associated with a lower risk than other coxibs and non-selective NSAIDs overall (**N**) (**Level I**).
18. Perioperative non-selective NSAIDs increase the risk of severe bleeding after a variety of other operations compared with placebo (**N**) (**Level II**).
19. Coxibs do not impair platelet function; this leads to reduced perioperative blood loss in comparison with non-selective NSAIDs (**S**) (**Level II**).
20. Short-term use of coxibs results in gastric ulceration rates similar to placebo (**U**) (**Level II**).
21. Use of parecoxib followed by valdecoxib after coronary artery bypass surgery increases the incidence of cardiovascular events and is therefore contraindicated (**S**) (**Level II**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Adverse effects of NSAIDs are significant and may limit their use (**U**).
- The risk of adverse renal effects of non-selective NSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension, use of other nephrotoxic agents and ACE inhibitors (**U**).

## 4.3 ADJUVANT DRUGS

### 4.3.1 Inhalational agents

#### **Nitrous oxide**

Nitrous oxide (N<sub>2</sub>O) has been used since the inception of anaesthesia for its modest analgesic and sedative properties, with minimal respiratory and cardiovascular depression. In many countries it is available as a 50% N<sub>2</sub>O /50% oxygen mixture called Entonox®. While it has a long history of use, there is a paucity of good studies examining its effectiveness in comparison with other analgesics.

In adults, N<sub>2</sub>O in oxygen has some analgesic efficacy in labour (Rosen, 2002 **Level I**) and is effective during painful procedures such as bone marrow aspiration (Gudgin et al, 2008 **Level III-3**), venous cannulation (Gerhardt et al, 2001 **Level II**), sigmoidoscopy (Harding & Gibson, 2000 **Level II**) and liver biopsy (Castera et al, 2001 **Level II**), and in relieving acute ischaemic chest pain (O'Leary et al, 1987 **Level II**). In elderly patients (median age 84 years), N<sub>2</sub>O provided better analgesia than morphine during bed sore and ulcer care (Paris et al, 2008 **Level II**).

In children, N<sub>2</sub>O was effective in reducing pain associated with IV cannulation (Henderson et al, 1990 **Level II**; Hee et al, 2003 **Level III-2**; Ekbom et al, 2005 **Level III-2**), urethral catheterisation (Zier et

al, 2007 **Level III-2**), and laceration repair (Burton et al, 1998 **Level II**; Luhmann et al, 2006 **Level II**). It has been reported to provide analgesia for the pain associated with fracture manipulation in children (Gregory & Sullivan, 1996 **Level III-1**; Evans et al, 1995 **Level III-1**), although its efficacy as an analgesic during very painful procedures may be limited (Babl et al, 2008 **Level IV**).

In the experimental setting, a study measuring changes in detection and pain thresholds to electrical tooth stimulation, reported the development of acute and chronic tolerance in response to single and repeated administration of N<sub>2</sub>O (38% or 35%) for 30 minutes (Ramsay et al, 2005 **Level II**). The significance of this finding in the clinical setting is unknown.

N<sub>2</sub>O diffuses more rapidly than nitrogen and can expand enclosed air-containing spaces within the body. Its use is therefore contraindicated in the presence of a pneumothorax, obstruction of middle ear and sinus cavities, recent vitreoretinal surgery, pneumocephalus, bowel obstruction and gas embolism (Shaw & Morgan, 1998).

### **Toxicity**

N<sub>2</sub>O oxidises the cobalt ion of cobalamin (vitamin B12) preventing it from acting as a coenzyme for methionine synthetase (MS); MS also requires 5-methyltetrahydrofolate as a coenzyme (Sanders et al, 2008). MS is required for the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), and therefore the production of rapidly dividing tissues such as bone marrow and GI mucosa, as well as the synthesis of myelin (Sanders et al, 2008).

Bone marrow and neurological complications have been reported in patients exposed to N<sub>2</sub>O. The risk may be greater in critically ill patients with increased metabolic demands or poor nutrition (Amos et al, 1982 **Level IV**).

N<sub>2</sub>O-induced bone marrow toxicity leading to megaloblastic anaemia is usually progressive but reversible. The bone marrow changes are almost completely prevented by administration of folic acid (Amos et al, 1982).

Neurotoxicity associated with N<sub>2</sub>O use is rare but can be rapid and may be irreversible.

Patients deficient in vitamin B12, including those with a subclinical deficiency (ie without an associated anaemia), may develop a severe and progressive myeloneuropathy even after brief exposure to N<sub>2</sub>O. There are many examples of such case reports (Schilling, 1986; Holloway & Alberico, 1990; Flippo & Holder, 1993; Kinsella & Green, 1995; Nestor & Stark, 1996; Rosener & Dichgans, 1996; Sesso et al, 1999; Marie et al, 2000; Waters et al, 2005; Cartner et al, 2007; Wu et al, 2007; Meyers & Judge, 2008; Singer et al, 2008; Somyreddy & Kothari, 2008). Those at risk of vitamin B12 deficiency include some vegetarians (in particular vegans), the newborn of vegetarian mothers, patients with GI pathology, elderly people or patients taking PPIs and H2 blockers, and alcoholics (Schilling, 1986; Rosener & Dichgans, 1996; Nilsson-Ehle, 1998; Schenk et al, 1999; Carmel, 2000; McNeely et al, 2000; Sanders et al, 2008). In individuals who are not vitamin B12 deficient, larger quantities or more prolonged use of N<sub>2</sub>O seems to be required before neurotoxicity is seen. Examples have been reported in those abusing the drug (Sanders et al, 2008).

The neuropathy appears to be the result of decreased methionine and subsequent defective myelin formation. The clinical and radiological (magnetic resonance imaging [MRI]) picture is that of a vitamin B12 deficiency where subacute combined degeneration (SACD) of the spinal cord causes numbness, tingling, paresthesiae, ataxia and spasticity (Weimann, 2003). Involvement of peripheral, autonomic and central nervous systems may also lead to incontinence, diplopia, confusion or impaired cognitive function (Weimann, 2003). In patients with pernicious anaemia, SACD usually responds well to treatment with vitamin B12, although it may take many months and response to treatment may be incomplete (Toh et al, 1997). Patients with SACD related to N<sub>2</sub>O exposure may sometimes show improvement after

administration of vitamin B12 +/- methionine (Wu et al, 2007; Meyers & Judge, 2008; Singer et al, 2008) although this is not always the case.

In monkeys exposed continuously to N<sub>2</sub>O, SADC is prevented by a diet supplemented with methionine (Scott et al, 1981) and in cultured human fibroblasts, a methionine-rich media diminished the rate of MS activation (Christensen & Ueland, 1993). Despite the lack of any good data assessing efficacy in humans, and even though the bone marrow changes are usually reversible, it may be reasonable to give patients repeatedly exposed to N<sub>2</sub>O, vitamin B12 and folic or folinic acid supplements (Weimann, 2003).

Another consequence of N<sub>2</sub>O-induced inactivation of MS is elevation of plasma homocysteine (a known risk factor for coronary artery and cerebrovascular disease), the levels of which rise after anaesthesia using N<sub>2</sub>O (Badner et al, 1998 **Level II**; Myles, Chan, Leslie et al, 2008 **Level II**; Nagele et al, 2008 **Level III-3**). Patients who are homozygous for polymorphisms in the gene encoding the enzyme that is an antecedent to MS are at a higher risk of developing abnormal plasma homocysteine concentrations after N<sub>2</sub>O anaesthesia (Nagele et al, 2008 **Level III-3**). A subset analysis of data from a large trial of 2050 patients — the ENIGMA trial (Myles et al, 2007) — found a relationship between increased plasma homocysteine levels and all major postoperative complications (Myles, Chan, Leslie et al, 2008 **Level II**) as well as marked impairment of endothelial function (Myles, Chan, Kaye et al, 2008 **Level II**). However, the ENIGMA study looked at patients who were undergoing major surgery that lasted for 2 hours or longer and were given N<sub>2</sub>O in a concentration of 70% (compared with a nitrous-free anaesthetic), and not at N<sub>2</sub>O used as an analgesic agent in a non-operative setting. The significance of this in respect to N<sub>2</sub>O use in this group of patients is unknown.

Methionine given preoperatively to patients undergoing N<sub>2</sub>O anaesthesia improved the rate of recovery of MS and prevented the prolonged postoperative rise in plasma homocysteine concentrations (Christensen et al, 1994 **Level IV**). Preoperative administration of oral B vitamins (folate, B6 and B12) also prevent the postoperative increase in homocysteine following N<sub>2</sub>O anaesthesia (Badner et al, 2001 **Level II**).

The information about the complications of N<sub>2</sub>O comes from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to N<sub>2</sub>O in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to N<sub>2</sub>O. Nevertheless, the severity of the potential problems requires highlighting. The suggestions for the use of N<sub>2</sub>O outlined below are extrapolations only from the information above.

### ***Suggestions for the use of nitrous oxide as an analgesic***

When N<sub>2</sub>O is to be used repeatedly for painful short procedures, it may be reasonable to:

- exclude patients with a known vitamin B12 deficiency;
- screen patients at risk of B12 deficiency by examination of the blood picture and serum B12 concentrations before using N<sub>2</sub>O;
- exclude asymptomatic patients with macrocytic anaemia or hypersegmentation of neutrophils until it is established that vitamin B12 or folate deficiency is not the cause;
- exclude females who may be in the early stages of pregnancy, although this will depend on the relative harm of any alternative methods;
- limit exposure to N<sub>2</sub>O to the briefest possible time — restricting the duration of exposure may require strict supervision and limited access to the gas;

- administer methionine, vitamin B12 (both inexpensive and with a good safety profile) and possibly folic or folinic acid to patients repeatedly exposed to N<sub>2</sub>O. The doses that may prevent the complications of exposure to N<sub>2</sub>O have not been established; and
- monitor for clinical signs and symptoms of neuropathy on a regular basis.

### **Methoxyflurane**

Methoxyflurane is a volatile anaesthetic agent with analgesic properties. It was first marketed in 1962 and later withdrawn from sale in 2001. The FDA withdrew the drug because of the risk of nephrotoxicity and hepatotoxicity and stated that it would not consider reintroduction into the market until new clinical trials were undertaken (FDA-Penthrane, 2005). Methoxyflurane is also not licensed in the United Kingdom. Although no longer used as an anaesthetic, methoxyflurane has been reintroduced into the health-care market in Australia and New Zealand for use as an analgesic, and is available as a self-administered ‘Penthrox®’ inhaler, which dispenses 0.2% to 0.4% methoxyflurane (Medical Devices International, 2009).

Methoxyflurane was first described for obstetric analgesia in 1966 (Bodley et al, 1966 **Level IV**) and then used as an analgesic for burns dressings (Packer & Titel, 1969 **Level IV**; Calverley, 1972 **Level IV**; Firm, 1972 **Level IV**; Marshall & Ozorio, 1972 **Level IV**).

There are few studies examining the effectiveness of methoxyflurane as an analgesic for painful procedures. A review of its use as an analgesic in prehospital and emergency care settings found a total of 48 relevant papers although all but one (an abstract only) were observational studies; however, this limited data would suggest that it is effective (Grindlay & Babl, 2009). For example, use of the Penthrox® inhaler in children reduced pain associated with extremity injuries (Babl et al, 2006 **Level IV**) but did not provide adequate analgesia for subsequent fracture manipulation (Babl et al, 2007 **Level IV**). It also provided effective pain relief for adult patients in the prehospital setting (Buntine et al, 2007 **Level IV**). Side effects included hallucinations, vomiting, confusion and dizziness, and sedation/drowsiness was common (26%) in children (Babl et al, 2006 **Level IV**; Buntine et al, 2007 **Level IV**).

Methoxyflurane causes a dose-dependent renal toxicity and, as noted above, renal failure was a key reason behind the withdrawal of the drug from use. Use of an analgesic device delivering higher concentrations of methoxyflurane was reported to have led to two fatalities from renal toxicity (Toomath & Morrison, 1987). However, the amount of methoxyflurane delivered using the Penthrox® inhaler is said to be significantly less than the dose that has been associated with subclinical nephrotoxicity (Grindlay & Babl, 2009).

#### **Key messages**

1. Nitrous oxide has some analgesic efficacy and is safe during labour (**U**) (**Level I**).
2. Nitrous oxide is an effective analgesic agent in a variety of other acute pain situations (**U**) (**Level II**).
3. Methoxyflurane, in low concentrations, may be an effective analgesia in the hospital and prehospital setting (**N**) (**Level IV**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Neuropathy and bone marrow suppression are rare but potentially serious complications of nitrous oxide use, particularly in at-risk patients (**U**).
- The information about the complications of nitrous oxide is from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to nitrous oxide in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to nitrous oxide. The suggestions for the use of nitrous oxide are extrapolations only from the information above. Consideration should be given to duration of exposure and supplementation with vitamin B12, methionine, and folic or folinic acid (**U**).
- If nitrous oxide is used with other sedative or analgesic agents, appropriate clinical monitoring should be used (**U**).

### 4.3.2 NMDA-receptor antagonists

NMDA receptor/ion channel complexes are sited peripherally and centrally within the nervous system (De Kock & Lavand'homme, 2007). Activation of NMDA receptors via glutamate release from excitatory synapses augments the propagation of nociceptive information and is linked to learning and memory, neural development and neuroplasticity, as well as acute and chronic pain states and opioid-induced tolerance. At the spinal level, NMDA receptor activation results in the development of central sensitisation manifested clinically as hyperalgesia and allodynia (De Kock & Lavand'homme, 2007; Hocking et al, 2007).

The NMDA-receptor antagonists ketamine, dextromethorphan, amantadine, memantine and magnesium have been investigated for the management of acute pain.

#### **Ketamine**

In low (sub-anaesthetic) doses, ketamine acts primarily as a non-competitive antagonist of the NMDA receptor, although it also binds to many other sites in the peripheral and central nervous systems (Visser & Schug, 2006; Hocking et al, 2007). The principal effect of ketamine at these doses is as an 'antihyperalgesic', 'antiallodynic' and 'antitolerance' agent and not as a primary analgesic *per se* (Hocking et al, 2007). Consequently, ketamine's main role is as an adjuvant in the treatment of pain associated with central sensitisation such as in severe acute pain, neuropathic pain and 'opioid-resistant' pain. It may also reduce the incidence of chronic postsurgical pain (CPSP) (see Section 9.1) and attenuate opioid-induced tolerance and hyperalgesia (see Section 11.7).

Ketamine may also be useful for the treatment of opioid-resistant or 'breakthrough' cancer pain and, in higher doses or combined with agents such as midazolam, it can provide effective and safe analgesia for painful procedures (see below).

Elia and Tramer (Elia & Tramer, 2005 **Level I**) reviewed a heterogeneous group of studies, with varying routes of ketamine administration (parenteral and non-parenteral) and dosing regimens. They found no clinically significant effect on pain scores for up to 48 hours after surgery (although the difference was significant up to 24 hours, pain scores were reduced, on average, by less than 1 cm on a 10 cm VAS). Despite demonstrating a significant (30%) opioid-sparing effect, there was no reduction in opioid-related adverse effects, including PONV.

Bell et al (Bell et al, 2006 **Level I**) also reviewed studies of ketamine given by a variety of routes at a variety of times relative to the surgery, but concentrated their meta-analysis on ketamine infusions used in conjunction with morphine PCA. They also reported opioid-sparing but, in

addition, showed a reduction in the incidence of PONV. Later studies, where continuous ketamine infusions were used for 48 hours after abdominal surgery, have shown similar results. One reported significantly reduced pain scores, PCA morphine consumption, nausea and vomiting, with no ketamine-related adverse effects, compared with placebo (Zakine et al, 2008 **Level II**). The other also reported lower PCA morphine requirements, better pain scores at rest and with movement, as well as less sedation; there were no differences in trail-making test times and errors, dreams or hallucinations (Webb et al, 2007 **Level II**). A 24-hour postoperative infusion of 83 mcg/kg/hr but not 42 mcg/kg/hr in addition to PCA fentanyl after cervical spine surgery was opioid-sparing and improved pain relief (Yamauchi et al, 2008 **Level II**). While concurrent administration of ketamine reduced PCA opioid requirements and the incidence of nausea and vomiting (Bell et al, 2006 **Level I**), there is conflicting evidence regarding the benefit derived from adding ketamine to the PCA opioid solution. In six studies where ketamine was added to the PCA opioid, results were mixed; pain was reduced in four of these studies and morphine consumption in three (Bell et al, 2006 **Level I**). Three more recent studies showed a lack of benefit after gynaecological (Aubrun et al, 2008 **Level II**) and orthopaedic surgery (Sveticic et al, 2008 **Level II**), or uterine artery embolisation (Jensen et al, 2008 **Level II**). In another, however, the addition of ketamine to morphine PCA reduced pain scores and the incidence of nausea and vomiting, was opioid-sparing, and led to shorter duration of use of PCA compared with PCA morphine alone (Kollender et al, 2008 **Level II**). In a study of post-thoracotomy patients, the addition of ketamine to morphine for PCA was opioid-sparing but failed to improve analgesia; however patients in the ketamine group had better respiratory parameters (Michelet et al, 2007 **Level II**).

Use of a low-dose IV ketamine infusion postoperatively significantly reduced acute pain in patients receiving epidural ropivacaine and morphine analgesia following thoracotomy (Suzuki et al, 2006 **Level II**).

Other outcomes have also been investigated. Parenteral ketamine improved rehabilitation after total knee arthroplasty (Adam et al, 2005 **Level II**). There was no significant difference in postoperative morphine consumption or area of stump allodynia between patients who received either a ketamine or saline infusion for 3 days after leg amputation; interestingly, the incidence of acute stump pain was significantly increased in the ketamine group (Hayes et al, 2004 **Level II**).

Based on these data, the 'routine' use of IV perioperative ketamine is not indicated and the place of ketamine in the treatment of chronic pain and the effects of long-term use remains unclear (Visser & Schug, 2006).

Bolus dose ketamine (0.25 mg/kg) was an effective 'rescue analgesic' in patients with acute postoperative pain that was poorly responsive to morphine (Weinbroum, 2003 **Level II**). In contrast, in a later study, the addition of bolus dose ketamine (0.25 mg/kg) to morphine for rescue analgesia in the recovery room failed to improve analgesia or reduce the incidence of nausea or vomiting (Gillies et al, 2007 **Level II**).

In the emergency department, ketamine used to treat severe trauma pain had a significant morphine-sparing effect without a change in pain scores (Galinski et al, 2007 **Level II**). A low-dose SC ketamine infusion provided better analgesia for acute musculoskeletal trauma pain with less nausea, vomiting and sedation, and improved respiratory function, than intermittent SC morphine injections (Gurnani et al, 1996 **Level II**). Ketamine-midazolam mixtures used for fracture reductions in paediatric patients in the emergency department were associated with less distress and fewer airway interventions than fentanyl-midazolam or propofol-fentanyl combinations (Migita et al, 2006 **Level I**).



Low-dose parenteral ketamine may also improve analgesia in patients with opioid-induced tolerance or hyperalgesia. In patients taking opioids on a long-term basis, the administration of ketamine has been reported to lead to improved pain relief and reduced opioid requirements (Bell, 1999; Eilers et al, 2001; Mitra, 2008). After spinal fusion in opioid-tolerant patients, use of a continuous ketamine infusion resulted in significantly less pain but did not reduce PCA opioid requirements (Urban et al, 2008 **Level II**). The evidence for the ability of ketamine to attenuate the acute tolerance and/or OIH seen after intraoperative use of remifentanyl infusions is conflicting. Ketamine infusion reduced the area of punctate mechanical hyperalgesia around the wound and postoperative morphine consumption, following high-dose remifentanyl infusion during laparotomy (Joly et al, 2005 **Level II**). In paediatric scoliosis surgery, ketamine did not decrease postoperative morphine requirements after remifentanyl-based anaesthesia (Engelhardt et al, 2008 **Level II**).

Perioperative ketamine has 'preventive' (Katz & Clarke, 2008 **Level I**), but not 'pre-emptive' (Ong et al, 2005 **Level I**) analgesic effects in the immediate postoperative period. Ketamine reduced the area of wound hyperalgesia and allodynia after nephrectomy (Stubhaug et al, 1997 **Level II**) and laparotomy (De Kock et al, 2001 **Level II**). Perioperative ketamine administration reduced the incidence of CPSP following thoracotomy (Suzuki et al, 2006 **Level II**) and laparotomy (De Kock et al, 2001 **Level II**), possibly reflecting a prolonged 'preventive analgesia' effect. However, there was no significant effect on CPSP following total knee replacement (Adam et al, 2005 **Level II**) or radical prostatectomy (Katz et al, 2004 **Level II**), or on the incidence of phantom or stump pain 6 months after lower limb amputation (Hayes et al, 2004 **Level II**), although this latter study may have been underpowered.

Ketamine showed a significant analgesic effect in patients with neuropathic pain after spinal cord injury (Kvarnstrom et al, 2004 **Level II**).

#### ***Adverse effects with short-term systemic administration of ketamine***

The addition of low-dose ketamine did not alter the overall incidence of adverse effects compared with opioids alone (Elia & Tramer, 2005 **Level I**). When used in conjunction with PCA morphine, adverse effects were noted to be mild or absent (Bell et al, 2006 **Level I**).

#### ***Routes of systemic administration and bioavailability***

Ketamine is most commonly administered as a continuous low-dose intravenous infusion, however SC infusion is also used, especially in palliative care, with a bioavailability (similar to IM) of approximately 90% (Clements et al, 1982). Sublingual, intranasal (IN) and transdermal routes have also been used for acute pain management (see Section 6).

A pharmacokinetic study in healthy volunteers calculated the bioavailability of oral ketamine as 20%, sublingual 30% and IN 45%: the pharmacodynamic effects of the active metabolite norketamine were thought to be of potential significance (Yanagihara et al, 2003). The bioavailability of a 25 mg ketamine lozenge was 24% when given by both sublingual and oral routes; peak plasma levels were seen at 30 minutes and 120 minutes respectively and terminal half-lives were similar at around 5 hours (Chong et al, 2009). For both routes, norketamine concentrations exceeded the concentrations of ketamine, and given its pharmacological activity profile, norketamine is therefore likely to be a major contributor to the overall analgesic effect.

#### ***Dextromethorphan***

A review of dextromethorphan for perioperative analgesia concluded that while some studies showed a decrease in opioid consumption and opioid-related side effects, any reduction in pain was not clinically significant and that, 'the consistency of the potential opioid-sparing and pain reducing effect must be questioned' (Duedahl et al, 2006). A meta-analysis was not



performed because of the marked differences in methodology and reporting between trials (Duedahl et al, 2006 2006). However, a systematic review reported that dextromethorphan had 'preventive analgesia' effects (Katz & Clarke, 2008 **Level I**). A later study looking at the effect of four oral doses of dextromethorphan given over 24 hours to patients after abdominal hysterectomy showed better pain relief immediately after surgery but not later at 6 hours and 24 hours (Chau-In et al, 2007 **Level II**).

## **Magnesium**

Systematic reviews of perioperative magnesium, failed to find convincing evidence of improved analgesia (Lysakowski et al, 2007 **Level I**) or any 'preventive analgesic' effects (McCartney et al, 2004 **Level I**). Magnesium added to morphine for PCA was opioid-sparing and led to better pain relief (Unlugenc et al, 2003 **Level II**); added to tramadol it was opioid-sparing but only provided better pain relief for the first 2 hours (Unlugenc et al, 2002 **Level II**).

IV magnesium may be useful in the treatment of migraine, however the studies are contradictory (see Section 9.6.5 for details).

## **Amantadine and memantine**

A bolus dose of IV amantadine had no effect on postoperative analgesia after abdominal hysterectomy (Gottschalk et al, 2001 **Level II**). However perioperative oral amantadine reduced morphine consumption, wound pain on palpation and bladder spasms, after radical prostatectomy (Snijdelaar et al, 2004 **Level II**).

Oral memantine reduced the number of demands for bolus doses of ropivacaine for analgesia via a brachial plexus catheter and, in combination with a continuous ropivacaine infusion, led to a reduction in the incidence of phantom limb pain at 6 months but not 12 months, following traumatic upper limb amputation (Schley et al, 2007 **Level II**). It was not effective in reducing the incidence of postmastectomy pain syndrome (Eisenberg et al, 2007 **Level II**).

### **Key messages**

1. Perioperative low-dose ketamine used in conjunction with patient-controlled analgesia morphine is opioid-sparing and reduces the incidence of nausea and vomiting (**N**) (**Level I** [Cochrane Review]).
2. In general, a perioperative low-dose ketamine infusion is opioid-sparing, but does not produce a clinically significant reduction in pain scores or opioid-related adverse effects (**S**) (**Level I**).
3. Ketamine is a safe and effective analgesic for painful procedures in children (**N**) (**Level I**).
4. Ketamine and dextromethorphan have preventive (**U**) but not pre-emptive analgesic effects (**N**) (**Level I**).
5. Magnesium does not reduce postoperative pain scores or opioid consumption and has no preventive analgesic effect (**N**) (**Level I**).
6. Ketamine may improve analgesia in patients with severe acute pain that is poorly responsive to opioids, although evidence is conflicting (**W**) (**Level II**).
7. Ketamine reduces postoperative pain in opioid-tolerant patients (**N**) (**Level II**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- The primary role of low dose ketamine is as an 'antihyperalgesic', 'antiallodynic', 'tolerance-protective' and preventive analgesic, rather than as an analgesic *per se* (**N**).

### 4.3.3 Antidepressant drugs

There are no published data on the use of antidepressants in the management of acute neuropathic pain, however antidepressants are effective in the treatment of a variety of chronic neuropathic pain states (Collins, Moore, McQuay & Wiffen, 2000 **Level I**; Saarto & Wiffen, 2007 **Level I**; Sultan et al, 2008 **Level I**). When used for the management of pain, the onset of effect is more rapid than when these drugs are used to treat depression.

The updated Cochrane meta-analysis (Saarto & Wiffen, 2007 **Level I**<sup>8</sup>) looking at the use of antidepressant drugs in the treatment of neuropathic pain confirmed the effectiveness of tricyclic antidepressants (TCAs) but that there is very limited evidence for the role of selective serotonin reuptake inhibitor (SSRIs). This analysis also concluded that venlafaxine appears to be as effective as TCAs, but the result is no longer significant as one of the positive venlafaxine studies has subsequently been retracted.

See Table 4.1 for NNTs and NNHs.

**Table 4.1 Antidepressants for the treatment of neuropathic pain**

Efficacy	NNT (95% CI)
Overall	
TCAs	3.6 (3.0–4.5)
SSRIs	limited evidence of benefit
Duloxetine	5.8 (4.5–8.4)
Diabetic neuropathy	1.3 (1.2–1.5)
Postherpetic neuralgia	2.7 (2.0–4.1)
HIV-related neuropathies	no evidence of benefit
Minor adverse effects	NNH (95% CI)
Pooled diagnoses	
Amitriptyline	6.0 (4.2–10.7)
SSRIs	no dichotomous data available
Major adverse effects (withdrawal from study)	NNH (95% CI)
Pooled diagnoses	
Amitriptyline	28.0 (17.6–68.9)
Duloxetine	15 (11–25)
SSRIs	not different from placebo

Note: CI: confidence interval; TCA: tricyclic antidepressants; SSRI: selective serotonin re-uptake inhibitors.

Source: Adapted from Collins, Moore, McQuay & Wiffen (2000), Saarto & Wiffen (2007), Sultan et al 2008<sup>8</sup>

Currently the use of antidepressants for acute neuropathic pain is mainly based on extrapolation of the above data.

Amitriptyline (Kalso et al, 1996 **Level II**) but not venlafaxine (Tasmuth et al, 2002 **Level II**) was effective in the treatment of neuropathic pain following breast surgery, however the amitriptyline side effects were not well-tolerated. Amitriptyline given to patients with herpes zoster reduced the incidence of postherpetic neuralgia at 6 months (Bowsher, 1997 **Level II**).

<sup>8</sup> This meta-analysis includes a study on venlafaxine that has since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. Independent reanalysis of this meta-analysis using a random effects model ( $I^2 = 51.3\%$ ) shows RR 1.87 (95% CI 0.66–5.30). The results for venlafaxine are no longer significant and have been excluded from Table 4.1.

Amitriptyline also provided good control of phantom limb pain and stump pain in amputees (Wilder-Smith et al, 2005 **Level III-1**). There was no significant difference in pain or disability with amitriptyline compared with placebo in spinal cord injury patients with chronic pain (Cardenas et al, 2002 **Level II**), however amitriptyline improved below-level neuropathic pain in patients with depression (Rintala et al, 2007 **Level II**). There are no studies of SSRIs in the treatment of central pain (Sindrup & Jensen, 1999 **Level I**).

Duloxetine is effective for the treatment of both painful diabetic neuropathy and fibromyalgia (Sultan et al, 2008 **Level I**).

There are very limited data on the use of antidepressants in acute nociceptive pain. Desipramine given prior to dental surgery increased and prolonged the analgesic effect of a single dose of morphine but had no analgesic effect in the absence of morphine (Levine et al, 1986 **Level II**). However, when used in experimental pain, desipramine had no effect on pain or hyperalgesia (Wallace et al, 2002 **Level II**). Amitriptyline given prior to dental surgery (Levine et al, 1986 **Level II**) or after orthopaedic surgery (Kerrick et al, 1993 **Level II**) did not improve morphine analgesia.

There is no good evidence that antidepressants given to patients with chronic low back pain improve pain relief (Urquhart et al, 2008 **Level I**).

**Note: reversal of conclusions**

This reverses the Level 1 conclusion in the previous edition of this document; an earlier meta-analysis had reported improved pain relief.

However, this and the earlier meta-analysis did not differentiate between TCAs and SSRIs, and the former have been shown to be effective compared with the latter (Staiger et al, 2003 **Level I**). There is good evidence for antidepressants in the treatment and prophylaxis of chronic headaches (Tomkins et al, 2001 **Level I**).

Clinical experience in chronic pain suggests that TCAs should be started at low doses (eg amitriptyline 5 to 10 mg at night) and subsequent doses increased slowly if needed, in order to minimise the incidence of adverse effects.

**Key messages**

1. In neuropathic pain, tricyclic antidepressants are more effective than selective serotonergic re-uptake inhibitors (**S**) (**Level I** [Cochrane Review]).
2. Duloxetine is effective in painful diabetic neuropathy and fibromyalgia (**N**) (**Level I** [Cochrane Review]).
3. There is no good evidence that antidepressants are effective in the treatment of chronic low back pain (**R**) (**Level I** [Cochrane Review]).
4. Tricyclic antidepressants are effective in the treatment of chronic headaches (**U**) and fibromyalgia (**N**) (**Level I**).
5. Antidepressants reduce the incidence of chronic neuropathic pain after herpes zoster (**U**) (**Level II**).

**Note: withdrawal of previous key message:**

*Antidepressants reduce the incidence of chronic neuropathic pain after breast surgery*  
This has been deleted as the information and evidence supporting it has been withdrawn.

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- Based on the experience in chronic neuropathic pain states, it would seem reasonable to use tricyclic antidepressants and selective serotonin re-uptake inhibitors in the management of acute neuropathic pain (**S**).
- To minimise adverse effects, particularly in elderly people, it is advisable to initiate treatment with low doses (**U**).

#### 4.3.4 Anticonvulsant drugs

##### **Specific anticonvulsant agents used in the treatment of acute pain**

###### ***Gabapentinoids (gabapentin/pregabalin)***

A number of meta-analyses have shown that perioperative gabapentinoids improved analgesia (at rest and with movement) and reduced postoperative opioid consumption, but increased the incidence of sedation compared with placebo (Ho et al, 2006 **Level I**; Hurley et al, 2006 **Level I**; Peng et al, 2007 **Level I**; Tiippana et al, 2007 **Level I**). Three of these meta-analyses (Ho et al, 2006 **Level I**; Peng et al, 2007 **Level I**; Tiippana et al, 2007 **Level I**) also reported a decrease in vomiting and pruritus; the NNT was 25 for nausea, 6 for vomiting and 7 for urinary retention (Tiippana et al, 2007 **Level I**). The effects of gabapentin were not dose-dependent in the range of 300 to 1200 mg. (Tiippana et al, 2007 **Level I**). After hysterectomy and spinal surgery specifically, gabapentin improved pain relief and was opioid-sparing, nausea was less in patients after hysterectomy, and there was no difference in sedation (Mathiesen et al, 2007 **Level I**).

Trials analysed in these meta-analyses used a wide variety of gabapentin dosing regimens. It is therefore not possible to recommend a particular regimen and furthermore, conclusions cannot be drawn regarding optimal treatment duration or potential long-term benefits (such as reduced CPSP).

Used as an adjunct to epidural analgesia, perioperative gabapentin reduced pain scores and epidural analgesic requirements and improved patient satisfaction, despite an increase in dizziness (Turan et al, 2006 **Level II**).

Gabapentin reduced pain and opioid consumption following acute burns (Cuignet et al, 2007 **Level III-3**) and reduced neuropathic pain descriptors in a small case series of patients with burns injuries (Gray et al, 2008 **Level IV**). Pregabalin reduced the intensity of itch and the Neuropathic Pain Scale descriptor of 'hot pain' (Gray et al, 2008 **Level II**). It was also effective for the treatment of neuropathic pain caused by traumatic or postsurgical nerve injury (Gordh et al, 2008 **Level II**). The incidence and intensity of postamputation pain was not reduced by gabapentin administered in the first 30 days after amputation (Nikolajsen, Finnerup et al, 2006 **Level II**).

###### ***Sodium valproate***

Sodium valproate did not improve acute nociceptive pain after surgery (Martin et al, 1988 **Level II**) and IV sodium valproate was ineffective in treating acute migraine (Tanen et al, 2003 **Level II**).

##### **Specific anticonvulsant agents used in the treatment of chronic pain**

###### ***Carbamazepine***

A review of carbamazepine for the treatment of chronic neuropathic pain calculated a NNT of 1.8 (CI 1.4 to 2.8) for relief of trigeminal neuralgia; there were insufficient data for a NNT for painful diabetic neuropathy to be calculated. The NNH for a minor adverse effect compared

with placebo was 3.7 (CI 2.4 to 7.8); the NNH for a major adverse event was insignificant (Wiffen, McQuay & Moore, 2005 **Level I**).

### **Phenytoin**

A review of phenytoin for the treatment of chronic neuropathic pain calculated a NNT of 2.1 (CI 1.5 to 3.6) for painful diabetic neuropathy. The NNH for a minor adverse effect compared with placebo was 3.2 (CI 2.1 to 6.3); the NNH for a major adverse event was not significant (Wiffen, Collins et al, 2005 **Level I**).

### **Gabapentin**

A review of gabapentin for the treatment of chronic neuropathic pain calculated a NNT of 4.3 (CI 3.5 to 5.7) overall; the NNTs for painful diabetic neuropathy and postherpetic neuralgia were 2.9 (CI 2.2 to 4.3) and 3.9 (CI 3 to 5.7) respectively (Wiffen, McQuay, Edwards et al, 2005 **Level I**). The NNH for a minor adverse effects compared with a placebo was 3.7 (CI 2.4 to 5.4); the NNH for a major adverse event was not significant. Gabapentin was effective in the treatment of phantom limb pain (Bone et al, 2002 **Level I**) and smaller later trials support the effectiveness of gabapentin in the treatment of central pain after spinal cord injury (Levendoglu et al, 2004 **Level II**; Tai et al, 2002 **Level II**).

### **Pregabalin**

Pregabalin was effective for the management of pain related to diabetic neuropathy (Hurley et al, 2008 **Level I**; Gutierrez-Alvarez et al, 2007 **Level I**) with an NNT of 3.24 (Gutierrez-Alvarez et al, 2007 **Level I**) and an increased risk of sedation and dizziness (Hurley et al, 2008 **Level I**). Pregabalin was effective for persistent neuropathic spinal cord injury pain (Siddall et al, 2006 **Level II**).

### **Sodium valproate**

Sodium valproate was effective for the prevention of migraine (Mulleners & Chronicle, 2008 **Level I**) but ineffective in the treatment of spinal cord injury pain (Drewes et al, 1994 **Level II**).

### **Lamotrigine**

A review of lamotrigine concluded that it was unlikely to be of benefit for the treatment of neuropathic pain (Wiffen & Rees, 2007 **Level I**).

### **Key messages**

1. Gabapentin is effective in the treatment of chronic neuropathic pain (**Q**); lamotrigine is most likely ineffective (**N**) (**Level I** [Cochrane Review]).
2. Carbamazepine is effective in the treatment of trigeminal neuralgia (**N**) (**Level I** [Cochrane Review]).
3. Pregabalin is effective in the treatment of chronic neuropathic pain related to diabetic neuropathy (**N**) (**Level I**).
4. Perioperative gabapentinoids (gabapentin/ pregabalin) reduce postoperative pain and opioid requirements (**U**) and reduce the incidence of vomiting, pruritus and urinary retention, but increase the risk of sedation (**N**) (**Level I**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Based on the experience in chronic neuropathic pain states, it would seem reasonable to use anticonvulsants in the management of acute neuropathic pain (**U**).

### 4.3.5 Membrane stabilisers

Perioperative IV lignocaine (lidocaine) infusion was opioid-sparing and significantly reduced pain scores, nausea, vomiting and duration of ileus up to 72 hours after abdominal surgery and also reduced length of hospital stay (Marret et al, 2008 **Level I**). The addition of lignocaine to morphine PCA conferred no benefit in terms of pain relief or side effects (Cepeda et al, 1996 **Level II**).

Intraoperative epidural lignocaine infusion resulted in significantly lower use of patient-controlled epidural analgesia (PCEA) and earlier return of bowel function in the 72 hours following colectomy compared with IV lignocaine; however the latter was still significantly better than placebo (Kuo et al, 2006 **Level II**). Mexiletine improved pain relief and reduced analgesic requirements after breast surgery (Fassoulaki et al, 2002 **Level II**).

IV lignocaine has been used to provide analgesia for burns procedures, however a Cochrane review reported that more trials were required to determine its efficacy (Wasiak & Cleland, 2007 **Level I**).

The efficacy of lignocaine in the treatment of acute migraine is unclear. Analgesia provided by IV lignocaine was similar to dihydroergotamine, but not as effective as chlorpromazine (Bell et al, 1990 **Level II**) and in one trial no better than placebo (Reutens et al, 1991 **Level II**). Results for IN lignocaine are conflicting (Maizels et al, 1996 **Level II**; Blanda et al, 2001 **Level II**).

Under experimental conditions, IV lignocaine reduced neuropathic pain in spinal cord injury (Finnerup et al, 2005 **Level II**) and reduced spontaneous pain and brush allodynia in central pain (Attal et al, 2000 **Level II**). Also after spinal cord injury, lignocaine reduced pain in only one of ten patients (Kvarnstrom et al, 2004 **Level II**); mexiletine did not reduce dysesthetic pain (Chiou-Tan et al, 1996 **Level II**).

Both lignocaine and mexiletine were more effective than placebo in treating chronic neuropathic pain, however there was no difference in efficacy or adverse effects when compared with carbamazepine, amantadine, or morphine (Challapalli et al, 2005 **Level I**). There was strong evidence of benefit for use of membrane stabilisers in pain due to peripheral nerve trauma (Kalso et al, 1998 **Level I**). Stump pain but not phantom pain was reduced by IV lignocaine (Wu et al, 2002 **Level II**).

Currently, the use of membrane stabilisers for acute neuropathic pain can only be based on extrapolation of the above data.

#### Key messages

1. Both lignocaine (lidocaine) and mexiletine are effective in the treatment of chronic neuropathic pain (**S**); there is no difference in efficacy or adverse effects compared with carbamazepine, amantadine, or morphine (**N**) (**Level I** [Cochrane Review]).
2. Perioperative intravenous lignocaine reduces pain and opioid requirements following abdominal surgery (**S**) as well as nausea, vomiting, duration of ileus and length of hospital stay (**N**) (**Level I**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- Based on the experience in chronic neuropathic pain states, it would seem reasonable to use membrane stabilisers in the management of acute neuropathic pain (**U**).
- Lignocaine (intravenous or subcutaneous) may be a useful agent to treat acute neuropathic pain (**U**).

### 4.3.6 Alpha-2 agonists

Systemic administration (oral, IM, IV) of single doses of the alpha-2 agonists clonidine (Bernard et al, 1991 **Level II**; De Kock et al, 1992 **Level II**; Park et al, 1996 **Level II**); and dexmedetomidine (Aho et al, 1991 **Level II**; Jalonen et al, 1997 **Level II**; Arain et al, 2004 **Level II**) decreased perioperative opioid requirements in surgical patients.

The addition of clonidine to morphine for PCA significantly improved postoperative analgesia (for the first 12 hours only) with less nausea and vomiting compared with morphine alone; however there was no reduction in morphine requirements (Jefferies et al, 2002 **Level II**). Higher doses of clonidine resulted in a significant reduction in opioid requirements but a greater degree of sedation and hypotension (Marinangeli et al, 2002 **Level II**).

Intraoperative dexmedetomidine infusion significantly reduced opioid requirements, nausea, vomiting and itch, but not pain or sedation scores compared with placebo, for up to 48 hours after abdominal hysterectomy (Gurbet et al, 2006 **Level II**). A combination of dexmedetomidine and morphine for PCA resulted in significantly better pain relief, a lower incidence of nausea but not vomiting and significant opioid-sparing compared with morphine alone (Lin et al, 2009 **Level II**).

In the intensive care setting, IV dexmedetomidine infusions used for sedation of ventilated patients resulted in a 50% reduction in morphine requirements (Venn et al, 1999 **Level II**).

#### Key message

1. The use of systemic alpha-2-agonists consistently improves perioperative opioid analgesia but the frequency and severity of side effects may limit their clinical usefulness (**U**) (**Level II**).

### 4.3.7 Salmon calcitonin and bisphosphonates

#### Calcitonin

Calcitonin is a 32 amino acid peptide hormone that regulates calcium homeostasis in vertebrates. It also has analgesic properties, primarily through receptor-mediated modulation of serotonergic activity in pain pathways of the central nervous system. Salmon calcitonin has a greater potency than mammalian forms of the hormone and is therefore reproduced as a synthetic drug for pharmaceutical use. The adverse effects of calcitonin therapy such as sedation, nausea, skin flushing and diarrhoea may reflect increased serotonergic activity. In rodents, the 5HT<sub>3</sub> antagonist tropisetron reduced its analgesic efficacy, which may be relevant in humans during the treatment of nausea and vomiting (Visser, 2005).

Salmon calcitonin, (IV, SC, IM, IN or rectal) reduces acute pain at rest and on movement and improves mobilisation (in 7 to 28 days) in patients with osteoporotic vertebral fractures and side effects are usually minor and mainly gastrointestinal (Blau & Hoehns, 2003 **Level I**; Knopp et al, 2005 **Level I**).

IV (and likely SC) salmon calcitonin is effective in the treatment of acute phantom limb pain (Jaeger & Maier, 1992 **Level II**). However, it was not effective for chronic phantom limb pain (Eichenberger et al, 2008 **Level II**).

A meta-analysis concluded that salmon calcitonin was beneficial in the treatment of chronic regional pain syndrome (CRPS) (Perez et al, 2001 **Level I**). However, the two placebo-controlled trials of the five in the meta-analysis produced conflicting results. A more recent study found that calcitonin was no more effective than paracetamol in improving pain and function in CRPS over a 2-month period in patients receiving physical therapy following upper limb trauma (Sahin et al, 2006 **Level II**).

The limited evidence available does not support the effectiveness of salmon calcitonin in the treatment of acute and persistent metastatic bone pain (Martinez-Zapata et al, 2006 **Level I**).

### **Bisphosphonates**

IV pamidronate (3 daily doses) reduced pain associated with acute osteoporotic vertebral fractures for up to 30 days post-treatment (Armingeat et al, 2006 **Level II**).

Bisphosphonates reduced sub-acute bone pain associated with metastatic carcinoma of the breast (Pavlakis et al, 2005 **Level I**) or prostate (Yuen et al, 2006 **Level I**) and in multiple myeloma (Djulbegovic et al, 2002 **Level I**).

#### **Key messages**

1. Bisphosphonates reduce bone pain associated with metastatic cancer and multiple myeloma (**N**) (**Level I** [Cochrane Review]).
2. Salmon calcitonin reduces pain and improves mobilisation after osteoporosis-related vertebral fractures (**S**) (**Level I**).
3. Salmon calcitonin reduces acute but not chronic phantom limb pain (**N**) (**Level II**).
4. Pamidronate reduces pain associated with acute osteoporotic vertebral fractures (**N**) (**Level II**).

### **4.3.8 Cannabinoids**

Cannabinoids are a diverse group of substances derived from natural (plant and animal) and synthetic sources whose effects are mediated via cannabinoid receptors. Although over 60 cannabinoids have been identified in products of the cannabis plants, the most potent psychoactive agent is delta9-tetrahydrocannabinol (delta9-THC) (Hosking & Zajicek, 2008). Potentially useful actions of cannabis include mood elevation, appetite stimulation, an antiemetic effect and antinociception. The clinical use of naturally occurring cannabis is unfortunately limited due to a wide range of side effects, including dysphoria, sedation and impaired psychomotor performance, memory and concentration. Cannabis withdrawal symptoms resemble those of opioid and alcohol withdrawal (Hosking & Zajicek, 2008). There is also concern that chronic exposure can predispose to the development of psychosis in susceptible individuals (Luzi et al, 2008 **Level IV**).

A number of expert committees have examined the scientific evidence assessing the efficacy and safety of cannabinoids in clinical practice (House of Lords, 1998; Joy et al, 1999; NSW Working Party, 2000). Insufficient rigorous scientific evidence was found to support the use of cannabinoids in clinical practice.

In 2001 a qualitative systematic review examined the evidence for cannabinoids as analgesics (Campbell et al, 2001 **Level I**) and found no evidence for clinically relevant effectiveness, but significant side effects.

In acute pain, a number of studies investigated different cannabinoid presentations for postoperative analgesia. No benefit was found with a single dose of oral THC on the second day following hysterectomy in 20 women (Buggy et al, 2003 **Level II**). Unexpectedly, high-dose (2 mg) nabilone in the presence of morphine was associated with increased pain scores in patients who underwent major orthopaedic or gynaecologic surgery (Beaulieu, 2006 **Level II**). A dose escalating study using an oral mixture of THC and cannabidiol (Cannador®) following cessation of PCA after a range of surgical procedures found that the need for rescue analgesia was reduced with increasing dose, but that side effects occurred at the higher dose (Holdcroft



et al, 2006 **Level III-3**). In patients having radical prostatectomy, the addition of daily dronabinol did not alter the analgesic requirement for piritramide (Seeling et al, 2006 **Level II**).

Although the number of clinical trials was small, cannabinoids were mildly effective in the treatment of chronic neuropathic and multiple sclerosis-related pain; the most common adverse effect was dizziness (35% of patients) (Iskedjian et al, 2007 **Level I**).

In patients with a variety of causes for both peripheral and central neuropathic pain, smoking cannabis (low and high dose) was significantly more effective than smoking placebo cigarettes in reducing neuropathic pain; acute cognitive impairment, particularly of memory, was significantly greater at higher cannabis doses, but psychoactive effects ('feeling high', 'feeling stoned') with both high and low doses were minimal and well-tolerated (Wilsey et al, 2008 **Level II**). Smoked cannabis was also more effective than placebo cigarettes in HIV-associated neuropathic pain (Abrams et al, 2007 **Level II**); the rate of responders (30% reduction in pain) in one trial was 46% with cannabis and 18% with placebo (Ellis et al 2009 **Level II**). A cannabidiol/THC oromucosal spray was more effective than a placebo spray for multiple sclerosis-related neuropathic pain (Rog et al, 2005 **Level II**). Compared with placebo, oromucosal administration of both combined cannabidiol/THC and THC alone were effective for the relief of intractable central neuropathic pain resulting from brachial plexus avulsion (Berman et al, 2004 **Level II**).

It should be noted that all clinical studies to date have design limitations, involve small numbers of patients and only used non-selective highly lipophilic cannabinoid compounds. The possible benefits from more selective agonists have yet to be investigated in the clinical setting.

#### Key message

1. Current evidence does not support the use of cannabinoids in acute pain management (**S**) but these drugs appear to be mildly effective when used in the treatment of chronic neuropathic pain, including multiple sclerosis-related pain (**N**) (**Level I**).

### 4.3.9 Glucocorticoids

Surgical tissue trauma leads to the conversion of arachidonic acid to prostaglandins and leukotrienes. NSAIDs inhibit the formation of prostaglandins whereas glucocorticoids also inhibit the production of prostaglandins, leukotrienes and cytokines (Gilon, 2004; Romundstad & Stubhaug, 2007). Several randomised controlled studies have shown that the addition of glucocorticoids reduces postoperative pain and analgesic requirement (see below). Additional benefits include decreased PONV and fatigue (Romundstad et al, 2006; Kehlet, 2007).

However more information is still needed about dose-finding, the effects of repeat dosing, procedure-specific effectiveness and safety (Kehlet, 2007). While good data regarding side effects are still lacking, high doses have been used in elective and emergency surgical patients without an increase in morbidity (Sauerland et al, 2000 **Level I**).

Earlier studies have shown benefit after oral surgery, tonsillectomy, lumbar disc surgery, laparoscopic cholecystectomy, arthroscopic surgery and lung resection (Gilon, 2004; Kehlet, 2007).

Studies looking at the effect of glucocorticoids after surgery include those where comparisons have been made with placebo only and those where comparisons have been made with other analgesics +/- placebo.

Preoperative administration of dexamethasone in patients undergoing total hip arthroplasty led to better dynamic pain relief than placebo, but there were no differences in pain at rest, PCA morphine requirements, wound complications or infection at one month after surgery

(Kardash et al, 2008 **Level II**). Similarly, after ambulatory breast surgery, dexamethasone improved pain relief on movement between 24 and 72 hours postoperatively compared with placebo, but the differences at other time periods were not significant; the power of this study was possibly limited because of the low pain scores in both patient groups — all were also given paracetamol and rofecoxib (Hval et al, 2007 **Level II**). Dexamethasone was no more effective than placebo in reducing back pain after lumbar discectomy, but there was a significant reduction in postoperative radicular leg pain and opioid consumption (Aminmansour et al, 2006 **Level II**). Pain after tonsillectomy was reduced on postoperative day 1 in patients given dexamethasone, although by a score of just 1 out of 10 (Afman et al, 2006 **Level I**); pain relief was also better from day 1 to day 7 (McKean et al, 2006 **Level II**). Compared with lower doses of dexamethasone and placebo, 15 mg IV dexamethasone significantly reduced 24-hour oxycodone requirements after laparoscopic hysterectomy, but there were no differences in pain scores at rest or with movement between any of the study groups (Jokela et al, 2009 **Level II**). While preoperative dexamethasone reduced pain, fatigue, nausea and vomiting in patients undergoing laparoscopic cholecystectomy compared with placebo (Bisgaard et al, 2003 **Level II**), no differences were found in these factors in patients given oral prednisone or placebo (Bisgaard et al, 2008 **Level II**).

After orthopaedic surgery, there was no difference in analgesic effect between methylprednisolone and ketorolac (both were better than placebo); methylprednisolone led to greater opioid-sparing but there was no difference in the incidence of adverse effects (Romundstad et al, 2004 **Level II**). After mixed ambulatory surgery, ketorolac provided better pain relief than either dexamethasone or betamethasone in the immediate postoperative period, but there were no differences in pain relief or analgesic use in the 4 to 72 hour period after surgery (Thagaard et al, 2007 **Level II**). Similarly, after breast augmentation, methylprednisolone and parecoxib provided similar analgesia; however, PONV and fatigue scores were lower in the patients given methylprednisolone (Romundstad et al, 2006).

A combination of gabapentin and dexamethasone provided better pain relief and led to less PONV than either drug given alone after varicocoele surgery; both the combination and the individual drugs were more effective than placebo (Koç et al, 2007 **Level II**). There was no difference in pain scores or PCA morphine requirements during the first 24 hours postoperatively in patients given pregabalin, pregabalin with dexamethasone, or placebo after hysterectomy (Mathiesen et al, 2009 **Level II**).

Glucocorticoids have also been shown to have antihyperalgesic effects in animals and humans (Romundstad & Stubhaug, 2007; Kehlet, 2007). Using experimental burn injury pain, both methylprednisolone and ketorolac reduced secondary hyperalgesia and increased pain pressure tolerance threshold compared with placebo, although the increase in pain pressure tolerance threshold was greater with ketorolac (Stubhaug et al, 2007 **Level II**). In surgical patients, preoperative administration of methylprednisolone resulted in significantly less hyperesthesia compared with parecoxib and placebo, but there was no reduction in persistent spontaneous or evoked pain (Romundstad et al, 2006 **Level II**).

### Key message

1. Dexamethasone, compared with placebo, reduces postoperative pain, nausea and vomiting, and fatigue (**Level II**).

### 4.3.10 Complementary and alternative medicines

Herbal, traditional Chinese and homeopathic medicines may be described as complementary or alternative medicines (CAMs) because their use lies outside the dominant, 'orthodox' health system of Western industrialised society (Belgrade, 2003). In other cultures these therapies may be mainstream.

CAMs include:

- herbal medicine — substances derived from plant parts such as roots, leaves or flowers;
- traditional Chinese medicine — herbal medicines, animal and mineral substances;
- homeopathy — ultra-diluted substances; and
- others — vitamins, minerals, animal substances, metals and chelation agents.

A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states (WHO, 1996). While the use of CAMs is commonplace, their efficacy in many areas, including in the management of acute pain, has not yet been subject to adequate scientific evaluation and there are limited data.

Preoperative melatonin administration led to reduced PCA morphine requirements and anxiety after surgery (Caumo et al, 2007 **Level II**). Treatment with lavender aromatherapy in the postanaesthesia care unit reduced the opioid requirements of morbidly obese patients after laparoscopic gastric banding (Kim et al, 2007 **Level II**). There is insufficient evidence that aromatherapy is effective for labour pain (Smith et al, 2006 **Level I**).

A review of trials looking at the effectiveness of herbal medicines for acute low back pain (a mix of acute, subacute and chronic pain) found that white willow bark (*Salix alba*), containing salicin, which is metabolised to salicylic acid, provided better analgesia than placebo and was similar to a coxib (rofecoxib) (Gagnier et al, 2006 **Level I**). Devil's claw (*Harpagophytum procumbens*) was also effective and there was moderate evidence that cayenne (*Capsicum frutescens*) may be better than placebo (Gagnier et al, 2006 **Level I**).

In dysmenorrhoea, vitamin B1 (Proctor & Murphy, 2001 **Level I**), vitamin E (Ziaei et al, 2005 **Level II**), Chinese herbal medicine (Zhu et al, 2007 **Level I**), rose tea (Tseng et al, 2005 **Level II**), guava leaf extract (*Psidium guajavae*) (Doubova et al, 2007 **Level II**), aromatherapy (Han et al, 2006 **Level II**) and fennel (*Foeniculum vulgare*) (Namavar Jahromi et al, 2003 **Level III-2**) provided effective analgesia.

Homeopathic arnica provided a statistically significant reduction in acute pain after tonsillectomy (Robertson et al, 2007 **Level II**), however it was ineffective for pain relief after hand surgery (Stevinson et al, 2003 **Level II**) and abdominal hysterectomy (Hart et al, 1997 **Level II**).

Peppermint oil has a NNT of 2.5 for improvement of pain or symptoms in irritable bowel syndrome (Ford et al, 2008 **Level I**).

Adverse effects and interactions with medications have been described with CAMs and must be considered before their use.

#### Key message

The following tick box represents conclusions based on clinical experience and expert opinion.

- There is some evidence that some complementary and alternative medicines may be effective in some acute pain states. Adverse effects and interactions with medications have been described with complementary and alternative medicines and must be considered before their use (**N**).

## REFERENCES

- Abrams DI, Jay CA, Shade SB et al (2007) Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* **68**(7): 515–21.
- Adam F, Chauvin M, Du Manoir B et al (2005) Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. *Anesth Analg* **100**(2): 475–80.
- Adunsky A, Levy R, Heim M et al (2002) Meperidine analgesia and delirium in aged hip fracture patients. *Arch Gerontol Geriatr* **35**(3): 253–9.
- Afman CE, Welge JA & Steward DL (2006) Steroids for post-tonsillectomy pain reduction: meta-analysis of randomized controlled trials. *Otolaryngol Head Neck Surg* **134**(2): 181–6.
- Aho MS, Erkola OA, Scheinin H et al (1991) Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesth Analg* **73**(2): 112–8.
- Aminmansour B, Khalili HA, Ahmadi J et al (2006) Effect of high-dose intravenous dexamethasone on postlumbar discectomy pain. *Spine* **31**(21): 2415–7.
- Amos RJ, Amess JA, Hinds CJ et al (1982) Incidence and pathogenesis of acute megaloblastic bone-marrow change in patients receiving intensive care. *Lancet* **2**(8303): 835–8.
- Angst MS & Clark JD (2006) Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* **104**(3): 570–87.
- Angst MS, Chu LF, Tingle MS et al (2009) No evidence for the development of acute tolerance to analgesic, respiratory depressant and sedative opioid effects in humans. *Pain* **142**: 17–26.
- Antman EM, Bennett JS, Daugherty A et al (2007) Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation* **115**(12): 1634–42.
- Aouad MT, Siddik-Sayyid SM, Taha SK et al (2007) Haloperidol vs. ondansetron for the prevention of postoperative nausea and vomiting following gynaecological surgery. *Eur J Anaesthesiol* **24**(2): 171–8.
- Apfel CC, Korttila K, Abdalla M et al (2004) A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* **350**(24): 2441–51.
- Arain SR, Ruehlow RM, Uhrich TD et al (2004) The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. *Anesth Analg* **98**(1): 153–8.
- Arcioni R, della Rocca M, Romano S et al (2002) Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT(3) spinal receptor involvement in acute pain in humans. *Anesth Analg* **94**(6): 1553–7.
- Armingeat T, Brondino R, Pham T et al (2006) Intravenous pamidronate for pain relief in recent osteoporotic vertebral compression fracture: a randomized double-blind controlled study. *Osteoporos Int* **17**(11): 1659–65.
- Athanasos P, Smith CS, White JM et al (2006) Methadone maintenance patients are cross-tolerant to the antinociceptive effects of very high plasma morphine concentrations. *Pain* **120**(3): 267–75.
- Attal N, Gaude V, Brasseur L et al (2000) Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology* **54**(3): 564–74.
- Aubrun F, Salvi N, Coriat P et al (2005) Sex- and age-related differences in morphine requirements for postoperative pain relief. *Anesthesiology* **103**(1): 156–60.
- Aubrun F, Gaillat C, Rosenthal D et al (2008) Effect of a low-dose ketamine regimen on pain, mood, cognitive function and memory after major gynaecological surgery: a randomized, double-blind, placebo-controlled trial. *Eur J Anaesthesiol* **25**(2): 97–105.
- Babl F, Jamison S, Spicer M et al (2006) Inhaled methoxyflurane as a prehospital analgesic in children. *Emerg Med Australas* **18**(4): 404–10.
- Babl F, Barnett P, Palmer G et al (2007) A pilot study of inhaled methoxyflurane for procedural analgesia in children. *Paediatr Anaesth* **17**(2): 148–53.
- Babl FE, Oakley E, Puspitadewi A et al (2008) Limited analgesic efficacy of nitrous oxide for painful procedures in children. *Emerg Med J* **25**(11): 717–21.
- Badner NH, Drader K, Freeman D et al (1998) The use of intraoperative nitrous oxide leads to postoperative increases in plasma homocysteine. *Anesth Analg* **87**(3): 711–3.

- Badner NH, Freeman D & Spence JD (2001) Preoperative oral B vitamins prevent nitrous oxide-induced postoperative plasma homocysteine increases. *Anesth Analg* **93**(6): 1507–10.
- Bainbridge D, Cheng DC, Martin JE et al (2006) NSAID-analgesia, pain control and morbidity in cardiothoracic surgery. *Can J Anaesth* **53**(1): 46–59
- Bandolier (2004) *NSAIDs, coxibs, smoking and bone*.  
www.jr2.ox.ac.uk/bandolier/booth/painpag/wisdom/NSB.pdf Bandolier Extra: www.ebandolier.com. Accessed January 2009.
- Barkin RL, Barkin SJ & Barkin DS (2006) Propoxyphene (dextropropoxyphene): a critical review of a weak opioid analgesic that should remain in antiquity. *Am J Ther* **13**(6): 534–42.
- Barnung SK, Treschow M & Borgbjerg FM (1997) Respiratory depression following oral tramadol in a patient with impaired renal function. *Pain* **71**(1): 111–2.
- Barratt SM, Smith RC, Kee AJ et al (2002) Multimodal analgesia and intravenous nutrition preserves total body protein following major upper gastrointestinal surgery. *Reg Anesth Pain Med* **27**(1): 15–22.
- Beaulieu P (2006) Effects of nabilone, a synthetic cannabinoid, on postoperative pain. *Can J Anaesth* **53**(8): 769–75.
- Beaussier M, Weickmans H, Paugam C et al (2005) A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients. *Anesth Analg* **100**(5): 1309–15.
- Belgrade MJ (2003) Alternative and complementary therapies. In: *Clinical Pain Management: Chronic Pain* edn. Jensen TS, Wilson PR and Rice ASC (eds). London, Arnold.
- Bell R, Montoya D, Shuaib A et al (1990) A comparative trial of three agents in the treatment of acute migraine headache. *Ann Emerg Med* **19**(10): 1079–82.
- Bell RF (1999) Low-dose subcutaneous ketamine infusion and morphine tolerance. *Pain* **83**(1): 101–3.
- Bell RF, Dahl JB, Moore RA et al (2006) Perioperative ketamine for acute postoperative pain. *Cochrane Database Syst Rev*(1): CD004603.
- Benson GD, Koff RS & Tolman KG (2005) The therapeutic use of acetaminophen in patients with liver disease. *Am J Ther* **12**(2): 133–41.
- Berman JS, Symonds C & Birch R (2004) Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* **112**(3): 299–306.
- Bernard JM, Hommeril JL, Passuti N et al (1991) Postoperative analgesia by intravenous clonidine. *Anesthesiology* **75**(4): 577–82.
- Bertolini A, Ferrari A, Ottani A et al (2006) Paracetamol: new vistas of an old drug. *CNS Drug Rev* **12**(3-4): 250–75.
- Bisgaard T, Klarskov B, Kehlet H et al (2003) Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. *Ann Surg* **238**(5): 651–60.
- Bisgaard T, Schulze S, Christian Hjortsø N et al (2008) Randomized clinical trial comparing oral prednisone (50 mg) with placebo before laparoscopic cholecystectomy. *Surg Endosc* **22**(2): 566–72.
- Blanda M, Rench T, Gerson LW et al (2001) Intranasal lidocaine for the treatment of migraine headache: a randomized, controlled trial. *Acad Emerg Med* **8**(4): 337–42.
- Blau LA & Hoehns JD (2003) Analgesic efficacy of calcitonin for vertebral fracture pain. *Ann Pharmacother* **37**(4): 564–70.
- Bodley PO, Mirza V, Spears JR et al (1966) Obstetric analgesia with methoxyflurane. A clinical trial. *Anaesthesia* **21**(4): 457–63.
- Bone M, Critchley P & Buggy DJ (2002) Gabapentin in postamputation phantom limb pain: A randomized, double-blind, placebo-controlled, cross-over study. *Reg Anesth Pain Med* **27**(5): 481–6.
- Bonnet MP, Marret E, Jossierand J et al (2008) Effect of prophylactic 5-HT<sub>3</sub> receptor antagonists on pruritus induced by neuraxial opioids: a quantitative systematic review. *Br J Anaesth* **101**(3): 311–9.

- Bostrom E, Hammarlund-Udenaes M & Simonsson US (2008) Blood-brain barrier transport helps to explain discrepancies in in vivo potency between oxycodone and morphine. *Anesthesiology* **108**(3): 495–505.
- Botting RM (2006) Inhibitors of cyclooxygenases: mechanisms, selectivity and uses. *J Physiol Pharmacol* **57** Suppl 5: 113–24.
- Bowsher D (1997) The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage* **13**(6): 327–31.
- Brodner G, Van Aken H, Hertle L et al (2001) Multimodal perioperative management - Combining thoracic epidural analgesia, forced mobilization, and oral nutrition - Reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. *Anesth Analg* **92**(6): 1594–600.
- Brosen K, Gram LF, Schou J et al (1985) Dextropropoxyphene kinetics after single and repeated oral doses in man. *Eur J Clin Pharmacol* **29**(1): 79–84.
- Buggy DJ, Toogood L, Maric S et al (2003) Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. *Pain* **106**(1-2): 169–72.
- Buntine P, Thom O, Babl F et al (2007) Prehospital analgesia in adults using inhaled methoxyflurane. *Emerg Med Australas* **19**(6): 509–14.
- Burns JW, Hodsman NB, McLintock TT et al (1989) The influence of patient characteristics on the requirements for postoperative analgesia. A reassessment using patient-controlled analgesia. *Anaesthesia* **44**(1): 2–6.
- Burton JH, Auble TE & Fuchs SM (1998) Effectiveness of 50% nitrous oxide/50% oxygen during laceration repair in children. *Acad Emerg Med* **5**(2): 112–7.
- Buttner M, Walder B, von Elm E et al (2004) Is low-dose haloperidol a useful antiemetic?: A meta-analysis of published and unpublished randomized trials. *Anesthesiology* **101**(6): 1454–63.
- Calverley RK (1972) Repeated methoxyflurane analgesia for burns dressings. *British Journal of Anaesthesia* **44**(6): 628.
- Campbell FA, Tramer MR, Carroll D et al (2001) Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* **323**(7303): 13–6.
- Cann C, Curran J, Milner T et al (2002) Unwanted effects of morphine-6-glucuronide and morphine. *Anaesthesia* **57**(12): 1200–3.
- Cardenas DD, Warmis CA, Turner JA et al (2002) Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. *Pain* **96**(3): 365–73.
- Cardwell M, Siviter G & Smith A (2005) Non-steroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane Database Syst Rev*(2): CD003591.
- Carlisle JB & Stevenson CA (2006) Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* **3**: CD004125.
- Carmel R (2000) Current concepts in cobalamin deficiency. *Annu Rev Med* **51**: 357–75.
- Cartner M, Sinnott M & Silburn P (2007) Paralysis caused by "nagging". *Med J Aust* **187**(6): 366–7.
- Cashman JN & Dolin SJ (2004) Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. *Br J Anaesth* **93**(2): 212–23.
- Castera L, Negre I, Samii K et al (2001) Patient-administered nitrous oxide/oxygen inhalation provides safe and effective analgesia for percutaneous liver biopsy: a randomized placebo-controlled trial. *Am J Gastroenterol* **96**(5): 1553–7.
- Catley DM, Thornton C, Jordan C et al (1985) Pronounced, episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* **63**(1): 20–8.
- Caumo W, Torres F, Moreira NL, Jr. et al (2007) The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg* **105**(5): 1263–71.
- Celik JB, Gormus N, Gormus ZI et al (2005) Preoperative analgesia management with rofecoxib in thoracotomy patients. *J Cardiothorac Vasc Anesth* **19**(1): 67–70.



- Cepeda MS, Delgado M, Ponce M et al (1996) Equivalent outcomes during postoperative patient-controlled intravenous analgesia with lidocaine plus morphine versus morphine alone. *Anesth Analg* **83**(1): 102–6.
- Cepeda MS & Carr DB (2003) Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. *Anesth Analg* **97**(5): 1464–8.
- Challapalli V, Tremont-Lukats IW, McNicol ED et al (2005) Systemic administration of local anesthetic agents to relieve neuropathic pain. *Cochrane Database Syst Rev*(4): CD003345.
- Chan FK, Wong VW, Suen BY et al (2007) Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet* **369**(9573): 1621–6.
- Chan MT, Choi KC, Gin T et al (2006) The additive interactions between ondansetron and droperidol for preventing postoperative nausea and vomiting. *Anesth Analg* **103**(5): 1155–62.
- Chang G, Chen L & Mao J (2007) Opioid tolerance and hyperalgesia. *Med Clin North Am* **91**(2): 199–211.
- Charbit B, Albaladejo P, Funck-Brentano C et al (2005) Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. *Anesthesiology* **102**(6): 1094–100.
- Charbit B, Alvarez JC, Dasque E et al (2008) Droperidol and ondansetron-induced QT interval prolongation: a clinical drug interaction study. *Anesthesiology* **109**(2): 206–12.
- Chau-In W, Sukmuan B, Ngamsangsisrisapt K et al (2007) Efficacy of pre- and postoperative oral dextromethorphan for reduction of intra- and 24-hour postoperative morphine consumption for transabdominal hysterectomy. *Pain Med* **8**(5): 462–7.
- Cheng HF & Harris RC (2004) Cyclooxygenases, the kidney, and hypertension. *Hypertension* **43**(3): 525–30.
- Chia YY, Chow LH, Hung CC et al (2002) Gender and pain upon movement are associated with the requirements for postoperative patient-controlled iv analgesia: a prospective survey of 2,298 Chinese patients. *Can J Anaesth* **49**(3): 249–55.
- Chiou-Tan FY, Tuel SM, Johnson JC et al (1996) Effect of mexiletine on spinal cord injury dysesthetic pain. *Am J Phys Med Rehabil* **75**(2): 84–7.
- Chong C, Schug SA, Page-Sharp M et al (2009) Development of a sublingual/oral formulation of ketamine for use in neuropathic pain: preliminary findings from a three-way randomized, crossover study. *Clin Drug Investig* **29**(5): 317–24.
- Chou WY, Wang CH, Liu PH et al (2006) Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. *Anesthesiology* **105**(2): 334–7.
- Chou WY, Yang LC, Lu HF et al (2006) Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. *Acta Anaesthesiol Scand* **50**(7): 787–92.
- Christensen B & Ueland PM (1993) Methionine synthase inactivation by nitrous oxide during methionine loading of normal human fibroblasts. Homocysteine remethylation as determinant of enzyme inactivation and homocysteine export. *J Pharmacol Exp Ther* **267**(3): 1298–303.
- Christensen B, Guttormsen AB, Schneede J et al (1994) Preoperative methionine loading enhances restoration of the cobalamin-dependent enzyme methionine synthase after nitrous oxide anesthesia. *Anesthesiology* **80**(5): 1046–56.
- Chu CC, Shieh JP, Tzeng JI et al (2008) The prophylactic effect of haloperidol plus dexamethasone on postoperative nausea and vomiting in patients undergoing laparoscopically assisted vaginal hysterectomy. *Anesth Analg* **106**(5): 1402–6.
- Chu LF, Clark DJ & Angst MS (2006) Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. *J Pain* **7**(1): 43–8.
- Chu LF, Angst MS & Clark D (2008) Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin J Pain* **24**(6): 479–96.
- Clements JA, Nimmo WS & Grant IS (1982) Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. *J Pharm Sci* **71**(5): 539–42.

- Cohen SP, Christo PJ, Wang S et al (2008) The effect of opioid dose and treatment duration on the perception of a painful standardized clinical stimulus. *Reg Anesth Pain Med* **33**(3): 199–206.
- Collins SL, Moore RA, McQuay HJ & Wiffen P (2000) Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. *J Pain Symptom Manage* **20**(6): 449–58.
- Coluzzi F & Mattia C (2005) Oxycodone. Pharmacological profile and clinical data in chronic pain management. *Minerva Anestesiol* **71**(7-8): 451–60.
- Compton P, Charuvastra VC, Kintaudi K et al (2000) Pain responses in methadone-maintained opioid abusers. *J Pain Symptom Manage* **20**(4): 237–45.
- Compton P, Charuvastra VC & Ling W (2001) Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. *Drug Alcohol Depend* **63**(2): 139–46.
- Coulbault L, Beaussier M, Verstuylt C et al (2006) Environmental and genetic factors associated with morphine response in the postoperative period. *Clin Pharmacol Ther* **79**(4): 316–24.
- Cruciani RA (2008) Methadone: to ECG or not to ECG...That is still the question. *J Pain Symptom Manage* **36**(5): 545–52.
- Cuignet O, Pirson J, Soudon O et al (2007) Effects of gabapentin on morphine consumption and pain in severely burned patients. *Burns* **33**(1): 81–6.
- Curtis SP, Ng J, Yu Q et al (2004) Renal effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs in controlled clinical trials. *Clin Ther* **26**(1): 70–83.
- Dahan A, Yassen A, Bijl H et al (2005) Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* **94**(6): 825–34.
- Dahan A, Yassen A, Romberg R et al (2006) Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth* **96**(5): 627–32.
- Dahan A, Kest B, Waxman AR et al (2008) Sex-specific responses to opiates: animal and human studies. *Anesth Analg* **107**(1): 83–95.
- Dahan A, van Dorp E, Smith T et al (2008) Morphine-6-glucuronide (M6G) for postoperative pain relief. *Eur J Pain* **12**(4): 403–11.
- Davies G, Kingswood C & Street M (1996) Pharmacokinetics of opioids in renal dysfunction. *Clin Pharmacokinet* **31**(6): 410–22.
- De Cosmo G, Congedo E, Lai C et al (2008) Preoperative psychologic and demographic predictors of pain perception and tramadol consumption using intravenous patient-controlled analgesia. *Clin J Pain* **24**(5): 399–405.
- De Kock MF, Pichon G & Scholtes JL (1992) Intraoperative clonidine enhances postoperative morphine patient-controlled analgesia. *Can J Anaesth* **39**(6): 537–44.
- De Kock M, Lavand'homme P & Waterloos H (2001) 'Balanced analgesia' in the perioperative period: is there a place for ketamine? *Pain* **92**(3): 373–80.
- De Kock MF & Lavand'homme PM (2007) The clinical role of NMDA receptor antagonists for the treatment of postoperative pain. *Best Pract Res Clin Anaesthesiol* **21**(1): 85–98.
- De Witte JL, Schoenmaekers B, Sessler DI et al (2001) The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesth Analg* **92**(5): 1319–21.
- Derry C, Derry S, Moore RA et al (2009a) Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database Syst Rev*(3): CD001548.
- Derry C, Derry S, Moore RA et al (2009b) Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. *Cochrane Database Syst Rev* (1) CD004234.
- Derry P, Derry S, Moore RA et al (2009c) Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database Syst Rev*(2): CD004768.
- Diemunsch P, Gan TJ, Philip BK et al (2007) Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. *Br J Anaesth* **99**(2): 202–11.
- Djulgovic B, Wheatley K, Ross J et al (2002) Bisphosphonates in multiple myeloma. *Cochrane Database Syst Rev*(3): CD003188.



- Dolin SJ, Cashman JN & Bland JM (2002) Effectiveness of acute postoperative pain management: I. Evidence from published data. *Br J Anaesth* **89**(3): 409–23.
- Dolin SJ & Cashman JN (2005) Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritus, and urinary retention. Evidence from published data. *Br J Anaesth* **95**(5): 584–91.
- Dobova SV, Morales HR, Hernandez SF et al (2007) Effect of a *Psidium guajavae* folium extract in the treatment of primary dysmenorrhea: a randomized clinical trial. *J Ethnopharmacol* **110**(2): 305–10.
- Doverly M, White JM, Somogyi AA et al (2001) Hyperalgesic responses in methadone maintenance patients. *Pain* **90**(1-2): 91–6.
- Drewes AM, Andreassen A & Poulsen LH (1994) Valproate for treatment of chronic central pain after spinal cord injury. A double-blind cross-over study. *Paraplegia* **32**(8): 565–9.
- Duedahl TH, Romsing J, Moiniche S et al (2006) A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. *Acta Anaesthesiol Scand* **50**(1): 1–13.
- Eichenberger U, Neff F, Svetlicic G et al (2008) Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg* **106**(4): 1265–73.
- Eilers H, Philip LA, Bickler PE et al (2001) The reversal of fentanyl-induced tolerance by administration of "small-dose" ketamine. *Anesth Analg* **93**(1): 213–4.
- Eisenberg E, Pud D, Koltun L et al (2007) Effect of early administration of the N-methyl-d-aspartate receptor antagonist amantadine on the development of postmastectomy pain syndrome: a prospective pilot study. *J Pain* **8**(3): 223–9.
- Ekbom K, Jakobsson J & Marcus C (2005) Nitrous oxide inhalation is a safe and effective way to facilitate procedures in paediatric outpatient departments. *Arch Dis Child* **90**(10): 1073–6.
- Elia N, Lysakowski C & Tramer MR (2005) Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology* **103**(6): 1296–304.
- Elia N, Tramer MR (2005) Ketamine and postoperative pain—a quantitative systematic review of randomised trials. *Pain* **113**(1-2):61–70.
- Ellis RJ, Toperoff W, Vaida F et al (2009) Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology* **34**(3): 672–80.
- Engelhardt T, Zaarour C, Naser B et al (2008) Intraoperative low-dose ketamine does not prevent a remifentanyl-induced increase in morphine requirement after pediatric scoliosis surgery. *Anesth Analg* **107**(4): 1170–5.
- Evans JK, Buckley SL, Alexander AH et al (1995) Analgesia for the reduction of fractures in children: a comparison of nitrous oxide with intramuscular sedation. *J Pediatr Orthop* **15**(1): 73–7.
- Ezri T, Lurie S, Stein A et al (2002) Postoperative nausea and vomiting: comparison of the effect of postoperative meperidine or morphine in gynecologic surgery patients. *J Clin Anesth* **14**(4): 262–6.
- Fassoulaki A, Patris K, Sarantopoulos C et al (2002) The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* **95**(4): 985–91.
- Faura CC, Collins SL, Moore RA et al (1998) Systematic review of factors affecting the ratios of morphine and its major metabolites. *Pain* **74**(1): 43–53.
- FDA-Penthane (2005) Determination that Penthrane (methoxyflurane) inhalational liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness. *Federal Register* **70**(171): 53019.
- FDA (2005) *Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk* <http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf>. Accessed March 2009.
- FDA (2006) *New Information [9/2006] - Concomitant Use of Ibuprofen and Aspirin*. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm>. Accessed March 2009.
- Filligim RB, King CD, Ribeiro-Dasilva MC et al (2009) Sex, gender, and pain: a review of recent clinical and experimental findings. *J Pain* **10**(5): 447–85.

- Finnerup NB, Biering-Sorensen F, Johannesen IL et al (2005) Intravenous lidocaine relieves spinal cord injury pain: a randomized controlled trial. *Anesthesiology* **102**(5): 1023–30.
- Firn S (1972) Methoxyflurane analgesia for burns dressings and other painful ward procedures in children. *Br J Anaesth* **44**(5): 517–22.
- Flippo TS & Holder WD, Jr. (1993) Neurologic degeneration associated with nitrous oxide anesthesia in patients with vitamin B12 deficiency. *Arch Surg* **128**(12): 1391–5.
- Fong HK, Sands LP & Leung JM (2006) The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesth Analg* **102**(4): 1255–66.
- Ford AC, Talley NJ, Spiegel BM et al (2008) Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ* **337**: a2313.
- Fransen M, Anderson C, Douglas J et al (2006) Safety and efficacy of routine postoperative ibuprofen for pain and disability related to ectopic bone formation after hip replacement surgery (HIPAID): randomised controlled trial. *BMJ* **333**(7567): 519.
- Fredheim OM, Moksnes K, Borchgrevink PC et al (2008) Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand* **52**(7): 879–89.
- Gagliese L, Jackson M, Ritvo P et al (2000) Age is not an impediment to effective use of patient-controlled analgesia by surgical patients. *Anesthesiology* **93**(3): 601–10.
- Gagliese L, Gauthier LR, Macpherson AK et al (2008) Correlates of postoperative pain and intravenous patient-controlled analgesia use in younger and older surgical patients. *Pain Med* **9**(3): 299–314.
- Gagnier JJ, van Tulder M, Berman B et al (2006) Herbal medicine for low back pain. *Cochrane Database Syst Rev*(2): CD004504.
- Gajraj NM & Joshi GP (2005) Role of cyclooxygenase-2 inhibitors in postoperative pain management. *Anesthesiol Clin North America* **23**(1): 49–72.
- Galinski M, Dolveck F, Combes X et al (2007) Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. *Am J Emerg Med* **25**(4): 385–90.
- Gammaitoni AR, Fine P, Alvarez N et al (2003) Clinical application of opioid equianalgesic data. *Clin J Pain* **19**(5): 286–97.
- Gan TJ, Joshi GP, Zhao SZ et al (2004) Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid-related adverse effects. *Acta Anaesthesiol Scand* **48**(9): 1194–207.
- Gan TJ (2006) Risk factors for postoperative nausea and vomiting. *Anesth Analg* **102**(6): 1884–98.
- Gan TJ, Apfel CC, Kovac A et al (2007) A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. *Anesth Analg* **104**(5): 1082–9.
- Gan TJ, Meyer TA, Apfel CC et al (2007) Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* **105**(6): 1615–28.
- Ganesh A & Maxwell LG (2007) Pathophysiology and management of opioid-induced pruritus. *Drugs* **67**(16): 2323–33.
- Gasse C, Derby L, Vasilakis-Scaramozza C et al (2000) Incidence of first-time idiopathic seizures in users of tramadol. *Pharmacotherapy* **20**(6): 629–34.
- Gerhardt RT, King KM & Wiegert RS (2001) Inhaled nitrous oxide versus placebo as an analgesic and anxiolytic adjunct to peripheral intravenous cannulation. *Am J Emerg Med* **19**(6): 492–4.
- Gerstenfeld LC & Einhorn TA (2004) COX inhibitors and their effects on bone healing. *Expert Opin Drug Saf* **3**(2): 131–6.
- Gillies A, Lindholm D, Angliss M et al (2007) The use of ketamine as rescue analgesia in the recovery room following morphine administration—a double-blind randomised controlled trial in postoperative patients. *Anaesth Intensive Care* **35**(2): 199–203.
- Gilron I (2004) Corticosteroids in postoperative pain management: future research directions for a multifaceted therapy. *Acta Anaesthesiol Scand* **48**(10): 1221–2.

- Goldstein JL, Kivitz AJ, Verburg KM et al (2003) A comparison of the upper gastrointestinal mucosal effects of valdecoxib, naproxen and placebo in healthy elderly subjects. *Aliment Pharmacol Ther* **18**(1): 125–32.
- Gordh TE, Stubhaug A, Jensen TS et al (2008) Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross-over, multi-center study. *Pain* **138**(2): 255–66.
- Gottschalk A, Schroeder F, Ufer M et al (2001) Amantadine, a N-methyl-D-aspartate receptor antagonist, does not enhance postoperative analgesia in women undergoing abdominal hysterectomy. *Anesth Analg* **93**(1): 192–6.
- Grace D & Fee JP (1996) A comparison of intrathecal morphine-6-glucuronide and intrathecal morphine sulfate as analgesics for total hip replacement. *Anesth Analg* **83**(5): 1055–9.
- Graham GG, Scott KF & Day RO (2005) Tolerability of paracetamol. *Drug Saf* **28**(3): 227–40.
- Gray P, Williams B & Cramond T (2008) Successful use of gabapentin in acute pain management following burn injury: a case series. *Pain Med* **9**(3): 371–6.
- Greco L, Bittner EA, Kher J et al (2008) Haloperidol plus ondansetron versus ondansetron alone for prophylaxis of postoperative nausea and vomiting. *Anesth Analg* **106**(5): 1410–3.
- Green RJ, Chambers J, Thomas PW et al (2007) Comparison of the relative analgesic efficacies of epidural or intramuscular diamorphine following total knee arthroplasty. *Eur J Anaesthesiol* **24**(11): 951–7.
- Gregory PR & Sullivan JA (1996) Nitrous oxide compared with intravenous regional anesthesia in pediatric forearm fracture manipulation. *J Pediatr Orthop* **16**(2): 187–91.
- Grindlay J & Babl FE (2009) Review article: Efficacy and safety of methoxyflurane analgesia in the emergency department and prehospital setting. *Emergency Medicine Australasia* **21**(1): 4–11.
- Gudgin EJ, Besser MW & Craig JI (2008) Entonox as a sedative for bone marrow aspiration and biopsy. *Int J Lab Hematol* **30**(1): 65–7.
- Gupta A, Lawrence AT, Krishnan K et al (2007) Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J* **153**(6): 891–9.
- Gurbet A, Basagan-Mogol E, Turker G et al (2006) Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. *Can J Anaesth* **53**(7): 646–52.
- Gurnani A, Sharma PK, Rautela RS et al (1996) Analgesia for acute musculoskeletal trauma: low-dose subcutaneous infusion of ketamine. *Anaesth Intensive Care* **24**(1): 32–6.
- Gutierrez-Alvarez AM, Beltran-Rodriguez J & Moreno CB (2007) Antiepileptic drugs in treatment of pain caused by diabetic neuropathy. *J Pain Symptom Manage* **34**(2): 201–8.
- Habib AS & Gan TJ (2008a) The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesia. *J Clin Anesth* **20**(1): 35–9.
- Habib AS & Gan TJ (2008b) Haloperidol for postoperative nausea and vomiting: are we reinventing the wheel? *Anesth Analg* **106**(5): 1343–5.
- Hahn TW, Mogensen T, Lund C et al (2003) Analgesic effect of i.v. paracetamol: possible ceiling effect of paracetamol in postoperative pain. *Acta Anaesthesiol Scand* **47**(2): 138–45.
- Han SH, Hur MH, Buckle J et al (2006) Effect of aromatherapy on symptoms of dysmenorrhea in college students: A randomized placebo-controlled clinical trial. *J Altern Complement Med* **12**(6): 535–41.
- Hanna MH, Elliott KM & Fung M (2005) Randomized, double-blind study of the analgesic efficacy of morphine-6-glucuronide versus morphine sulfate for postoperative pain in major surgery. *Anesthesiology* **102**(4): 815–21.
- Hans G (2007) Buprenorphine—a review of its role in neuropathic pain. *J Opioid Manag* **3**(4): 195–206.
- Harding TA & Gibson JA (2000) The use of inhaled nitrous oxide for flexible sigmoidoscopy: a placebo-controlled trial. *Endoscopy* **32**(6): 457–60.
- Harris SI, Kuss M, Hubbard RC et al (2001) Upper gastrointestinal safety evaluation of parecoxib sodium, a new parenteral cyclooxygenase-2-specific inhibitor, compared with ketorolac, naproxen, and placebo. *Clin Ther* **23**(9): 1422–8.

- Hart O, Mullee MA, Lewith G et al (1997) Double-blind, placebo-controlled, randomized clinical trial of homoeopathic arnica C30 for pain and infection after total abdominal hysterectomy. *J R Soc Med* **90**(2): 73–8.
- Hawton K, Bergen H, Simkin S et al (2009) Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. *BMJ* **338**: b2270.
- Hay JL, White JM, Bochner F et al (2009) Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. *J Pain* **10**(3): 316–22.
- Hayes C, Armstrong-Brown A & Burstal R (2004) Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: a randomized, controlled trial. *Anaesth Intensive Care* **32**(3): 330–8.
- Health Canada (2006) *Notice to Hospitals: Health Canada Issued Important Safety Information on Anzemet (dolasetron mesylate): New Contraindications*. [www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/\\_2006/anzemet\\_nth-aah-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/anzemet_nth-aah-eng.php). Accessed April 2009.
- Hee HI, Goy RW & Ng AS (2003) Effective reduction of anxiety and pain during venous cannulation in children: a comparison of analgesic efficacy conferred by nitrous oxide, EMLA and combination. *Paediatr Anaesth* **13**(3): 210–6.
- Hegi TR, Bombeli T, Seifert B et al (2004) Effect of rofecoxib on platelet aggregation and blood loss in gynaecological and breast surgery compared with diclofenac. *Br J Anaesth* **92**(4): 523–31.
- Henderson JM, Spence DG, Komocar LM et al (1990) Administration of nitrous oxide to pediatric patients provides analgesia for venous cannulation. *Anesthesiology* **72**(2): 269–71.
- Hernandez-Diaz S, Varas-Lorenzo C & Garcia Rodriguez LA (2006) Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol* **98**(3): 266–74.
- Herrick IA, Ganapathy S, Komar W et al (1996) Postoperative cognitive impairment in the elderly. Choice of patient-controlled analgesia opioid. *Anaesthesia* **51**(4): 356–60.
- Hippisley-Cox J & Coupland C (2005) Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* **330**(7504): 1366.
- Hippisley-Cox J, Coupland C & Logan R (2005) Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* **331**(7528): 1310–6.
- Ho KY, Gan TJ & Habib AS (2006) Gabapentin and postoperative pain—a systematic review of randomized controlled trials. *Pain* **126**(1-3): 91–101.
- Hocking G, Visser EJ & Schug SA (2007) Ketamine: does life begin at 40? *Pain: Clinical Updates (IASP)* **15**(3): 1–6.
- Holdcroft A, Maze M, Dore C et al (2006) A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. *Anesthesiology* **104**(5): 1040–6.
- Holdgate A & Pollock T (2004) Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. *BMJ* **328**(7453): 1401.
- Hollingshead J, Duhme RM & Cornblath DR (2006) Tramadol for neuropathic pain. *Cochrane Database Syst Rev* **3**: CD003726.
- Holloway KL & Alberico AM (1990) Postoperative myeloneuropathy: a preventable complication in patients with B12 deficiency. *J Neurosurg* **72**(5): 732–6.
- Holmquist GL (2009) Opioid metabolism and effects of cytochrome P450. *Pain Med* **10**(S1): S20–29.
- Horlocker TT, Burton AW, Connis RT et al (2009) Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. *Anesthesiology* **110**(2): 218–30.
- Horta ML, Morejon LC, da Cruz AW et al (2006) Study of the prophylactic effect of droperidol, alizapride, propofol and promethazine on spinal morphine-induced pruritus. *Br J Anaesth* **96**(6): 796–800.
- Hosking RD & Zajicek JP (2008) Therapeutic potential of cannabis in pain medicine. *Br J Anaesth* **101**(1): 59–68.

- House of Lords (1998) *Cannabis: the scientific and medical evidence*. House of Lords Committee on Science and Technology. Science and Technology 9th report. London, The United Kingdom Parliament.
- Hubbard RC, Naumann TM, Traylor L et al (2003) Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia. *Br J Anaesth* **90**(2): 166–72.
- Hudcova J, McNicol E, Quah C et al (2005) Patient controlled intravenous opioid analgesia versus conventional opioid analgesia for postoperative pain control; a quantitative systematic review. *Acute Pain* **7**: 115–32.
- Hudson M, Baron M, Rahme E et al (2005) Ibuprofen may abrogate the benefits of aspirin when used for secondary prevention of myocardial infarction. *J Rheumatol* **32**(8): 1589–93.
- Hurley RW, Cohen SP, Williams KA et al (2006) The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. *Reg Anesth Pain Med* **31**(3): 237–47.
- Hurley RW & Adams MC (2008) Sex, gender, and pain: an overview of a complex field. *Anesth Analg* **107**(1): 309–17.
- Hurley RW, Lesley MR, Adams MC et al (2008) Pregabalin as a treatment for painful diabetic peripheral neuropathy: a meta-analysis. *Reg Anesth Pain Med* **33**(5): 389–94.
- Hval K, Kjetil H, Thagaard KS et al (2007) The prolonged postoperative analgesic effect when dexamethasone is added to a nonsteroidal antiinflammatory drug (rofecoxib) before breast surgery. *Anesth Analg* **105**(2): 481–6.
- Hyllested M, Jones S, Pedersen JL et al (2002) Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *Br J Anaesth* **88**(2): 199–214.
- Hynes D, McCarrroll M & Hiesse-Provost O (2006) Analgesic efficacy of parenteral paracetamol (propacetamol) and diclofenac in post-operative orthopaedic pain. *Acta Anaesthesiol Scand* **50**(3): 374–81.
- Iskedjian M, Bereza B, Gordon A et al (2007) Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin* **23**(1): 17–24.
- Jaeger H & Maier C (1992) Calcitonin in phantom limb pain: a double-blind study. *Pain* **48**(1): 21–7.
- Jalonen J, Hynynen M, Kuitunen A et al (1997) Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. *Anesthesiology* **86**(2): 331–45.
- Janicki PK, Schuler G, Francis D et al (2006) A genetic association study of the functional A118G polymorphism of the human mu-opioid receptor gene in patients with acute and chronic pain. *Anesth Analg* **103**(4): 1011–7.
- Jasani NB, O'Conner RE & Bouzoukis JK (1994) Comparison of hydromorphone and meperidine for ureteral colic. *Acad Emerg Med* **1**(6): 539–43.
- Jeffs SA, Hall JE & Morris S (2002) Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia. *Br J Anaesth* **89**(3): 424–7.
- Jensen LL, Handberg G, Helbo-Hansen HS et al (2008) No morphine sparing effect of ketamine added to morphine for patient-controlled intravenous analgesia after uterine artery embolization. *Acta Anaesthesiol Scand* **52**(4): 479–86.
- Jick H, Derby LE, Vasilakis C et al (1998) The risk of seizures associated with tramadol. *Pharmacotherapy* **18**(3): 607–11.
- Johns RA, Hanousek J & Montgomery JE (2006) A comparison of cyclizine and granisetron alone and in combination for the prevention of postoperative nausea and vomiting. *Anaesthesia* **61**(11): 1053–7.
- Johnson RE, Fudala PJ & Payne R (2005) Buprenorphine: considerations for pain management. *J Pain Symptom Manage* **29**(3): 297–326.
- Jokela RM, Ahonen JV, Tallgren MK et al (2009) The effective analgesic dose of dexamethasone after laparoscopic hysterectomy. *Anesth Analg* **109**(2): 607–15.
- Joly V, Richebe P, Guignard B et al (2005) Remifentanyl-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* **103**(1): 147–55.
- Jones JG, Sapsford DJ & Wheatley RG (1990) Postoperative hypoxaemia: mechanisms and time course. *Anaesthesia* **45**(7): 566–73.

- Joo DT (2007) Mechanisms of opioid tolerance: merging evidence and therapeutic implications. *Can J Anaesth* **54**(12): 969–76.
- Joy JE, Watson SJ & Benson JA (1999) *Marijuana and Medicine: Assessing the Science Base*. Washington DC, National Academy Press.
- Juhl GI, Norholt SE, Tonnesen E et al (2006) Analgesic efficacy and safety of intravenous paracetamol (acetaminophen) administered as a 2 g starting dose following third molar surgery. *Eur J Pain* **10**(4): 371–7.
- Juhlin T, Bjorkman S & Hoglund P (2005) Cyclooxygenase inhibition causes marked impairment of renal function in elderly subjects treated with diuretics and ACE-inhibitors. *Eur J Heart Fail* **7**(6): 1049–56.
- Justo D, Gal-Oz A, Paran Y et al (2006) Methadone-associated Torsades de Pointes (polymorphic ventricular tachycardia) in opioid-dependent patients. *Addiction* **101**(9): 1333–8.
- Kalso E, Tasmuth T & Neuvonen PJ (1996) Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. *Pain* **64**(2): 293–302.
- Kalso E, Tramer MR, McQuay HJ et al (1998) Systemic local-anaesthetic-type drugs in chronic pain: a systematic review. *Eur J Pain* **2**(1): 3–14.
- Kam PCA & So A (2009) COX-3: uncertainties and controversies. *Curr Anaesth Crit Care* **20**: 50–53.
- Kardash KJ, Sarrazin F, Tessler MJ et al (2008) Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. *Anesth Analg* **106**(4): 1253–7.
- Katz J, Schmid R, Snijdelaar DG et al (2004) Pre-emptive analgesia using intravenous fentanyl plus low-dose ketamine for radical prostatectomy under general anesthesia does not produce short-term or long-term reductions in pain or analgesic use. *Pain* **110**(3): 707–18.
- Katz J & Clarke K (2008) Preventive analgesia and beyond: current status, evidence and future directions. In: *Clinical Pain Management: Acute Pain* edn. Macintyre PE, Walher SM and Rowbotham D, J. (eds). London, Hodder Arnold.
- Kearney PM, Baigent C, Godwin J et al (2006) Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* **332**(7553): 1302–8.
- Kehlet H (1997) Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* **78**(5): 606–17.
- Kehlet H (2007) Glucocorticoids for peri-operative analgesia: how far are we from general recommendations? *Acta Anaesthesiol Scand* **51**(9): 1133–5.
- Kerrick JM, Fine PG, Lipman AG et al (1993) Low-dose amitriptyline as an adjunct to opioids for postoperative orthopedic pain: a placebo-controlled trial. *Pain* **52**(3): 325–30.
- Kim JT, Ren CJ, Fielding GA et al (2007) Treatment with lavender aromatherapy in the post-anesthesia care unit reduces opioid requirements of morbidly obese patients undergoing laparoscopic adjustable gastric banding. *Obes Surg* **17**(7): 920–5.
- Kinsella LJ & Green R (1995) 'Anesthesia paresthetica': nitrous oxide-induced cobalamin deficiency. *Neurology* **45**(8): 1608–10.
- Kirchheiner J, Schmidt H, Tzvetkov M et al (2007) Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* **7**(4): 257–65.
- Kirchheiner J, Keulen JT, Bauer S et al (2008) Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. *J Clin Psychopharmacol* **28**(1): 78–83.
- Kjellberg F & Tramer MR (2001) Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *Eur J Anaesthesiol* **18**(6): 346–57.
- Klepstad P, Dale O, Kaasa S et al (2003) Influences on serum concentrations of morphine, M6G and M3G during routine clinical drug monitoring: a prospective survey in 300 adult cancer patients. *Acta Anaesthesiol Scand* **47**(6): 725–31.
- Klepstad P, Dale O, Skorpen F et al (2005) Genetic variability and clinical efficacy of morphine. *Acta Anaesthesiol Scand* **49**(7): 902–8.



- Kluger MT, Owen H, Watson D et al (1992) Oxyhaemoglobin saturation following elective abdominal surgery in patients receiving continuous intravenous infusion or intramuscular morphine analgesia. *Anaesthesia* **47**(3): 256–60.
- Knopp JA, Diner BM, Blitz M et al (2005) Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. *Osteoporos Int* **16**(10): 1281–90.
- Koç S, Memis D & Sut N (2007) The preoperative use of gabapentin, dexamethasone, and their combination in varicocele surgery: a randomized controlled trial. *Anesth Analg* **105**(4): 1137–42.
- Kollender Y, Bickels J, Stocki D et al (2008) Subanaesthetic ketamine spares postoperative morphine and controls pain better than standard morphine does alone in orthopaedic-oncological patients. *Eur J Cancer* **44**(7): 954–62.
- Kopka A, Wallace E, Reilly G et al (2007) Observational study of perioperative PtcCO<sub>2</sub> and SpO<sub>2</sub> in non-ventilated patients receiving epidural infusion or patient-controlled analgesia using a single earlobe monitor (TOSCA). *Br J Anaesth* **99**(4): 567–71.
- Koppert W, Ihmsen H, Korber N et al (2005) Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain* **118**(1-2): 15–22.
- Kovac AL (2006) Meta-analysis of the use of rescue antiemetics following PONV prophylactic failure with 5-HT<sub>3</sub> antagonist/dexamethasone versus single-agent therapies. *Ann Pharmacother* **40**(5): 873–87.
- Kramer BK, Kammerl MC & Komhoff M (2004) Renal cyclooxygenase-2 (COX-2). Physiological, pathophysiological, and clinical implications. *Kidney Blood Press Res* **27**(1): 43–62.
- Kress HG (2009) Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain* **13**(3): 219–30.
- Krishna S, Hughes LF & Lin SY (2003) Postoperative hemorrhage with nonsteroidal anti-inflammatory drug use after tonsillectomy: a meta-analysis. *Arch Otolaryngol Head Neck Surg* **129**(10): 1086–9.
- Kuo CP, Jao SW, Chen KM et al (2006) Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth* **97**(5): 640–6.
- Kvarnstrom A, Karlsten R, Quiding H et al (2004) The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. *Acta Anaesthesiol Scand* **48**(4): 498–506.
- Lalovic B, Kharasch E, Hoffer C et al (2006) Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin Pharmacol Ther* **79**(5): 461–79.
- Lanas A, Serrano P, Bajador E et al (2003) Risk of upper gastrointestinal bleeding associated with non-aspirin cardiovascular drugs, analgesics and nonsteroidal anti-inflammatory drugs. *Eur J Gastroenterol Hepatol* **15**(2): 173–8.
- Landau R (2006) One size does not fit all: genetic variability of mu-opioid receptor and postoperative morphine consumption. *Anesthesiology* **105**(2): 235–7.
- Landwehr S, Kiencke P, Giesecke T et al (2005) A comparison between IV paracetamol and IV metamizol for postoperative analgesia after retinal surgery. *Curr Med Res Opin* **21**(10): 1569–75.
- Latta KS, Ginsberg B & Barkin RL (2002) Meperidine: a critical review. *Am J Ther* **9**(1): 53–68.
- Lau H & Patil NG (2004) Acute pain after endoscopic totally extraperitoneal (TEP) inguinal hernioplasty: multivariate analysis of predictive factors. *Surg Endosc* **18**(1): 92–6.
- Laugesen S, Enggaard TP, Pedersen RS et al (2005) Paroxetine, a cytochrome P450 2D6 inhibitor, diminishes the stereoselective O-demethylation and reduces the hypoalgesic effect of tramadol. *Clin Pharmacol Ther* **77**(4): 312–23.
- Lee A & Done ML (2004) Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev*(3): CD003281.
- Lee A, Cooper MG, Craig JC et al (2007) Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. *Cochrane Database Syst Rev*(2): CD002765.
- Lee LH, Irwin MG, Yao TJ et al (2008) Timing of intraoperative parecoxib analgesia in colorectal surgery. *Acute Pain* **10**(3-4): 123–30.

- Lee Y, Wang PK, Lai HY et al (2007) Haloperidol is as effective as ondansetron for preventing postoperative nausea and vomiting. *Can J Anaesth* **54**(5): 349–54.
- Levendoglu F, Ogun CO, Ozerbil O et al (2004) Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine* **29**(7): 743–51.
- Levine JD, Gordon NC, Smith R et al (1986) Desipramine enhances opiate postoperative analgesia. *Pain* **27**(1): 45–9.
- Li Wan Po A & Zhang WY (1997) Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* **315**(7122): 1565–71.
- Lim AW & Schug SA (2001) Tramadol versus morphine as oral step-down analgesia after postoperative epidural analgesia. *Reg Anesth Pain Med* **26**: S133.
- Lin TF, Yeh YC, Lin FS et al (2009) Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth* **102**(1): 117–22.
- Logan DE & Rose JB (2004) Gender differences in post-operative pain and patient controlled analgesia use among adolescent surgical patients. *Pain* **109**(3): 481–7.
- Lotsch J (2005) Opioid metabolites. *J Pain Symptom Manage* **29**(5 Suppl): S10–24.
- Lotsch J, Rohrbacher M, Schmidt H et al (2009) Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? *Pain* **144**(1-2): 119–24.
- Ludwin DB & Shafer SL (2008) Con: The black box warning on droperidol should not be removed (but should be clarified!). *Anesth Analg* **106**(5): 1418–20.
- Lugo RA, Satterfield KL & Kern SE (2005) Pharmacokinetics of methadone. *J Pain Palliat Care Pharmacother* **19**(4): 13–24.
- Luhmann JD, Schootman M, Luhmann SJ et al (2006) A randomized comparison of nitrous oxide plus hematoma block versus ketamine plus midazolam for emergency department forearm fracture reduction in children. *Pediatrics* **118**(4): e1078–86.
- Luzi S, Morrison PD, Powell J et al (2008) What is the mechanism whereby cannabis use increases risk of psychosis? *Neurotox Res* **14**(2-3): 105–12.
- Lysakowski C, Dumont L, Czarnetzki C et al (2007) Magnesium as an adjuvant to postoperative analgesia: a systematic review of randomized trials. *Anesth Analg* **104**(6): 1532–9.
- MacDonald TM & Wei L (2003) Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* **361**(9357): 573–4.
- Macintyre PE & Jarvis DA (1996) Age is the best predictor of postoperative morphine requirements. *Pain* **64**(2): 357–64.
- Macintyre PE & Schug SA (2007) *Acute Pain Management: A Practical Guide*. London, Saunders Elsevier.
- Macintyre PE & Coldrey J (2008) Patient-controlled analgesia. In: *Clinical Pain Management: Acute Pain* edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
- Macintyre PE & Upton R (2008) Acute pain management in the elderly patient. In: *Clinical Pain Management: Acute Pain* 2nd edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
- Madadi P, Shirazi F, Walter FG et al (2008) Establishing causality of CNS depression in breastfed infants following maternal codeine use. *Paediatr Drugs* **10**(6): 399–404.
- Madadi P, Ross CJ, Hayden MR et al (2009) Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* **85**(1): 31–5.
- Mahe I, Bertrand N, Drouet L et al (2005) Paracetamol: a haemorrhagic risk factor in patients on warfarin. *Br J Clin Pharmacol* **59**(3): 371–4.
- Maizels M, Scott B, Cohen W et al (1996) Intranasal lidocaine for treatment of migraine: a randomized, double-blind, controlled trial. *JAMA* **276**(4): 319–21.
- Malan TP, Jr., Marsh G, Hakki SI et al (2003) Parecoxib sodium, a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty. *Anesthesiology* **98**(4): 950–6.
- Mallet C, Daulhac L, Bonnefont J et al (2008) Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. *Pain* **139**(1): 190–200.



- Mancini F, Landolfi C, Muzio M et al (2003) Acetaminophen down-regulates interleukin-1beta-induced nuclear factor-kappaB nuclear translocation in a human astrocytic cell line. *Neurosci Lett* **353**(2): 79–82.
- Mao J (2008) Opioid-induced hyperalgesia. *Pain: Clinical Updates (IASP)* **16**(2).
- Marcou TA, Marque S, Mazoit JX et al (2005) The median effective dose of tramadol and morphine for postoperative patients: a study of interactions. *Anesth Analg* **100**(2): 469–74.
- Marie RM, Le Biez E, Busson P et al (2000) Nitrous oxide anesthesia-associated myelopathy. *Arch Neurol* **57**(3): 380–2.
- Marinangeli F, Ciccozzi A, Donatelli F et al (2002) Clonidine for treatment of postoperative pain: a dose-finding study. *Eur J Pain* **6**(1): 35–42.
- Marjoribanks J, Proctor ML & Farquhar C (2003) Nonsteroidal anti-inflammatory drugs for primary dysmenorrhoea. *Cochrane Database Syst Rev*(4): CD001751.
- Marret E, Flahault A, Samama CM et al (2003) Effects of postoperative, nonsteroidal, antiinflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized, controlled trials. *Anesthesiology* **98**(6): 1497–502.
- Marret E, Kurdi O, Zufferey P et al (2005) Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. *Anesthesiology* **102**(6): 1249–60.
- Marret E, Rolin M, Beaussier M et al (2008) Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *Br J Surg* **95**(11): 1331–8.
- Marshall MA & Ozorio HP (1972) Analgesia for burns dressing using methoxyflurane. *Br J Anaesth* **44**(1): 80–2.
- Martin-Garcia C, Hinojosa M, Berges P et al (2003) Celecoxib, a highly selective COX-2 inhibitor, is safe in aspirin-induced asthma patients. *J Investig Allergol Clin Immunol* **13**(1): 20–5.
- Martin C, Martin A, Rud C et al (1988) [Comparative study of sodium valproate and ketoprofen in the treatment of postoperative pain]. *Ann Fr Anesth Reanim* **7**(5): 387–92.
- Martinez-Zapata MJ, Roque M, Alonso-Coello P et al (2006) Calcitonin for metastatic bone pain. *Cochrane Database Syst Rev* **3**: CD003223.
- Martinez V, Belbachir A, Jaber A et al (2007) The influence of timing of administration on the analgesic efficacy of parecoxib in orthopedic surgery. *Anesth Analg* **104**(6): 1521–7.
- Mathiesen O, Moiniche S & Dahl JB (2007) Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. *BMC Anesthesiol* **7**: 6.
- Mathiesen O, Rasmussen ML, Dierking G et al (2009) Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. *Acta Anaesthesiologica Scandinavica* **53**(2): 227–35.
- McCartney CJ, Sinha A & Katz J (2004) A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. *Anesth Analg* **98**(5): 1385–400.
- McCormack JG, Kelly KP, Wedgwood J et al (2008) The effects of different analgesic regimens on transcutaneous CO<sub>2</sub> after major surgery. *Anaesthesia* **63**(8): 814–21.
- McGettigan P & Henry D (2006) Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* **296**(13): 1633–44.
- McKean S, Kochilas X, Kelleher R et al (2006) Use of intravenous steroids at induction of anaesthesia for adult tonsillectomy to reduce post-operative nausea and vomiting and pain: a double-blind randomized controlled trial. *Clin Otolaryngol* **31**(1): 36–40.
- McNeely JK, Buczulinski B & Rosner DR (2000) Severe neurological impairment in an infant after nitrous oxide anesthesia. *Anesthesiology* **93**(6): 1549–50.
- McNicol ED, Boyce D, Schumann R et al (2008) Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database Syst Rev*(2): CD006332.
- McQuay HJ (1991) Opioid clinical pharmacology and routes of administration. *Br Med Bull* **47**(3): 703–17.
- McQuay HJ & Moore RA (2007) Dose-response in direct comparisons of different doses of aspirin, ibuprofen and paracetamol (acetaminophen) in analgesic studies. *Br J Clin Pharmacol* **63**(3): 271–8.

- Medical Devices International (2009) *Penthrox (methoxyflurane) Inhalation Product Information*. [http://www.medicaldev.com/pdf\\_files/Products\\_Pain\\_Relief\\_Healthcare\\_Professionals\\_Medical/Penthrox\\_Product%20Information%20sheet.pdf](http://www.medicaldev.com/pdf_files/Products_Pain_Relief_Healthcare_Professionals_Medical/Penthrox_Product%20Information%20sheet.pdf) Medical Devices International. Accessed March 2009.
- Merry AF, Webster CS, Holland RL et al (2004) Clinical tolerability of perioperative tenoxicam in 1001 patients—a prospective, controlled, double-blind, multi-centre study. *Pain* **111**(3): 313–22.
- Meyers LE & Judge BS (2008) Myeloneuropathy in a dentist. *Clin Toxicol (Phila)* **46**(10): 1095–6.
- Michelet P, Guervilly C, Helaine A et al (2007) Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation. *Br J Anaesth* **99**(3): 396–403.
- Migita RT, Klein EJ & Garrison MM (2006) Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. *Arch Pediatr Adolesc Med* **160**(1): 46–51.
- Mildh LH, Leino KA & Kirvela OA (1999) Effects of tramadol and meperidine on respiration, plasma catecholamine concentrations, and hemodynamics. *J Clin Anesth* **11**(4): 310–6.
- Minto CF, Schnider TW, Egan TD et al (1997) Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl. I. Model development. *Anesthesiology* **86**(1): 10–23.
- Mitra S (2008) Opioid-induced hyperalgesia: pathophysiology and clinical implications. *J Opioid Manag* **4**(3): 123–30.
- Miyoshi RH & Lackband SG (2001) Systemic Opioid Analgesics. In: *Bonica's Management of Pain* 3rd edn. Loeser JD (eds). Hagerstown, Md, Lippincott Williams & Wilkins 2208.
- Moiniche S, Romsing J, Dahl JB et al (2003) Nonsteroidal antiinflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. *Anesth Analg* **96**(1): 68–77.
- Moore RA, Derry S & McQuay HJ (2007) Cyclo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk. *BMC Musculoskelet Disord* **8**: 73.
- Morrison RS, Magaziner J, Gilbert M et al (2003) Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* **58**(1): 76–81.
- Mulleners WM & Chronicle EP (2008) Anticonvulsants in migraine prophylaxis: a Cochrane review. *Cephalalgia* **28**(6): 585–97.
- Munsterhjelm E, Niemi TT, Ylikorkala O et al (2006) Influence on platelet aggregation of i.v. parecoxib and acetaminophen in healthy volunteers. *Br J Anaesth* **97**(2): 226–31.
- Murray A & Hagen NA (2005) Hydromorphone. *J Pain Symptom Manage* **29**(5 Suppl): S57–66.
- Myles PS, Leslie K, Chan MT et al (2007) Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology* **107**(2): 221–31.
- Myles PS, Chan MT, Kaye DM et al (2008) Effect of nitrous oxide anesthesia on plasma homocysteine and endothelial function. *Anesthesiology* **109**(4): 657–63.
- Myles PS, Chan MT, Leslie K et al (2008) Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. *Br J Anaesth* **100**(6): 780–6.
- Nagele P, Zeugswetter B, Wiener C et al (2008) Influence of methylenetetrahydrofolate reductase gene polymorphisms on homocysteine concentrations after nitrous oxide anesthesia. *Anesthesiology* **109**(1): 36–43.
- Namavar Jahromi B, Tartifzadeh A & Khabnadideh S (2003) Comparison of fennel and mefenamic acid for the treatment of primary dysmenorrhea. *Int J Gynaecol Obstet* **80**(2): 153–7.
- Nestor PJ & Stark RJ (1996) Vitamin B12 myeloneuropathy precipitated by nitrous oxide anaesthesia. *Med J Aust* **165**(3): 174.
- Ng A, Smith G & Davidson AC (2003) Analgesic effects of parecoxib following total abdominal hysterectomy. *Br J Anaesth* **90**(6): 746–9.
- Ng KF, Yuen TS & Ng VM (2006) A comparison of postoperative cognitive function and pain relief with fentanyl or tramadol patient-controlled analgesia. *J Clin Anesth* **18**(3): 205–10.
- Nielsen CK, Ross FB, Lotfipour S et al (2007) Oxycodone and morphine have distinctly different pharmacological profiles: radioligand binding and behavioural studies in two rat models of neuropathic pain. *Pain* **132**(3): 289–300.

- Nikolajsen L, Brandsborg B, Lucht U et al (2006) Chronic pain following total hip arthroplasty: a nationwide questionnaire study. *Acta Anaesthesiol Scand* **50**(4): 495–500.
- Nikolajsen L, Finnerup NB, Kramp S et al (2006) A randomized study of the effects of gabapentin on postamputation pain. *Anesthesiology* **105**(5): 1008–15.
- Nilsson-Ehle H (1998) Age-related changes in cobalamin (vitamin B12) handling. Implications for therapy. *Drugs Aging* **12**(4): 277–92.
- NSW Working Party (2000) *The use of cannabis for medical purposes*. Working Party in the Use of Cannabis for Medical Purposes. Sydney, NSW Government.
- Nussmeier NA, Whelton AA, Brown MT et al (2005) Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* **352**(11): 1081–91.
- Nussmeier NA, Whelton AA, Brown MT et al (2006) Safety and efficacy of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib after noncardiac surgery. *Anesthesiology* **104**(3): 518–26.
- Nuttall GA, Eckerman KM, Jacob KA et al (2007) Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population? *Anesthesiology* **107**(4): 531–6.
- O'Connor A, Schug SA & Cardwell H (2000) A comparison of the efficacy and safety of morphine and pethidine as analgesia for suspected renal colic in the emergency setting. *J Accid Emerg Med* **17**(4): 261–4.
- O'Leary U, Puglia C, Friehling TD et al (1987) Nitrous oxide anesthesia in patients with ischemic chest discomfort: effect on beta-endorphins. *J Clin Pharmacol* **27**(12): 957–61.
- Oderda GM, Said Q, Evans RS et al (2007) Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. *Ann Pharmacother* **41**(3): 400–6.
- Ofman JJ, MacLean CH, Straus WL et al (2002) A metaanalysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. *J Rheumatol* **29**(4): 804–12.
- Ong CK, Lirk P, Seymour RA et al (2005) The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg* **100**(3): 757–73.
- Orhan-Sungur M, Kranke P, Sessler D et al (2008) Does supplemental oxygen reduce postoperative nausea and vomiting? A meta-analysis of randomized controlled trials. *Anesth Analg* **106**(6): 1733–8.
- Oscier CD & Milner QJ (2009) Peri-operative use of paracetamol. *Anaesthesia* **64**(1): 65–72.
- Packer KJ & Titel JH (1969) Methoxyflurane analgesia for burns dressings: experience with the analgizer. *Br J Anaesth* **41**(12): 1080–5.
- Paris A, Horvath R, Basset P et al (2008) Nitrous oxide-oxygen mixture during care of bedsores and painful ulcers in the elderly: a randomized, crossover, open-label pilot study. *J Pain Symptom Manage* **35**(2): 171–6.
- Park J, Forrest J, Kolesar R et al (1996) Oral clonidine reduces postoperative PCA morphine requirements. *Can J Anaesth* **43**(9): 900–6.
- Park SY, Moon SH, Park MS et al (2005) The effects of ketorolac injected via patient controlled analgesia postoperatively on spinal fusion. *Yonsei Med J* **46**(2): 245–51.
- Parra D, Beckey NP & Stevens GR (2007) The effect of acetaminophen on the international normalized ratio in patients stabilized on warfarin therapy. *Pharmacotherapy* **27**(5): 675–83.
- Pavlaklis N, Schmidt R & Stockler M (2005) Bisphosphonates for breast cancer. *Cochrane Database Syst Rev*(3): CD003474.
- Peng PW & Sandler AN (1999) A review of the use of fentanyl analgesia in the management of acute pain in adults. *Anesthesiology* **90**(2): 576–99.
- Peng PW, Wijeyesundera DN & Li CC (2007) Use of gabapentin for perioperative pain control – a meta-analysis. *Pain Res Manag* **12**(2): 85–92.
- Perez RS, Kwakkel G, Zuurmond WW et al (2001) Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. *J Pain Symptom Manage* **21**(6): 511–26.
- Philip BK, Reese PR & Burch SP (2002) The economic impact of opioids on postoperative pain management. *J Clin Anesth* **14**(5): 354–64.

- Pickering G, Lorient MA, Libert F et al (2006) Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. *Clin Pharmacol Ther* **79**(4): 371–8.
- Pickering G, Esteve V, Lorient MA et al (2008) Acetaminophen reinforces descending inhibitory pain pathways. *Clin Pharmacol Ther* **84**(1): 47–51.
- Pilotto A, Franceschi M, Leandro G et al (2003) The risk of upper gastrointestinal bleeding in elderly users of aspirin and other non-steroidal anti-inflammatory drugs: the role of gastroprotective drugs. *Aging Clin Exp Res* **15**(6): 494–9.
- Pradhan BB, Tatsumi RL, Gallina J et al (2008) Ketorolac and spinal fusion: does the perioperative use of ketorolac really inhibit spinal fusion? *Spine* **33**(19): 2079–82.
- Proctor ML & Murphy PA (2001) Herbal and dietary therapies for primary and secondary dysmenorrhoea. *Cochrane Database Syst Rev*(3): CD002124.
- Quigley C (2004) Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev*(3): CD004847.
- Radbruch L, Grond S & Lehmann KA (1996) A risk-benefit assessment of tramadol in the management of pain. *Drug Saf* **15**(1): 8–29.
- Raffa RB, Friderichs E, Reimann W et al (1992) Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther* **260**(1): 275–85.
- Ramsay DS, Leroux BG, Rothen M et al (2005) Nitrous oxide analgesia in humans: acute and chronic tolerance. *Pain* **114**(1-2): 19–28.
- Rapp SE, Egan KJ, Ross BK et al (1996) A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* **82**(5): 1043–8.
- RCA (1998) *Guidelines for the use of nonsteroidal antiinflammatory drugs in the perioperative period*. London, Royal College of Anaesthetists.
- Ready LB, Oden R, Chadwick HS et al (1988) Development of an anesthesiology-based postoperative pain management service. *Anesthesiology* **68**(1): 100–6.
- Remy C, Marret E & Bonnet F (2005) Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. *Br J Anaesth* **94**(4): 505–13.
- Reutens DC, Fatovich DM, Stewart-Wynne EG et al (1991) Is intravenous lidocaine clinically effective in acute migraine? *Cephalalgia* **11**(6): 245–7.
- Reynolds LW, Hoo RK, Brill RJ et al (2003) The COX-2 specific inhibitor, valdecoxib, is an effective, opioid-sparing analgesic in patients undergoing total knee arthroplasty. *J Pain Symptom Manage* **25**(2): 133–41.
- Riley J, Eisenberg E, Muller-Schwefe G et al (2008) Oxycodone: a review of its use in the management of pain. *Curr Med Res Opin* **24**(1): 175–92.
- Rintala DH, Holmes SA, Courtade D et al (2007) Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Arch Phys Med Rehabil* **88**(12): 1547–60.
- Roberts GW, Bekker TB, Carlsen HH et al (2005) Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. *Anesth Analg* **101**(5): 1343–8.
- Robertson A, Suryanarayanan R & Banerjee A (2007) Homeopathic *Arnica montana* for post-tonsillectomy analgesia: a randomised placebo control trial. *Homeopathy* **96**(1): 17–21.
- Robinson SL, Rowbotham DJ & Smith G (1991) Morphine compared with diamorphine. A comparison of dose requirements and side-effects after hip surgery. *Anaesthesia* **46**(7): 538–40.
- Rochford M, Kiernan TJ & Aziz A (2007) Dolasetron overdose resulting in prolonged QTc interval and severe hypotension: a case report and literature review. *Emerg Med J* **24**(7): 515–7.
- Roelofs PD, Deyo RA, Koes BW et al (2008) Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev*(1): CD000396.
- Rog DJ, Nurmikko TJ, Friede T et al (2005) Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* **65**(6): 812–9.

- Romberg R, Olofsen E, Sarton E et al (2003) Pharmacodynamic effect of morphine-6-glucuronide versus morphine on hypoxic and hypercapnic breathing in healthy volunteers. *Anesthesiology* **99**(4): 788–98.
- Romberg R, van Dorp E, Hollander J et al (2007) A randomized, double-blind, placebo-controlled pilot study of IV morphine-6-glucuronide for postoperative pain relief after knee replacement surgery. *Clin J Pain* **23**(3): 197–203.
- Romsing J, Moiniche S & Dahl JB (2002) Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. *Br J Anaesth* **88**(2): 215–26.
- Romsing J & Moiniche S (2004) A systematic review of COX-2 inhibitors compared with traditional NSAIDs, or different COX-2 inhibitors for post-operative pain. *Acta Anaesthesiol Scand* **48**(5): 525–46.
- Romsing J, Moiniche S, Mathiesen O et al (2005) Reduction of opioid-related adverse events: using opioid-sparing analgesia with COX-2 inhibitors lacks documentation: a systematic review. *Acta Anaesthesiol Scand* **49**(2): 133–42.
- Romundstad L, Breivik H, Niemi G et al (2004) Methylprednisolone intravenously 1 day after surgery has sustained analgesic and opioid-sparing effects. *Acta Anaesthesiol Scand* **48**(10): 1223–31.
- Romundstad L, Breivik H, Roald H et al (2006) Methylprednisolone reduces pain, emesis, and fatigue after breast augmentation surgery: a single-dose, randomized, parallel-group study with methylprednisolone 125 mg, parecoxib 40 mg, and placebo. *Anesth Analg* **102**(2): 418–25.
- Romundstad L & Stubhaug A (2007) Glucocorticoids for acute and persistent postoperative neuropathic pain: what is the evidence? *Anesthesiology* **107**(3): 371–3.
- Rosen MA (2002) Nitrous oxide for relief of labor pain: a systematic review. *Am J Obstet Gynecol* **186**(5 Suppl Nature): S110–26.
- Rosener M & Dichgans J (1996) Severe combined degeneration of the spinal cord after nitrous oxide anaesthesia in a vegetarian. *J Neurol Neurosurg Psychiatry* **60**(3): 354.
- Rosow CE, Gomery P, Chen TY et al (2007) Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone. *Clin Pharmacol Ther* **82**(1): 48–53.
- Rosow CE, Haspel KL, Smith SE et al (2008) Haloperidol versus ondansetron for prophylaxis of postoperative nausea and vomiting. *Anesth Analg* **106**(5): 1407–9.
- Rosseland LA & Stubhaug A (2004) Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. *Pain* **112**(3): 248–53.
- Rosseland LA, Solheim N & Stubhaug A (2008) Pain and disability 1 year after knee arthroscopic procedures. *Acta Anaesthesiol Scand* **52**(3): 332–7.
- Rusch D, Arndt C, Martin H et al (2007) The addition of dexamethasone to dolasetron or haloperidol for treatment of established postoperative nausea and vomiting. *Anaesthesia* **62**(8): 810–7.
- Saarto T & Wiffen P (2007) Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*(4): CD005454.
- Sahin F, Yilmaz F, Kotevoglou N et al (2006) Efficacy of salmon calcitonin in complex regional pain syndrome (type 1) in addition to physical therapy. *Clin Rheumatol* **25**(2): 143–8.
- Sanders RD, Weimann J & Maze M (2008) Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *Anesthesiology* **109**(4): 707–22.
- Sauerland S, Nagelschmidt M, Mallmann P et al (2000) Risks and benefits of preoperative high dose methylprednisolone in surgical patients: a systematic review. *Drug Saf* **23**(5): 449–61.
- Schenk BE, Kuipers EJ, Klinkenberg-Knol EC et al (1999) Atrophic gastritis during long-term omeprazole therapy affects serum vitamin B12 levels. *Aliment Pharmacol Ther* **13**(10): 1343–6.
- Schilling RF (1986) Is nitrous oxide a dangerous anesthetic for vitamin B12-deficient subjects? *JAMA* **255**(12): 1605–6.
- Schley M, Topfner S, Wiech K et al (2007) Continuous brachial plexus blockade in combination with the NMDA receptor antagonist memantine prevents phantom pain in acute traumatic upper limb amputees. *Eur J Pain* **11**(3): 299–308.
- Schug SA, Sidebotham DA, McGuinnety M et al (1998) Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. *Anesth Analg* **87**(2): 368–72.

- Schug SA, Joshi GP, Camu F et al (2009) Cardiovascular safety of the cyclooxygenase-2 selective inhibitors parecoxib and valdecoxib in the postoperative setting: an analysis of integrated data. *Anesth Analg* **108**(1): 299–307.
- Scott JC & Stanski DR (1987) Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* **240**(1): 159–66.
- Scott JM, Dinn JJ, Wilson P et al (1981) Pathogenesis of subacute combined degeneration: a result of methyl group deficiency. *Lancet* **2**(8242): 334–7.
- Seeling W, Kneer L, Buchele B et al (2006) [Delta(9)-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain]. *Anaesthesist* **55**(4): 391–400.
- Sesso RM, lunes Y & Melo AC (1999) Myeloneuropathy following nitrous oxide anaesthesia in a patient with macrocytic anaemia. *Neuroradiology* **41**(8): 588–90.
- Shapiro A, Zohar E, Zaslansky R et al (2005) The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth* **17**(7): 537–42.
- Shaw AD & Morgan M (1998) Nitrous oxide: time to stop laughing? *Anaesthesia* **53**(3): 213–5.
- Sheen MJ, Ho ST, Lee CH, Tsung YC & Chang FL (2008) Preoperative gabapentin prevents intrathecal morphine-induced pruritus after orthopedic surgery. *Anesth Analg* **106**(6): 1868–72.
- Sheen MJ, Ho ST, Lee CH, Tsung YC, Chang FL et al (2008) Prophylactic mirtazapine reduces intrathecal morphine-induced pruritus. *Br J Anaesth* **101**(5): 711–5.
- Sia AT, Lim Y, Lim EC et al (2008) A118G single nucleotide polymorphism of human mu-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. *Anesthesiology* **109**(3): 520–6.
- Siddall PJ, Cousins MJ, Otte A et al (2006) Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* **67**(10): 1792–800.
- Silvasti M, Svartling N, Pitkanen M et al (2000) Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. *Eur J Anaesthesiol* **17**(7): 448–55.
- Silverman ME, Shih RD & Allegra J (2004) Morphine induces less nausea than meperidine when administered parenterally. *J Emerg Med* **27**(3): 241–3.
- Simmons DL, Botting RM & Hla T (2004) Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. *Pharmacol Rev* **56**(3): 387–437.
- Simon RA & Namazy J (2003) Adverse reactions to aspirin and nonsteroidal antiinflammatory drugs (NSAIDs). *Clin Rev Allergy Immunol* **24**(3): 239–52.
- Simopoulos TT, Smith HS, Peeters-Asdourian C et al (2002) Use of meperidine in patient-controlled analgesia and the development of a normeperidine toxic reaction. *Arch Surg* **137**(1): 84–8.
- Sinatra RS, Jahr JS, Reynolds LW et al (2005) Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology* **102**(4): 822–31.
- Sindrup SH & Jensen TS (1999) Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* **83**(3): 389–400.
- Singer MA, Lazaridis C, Nations SP et al (2008) Reversible nitrous oxide-induced myeloneuropathy with pernicious anemia: case report and literature review. *Muscle Nerve* **37**(1): 125–9.
- Smith CA, Collins CT, Cyna AM et al (2006) Complementary and alternative therapies for pain management in labour. *Cochrane Database Syst Rev*(4): CD003521.
- Smith MT (2000) Neuroexcitatory effects of morphine and hydromorphone: evidence implicating the 3-glucuronide metabolites. *Clin Exp Pharmacol Physiol* **27**(7): 524–8.
- Smith TW, Binning AR & Dahan A (2009) Efficacy and safety of morphine-6-glucuronide (M6G) for postoperative pain relief: a randomized, double-blind study. *Eur J Pain* **13**(3): 293–9.
- Snabes MC, Jakimiuk AJ, Kotarski J et al (2007) Parecoxib sodium administered over several days reduces pain after gynecologic surgery via laparotomy. *J Clin Anesth* **19**(6): 448–55.



- Snijdelaar DG, Koren G & Katz J (2004) Effects of perioperative oral amantadine on postoperative pain and morphine consumption in patients after radical prostatectomy: results of a preliminary study. *Anesthesiology* **100**(1): 134–41.
- Somogyi AA, Barratt DT & Collier JK (2007) Pharmacogenetics of opioids. *Clin Pharmacol Ther* **81**(3): 429–44.
- Somyreddy K & Kothari M (2008) Nitrous oxide induced sub-acute combined degeneration of spinal cord: a case report. *Electromyogr Clin Neurophysiol* **48**(5): 225–8.
- Sorich M, Osborne GA, Jarvis DA et al (2004) Comparison of dextropropoxyphene and paracetamol with paracetamol after third molar dental extractions. *J Pharm Pract Res* **34**(1): 22–25.
- Stahl C, Christrup LL, Andersen SD et al (2006) A comparative study of oxycodone and morphine in a multi-modal, tissue-differentiated experimental pain model. *Pain* **123**(1-2): 28–36.
- Staiger TO, Gaster B, Sullivan MD et al (2003) Systematic review of antidepressants in the treatment of chronic low back pain. *Spine* **28**(22): 2540–5.
- Stamer UM, Lehnen K, Hothker F et al (2003) Impact of CYP2D6 genotype on postoperative tramadol analgesia. *Pain* **105**(1-2): 231–8.
- Stamer UM & Stuber F (2007) Genetic factors in pain and its treatment. *Curr Opin Anaesthesiol* **20**(5): 478–84.
- Stevenson C, Devaraj VS, Fountain-Barber A et al (2003) Homeopathic arnica for prevention of pain and bruising: randomized placebo-controlled trial in hand surgery. *J R Soc Med* **96**(2): 60–5.
- Stoltz RR, Harris SI, Kuss ME et al (2002) Upper GI mucosal effects of parecoxib sodium in healthy elderly subjects. *Am J Gastroenterol* **97**(1): 65–71.
- Straube S, Derry S, McQuay HJ et al (2005) Effect of preoperative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies. *Acta Anaesthesiol Scand* **49**(5): 601–13.
- Strom BL, Berlin JA, Kinman JL et al (1996) Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. *JAMA* **275**(5): 376–82.
- Stubhaug A, Breivik H, Eide PK et al (1997) Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* **41**(9): 1124–32.
- Stubhaug A, Romundstad L, Kaasa T et al (2007) Methylprednisolone and ketorolac rapidly reduce hyperalgesia around a skin burn injury and increase pressure pain thresholds. *Acta Anaesthesiol Scand* **51**(9): 1138–46.
- Sultan A, Gaskell H, Derry S et al (2008) Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. *BMC Neurol* **8**: 29.
- Sun T, Sacan O, White PF et al (2008) Perioperative versus postoperative celecoxib on patient outcomes after major plastic surgery procedures. *Anesth Analg* **106**(3): 950–8.
- Suzuki M, Haraguti S, Sugimoto K et al (2006) Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* **105**(1): 111–9.
- Sveticic G, Farzanegan F, Zmoos P et al (2008) Is the combination of morphine with ketamine better than morphine alone for postoperative intravenous patient-controlled analgesia? *Anesth Analg* **106**(1): 287–93.
- Sweeney BP (2007) Pharmacogenomics and anaesthesia: explaining the variability in response to opiates. *Eur J Anaesthesiol* **24**(3): 209–12.
- Szczeklik A & Stevenson DD (2003) Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* **111**(5): 913–21.
- Taenzer AH, Clark C & Curry CS (2000) Gender affects report of pain and function after arthroscopic anterior cruciate ligament reconstruction. *Anesthesiology* **93**(3): 670–5.
- Tai Q, Kirshblum S, Chen B et al (2002) Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial. *J Spinal Cord Med* **25**(2): 100–5.



- Tanen DA, Miller S, French T et al (2003) Intravenous sodium valproate versus prochlorperazine for the emergency department treatment of acute migraine headaches: a prospective, randomized, double-blind trial. *Ann Emerg Med* **41**(6): 847–53.
- Targownik LE, Metge CJ, Leung S et al (2008) The relative efficacies of gastroprotective strategies in chronic users of nonsteroidal anti-inflammatory drugs. *Gastroenterology* **134**(4): 937–44.
- Tarkkila P, Tuominen M & Lindgren L (1997) Comparison of respiratory effects of tramadol and oxycodone. *J Clin Anesth* **9**(7): 582–5.
- Tarkkila P, Tuominen M & Lindgren L (1998) Comparison of respiratory effects of tramadol and pethidine. *Eur J Anaesthesiol* **15**(1): 64–8.
- Tasmuth T, Hartel B & Kalso E (2002) Venlafaxine in neuropathic pain following treatment of breast cancer. *Eur J Pain* **6**(1): 17–24.
- Thagaard KS, Jensen HH & Raeder J (2007) Analgesic and antiemetic effect of ketorolac vs. betamethasone or dexamethasone after ambulatory surgery. *Acta Anaesthesiol Scand* **51**(3): 271–7.
- Thevenin A, Beloeil H, Blanie A et al (2008) The limited efficacy of tramadol in postoperative patients: a study of ED80 using the continual reassessment method. *Anesth Analg* **106**(2): 622–7.
- Tiippana EM, Hamunen K, Kontinen VK et al (2007) Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* **104**(6): 1545–56.
- Toh BH, van Driel IR & Gleeson PA (1997) Pernicious anemia. *N Engl J Med* **337**(20): 1441–8.
- Tomkins GE, Jackson JL, O'Malley PG et al (2001) Treatment of chronic headache with antidepressants: a meta-analysis. *Am J Med* **111**(1): 54–63.
- Toms L, McQuay HJ, Derry S et al (2008) Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database Syst Rev*(4): CD004602.
- Toomath RJ & Morrison RB (1987) Renal failure following methoxyflurane analgesia. *NZ Med J*.
- Tramer MR (2001) A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part II. Recommendations for prevention and treatment, and research agenda. *Acta Anaesthesiologica Scandinavica* **45**(1): 14–9.
- Tseng YF, Chen CH & Yang YH (2005) Rose tea for relief of primary dysmenorrhea in adolescents: a randomized controlled trial in Taiwan. *J Midwifery Womens Health* **50**(5): e51–7.
- Turan A, Kaya G, Karamanlioglu B et al (2006) Effect of oral gabapentin on postoperative epidural analgesia. *Br J Anaesth* **96**(2): 242–6.
- Uchiyama K, Kawai M, Tani M et al (2006) Gender differences in postoperative pain after laparoscopic cholecystectomy. *Surg Endosc* **20**(3): 448–51.
- Unlugenc H, Gunduz M, Ozalevli M et al (2002) A comparative study on the analgesic effect of tramadol, tramadol plus magnesium, and tramadol plus ketamine for postoperative pain management after major abdominal surgery. *Acta Anaesthesiol Scand* **46**(8): 1025–30.
- Unlugenc H, Ozalevli M, Guler T et al (2003) Postoperative pain management with intravenous patient-controlled morphine: comparison of the effect of adding magnesium or ketamine. *Eur J Anaesthesiol* **20**(5): 416–21.
- Urban MK, Ya Deau JT, Wukovits B et al (2008) Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. *HSS J* **4**(1): 62–5.
- Urquhart DM, Hoving JL, Assendelft WW et al (2008) Antidepressants for non-specific low back pain. *Cochrane Database Syst Rev*(1): CD001703.
- Van Aken H, Thys L, Veekman L et al (2004) Assessing analgesia in single and repeated administrations of propacetamol for postoperative pain: comparison with morphine after dental surgery. *Anesth Analg* **98**(1): 159–65.
- van Dorp EL, Yassen A, Sarton E et al (2006) Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology* **105**(1): 51–7.
- van Dorp EL, Romberg R, Sarton E et al (2006) Morphine-6-glucuronide: morphine's successor for postoperative pain relief? *Anesth Analg* **102**(6): 1789–97.

- Varrassi G, Marinangeli F, Agro F et al (1999) A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gynecologic surgery. *Anesth Analg* **88**(3): 611–6.
- Venn RM, Bradshaw CJ, Spencer R et al (1999) Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* **54**(12): 1136–42.
- Vila H, Jr., Smith RA, Augustyniak MJ et al (2005) The efficacy and safety of pain management before and after implementation of hospital-wide pain management standards: is patient safety compromised by treatment based solely on numerical pain ratings? *Anesth Analg* **101**(2): 474–80.
- Visser E (2005) A review of calcitonin and its use in the treatment of acute pain. *Acute Pain* **7**(4): 143–8.
- Visser E & Schug SA (2006) The role of ketamine in pain management. *Biomed Pharmacother* **60**(7): 341–8.
- Vondrackova D, Leyendecker P, Meissner W et al (2008) Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *J Pain* **9**(12): 1144–54.
- Wallace MS, Barger D & Schulteis G (2002) The effect of chronic oral desipramine on capsaicin-induced allodynia and hyperalgesia: a double-blinded, placebo-controlled, crossover study. *Anesth Analg* **95**(4): 973–8.
- Wallenborn J, Gelbrich G, Bulst D et al (2006) Prevention of postoperative nausea and vomiting by metoclopramide combined with dexamethasone: randomised double blind multicentre trial. *BMJ* **333**(7563): 324.
- Wang TF, Liu YH, Chu CC et al (2008) Low-dose haloperidol prevents post-operative nausea and vomiting after ambulatory laparoscopic surgery. *Acta Anaesthesiol Scand* **52**(2): 280–4.
- Warren PM, Taylor JH, Nicholson KE et al (2000) Influence of tramadol on the ventilatory response to hypoxia in humans. *Br J Anaesth* **85**(2): 211–6.
- Wasiak J & Cleland H (2007) Lidocaine for pain relief in burn injured patients. *Cochrane Database Syst Rev*(3): CD005622.
- Waters MF, Kang GA, Mazziotta JC et al (2005) Nitrous oxide inhalation as a cause of cervical myelopathy. *Acta Neurologica Scandinavica*.
- Webb AR, Skinner BS, Leong S et al (2007) The addition of a small-dose ketamine infusion to tramadol for postoperative analgesia: a double-blinded, placebo-controlled, randomized trial after abdominal surgery. *Anesth Analg* **104**(4): 912–7.
- Wedam EF, Bigelow GE, Johnson RE et al (2007) QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Intern Med* **167**(22): 2469–75.
- Weil K, Hooper L, Afzal Z et al (2007) Paracetamol for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database Syst Rev*(3): CD004487.
- Weimann J (2003) Toxicity of nitrous oxide. *Best Pract Res Clin Anaesthesiol* **17**(1): 47–61.
- Weinbroum AA (2003) A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. *Anesth Analg* **96**(3): 789–95.
- Weinger MB (2007) Dangers of postoperative opioids. *APSF Newsletter* **2006-2007**: 6107.
- Weschules DJ & Bain KT (2008) A systematic review of opioid conversion ratios used with methadone for the treatment of pain. *Pain Med* **9**(5): 595–612.
- Weschules DJ, Bain KT & Richeimer S (2008) Actual and potential drug interactions associated with methadone. *Pain Med* **9**(3): 315–44.
- West PM & Fernandez C (2003) Safety of COX-2 inhibitors in asthma patients with aspirin hypersensitivity. *Ann Pharmacother* **37**(10): 1497–501.
- Wheatley RG, Somerville ID, Sapsford DJ et al (1990) Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. *Br J Anaesth* **64**(3): 267–75.
- White PF, Song D, Abrao J et al (2005) Effect of low-dose droperidol on the QT interval during and after general anesthesia: a placebo-controlled study. *Anesthesiology* **102**(6): 1101–5.

- White PF, Sacan O, Tufanogullari B et al (2007) Effect of short-term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. *Can J Anaesth* **54**(5): 342–8.
- White WB, West CR, Borer JS et al (2007) Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. *Am J Cardiol* **99**(1): 91–8.
- WHO (1996) *Cancer Pain Relief: with a guide to opioid availability*. Geneva, World Health Organisation.
- Wiffen P, Collins S, McQuay H et al (2005) Anticonvulsant drugs for acute and chronic pain. *Cochrane Database Syst Rev*(3): CD001133.
- Wiffen PJ, McQuay HJ, Edwards JE et al (2005) Gabapentin for acute and chronic pain. *Cochrane Database Syst Rev*(3): CD005452.
- Wiffen PJ, McQuay HJ & Moore RA (2005) Carbamazepine for acute and chronic pain. *Cochrane Database Syst Rev*(3): CD005451.
- Wiffen PJ & Rees J (2007) Lamotrigine for acute and chronic pain. *Cochrane Database Syst Rev*(2): CD006044.
- Wilder-Smith CH, Hill L, Osler W et al (1999) Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. *Dig Dis Sci* **44**(6): 1107–16.
- Wilder-Smith CH, Hill L, Wilkins J et al (1999) Effects of morphine and tramadol on somatic and visceral sensory function and gastrointestinal motility after abdominal surgery. *Anesthesiology* **91**(3): 639–47.
- Wilder-Smith CH, Hill LT & Laurent S (2005) Postamputation pain and sensory changes in treatment-naïve patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo. *Anesthesiology* **103**(3): 619–28.
- Wilsey B, Marcotte T, Tsodikov A et al (2008) A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* **9**(6): 506–21.
- Woodhouse A, Ward ME & Mather LE (1999) Intra-subject variability in post-operative patient-controlled analgesia (PCA): is the patient equally satisfied with morphine, pethidine and fentanyl? *Pain* **80**(3): 545–53.
- Wright AW, Mather LE & Smith MT (2001) Hydromorphone-3-glucuronide: a more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. *Life Sci* **69**(4): 409–20.
- Wu CL, Tella P, Staats PS et al (2002) Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial. *Anesthesiology* **96**(4): 841–8.
- Wu MS, Hsu YD, Lin JC et al (2007) Spinal myoclonus in subacute combined degeneration caused by nitrous oxide intoxication. *Acta Neurol Taiwan* **16**(2): 102–5.
- Yamauchi M, Asano M, Watanabe M et al (2008) Continuous low-dose ketamine improves the analgesic effects of fentanyl patient-controlled analgesia after cervical spine surgery. *Anesth Analg* **107**(3): 1041–4.
- Yanagihara Y, Ohtani M, Kariya S et al (2003) Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharm Drug Dispos* **24**(1): 37–43.
- Yassen A, Olofsen E, Romberg R et al (2006) Mechanism-based pharmacokinetic-pharmacodynamic modeling of the antinociceptive effect of buprenorphine in healthy volunteers. *Anesthesiology* **104**(6): 1232–42.
- Yuen KK, Shelley M, Sze WM et al (2006) Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev*(4): CD006250.
- Zacharias M, De Silva RK, Hickling J et al (2007) Comparative safety and efficacy of two high dose regimens of oral paracetamol in healthy adults undergoing third molar surgery under local anaesthesia. *Anaesth Intensive Care* **35**(4): 544–9.
- Zakine J, Samarcq D, Lorne E et al (2008) Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. *Anesth Analg* **106**(6): 1856–61.
- Zhang J, Ding EL & Song Y (2006) Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. *JAMA* **296**(13): 1619–32.

- Zhao SZ, Chung F, Hanna DB et al (2004) Dose-response relationship between opioid use and adverse effects after ambulatory surgery. *J Pain Symptom Manage* **28**(1): 35–46.
- Zhou TJ, Tang J & White PF (2001) Propacetamol versus ketorolac for treatment of acute postoperative pain after total hip or knee replacement. *Anesth Analg* **92**(6): 1569–75.
- Zhu X, Proctor M, Bensoussan A et al (2007) Chinese herbal medicine for primary dysmenorrhoea. *Cochrane Database Syst Rev*(4): CD005288.
- Ziaei S, Zakeri M & Kazemnejad A (2005) A randomised controlled trial of vitamin E in the treatment of primary dysmenorrhoea. *BJOG* **112**(4): 466–9.
- Zier JL, Kvam KA, Kurachek SC et al (2007) Sedation with nitrous oxide compared with no sedation during catheterization for urologic imaging in children. *Pediatr Radiol* **37**(7): 678–84.

## 5. REGIONALLY AND LOCALLY ADMINISTERED ANALGESIC DRUGS

### 5.1 LOCAL ANAESTHETICS

Local anaesthetics exert their effect as analgesics by the blockade of sodium channels and hence impeding neuronal excitation and/or conduction.

#### 5.1.1 Short-duration local anaesthetics

Lignocaine (lidocaine) is the most widely used short-duration local anaesthetic in acute pain management. Although the plasma half-life is approximately 90 minutes, the duration of local anaesthetic effect depends very much on the site of administration, dose administered and the presence or absence of vasoconstrictors. Although lignocaine is hydrophilic, it is delivered in high concentrations and therefore usually diffuses well into nerve bundles, resulting in little separation of sensory and motor blocking actions (Covino & Wildsmith, 1998).

The use of lignocaine in ongoing acute pain management is usually restricted to the short-term re-establishment of a local anaesthetic infusion block; it is unsuited to long-term (ie days) use because of the development of tachyphylaxis or acute tolerance (Mogensen, 1995). For example, 24-hour continuous perineural infusions of lignocaine resulted in less effective analgesia and more motor block than infusions of the long-acting local anaesthetic agent ropivacaine (Casati, Vinciguerra et al, 2003 **Level II**).

#### 5.1.2 Long-duration local anaesthetics

The three commonly used long-duration local anaesthetic agents, bupivacaine, levobupivacaine and ropivacaine, are structurally related (Markham & Faulds, 1996; McLeod & Burke, 2001; Casati & Putzu, 2005). Whereas bupivacaine is a racemic mixture of S- and R-enantiomers, levobupivacaine is the S- (or levo) enantiomer of bupivacaine; ropivacaine is likewise an S-enantiomer.

The issue with relative potency emerges with lower doses and concentrations of local anaesthetics. When doses are carefully titrated, a minimum local anaesthetic concentration (MLAC) can be found at which 50% of patients will achieve a satisfactory analgesic block. In obstetric epidural analgesia, two separate studies found the MLAC of bupivacaine was 0.6 times that of ropivacaine (Capogna et al, 1999 **Level II**; Polley et al, 1999 **Level II**). The motor-blocking potency showed a similar ratio of 0.66 (Lacassie et al, 2002 **Level II**).

When comparing bupivacaine with levobupivacaine, the 'percentage' bupivacaine solution is by weight of bupivacaine hydrochloride, whereas % levobupivacaine solution is for the active molecule alone (even though presented as the hydrochloride). This means that the molar dose of equal 'percentage concentration' is 13% higher for levobupivacaine (Schug, 2001). The sensory MLAC potency ratio of levobupivacaine to bupivacaine is 0.98, although if correction is made for molar concentrations this falls to 0.87 (neither value being different from unity) (Lyons et al, 1998 **Level II**). Levobupivacaine has been shown to have slightly less motor-blocking capacity than bupivacaine with a levobupivacaine/ bupivacaine potency ratio for epidural motor blockade of 0.87 (95% CI, 0.77-0.98) (Lacassie & Columb, 2003 **Level II**). Another labour epidural analgesia study has found no difference in MLAC between levobupivacaine and

ropivacaine with a ropivacaine/ levobupivacaine potency ratio of 0.98 (95% CI 0.80 to 1.20) (Polley et al, 2003 **Level II**).

### **Epidural local anaesthetics**

For *postoperative* epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Scott et al, 1995 **Level II**; Schug et al, 1996 **Level II**). Therefore, most investigators compare infusions of bupivacaine or levobupivacaine at 0.1% or 0.125% with ropivacaine 0.2%, which removes any imbalance in comparative potency.

The majority of studies find similar analgesic outcomes with postoperative epidural infusions based on these strengths (Jorgensen et al, 2000 **Level II**; Macias et al, 2002 **Level II**; Casati, Santorsola et al, 2003 **Level II**). Motor block is of clinical relevance in low thoracic or lumbar epidural infusions and has been reported to be less intense with epidural ropivacaine than with bupivacaine (Zaric et al, 1996 **Level II**; Muldoon et al, 1998 **Level II**; Merson, 2001 **Level II**). However, this finding has not been supported by other authors.

Ropivacaine 0.2% and levobupivacaine 0.125% provided similar analgesia with similar adverse effects and no motor block when infused via thoracic epidural catheters for lung surgery (De Cosmo et al, 2008 **Level II**). Patient-controlled lumbar epidural analgesia for prostatectomy using ropivacaine 0.2% or levobupivacaine 0.125% resulted in similar pain relief, adverse effects and incidence of motor block (Heid et al, 2007 **Level II**). These two local anaesthetics in these concentrations were also equivalent to 0.125% bupivacaine after hip surgery (Koch et al, 2008 **Level II**). However, epidural ropivacaine 0.165% was inferior to levobupivacaine 0.125% after orthopaedic surgery (Smet et al, 2008 **Level II**). In a comparison between ropivacaine 0.2%, bupivacaine 0.125% and lignocaine 0.5%, the regression of sensory blockade under continuous infusion was least with ropivacaine (Kanai et al, 2007 **Level II**).

The relevance of dose, not concentration or volume of local anaesthetic infused, was confirmed in two trials. The same dose of a mixture of levobupivacaine in three different concentrations (0.5%, 0.25%, and 0.15%) and sufentanil administered during continuous thoracic epidural infusion for thoracotomy resulted in similar efficacy and adverse effects (Mendola et al, 2009 **Level II**) as did two concentrations (0.15% and 0.5%) of levobupivacaine in another trial (Dernedde et al, 2008 **Level II**).

Neither infusions of bupivacaine 0.125% nor ropivacaine 0.2% interfered with neurophysiological assessments after scoliosis surgery (Pham Dang et al, 2008 **Level II**).

At concentrations of 0.5% or greater, there were no significant differences in onset time and intensity or duration of sensory blockade between bupivacaine, levobupivacaine or ropivacaine used for epidural analgesia (Cheng et al, 2002 **Level II**; Casati, Santorsola et al, 2003 **Level II**)

### **Local anaesthetic/opioid combinations**

The quality of pain relief from low-dose epidural infusions of plain local anaesthetic consistently benefits from the addition of adjuvants such as opioids (Crews et al, 1999 **Level II**; Scott et al, 1999 **Level II**; Hubler et al, 2001 **Level II**; Senard et al, 2002 **Level II**) or alpha-2 adrenoceptor agonists (Milligan et al, 2000 **Level II**; Niemi & Breivik, 2002 **Level II**) (see Section 5.3). Potential dose-sparing benefits are more obvious for local anaesthetic side effects (hypotension and motor block) than for opioid-related side effects (Walker et al, 2002 **Level I**).

Comparisons of patient-controlled epidural analgesia (PCEA) using ropivacaine 0.2%, ropivacaine 0.125% and levobupivacaine 0.125%, all with sufentanil 1 mcg/mL (6 ml background plus 2 ml bolus), showed no differences in pain relief or motor block; patients given 0.2% ropivacaine used similar volumes, thus receiving more total dose of local anaesthetic and the same amount of sufentanil (Sitsen et al, 2007 **Level II**). Similarly, there was

no difference in analgesia and no motor blockade reported in a PCEA comparison of ropivacaine 0.05%, 0.075% and 0.1%, with fentanyl 4 mcg/mL and droperidol 25 mcg/mL added to all solutions (Iijima et al, 2007 **Level II**). In another comparison of PCEA 0.625% bupivacaine with fentanyl 3 mcg/mL and 0.15% ropivacaine alone, there was no difference in pain relief; patient satisfaction was lower with PCEA ropivacaine even though it led to fewer opioid-related effects (Pitimana-aree et al, 2005 **Level II**).

No studies directly compare fentanyl to morphine when added to local anaesthetic epidural infusions, although a retrospective audit of the use of high thoracic epidural following cardiac surgery suggested improved pain control and lowered infusion rate using ropivacaine 0.2% with morphine 20 mcg/ml compared with fentanyl 2 mcg/ml (Royse et al, 2005 **Level III-3**).

For information relating to the use of epidural local anaesthetics or opioid/local anaesthetic combinations for *labour* pain see Section 11.1.2.

### **Peripheral local anaesthetics**

A number of studies have compared different local anaesthetics or doses of local anaesthetics used for continuous peripheral nerve blockade (CPNB).

At concentrations of 0.5% or greater, there were no significant differences in onset time and intensity or duration of sensory blockade between bupivacaine, levobupivacaine or ropivacaine in sciatic (Casati et al, 2002 **Level II**), interscalene (Casati, Borghi et al, 2003 **Level II**) or axillary brachial plexus blocks (McGlade et al, 1998 **Level II**). The intensity and duration of motor block is frequently less with ropivacaine compared with bupivacaine or levobupivacaine, but this has little effect on the quality of block for surgery (McGlade et al, 1998 **Level II**; Casati, Borghi et al, 2003 **Level II**).

A comparison of three concentrations (0.1%, 0.2%, 0.3%) of ropivacaine for continuous femoral nerve blockade following total knee arthroplasty found that infusions of 0.2% and 0.3% ropivacaine had equivalent quality of postoperative analgesia (Brodner et al, 2007 **Level II**). After similar surgery, there was no difference in pain relief or motor block between patient-controlled femoral nerve blockade with 0.125% levobupivacaine and 0.2% ropivacaine (Heid et al, 2008 **Level II**).

Comparisons of two different patient-controlled CPNB regimens found different results depending on the location of the block; the regimens were ropivacaine at 4 mL/hr 0.4% (bolus 2 mL) or 8 mL/hr 0.2% (bolus 4 mL). For continuous popliteal nerve blockade, the larger volumes of the dilute local anaesthetic were more likely to cause an insensate limb (Ilfeld et al, 2008 **Level II**); for continuous interscalene nerve block there was no difference between the two solutions (Le et al, 2008 **Level II**), and for continuous infraclavicular nerve block the smaller volumes of the more concentrated local anaesthetic were more likely to cause an insensate limb (Ilfeld et al, 2009 **Level II**).

Another comparison of patient-controlled continuous interscalene blockade using 0.25% levobupivacaine, 0.25% ropivacaine and 0.4% ropivacaine reported less effective pain relief with the lower concentration of ropivacaine (Borghi et al, 2006 **Level II**).

Continuous popliteal sciatic nerve blockade using 0.2% ropivacaine, 0.2% levobupivacaine and 0.125% levobupivacaine resulted in similar pain relief after foot surgery, but fewer patients had complete recovery of motor function at 24 and 48 hours with 0.2% levobupivacaine (Casati et al, 2004 **Level II**).



### 5.1.3 Local anaesthetic toxicity

#### **Direct toxicity**

Lignocaine (5%) infused via lumbar subarachnoid microcatheters has been associated with case reports of cauda equina syndrome (Rigler et al, 1991 **Level IV**; Schell et al, 1991 **Level IV**). This suggested that high local concentrations of lignocaine were potentially neurotoxic and led to the technique falling into disfavour.

Transient Neurological Symptoms (TNS) is a clinical syndrome associated with spinal anaesthesia. Patients experience pain or muscle spasms in the buttocks or lower limbs following initial recovery from the spinal anaesthetic. The onset of symptoms is usually within 24 hours of the procedure and it fully resolves spontaneously within a few days. A meta-analysis was performed of all randomised and pseudo-randomised (Level II and Level III-1) studies comparing the frequency of TNS and neurological complications after spinal anaesthesia with lignocaine to other local anaesthetics; the overall incidence was 14.2% following lignocaine and the relative risk (RR) for developing TNS after spinal anaesthesia with lignocaine compared with other local anaesthetics (bupivacaine, prilocaine, procaine, levobupivacaine, ropivacaine and 2-chloroprocaine) was 7.31 (95% CI 4.16 to 12.86); there was no association with baricity or lignocaine concentration in the individual studies that compared these factors (Zaric et al, 2009 **Level I**).

#### **Systemic toxicity**

There are consistent laboratory data showing that the S-enantiomers of the long-acting amide local anaesthetics exhibit less central nervous system (CNS) or cardiac toxicity than the R-enantiomers or the racemic mixtures for doses resulting in equivalent sensory nerve conduction block. It is difficult to define relative toxicities for these agents because it depends on the parameters measured.

There is a lack of scientific data available to determine the safe dose of local anaesthetic. However the upper limit of a safe dose should take into account patient weight, age and comorbidities. There is a pharmacokinetic rationale to support fractional dosing by incremental injection of local anaesthetic. There are case reports of systemic local anaesthetic toxicity occurring using ultrasound guidance, although a meta-analysis found a significantly decreased risk of vascular puncture using ultrasound (RR 0.16; 95% CI 0.05 to 0.47) (Abrahams et al, 2008 **Level I**).

In blinded human volunteer studies, CNS symptoms were detected at IV doses and plasma levels that were 25% higher for ropivacaine compared with bupivacaine (Scott et al, 1989 **Level II**) and 16% higher for levobupivacaine than bupivacaine (Bardsley et al, 1998 **Level II**). Although these data show that CNS toxicity might occur less frequently or be less severe with the S-enantiomers, all local anaesthetics are toxic. A rapid IV bolus of any of these agents may overwhelm any of the more subtle differences found at lower plasma concentrations.

Severe myocardial depression and refractory ventricular fibrillation have been described as the hallmark of accidental IV administration of moderately large doses of bupivacaine. This has been attributed to the slow dissociation of bupivacaine from the myocardial sodium channel, which is less marked with levobupivacaine and ropivacaine (Mather & Chang, 2001; Mather et al, 2005). Animal studies confirm that higher systemic doses of ropivacaine and levobupivacaine are required to induce ventricular arrhythmias, circulatory collapse or asystole (Ohmura et al, 2001), with the ranking of toxicity risk being bupivacaine > levobupivacaine > ropivacaine (Groban & Dolinski, 2001).

Controlled human studies are only possible when looking at surrogate endpoints such as ECG changes or myocardial depression and suggest a similar ranking of effect (Scott et al, 1989 **Level II**; Knudsen et al, 1997 **Level II**; Bardsley et al, 1998 **Level II**; Mather & Chang, 2001 **Level II**), with bupivacaine being the most toxic and levobupivacaine being less toxic and similar to ropivacaine (Stewart et al, 2003 **Level II**).

Successful resuscitation from a massive overdose is of greater relevance in clinical practice. A canine study investigating resuscitation and survival following local anaesthetic-induced circulatory collapse showed survival rates of 50%, 70% and 90% with bupivacaine, levobupivacaine and ropivacaine respectively (Groban & Dolinski, 2001).

Case reports of accidental toxic overdose with ropivacaine and bupivacaine suggest that outcomes are more favourable and resuscitation more straightforward (in particular requiring less cardiovascular [CV] support) with ropivacaine (Pham-Dang et al, 2000; Chazalon et al, 2003; Huet et al, 2003; Klein et al, 2003; Soltesz et al, 2003; Khoo & Corbett, 2006; Kimura et al, 2007).

Total plasma levels of local anaesthetic tend to rise during the first 48 hours of postoperative infusion, although free levels remain relatively low (Emanuelsson et al, 1995; Scott et al, 1997). Thus, in published studies, toxicity due to systemic absorption from epidural or perineural infusions has not been a problem. However, the risk of accidental absolute overdose with postoperative infusions suggests that the less toxic agents should be used in preference and that the doses administered should be the minimum needed for efficacy.

There is basic scientific evidence and several case reports to support the use of IV lipid emulsion therapy for systemic local anaesthetic toxicity resulting in CV collapse (Felice & Schumann, 2008 **Level IV**). Animal experimental data (Weinberg et al, 2003; Weinberg et al, 1998) have been supported by a few case reports of successful resuscitation following bupivacaine (Rosenblatt et al, 2006), ropivacaine (Litz et al, 2006), levobupivacaine (Foxall et al, 2007), mepivacaine/prilocaine (Litz et al, 2008) and mepivacaine/bupivacaine (Warren et al, 2008) toxicity. The mechanism of action of the lipid emulsion may be due to partitioning of local anaesthetic within the emulsion itself (Weinberg, 2006) or mitochondrial substrate enhancement in the myocardium (Weinberg et al, 2000). Uncertainties relating to dosage, efficacy and side effects still remain and therefore it is recommended that lipid emulsion only be administered after advanced cardiac life support has commenced, including adrenaline administration, and convulsions controlled (Corman & Skledar, 2007 **Level IV**). Guidelines have been established to facilitate management of local anaesthetic toxicity, which now include reference to lipid emulsion therapy (AAGBI, 2007). It should be noted that local anaesthetic toxicity might recur following successful initial resuscitation, suggesting a need for continued intensive observation if a large dose of local anaesthetic has been administered (Marwick et al, 2009).

### Key messages

1. Lignocaine is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**N**) (**Level I** [Cochrane Review]).
2. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level 1**).
3. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blockade (**N**) (**Level I**).
4. Continuous perineural infusions of lignocaine (lidocaine) result in less effective analgesia and more motor block than long-acting local anaesthetic agents (**U**) (**Level II**).

5. There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine when given in low doses for regional analgesia (epidural and peripheral nerve blockade) in terms of quality of analgesia or motor blockade (**U**) (**Level II**).
6. Cardiovascular and central nervous system toxicity of the stereospecific isomers ropivacaine and levobupivacaine is less severe than with racemic bupivacaine (**U**) (**Level II**).
7. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity, however uncertainties relating to dosage, efficacy and side effects still remain and therefore it is appropriate to administer lipid emulsion once advanced cardiac life support has begun and convulsions are controlled (**N**) (**Level IV**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Case reports following accidental overdose with ropivacaine and bupivacaine suggest that resuscitation is likely to be more successful with ropivacaine (**U**).

## 5.2 OPIOIDS

### 5.2.1 Neuraxial opioids

Opioid receptors were described in the spinal cord of the rat in 1976 (Pert et al, 1976) and the same year a potent analgesic effect of directly applied intrathecal morphine was reported in these animals (Yaksh & Rudy, 1976). Opioid analgesia is spinally mediated via presynaptic and postsynaptic receptors in the substantia gelatinosa in the dorsal horn (Yaksh, 1981). Spinal opioid receptors are 70% mu, 24% delta and 6% kappa (Treman & Bonica, 2001), with 70% of all mu and delta receptors being presynaptic (predominantly small primary afferents) and commonly co-located, and kappa receptors being more commonly postsynaptic.

Antinociception may be further augmented by descending inhibition from mu-opioid receptor activation in the periaqueductal area of the brain, which may be potentiated by neuraxial opioids. In addition to this, a local anaesthetic action has been described for pethidine (meperidine), which may contribute to the clinical effect when administered intrathecally (Jaffe & Rowe, 1996). The first clinical use of intrathecal morphine was for analgesia in cancer patients (Wang et al, 1979).

Neuraxial opioids may cause respiratory depression, sedation, nausea, vomiting, pruritus, urinary retention and decreased gastrointestinal motility. Depending on type and dose of the opioid, a combination of spinal and systemic mechanisms may be responsible for these adverse effects. Many of these effects are more frequent with morphine and are to some extent dose related (Dahl et al, 1999 **Level I**; Cole et al, 2000 **Level I**). Late onset respiratory depression, which is believed to be a result of the cephalad spread of opioids within the cerebrospinal fluid, is also seen more commonly with hydrophilic opioids such as morphine (Cousins & Mather, 1984).

#### **Intrathecal opioids**

The lipid solubility of opioids largely determines the speed of onset and duration of intrathecal analgesia; hydrophilic drugs (eg morphine) have a slower onset of action and longer half-lives in cerebrospinal fluid with greater dorsal horn bioavailability and greater cephalad migration compared with lipophilic opioids (eg fentanyl) (Bernards et al, 2003).

Safety studies and widespread clinical experience with morphine, fentanyl and sufentanil have shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (Hodgson et al, 1999 **Level IV**). Other opioid agonists or partial agonists do not have animal or human safety data.

Early clinical studies used very high intrathecal morphine doses (ie 500 mcg or more), however adequate postoperative analgesia with fewer adverse effects may be obtained with significantly less morphine — although at lower doses there is not a clear dose-response relationship for some side effects or pain relief (Meylan et al, 2009 **Level I**). A meta-analysis comparing intrathecal morphine doses of less than 300 mcg, equal to or greater than 300 mcg, and placebo reported a greater risk of respiratory depression and of nausea and vomiting with the higher, but not lower, doses of morphine, while the incidence of pruritus was increased for all doses (Gehling & Tryba, 2009 **Level I**).

Following hip and knee arthroplasty, intrathecal morphine (100 to 300 mcg) provided excellent analgesia for 24 hours after surgery with no difference in side effects; after hip arthroplasty only there was a significant reduction in postoperative patient-controlled (PCA) morphine requirements (Rathmell et al, 2003 **Level II**). Following knee arthroplasty, intrathecal morphine 500 mcg compared with 200 mcg reduced supplemental rescue analgesia (tramadol) over 24 hours with no difference in adverse event rates (Bowrey et al, 2005 **Level II**), and 200 mcg was as effective as 300 mcg with no difference in side effects; both were superior to 100 mcg (Hassett et al, 2008 **Level II**). After hip arthroplasty, 100 mcg and 200 mcg doses of intrathecal morphine produced good and comparable pain relief and reductions in postoperative morphine requirements; 50 mcg was ineffective (Murphy et al, 2003 **Level II**).

When combined with low-dose bupivacaine for Caesarean section, 100 mcg intrathecal morphine produced analgesia comparable with doses as high as 400 mcg, with significantly less pruritus (Girgin et al, 2008 **Level II**). A single dose of morphine (100 mcg) added to a spinal anaesthetic for Caesarean section prolonged the time to first postoperative analgesic administration resulting in at least 11 hours of effective analgesia. Adverse effects included pruritus (43%), nausea (10%) and vomiting (12%). The rate of respiratory depression was low (see below). In these patients, sufentanil and fentanyl showed no analgesic benefits (Dahl et al, 1999 **Level I**).

The addition of 10 mcg sufentanil to 0.4 mg intrathecal morphine did not potentiate postoperative analgesia or reduce intraoperative opioid requirements in patients undergoing major colorectal surgery (Culebras et al, 2007 **Level II**). The addition of intrathecal fentanyl to low-dose spinal bupivacaine for anorectal surgery resulted in more pruritus but lower mean recovery and discharge times, with fewer analgesic requests in the fentanyl group (Gurbet et al, 2008 **Level II**).

In a more recent study, intrathecal sufentanil provided shorter postoperative analgesia (mean 6.3 hours) than intrathecal morphine (mean 19.5 hours) with no difference in side effects (Karaman et al, 2006 **Level II**). In another comparison of intrathecal morphine (100 mcg) and intrathecal pethidine (10 mg) for analgesia following Caesarean section in a non-blinded study, patients receiving morphine had longer analgesia and fewer intraoperative side effects than the pethidine group, but experienced more pruritus (Kumar et al, 2007 **Level II**).

For more information on effectiveness and side effects related to the use of intrathecal opioids see Section 7.3.

## Epidural opioids

The behaviour of epidural opioids is also governed largely by their lipid solubility. The greater sequestration of lipid soluble opioids into epidural fat and slow re-release back into the epidural space means that elimination from the epidural space is prolonged, resulting in relatively smaller fractions of drug reaching the cerebrospinal fluid (Bernards et al, 2003). Lipophilic opioids (eg fentanyl) have a faster onset but shorter duration of action compared with hydrophilic drugs (eg morphine) (de Leon-Casasola & Lema, 1996; Bernards, 2004).

Morphine is the least lipid soluble of the opioids administered epidurally; it has the slowest onset and offset of action (Cousins & Mather, 1984) and the highest bioavailability in the spinal cord after epidural administration (Bernards, 2004). As it has a prolonged analgesic effect it can be given by intermittent bolus dose or infusion; the risk of respiratory depression may be higher and analgesia less effective with bolus dose regimens (de Leon-Casasola & Lema, 1996).

The evidence that epidural fentanyl acts via a spinal rather than systemic effect is conflicting and it has been suggested that any benefit when comparing epidural with systemic fentanyl alone is marginal (Wheatley et al, 2001; Bernards, 2004). However, the conflicting results may be due to differing modes of administration. An infusion of epidural fentanyl appears to produce analgesia by uptake into the systemic circulation, whereas a bolus dose of fentanyl produces analgesia by a selective spinal mechanism (Ginosar et al, 2003 **Level IV**). There is no evidence of benefit of epidural versus systemic administration of alfentanil or sufentanil (Bernards, 2004)

Pethidine is effective when administered epidurally by bolus dose, continuous infusion and by PCEA. It is more lipid soluble than morphine (but less than fentanyl and its analogues), thus its onset and offset of epidural analgesic action is more rapid than morphine (Ngan Kee, 1998 **Level IV**). The analgesic effect of smaller doses appears to be spinally mediated but systemic effects are likely after larger doses; in the smaller doses it is not known whether the local anaesthetic properties of pethidine contribute significantly to pain relief (Ngan Kee, 1998 **Level IV**). Epidural pethidine has been used predominantly in the obstetric setting. After Caesarean section epidural pethidine resulted in better pain relief and less sedation than IV pethidine (Paech et al, 1994 **Level II**) but inferior analgesia compared with intrathecal morphine, albeit with less pruritus, nausea and drowsiness (Paech et al, 2000 **Level II**).

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to (monoacetylmorphine) MAM and morphine. Diamorphine and MAM are more lipid soluble than morphine and penetrate the CNS more rapidly, although it is MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine (Miyoshi & Lackband, 2001). Epidural administration of diamorphine is common in the United Kingdom and is effective whether administered by intermittent bolus dose or infusion (McLeod et al, 2005).

The quality of epidural analgesia with hydromorphone is similar to morphine (Chaplan et al, 1992 **Level II**). In a comparison of epidural and IV hydromorphone, patients required twice as much IV hydromorphone to obtain the same degree of analgesia (Liu et al, 1995 **Level II**).

The addition of butorphanol to epidural bupivacaine resulted in more rapid and prolonged pain relief compared with butorphanol alone (Bharti & Chari, 2009 **Level II**).

An extended-release suspension of morphine has been developed for epidural use (Depodur™) consisting of morphine molecules suspended in liposome complexes (lipifoam). Extended-release epidural morphine (EREM) has been shown to be effective compared with placebo after hip arthroplasty (Viscusi et al, 2005 **Level II**; Martin et al, 2006 **Level II**) and, using doses of 10 mg or more, to lead to better pain relief compared with standard epidural morphine (4 or 5 mg) and a reduction in the need for supplemental analgesics up to 48 hours after hip arthroplasty (Viscusi et al, 2006 **Level III-1**), lower abdominal surgery (Gambling et al, 2005 **Level II**) and Caesarean section (Carvalho et al, 2005 **Level II**; Carvalho et al, 2007 **Level II**).

Respiratory depression has been reported to occur in up to 5.4% of patients depending on the definition used (Carvalho et al, 2005 **Level II**; Gambling et al, 2005 **Level II**; Viscusi et al, 2005 **Level II**; Martin et al, 2006 **Level II**) and it may require prolonged treatment; in one patient naloxone was required for 62 hours (Martin et al, 2006 **Level II**).

It has been recommended that the liposome preparation of Depodur® not be administered while local anaesthetics are present in the epidural space as this may cause early release of the morphine (Viscusi et al, 2009 **Level II**). When Depodur® was administered within 3 to 15 minutes of a 3 mL test dose of 1.5% lignocaine with adrenaline, higher  $C_{max}$  values for morphine were indeed reported compared with  $C_{max}$  values when no lignocaine was administered; there was no difference in morphine  $C_{max}$  if the interval was greater than 30 minutes (Viscusi et al, 2009 **Level II**). The  $C_{max}$  of morphine was unchanged when Depodur® doses were given 15, 30 and 60 minutes after an anaesthetic dose of epidural bupivacaine – 20 ml of 0.25% (Gambling et al, 2009 **Level II**).

### 5.2.2 Peripheral opioids

Opioid receptors on sensory unmyelinated C nerve fibres mediate peripheral antinociceptive effects in animal studies (Stein et al, 1990). In the presence of inflammation, opioid receptors are transported to the periphery and increased amounts of endogenous opioid peptides are present in infiltrating immune cells (Schafer, 1999; Smith, 2008; Stein, 1995). An experimental model of inflammatory hyperalgesia caused by ultraviolet light showed that analgesia mediated via peripheral opioid mechanisms could also occur in humans (Koppert et al, 1999 **Level II**). In joint studies, the increase in opioid receptors and their endogenous peptides correlated with the degree of inflammation, being more abundant in rheumatoid arthritis than in osteoarthritis and joint trauma (Mousa et al, 2007), consistent with the clinical observation that peripheral opioids are more effective in the presence of inflammation. Intra-articular bupivacaine was less effective than morphine in providing analgesia in patients having 'high inflammatory arthroscopic knee surgery', whereas bupivacaine was more effective than morphine in those having 'low inflammatory surgery' (Marchal et al, 2003 **Level II**) (see also Section 7.5).

In clinical practice, morphine injected as a single dose into the knee intra-articular space produced analgesia that lasted up to 24 hours, but evidence for a peripheral rather than a systemic effect was not conclusive (Gupta et al, 2001 **Level I**; Kalso et al, 2002 **Level I**).

Confounding variables that hinder analysis included the pre-existing degree of inflammation, type of surgery, the baseline pain severity and the overall relatively weak clinical effect (Gupta et al, 2001 **Level I**). When published trials were analysed taking these confounding factors into consideration, including the intensity of early postoperative pain, the data did not support an analgesic effect for intra-articular morphine following arthroscopy compared with placebo (Rosseland, 2005 **Level I**).

#### **Note: reversal of conclusions**

This reverses the Level 1 conclusion in the previous edition of this document; the earlier meta-analyses performed without taking confounding factors into consideration had reported improved pain relief with intra-articular morphine.

The addition of intra-articular sufentanil to a mixture of ropivacaine and clonidine following anterior cruciate ligament repair provided no additional analgesic benefits (Armellin et al, 2008 **Level II**). A mixture of intra-articular bupivacaine and 100 mg tramadol resulted in better pain relief and lower rescue analgesic requirements than use of either drug alone (Zeidan et al, 2008 **Level II**).

There is no evidence for analgesic efficacy of peripheral opioids at non-intra-articular sites, including use with perineural blockade (Picard et al, 1997 **Level I**). While opioid receptors have been identified in the cornea and skin, topically applied opioids have not consistently demonstrated efficacy in pain states such as corneal ulceration (fentanyl) (Zollner et al, 2008 **Level II**), partial thickness burns (morphine) (Welling, 2007 **Level II**), or chronic skin ulceration (morphine) (Vernassiere et al, 2005 **Level II**).

Although commonly used, oral morphine mouthwash in chemotherapy-induced mucositis pain has only limited supporting evidence; a dose-response (beneficial) effect was seen in a small pilot study using 1 mg/mL and 2 mg/mL morphine mouthwash (Cerchiatti et al, 2003 **Level II**). Benefit was also evident in a small comparison of morphine mouthwash 30 mg 3-hourly, with a local anaesthetic-based solution, in mucositis associated with chemoradiotherapy in head and neck cancer patients (Cerchiatti et al, 2002 **Level II**).

#### Key messages

1. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl after Caesarean section (**U**) (**Level I**).
2. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**N**) (**Level I**).
3. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo when administered after surgery (**R**) (**Level I**).
4. Evidence for a clinically relevant peripheral opioid effect at non-articular sites, including perineural, is inconclusive (**U**) (**Level I**).
5. Epidural pethidine produces better pain relief and less sedation than IV pethidine after Caesarean section (**U**) (**Level II**).
6. Extended release epidural morphine provides analgesia for up to 48 hours, however central depressant effects, including respiratory depression, may also be increased and prolonged (**N**) (**Level II**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- No neurotoxicity has been shown at normal clinical intrathecal doses of morphine, fentanyl and sufentanil (**U**).
- Neuraxial administration of bolus doses of hydrophilic opioids carries an increased risk of delayed sedation and respiratory depression compared with lipophilic opioids (**U**).



## 5.3 ADJUVANT DRUGS

### 5.3.1 Alpha-2 agonists

#### **Neuraxial**

Clonidine is an alpha-2 adrenoceptor agonist that acts as an analgesic at the level of the spinal cord. There is no human or animal evidence of neurotoxicity when preservative-free clonidine is administered intrathecally (Hodgson et al, 1999). Epidural clonidine is approved by the United States Food and Drug Administration (FDA) for relief of chronic cancer pain.

Intrathecal clonidine given in doses from 15 to 150 mcg combined with intrathecal local anaesthetic, significantly prolonged the time to two segment block regression but did not affect the rate of onset of a complete block (Elia et al, 2008 **Level I**). Intrathecal clonidine also prolonged the time to first analgesic request (median 101 min, range 35 to 310 min) and duration of motor block but in a non-dose-dependent manner; intraoperative pain was reduced but hypotension was more frequent (RR 1.8; 95% CI 1.4 to 2.3) (Elia et al, 2008 **Level I**). Others have reported that the addition of either clonidine or dexmedetomidine to intrathecal bupivacaine increased the speed of onset and duration of motor and sensory block without additional side effects (Kanazi et al, 2006 **Level II**).

Intrathecal clonidine 100 mcg added to 500 mcg intrathecal morphine resulted in better pain relief and faster time to extubation after cardiac surgery compared with intrathecal morphine alone (Nader et al, 2009 **Level II**). In patients undergoing radical prostatectomy, the addition of clonidine to intrathecal morphine prolonged analgesia compared with intrathecal morphine alone and PCA morphine; intrathecal morphine alone was better than PCA (Andrieu et al, 2009 **Level II**).

A review by Roelants of multiple randomised controlled trials (RCTs) concluded that small doses of intrathecal clonidine (30 mcg) combined with local anaesthetics and opioids prolonged labour analgesia; hypotension may occur and was more common with higher doses of clonidine (Roelants, 2006 **Level II**). Intrathecal clonidine combined with bupivacaine had a postoperative antihyperalgesic effect at 48 hours after elective Caesarean delivery compared with intrathecal bupivacaine-sufentanil and intrathecal clonidine 75 mcg-bupivacaine-sufentanil, however no reduction in pain scores or opioid requirements was observed (Lavand'homme et al, 2008 **Level II**). In another study, the combination of subarachnoid bupivacaine, fentanyl, morphine and clonidine significantly prolonged pain relief following Caesarean section, but with increased sedation (Paech et al, 2004 **Level II**).

The addition of clonidine to PCEA with ropivacaine and morphine after total knee arthroplasty decreased opioid requirements and improved analgesia without increasing side effects (Huang et al, 2007 **Level II**). The addition of clonidine to epidural levobupivacaine, also after hip arthroplasty, significantly reduced postoperative morphine requirements compared with either drug alone (Milligan et al, 2000 **Level II**). Low-dose infusion of clonidine alone via thoracic epidural catheters after spinal surgery reduced systemic opioid requirements and nausea without causing significant sedation or hypotension (Farmery & Wilson-MacDonald, 2009 **Level II**).

In children, addition of clonidine to bupivacaine caudal injection increased the duration (Ansermino et al, 2003 **Level I**) and quality of analgesia without an increase in side effects (Yildiz et al, 2006 **Level II**) (see also Section 10.7.2).

## **Plexus block**

There is evidence of analgesic benefit with the addition of clonidine to local anaesthetics for brachial plexus blocks (Murphy et al, 2000 **Level I**) but many of the studies have methodological limitations.

Clonidine improved duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for axillary and peribulbar blocks; side effects appeared to be limited at doses up to 150 mcg (McCartney et al, 2007 **Level I**<sup>9</sup>). The addition of clonidine to local anaesthetic solutions used for single-shot peripheral nerve or plexus blocks also prolonged duration of analgesia and motor block (Popping et al, 2009 **Level I**). The effects of the addition of clonidine to lignocaine were similar to those of adding adrenaline in cervical plexus blockade in terms of block onset and duration, although lignocaine absorption was faster when clonidine was used (Molnar et al, 1997 **Level II**). Addition of clonidine to a popliteal fossa nerve block with bupivacaine did not result in any difference in pain relief but did prolong the analgesic effects (YaDeau et al, 2008 **Level II**). There was no difference in pain relief when clonidine was added to a continuous femoral nerve infusion with ropivacaine (Casati et al, 2005 **Level II**).

The use of clonidine with local anaesthetic or opioid also extended analgesia with thoracic paravertebral blocks (Bhatnagar et al, 2006 **Level II**; Burlacu et al, 2006 **Level II**).

Evidence is lacking for the use of clonidine as an adjunct to local anaesthetics for continuous catheter techniques (McCartney et al, 2007 **Level I**<sup>9</sup>).

### **Intravenous regional anaesthesia**

Addition of dexmedetomidine to lignocaine IV regional anaesthesia (IVRA) increased duration and quality of analgesia (Memis et al, 2004 **Level II**). Clonidine was effective in delaying tourniquet pain with IVRA in volunteers (Lurie et al, 2000 **Level III-2**).

### **Intra-articular**

The use of intra-articular clonidine on its own or in addition to local anaesthetic agents improved analgesia after knee joint arthroscopy and decreased opioid consumption (Brill & Plaza, 2004 **Level II**; Alagol et al, 2005 **Level II**).

Intra-articular dexmedetomidine resulted in a longer duration of pain relief compared with IV dexmedetomidine (Al-Metwalli et al, 2008 **Level II**).

## **5.3.2 Adrenaline**

### **Neuraxial**

In postoperative thoracic epidural infusions, the addition of adrenaline (epinephrine) to fentanyl and ropivacaine or bupivacaine improved analgesia (Sakaguchi et al, 2000 **Level II**; Niemi & Breivik, 2002 **Level II**; Niemi & Breivik, 2003 **Level II**). This was not demonstrated with lumbar epidural infusions (Forster et al, 2003 **Level II**). The efficacy of thoracic epidural pethidine infusions after thoracotomy was not improved by addition of adrenaline (Bryson et al, 2007 **Level II**).

The addition of adrenaline (0.2 mg) to intrathecal bupivacaine prolonged motor block and some sensory block modalities (Moore JM et al, 1998 **Level II**).

---

<sup>9</sup> This systematic review includes a study or studies that have since been withdrawn from publication. Please refer to the Introduction at the beginning of this document for comments regarding the management of retracted articles. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) re-examined the data included in this review and concluded that exclusion of data obtained from the retracted publications did not significantly alter the results.

### 5.3.3 Ketamine

#### **Neuraxial**

Some commercially available preparations of ketamine contain an untested preservative (benzethonium chloride) and a low pH (pH 3.5 to 5.5) and so cannot be recommended for intrathecal use in humans (Hodgson et al, 1999).

The addition of intrathecal ketamine to bupivacaine did not prolong postoperative analgesia or reduce analgesic requirements, but did lead to significantly more nausea and vomiting, sedation, dizziness, nystagmus and 'strange feelings' (Kathirvel et al, 2000 **Level II**).

Early postoperative analgesia was improved by the use of epidural racemic ketamine with bupivacaine for lower limb amputations, although pain at 1 year was not different; perioperative opioids were not used (Wilson et al, 2008 **Level II**). The combination of ketamine with opioid-based (+/- local anaesthetic) solutions for epidural analgesia improved pain relief (Subramaniam et al, 2004 **Level I**) and may reduce overall opioid requirements (Walker et al, 2002 **Level I**) without increasing the incidence of adverse effects (Walker et al, 2002 **Level I**; Subramaniam et al, 2004 **Level I**).

A combination of bupivacaine, ketamine and midazolam administered intrathecally prolonged the analgesic time following lower limb surgery compared with bupivacaine alone or bupivacaine with ketamine; however the authors cautioned that the safety of such combinations has not yet been established (Murali Krishna et al, 2008 **Level II**).

Use of intrathecal S(+) ketamine with bupivacaine for Caesarean section decreased time to onset and increased spread of the block, but did not prolong the duration compared with fentanyl (Unlugenc et al, 2006 **Level II**).

Caudal epidural ketamine 0.25 to 0.5 mg/kg in children, in combination with local anaesthetic prolonged analgesia with few side effects (Ansermino et al, 2003 **Level I**; Tsui & Berde, 2005) (see also Section 10.7.2).

#### **Peripheral sites**

Most studies on the use of ketamine alone or with local anaesthesia, show no analgesic benefit for peripheral neural blockade, such as brachial plexus block for arm surgery, (Lee et al, 2002 **Level II**), intra-articular injection (Rosseland et al, 2003 **Level II**) or wound infiltration such as following Caesarean section (Zohar et al, 2002 **Level II**) or inguinal hernia repair (Clerc et al, 2005 **Level II**), although pain scores were lower with preincisional ketamine versus saline in circumcision (Tan et al, 2007 **Level II**). Adding ketamine to lignocaine IVRA did not result in better pain relief compared with ketamine given intravenously (Viscomi et al, 2009 **Level II**).

#### **Topical**

Topical administration of ketamine might result in effective systemic plasma concentrations making it difficult to interpret any local effects (Poyhia & Vainio, 2006). A transdermal ketamine patch (delivering 25 mg over 24 hours) reduced analgesic consumption after gynaecological surgery (Azevedo et al, 2000 **Level II**) but analgesic effects from topical ketamine (3 mL 0.3%) applied to the tonsillar fossa after tonsillectomy, although superior to placebo, added no benefit to topical morphine (Canbay et al, 2008 **Level II**).

Topical ketamine as a mouthwash has been reported to be effective in reducing pain and opioid consumption from oral mucositis at rest and with eating (Slatkin & Rhiner, 2003).

### 5.3.4 Midazolam

Midazolam, the preservative-free preparation, has been proposed as a potential spinal analgesic due to its action on GABA<sub>A</sub> receptors. It is not approved for this indication and efficacy and safety issues remain unclear.

Reports of intrathecal midazolam administration have appeared in the literature for many years, despite concerns regarding potential neurotoxicity (Yaksh & Allen, 2004). Early clinical series (Tucker, Lai et al, 2004 **Level III-2**; Tucker, Mezzatesta et al, 2004 **Level III-2**) and laboratory investigations (Johansen et al, 2004) suggested a low risk of toxicity — neurotoxic damage was not seen in sheep and pigs given continuous intrathecal midazolam (Johansen et al, 2004) and a 1-month questionnaire follow-up of patients who had received intrathecal midazolam failed to show any evidence of neurological or urological complications (Tucker, Lai et al, 2004 **Level III-2**).

A meta-analysis of intrathecal midazolam in perioperative and peripartum patients showed the addition of intrathecal midazolam (typically 2 mg or more) to other spinal medications reduced the incidence of nausea and vomiting and delayed the time to request for rescue analgesia, but had little effect beyond 12 hours (Ho & Ismail, 2008 **Level I**). The incidence of neurological symptoms after intrathecal midazolam was uncommon (1.8%) and did not differ from placebo (Ho & Ismail, 2008 **Level I**). There are insufficient data to exclude the possibility of long-term neurological complications from intrathecal midazolam, although none have yet been reported.

Another study reported that the addition of subarachnoid midazolam for labour pain produced no effect on its own, but potentiated the analgesic effect of intrathecal fentanyl (Tucker, Mezzatesta et al, 2004 **Level II**). Combining intrathecal midazolam (2 mg) with bupivacaine for Caesarean section significantly prolonged the block and reduced nausea without CV or neurological side effects (Prakash et al, 2006 **Level II**).

Midazolam added to bupivacaine for epidural infusion improved analgesia but increased sedation (Nishiyama et al, 2002 **Level II**). In patients having a gastrectomy, single dose preoperative epidural midazolam combined with ketamine improved analgesia and prolonged the time to rescue analgesia compared with epidural ketamine or placebo, with no significant adverse effects (Wang et al, 2006 **Level II**).

Midazolam has been added to caudal epidural analgesia in paediatric surgery; age-related toxicity issues have not been addressed. In combination with bupivacaine it prolonged postoperative analgesia (Kumar et al, 2005 **Level II**; Ansermino et al, 2003 **Level I**).

### 5.3.5 Neostigmine

Neostigmine acts as a spinal analgesic by potentiation of muscarinic cholinergic activity. In a literature review of animal and human studies there was no evidence of neurotoxicity with spinal neostigmine (Hodgson et al, 1999).

Intrathecal neostigmine for perioperative and peripartum analgesia resulted in a slight improvement in pain scores and reduced the need for rescue medication; however, it increased nausea and vomiting (OR 5), bradycardia requiring atropine (OR 2.7) and anxiety, agitation and restlessness (OR 10.3) (Ho et al, 2005 **Level I**). The authors concluded that the significant side effects outweighed any clinical benefit.

Epidural neostigmine combined with an opioid reduced the dose of epidural opioid that is required for analgesia but there may not be any decrease in opioid-related side effects compared with the opioid alone (Walker et al, 2002 **Level I**). Epidural neostigmine in the obstetric population improved postoperative analgesia in most studies without increasing the incidence of adverse events (Habib & Gan, 2006 **Level I**). Epidural neostigmine combined with

sufentanil or clonidine, as initial labour analgesia, was without side effects and allowed a 'mobile epidural'; at the doses studied it produced modest analgesia following Caesarean section (Roelants, 2006 **Level II**). The addition of epidural clonidine to bupivacaine reduced hourly patient-controlled epidural bupivacaine requirements during labour (Ross et al, 2009 **Level I**).

Intra-articular administration of neostigmine produced a useful analgesic effect in the postoperative period and was not associated with an increase in the incidence of adverse effects (Habib & Gan, 2006 **Level I**).

Studies investigating the efficacy of adding neostigmine to the local anaesthetics used for brachial plexus block and intravenous regional anaesthesia reported conflicting results indicating the need for further studies (Habib & Gan, 2006 **Level I**).

### 5.3.6 Magnesium

The long-term effects of perineural or neuraxial magnesium have not been clarified.

In patients undergoing orthopaedic surgery, supplementation of spinal anaesthesia with combined intrathecal and epidural magnesium sulphate significantly reduced patients' postoperative morphine requirements (Arcioni et al, 2007 **Level II**). Addition of magnesium sulphate to lignocaine IVRA improved intra- and postoperative analgesia and tolerance of the tourniquet (Turan et al, 2005 **Level II**; Kashefi et al, 2008 **Level II**). While the addition of magnesium to intrathecal bupivacaine prolonged the times for block regression and first request for analgesia after knee arthroscopy, time to ambulation was longer in the magnesium group (Dayioglu et al, 2009 **Level II**).

Intra-articular magnesium combined with bupivacaine resulted in better pain relief than either drug given alone or placebo (Elsharnouby et al, 2008 **Level II**).

### 5.3.7 Botulinum toxin A

Following direct IM injection, botulinum toxin acts to irreversibly bind to the acetylcholine receptor and induce a chemical denervation with resultant muscular paralysis. The extent and duration of paralysis depends on the dose administered. Systemic weakness may follow high cumulative doses. Reinnervation may occur over a period of weeks to months.

In treating pain and related muscle spasm in multiple sclerosis, data on the use of botulinum toxin are conflicting and of low quality (Shakespeare et al, 2003). Similarly, the current evidence does not support the use of botulinum toxin injection in trigger points for myofascial pain (Ho & Tan, 2007 **Level I**). In subacute and chronic neck disorders IM botulinum toxin injections have similar effects to saline in improving pain (pooled mean difference: -0.39; CI -1.25 to 0.47) (Peloso et al, 2007 **Level I**); although there is benefit in cervical dystonia (Simpson et al, 2008 **Level I**).

#### Key messages

1. Intrathecal clonidine improves duration of analgesia and anaesthesia when used as an adjunct to intrathecal local anaesthetics (**N**) (**Level I**).
2. Clonidine improves duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for peribulbar, peripheral nerve and plexus blocks (**N**) (**Level I**).
3. Intrathecal neostigmine marginally improves perioperative and peripartum analgesia in combination with other spinal medications but is associated with significant side effects (**S**) (**Level I**).

4. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia (**U**) (**Level I**).
5. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing side effects (**U**) (**Level I**).
6. Intrathecal midazolam combined with a local anaesthetic prolongs the time to first analgesia and reduces postoperative nausea and vomiting (**N**) (**Level I**).
7. Following Caesarean section, intrathecal morphine provides improved analgesia compared with placebo (**N**) (**Level I**) and more prolonged analgesia compared with more lipophilic opioids (**N**) (**Level II**).
8. Intrathecal clonidine added to intrathecal morphine improves and prolongs analgesia (**N**) (**Level II**).
9. Epidural clonidine reduces postoperative systemic opioid requirements (**N**) (**Level II**).
10. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia (**U**) (**Level II**).
11. In obstetrics, epidural neostigmine improves postoperative analgesia without increasing the incidence of adverse events (**N**) (**Level II**).
12. Addition of either clonidine or dexmedetomidine to intrathecal bupivacaine increases the speed of onset and duration of motor and sensory block without additional side effects (**N**) (**Level II**).

## 5.4 ANTI-INFLAMMATORY DRUGS

### 5.4.1 Corticosteroids

#### **Neuraxial**

Use of epidural methylprednisolone resulted in no difference in morphine requirements or pain scores following thoracotomy compared with epidural saline (Blanloeil et al, 2001 **Level II**). Following lumbar disc surgery, the combination of wound infiltration with bupivacaine and epidural/ perineural methylprednisolone improved analgesia and decreased opioid consumption compared with placebo (Mirzai et al, 2002 **Level II**; Jirattanaphochai et al, 2007 **Level II**). However, epidural administration of either drug on its own was not superior to placebo (Loffinia et al, 2007 **Level II**). Preoperative single dose epidural administration of dexamethasone, with or without bupivacaine, was shown to reduce postoperative pain and morphine consumption following laparoscopic cholecystectomy (Thomas & Beevi, 2006 **Level II**).

#### **Peripheral sites**

Intra-articular corticosteroid injections would be expected to have an analgesic effect in inflammatory arthropathies. Following knee joint arthroscopy, intra-articular steroids were more effective than placebo in reducing pain, analgesic consumption and duration of immobilisation either alone (Wang et al, 1998 **Level II**), in conjunction with opioids (Kizilkaya et al, 2004 **Level II**; Kizilkaya et al, 2005 **Level II**) and/or local anaesthetics (Rasmussen et al, 2002 **Level II**). Dexamethasone on its own was less effective than pethidine or fentanyl (Saryazdi et al, 2006 **Level II**). There may be a higher risk of septic arthritis with intra-articular steroids (Armstrong et al, 1992 **Level IV**). Subacromial injections of corticosteroids have been shown to be effective in treating rotator cuff tendonitis for up to 9 months, and were superior to oral NSAIDs (NNT 2.5; CI 1 to 9)) (Arroll & Goodyear-Smith, 2005 **Level I**).

In patients having hand surgery, IVRA using a combination of lignocaine and dexamethasone resulted in lower pain scores and lower analgesic requirements for 24 hours compared with lignocaine alone or lignocaine IVRA with dexamethasone in the non-operative arm (Bigat et al, 2006 **Level II**).

The addition of dexamethasone to lignocaine for axillary brachial plexus block prolonged the duration of sensory and motor blockade compared with lignocaine alone (Movafegh et al, 2006 **Level II**).

There is insufficient evidence to support the use of injection therapy, including corticosteroids, in subacute and chronic low-back pain. However, it cannot be ruled out that specific subgroups of patients may respond to a specific type of injection therapy (Staal et al, 2009 **Level I**). Lumbar epidural steroid injections may provide short-term relief from acute radicular pain but did not impact on function, need for surgery, or provide long-term pain relief beyond 3 months (Armon et al, 2007 **Level I**).

### **Topical**

Topical corticosteroids have not been shown to have consistent efficacy in acute herpes zoster (Hempenstall et al, 2005 **Level I**).

#### **Key messages**

1. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**N**) (**Level I**).
2. Lumbar epidural steroid administration is effective for short-term relief of acute radicular pain (**N**) (**Level I**).
3. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**N**) (**Level II**).
4. Intravenous regional anaesthesia combining dexamethasone with lignocaine improves analgesia for up to 24 hours (**N**) (**Level II**).
5. There is a risk of septic arthritis with intra-articular steroids (**N**) (**Level IV**).

## **5.4.2 Non-steroidal anti-inflammatory drugs**

### **Peripheral sites**

Intra-articular nsNSAIDs such as tenoxicam and ketorolac resulted in improved pain relief after surgery (Elhakim et al, 1996 **Level II**; Cook et al, 1997 **Level II**; Convery et al, 1998 **Level II**; Colbert et al, 1999 **Level II**; Gupta et al, 1999 **Level II**); no long-term follow-up looking at any effect on bone healing has been undertaken.

### **Topical**

With topical application of diclofenac, tissue levels are higher and plasma levels lower than following oral administration (Zacher et al, 2008). Topical diclofenac significantly reduced pain and inflammation in a range of sports, traumatic and inflammatory acute and chronic conditions compared with placebo and was comparable to other topical NSAIDs (although there were no direct comparisons) and oral diclofenac, ibuprofen and naproxen. (Zacher et al, 2008 **Level I**). Topical ketoprofen used for up to one week in acute painful conditions (sprains, sprains or sports injuries) had a NNT of 3.8, which was significantly better than other topical NSAIDs, although in non-comparative (head-to-head) trials. (Mason et al, 2004 **Level I**). Topical indomethacin did not have proven efficacy (Moore RA et al, 1998 **Level I**).



There was a small but significant reduction of pain with the use of topical NSAIDs for traumatic corneal abrasions (Calder et al, 2005 **Level I**).

Use of topical ketoprofen patches showed mild clinical benefit over placebo in tendinitis and ankle sprain (NNT 5 to 6) (Mazieres, Rouanet, Guillon et al, 2005 **Level II**; Mazieres, Rouanet, Velicy et al, 2005 **Level II**).

Topical NSAIDs were of limited efficacy in lateral elbow pain providing short-term functional improvement for up to 2 weeks. They resulted in fewer GI side effects compared with oral NSAIDs (Green et al, 2001 **Level I**).

Overall, there are insufficient data to support the use of topical NSAID analgesia in acute and chronic Achilles tendinitis (McLauchlan & Handoll, 2001 **Level I**) or in superficial venous thrombosis of the leg (Di Nisio et al, 2007 **Level I**).

There is insufficient evidence to differentiate between routes of administration of NSAIDs in the treatment of low back pain (Roelofs et al, 2008 **Level I**).

### Key messages

1. Topical NSAIDs are of limited efficacy in lateral elbow pain and provide short-term functional improvement; they result in fewer gastrointestinal side effects compared with oral NSAIDs (**N**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs added to local anaesthetic solutions for IVRA improve postoperative analgesia (**N**) (**Level I**).
3. Topical NSAIDs are effective in treating acute strains, sprains or sports injuries for up to 1 week with ketoprofen being significantly better than all other topical NSAIDs, and indomethacin similar to placebo (**N**) (**Level I**).
4. Topical diclofenac significantly reduces pain and inflammation in a range of sports, traumatic and inflammatory conditions and in acute musculoskeletal injuries is at least comparable to oral naproxen (**N**) (**Level I**).
5. Topical NSAIDs are effective analgesics for traumatic corneal abrasions (**N**) (**Level I**).

## REFERENCES

- AAGBI (2007) *Management of Local Anaesthetic Toxicity*. <http://www.aagbi.org/publications/guidelines/docs/latotoxicity07.pdf> Association of Anaesthetists of Great Britain and Ireland. Accessed May 2009.
- Abrahams MS, Panzer O, Atchabahian A et al (2008) Case report: limitation of local anesthetic spread during ultrasound-guided interscalene block. Description of an anatomic variant with clinical correlation. *Reg Anesth Pain Med* **33**(4): 357–9.
- Al-Metwalli RR, Mowafi HA, Ismail SA et al (2008) Effect of intra-articular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. *Br J Anaesth* **101**(3): 395–9.
- Alagol A, Calpur OU, Usar PS et al (2005) Intraarticular analgesia after arthroscopic knee surgery: comparison of neostigmine, clonidine, tenoxicam, morphine and bupivacaine. *Knee Surg Sports Traumatol Arthrosc* **13**(8): 658–63.
- Andrieu G, Roth B, Ousmane L et al (2009) The efficacy of intrathecal morphine with or without clonidine for postoperative analgesia after radical prostatectomy. *Anesth Analg* **108**(6): 1954–7.
- Ansermino M, Basu R, Vandebek C et al (2003) Nonopioid additives to local anaesthetics for caudal blockade in children: a systematic review. *Paediatr Anaesth* **13**(7): 561–73.

- Arcioni R, Palmisani S, Tigano S et al (2007) Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce post-operative analgesic requirements: A prospective, randomized, double-blind, controlled trial in patients undergoing major orthopedic surgery. *Acta Anaesthesiologica Scandinavica* **51**(4): 482–89.
- Armellini G, Nardacchione R & Ori C (2008) Intra-articular sufentanil in multimodal analgesic management after outpatient arthroscopic anterior cruciate ligament reconstruction: a prospective, randomized, double-blinded study. *Arthroscopy* **24**(8): 909–13.
- Armon C, Argoff CE, Samuels J et al (2007) Assessment: use of epidural steroid injections to treat radicular lumbosacral pain: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **68**(10): 723–9.
- Armstrong R, Bolding F & Joseph R (1992) Septic arthritis following arthroscopy: clinical syndromes and analysis of risk factors. *Arthroscopy* **8**: 213–23.
- Arroll B & Goodyear-Smith F (2005) Corticosteroid injections for painful shoulder: a meta-analysis. *Br J Gen Pract* **55**(512): 224–8.
- Azevedo VM, Lauretti GR, Pereira NL et al (2000) Transdermal ketamine as an adjuvant for postoperative analgesia after abdominal gynecological surgery using lidocaine epidural blockade. *Anesth Analg* **91**(6): 1479–82.
- Bardsley H, Gristwood R, Baker H et al (1998) A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol* **46**(3): 245–9.
- Bernards CM, Shen DD, Sterling ES et al (2003) Epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidural opioids (part 1): differences among opioids. *Anesthesiology* **99**(2): 455–65.
- Bernards CM (2004) Recent insights into the pharmacokinetics of spinal opioids and the relevance to opioid selection. *Curr Opin Anaesthesiol* **17**(5): 441–7.
- Bharti N & Chari P (2009) Epidural butorphanol-bupivacaine analgesia for postoperative pain relief after abdominal hysterectomy. *J Clin Anesth* **21**(1): 19–22.
- Bhatnagar S, Mishra S, Madhurima S et al (2006) Clonidine as an analgesic adjuvant to continuous paravertebral bupivacaine for post-thoracotomy pain. *Anaesth Intensive Care* **34**(5): 586–91.
- Bigat Z, Boztug N, Hadimioglu N et al (2006) Does dexamethasone improve the quality of intravenous regional anesthesia and analgesia? A randomized, controlled clinical study. *Anesth Analg* **102**(2): 605–9.
- Blanloeil Y, Bizouarn P, Le Teurnier Y et al (2001) Postoperative analgesia by epidural methylprednisolone after posterolateral thoracotomy. *Br J Anaesth* **87**(4): 635–8.
- Brill S & Plaza M (2004) Non-narcotic adjuvants may improve the duration and quality of analgesia after knee arthroscopy: a brief review. *Can J Anaesth* **51**(10): 975–8.
- Borghi B, Facchini F, Agnoletti V et al (2006) Pain relief and motor function during continuous interscalene analgesia after open shoulder surgery: a prospective, randomized, double-blind comparison between levobupivacaine 0.25%, and ropivacaine 0.25% or 0.4%. *Eur J Anaesthesiol* **23**(12): 1005–9.
- Bowrey S, Hamer J, Bowler I et al (2005) A comparison of 0.2 and 0.5 mg intrathecal morphine for postoperative analgesia after total knee replacement. *Anaesthesia* **60**(5): 449–52.
- Brodner G, Buerkle H, Van Aken H et al (2007) Postoperative analgesia after knee surgery: a comparison of three different concentrations of ropivacaine for continuous femoral nerve blockade. *Anesth Analg* **105**(1): 256–62.
- Bryson GL, Thompson C, Gagne S et al (2007) The addition of adrenaline to thoracic epidural meperidine does not improve analgesia following thoracotomy. *Can J Anaesth* **54**(11): 882–90.
- Burlacu CL, Frizelle HP, Moriarty DC et al (2006) Fentanyl and clonidine as adjunctive analgesics with levobupivacaine in paravertebral analgesia for breast surgery. *Anaesthesia* **61**(10): 932–7.
- Calder LA, Balasubramanian S & Fergusson D (2005) Topical nonsteroidal anti-inflammatory drugs for corneal abrasions: meta-analysis of randomized trials. *Academic Emergency Medicine* **12**(5): 467–73.
- Canbay O, Celebi N, Uzun S et al (2008) Topical ketamine and morphine for post-tonsillectomy pain. *Eur J Anaesthesiol* **25**(4): 287–92.

- Capogna G, Celleno D, Fusco P et al (1999) Relative potencies of bupivacaine and ropivacaine for analgesia in labour. *Br J Anaesth* **82**(3): 371–3.
- Carvalho B, Riley E, Cohen SE et al (2005) Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: results of a multicenter randomized controlled study. *Anesth Analg* **100**(4): 1150–8.
- Carvalho B, Roland LM, Chu LF et al (2007) Single-dose, extended-release epidural morphine (DepoDur) compared to conventional epidural morphine for post-cesarean pain. *Anesth Analg* **105**(1): 176–83.
- Casati A, Borghi B, Fanelli G et al (2002) A double-blinded, randomized comparison of either 0.5% levobupivacaine or 0.5% ropivacaine for sciatic nerve block. *Anesth Analg* **94**(4): 987–90.
- Casati A, Borghi B, Fanelli G et al (2003) Interscalene brachial plexus anesthesia and analgesia for open shoulder surgery: a randomized, double-blinded comparison between levobupivacaine and ropivacaine. *Anesth Analg* **96**(1): 253–9.
- Casati A, Santorsola R, Aldegheri G et al (2003) Intraoperative epidural anesthesia and postoperative analgesia with levobupivacaine for major orthopedic surgery: a double-blind, randomized comparison of racemic bupivacaine and ropivacaine. *J Clin Anesth* **15**(2): 126–31.
- Casati A, Vinciguerra F, Scarioni M et al (2003) Lidocaine versus ropivacaine for continuous interscalene brachial plexus block after open shoulder surgery. *Acta Anaesthesiol Scand* **47**(3): 355–60.
- Casati A, Vinciguerra F, Cappelleri G et al (2004) Levobupivacaine 0.2% or 0.125% for continuous sciatic nerve block: a prospective, randomized, double-blind comparison with 0.2% ropivacaine. *Anesth Analg* **99**(3): 919–23.
- Casati A & Putzu M (2005) Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? *Best Pract Res Clin Anaesthesiol* **19**(2): 247–68.
- Casati A, Vinciguerra F, Cappelleri G et al (2005) Adding clonidine to the induction bolus and postoperative infusion during continuous femoral nerve block delays recovery of motor function after total knee arthroplasty. *Anesth Analg* **100**(3): 866–72.
- Cerchiotti LC, Navigante AH, Bonomi MR et al (2002) Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer* **95**(10): 2230–6.
- Cerchiotti LC, Navigante AH, Korte MW et al (2003) Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study. *Pain* **105**(1-2): 265–73.
- Chaplan SR, Duncan SR, Brodsky JB et al (1992) Morphine and hydromorphone epidural analgesia. A prospective, randomized comparison. *Anesthesiology* **77**(6): 1090–4.
- Chazalon P, Tourtier JP, Villevielle T et al (2003) Ropivacaine-induced cardiac arrest after peripheral nerve block: successful resuscitation. *Anesthesiology* **99**(6): 1449–51.
- Cheng CR, Su TH, Hung YC et al (2002) A comparative study of the safety and efficacy of 0.5% levobupivacaine and 0.5% bupivacaine for epidural anesthesia in subjects undergoing elective caesarean section. *Acta Anaesthesiol Sin* **40**(1): 13–20.
- Chia YY, Chang TH, Liu K et al (2006) The efficacy of thoracic epidural neostigmine infusion after thoracotomy. *Anesth Analg* **102**(1): 201–8.
- Clerc S, Vuilleumier H, Frascarolo P et al (2005) Is the effect of inguinal field block with 0.5% bupivacaine on postoperative pain after hernia repair enhanced by addition of ketorolac or S(+) ketamine? *Clin J Pain* **21**(1): 101–5.
- Colbert ST, Curran E, O'Hanlon DM et al (1999) Intra-articular tenoxicam improves postoperative analgesia in knee arthroscopy. *Can J Anaesth* **46**(7): 653–7.
- Cole PJ, Craske DA & Wheatley RG (2000) Efficacy and respiratory effects of low-dose spinal morphine for postoperative analgesia following knee arthroplasty. *Br J Anaesth* **85**(2): 233–7.
- Convery PN, Milligan KR, Quinn P et al (1998) Low-dose intra-articular ketorolac for pain relief following arthroscopy of the knee joint. *Anaesthesia* **53**(11): 1125–9.
- Cook TM, Tuckey JP & Nolan JP (1997) Analgesia after day-case knee arthroscopy: double-blind study of intra-articular tenoxicam, intra-articular bupivacaine and placebo. *Br J Anaesth* **78**(2): 163–8.
- Corman SL & Skledar SJ (2007) Use of lipid emulsion to reverse local anesthetic-induced toxicity. *Ann Pharmacother* **41**(11): 1873–7.

- Cousins MJ & Mather LE (1984) Intrathecal and epidural administration of opioids. *Anesthesiology* **61**(3): 276–310.
- Covino BG & Wildsmith JA (1998) Clinical pharmacology of local anaesthetic agents. In: *Neural Blockade* 3rd edn. Cousins MJ and Bridenbaugh P (eds). Philadelphia, Lippincott-Raven.
- Crews JC, Hord AH, Denson DD et al (1999) A comparison of the analgesic efficacy of 0.25% levobupivacaine combined with 0.005% morphine, 0.25% levobupivacaine alone, or 0.005% morphine alone for the management of postoperative pain in patients undergoing major abdominal surgery. *Anesth Analg* **89**(6): 1504–9.
- Culebras X, Savoldelli GL, Van Gessel E et al (2007) Low-dose sufentanil does not potentiate intrathecal morphine for perioperative analgesia after major colorectal surgery. *Can J Anaesth* **54**(10): 811–7.
- Dahl JB, Jeppesen IS, Jorgensen H et al (1999) Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. *Anesthesiology* **91**(6): 1919–27.
- Dayioglu H, Baykara ZN, Salbes A et al (2009) Effects of adding magnesium to bupivacaine and fentanyl for spinal anesthesia in knee arthroscopy. *J Anesth* **23**(1): 19–25.
- De Cosmo G, Congedo E, Lai C et al (2008) Ropivacaine vs. levobupivacaine combined with sufentanil for epidural analgesia after lung surgery. *Eur J Anaesthesiol* **25**(12): 1020–5.
- de Leon-Casasola OA & Lema MJ (1996) Postoperative epidural opioid analgesia: what are the choices? *Anesth Analg* **83**(4): 867–75.
- Dernedde M, Stadler M, Taviaux N et al (2008) Postoperative patient-controlled thoracic epidural analgesia: importance of dose compared to volume or concentration. *Anaesth Intensive Care* **36**(6): 814–21.
- Di Nisio M, Wichers IM & Middeldorp S (2007) Treatment for superficial thrombophlebitis of the leg. *Cochrane Database of Systematic Reviews*(2): CD004982.
- Elhakim M, Fathy A, Elkott M et al (1996) Intra-articular tenoxicam relieves post-arthroscopy pain. *Acta Anaesthesiol Scand* **40**(10): 1223–6.
- Elia N, Culebras X, Mazza C et al (2008) Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med* **33**(2): 159–67.
- Elsharnouby NM, Eid HE, Abou Elezz NF et al (2008) Intraarticular injection of magnesium sulphate and/or bupivacaine for postoperative analgesia after arthroscopic knee surgery. *Anesth Analg* **106**(5): 1548–52.
- Emanuelsson BM, Zaric D, Nydahl PA et al (1995) Pharmacokinetics of ropivacaine and bupivacaine during 21 hours of continuous epidural infusion in healthy male volunteers. *Anesth Analg* **81**(6): 1163–8.
- Farmery AD & Wilson-MacDonald J (2009) The analgesic effect of epidural clonidine after spinal surgery: a randomized placebo-controlled trial. *Anesth Analg* **108**(2): 631–4.
- Felice K & Schumann H (2008) Intravenous lipid emulsion for local anesthetic toxicity: a review of the literature. *J Med Toxicol* **4**(3): 184–91.
- Forster JG, Niemi TT, Aromaa U et al (2003) Epinephrine added to a lumbar epidural infusion of a small-dose ropivacaine-fentanyl mixture after arterial bypass surgery of the lower extremities. *Acta Anaesthesiol Scand* **47**(9): 1106–13.
- Forster JG, Lumme HM, Palkama VJ et al (2008) Epinephrine 4 microg/mL added to a low-dose mixture of ropivacaine and fentanyl for lumbar epidural analgesia after total knee arthroplasty. *Anesth Analg* **106**(1): 301–4.
- Foxall G, McCahon R, Lamb J et al (2007) Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid. *Anaesthesia* **62**(5): 516–8.
- Gambling D, Hughes T, Martin G et al (2005) A comparison of Depodur, a novel, single-dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery. *Anesth Analg* **100**(4): 1065–74.
- Gehling M & Tryba M (2009) Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia* **64**(6): 643–51.

- Ginosar Y, Riley ET & Angst MS (2003) The site of action of epidural fentanyl in humans: the difference between infusion and bolus administration. *Anesth Analg* **97**(5): 1428–38.
- Girgin NK, Gurbet A, Turker G et al (2008) Intrathecal morphine in anesthesia for cesarean delivery: dose-response relationship for combinations of low-dose intrathecal morphine and spinal bupivacaine. *J Clin Anesth* **20**(3): 180–5.
- Green S, Buchbinder R, Barnsley L et al (2001) Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. *Cochrane Database of Systematic Reviews*(4): CD003686.
- Groban L & Dolinski SY (2001) Differences in cardiac toxicity among ropivacaine, levobupivacaine, bupivacaine, and lidocaine. *Techniques in Regional Anesthesia and Pain Management* **5**(2): 48–55.
- Gupta A, Axelsson K, Allvin R et al (1999) Postoperative pain following knee arthroscopy: the effects of intra-articular ketorolac and/or morphine. *Reg Anesth Pain Med* **24**(3): 225–30.
- Gupta A, Bodin L, Holmstrom B et al (2001) A systematic review of the peripheral analgesic effects of intraarticular morphine. *Anesth Analg* **93**(3): 761–70.
- Gurbet A, Turker G, Girgin NK et al (2008) Combination of ultra-low dose bupivacaine and fentanyl for spinal anaesthesia in out-patient ano-rectal surgery. *J Int Med Res* **36**(5): 964–70.
- Habib AS & Gan TJ (2006) Use of neostigmine in the management of acute postoperative pain and labour pain: a review. *CNS Drugs* **20**(10): 821–39.
- Hassett P, Ansari B, Gnanamoorthy P et al (2008) Determination of the efficacy and side-effect profile of lower doses of intrathecal morphine in patients undergoing total knee arthroplasty. *BMC Anesthesiol* **8**: 5.
- Heid F, Schmidt-Glitzner A, Piepho T et al (2007) Epidural ropivacaine -- where are the benefits? A prospective, randomized, double-blind trial in patients with retropubic prostatectomy. *Acta Anaesthesiol Scand* **51**(3): 294–8.
- Heid F, Muller N, Piepho T et al (2008) Postoperative analgesic efficacy of peripheral levobupivacaine and ropivacaine: a prospective, randomized double-blind trial in patients after total knee arthroplasty. *Anesth Analg* **106**(5): 1559–61.
- Hempenstall K, Nurmikko TJ, Johnson RW et al (2005) Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. *PLoS Med* **2**(7): e164.
- Ho KM, Ismail H, Lee KC et al (2005) Use of intrathecal neostigmine as an adjunct to other spinal medications in perioperative and peripartum analgesia: a meta-analysis. *Anaesth Intensive Care* **33**(1): 41–53.
- Ho KM & Ismail H (2008) Use of intrathecal midazolam to improve perioperative analgesia: a meta-analysis. *Anaesth Intensive Care* **36**(3): 365–73.
- Ho KY & Tan KH (2007) Botulinum toxin A for myofascial trigger point injection: a qualitative systematic review. *Eur J Pain* **11**(5): 519–27.
- Hodgson PS, Neal JM, Pollock JE et al (1999) The neurotoxicity of drugs given intrathecally (spinal). *Anesth Analg* **88**(4): 797–809.
- Huang YS, Lin LC, Huh BK et al (2007) Epidural clonidine for postoperative pain after total knee arthroplasty: a dose-response study. *Anesth Analg* **104**(5): 1230–5.
- Hubler M, Litz RJ, Sengebusch KH et al (2001) A comparison of five solutions of local anaesthetics and/or sufentanil for continuous, postoperative epidural analgesia after major urological surgery. *Eur J Anaesthesiol* **18**(7): 450–7.
- Huet O, Eyrolle LJ, Mazoit JX et al (2003) Cardiac arrest after injection of ropivacaine for posterior lumbar plexus blockade. *Anesthesiology* **99**(6): 1451–3.
- Iijima T, Ishiyama T, Kashimoto S et al (2007) A comparison of three different concentrations of ropivacaine with fentanyl for patient-controlled epidural analgesia. *Anesth Analg* **105**(2): 507–11.
- Ilfeld BM, Loland VJ, Gerancher JC et al (2008) The effects of varying local anesthetic concentration and volume on continuous popliteal sciatic nerve blocks: a dual-center, randomized, controlled study. *Anesth Analg* **107**(2): 701–7.

- Iffeld BM, Le LT, Ramjohn J et al (2009) The effects of local anesthetic concentration and dose on continuous infraclavicular nerve blocks: a multicenter, randomized, observer-masked, controlled study. *Anesth Analg* **108**(1): 345–50.
- Jaffe RA & Rowe MA (1996) A comparison of the local anesthetic effects of meperidine, fentanyl, and sufentanil on dorsal root axons. *Anesth Analg* **83**(4): 776–81.
- Jirattananaphochai K, Jung S, Thienthong S et al (2007) Peridural methylprednisolone and wound infiltration with bupivacaine for postoperative pain control after posterior lumbar spine surgery: a randomized double-blinded placebo-controlled trial. *Spine* **32**(6): 609–16.
- Johansen MJ, Gradert TL, Satterfield WC et al (2004) Safety of continuous intrathecal midazolam infusion in the sheep model. *Anesth Analg* **98**(6): 1528–35.
- Jorgensen H, Fomsgaard JS, Dirks J et al (2000) Effect of continuous epidural 0.2% ropivacaine vs 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy. *Br J Anaesth* **84**(2): 144–50.
- Kalso E, Smith L, McQuay HJ et al (2002) No pain, no gain: clinical excellence and scientific rigour—lessons learned from IA morphine. *Pain* **98**(3): 269–75.
- Kanai A, Osawa S, Suzuki A et al (2007) Regression of sensory and motor blockade, and analgesia during continuous epidural infusion of ropivacaine and fentanyl in comparison with other local anesthetics. *Pain Med* **8**(7): 546–53.
- Kanazi GE, Aouad MT, Jabbour-Khoury SI et al (2006) Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. *Acta Anaesthesiologica Scandinavica* **50**(2): 222–7.
- Karaman S, Kocabas S, Uyar M et al (2006) The effects of sufentanil or morphine added to hyperbaric bupivacaine in spinal anaesthesia for caesarean section. *Eur J Anaesthesiol* **23**(4): 285–91.
- Kashefi P, Montazeri K, Honarmand A et al (2008) Adding magnesium to lidocaine for intravenous regional anesthesia. *JRMS* **13**(3): 108–14.
- Kathirvel S, Sadhasivam S, Saxena A et al (2000) Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. *Anaesthesia* **55**(9): 899–904.
- Kato R, Shimamoto H, Terui K et al (2008) Delayed respiratory depression associated with 0.15 mg intrathecal morphine for cesarean section: a review of 1915 cases. *J Anesth* **22**(2): 112–6.
- Khoo LP & Corbett AR (2006) Successful resuscitation of an ASA 3 patient following ropivacaine-induced cardiac arrest. *Anaesth Intensive Care* **34**(6): 804–7.
- Kimura Y, Kamada Y, Kimura A et al (2007) Ropivacaine-induced toxicity with overdose suspected after axillary brachial plexus block. *J Anesth* **21**(3): 413–6.
- Kizilkaya M, Yildirim OS, Dogan N et al (2004) Analgesic Effects of Intraarticular Sufentanil and Sufentanil Plus Methylprednisolone after Arthroscopic Knee Surgery. *Anesth Analg* **98**(4): 1062–65.
- Kizilkaya M, Yildirim OS, Ezirmik N et al (2005) Comparisons of analgesic effects of different doses of morphine and morphine plus methylprednisolone after knee surgery. *Eur J Anaesthesiol* **22**(8): 603–08.
- Klein SM, Pierce T, Rubin Y et al (2003) Successful resuscitation after ropivacaine-induced ventricular fibrillation. *Anesth Analg* **97**(3): 901–3.
- Knudsen K, Beckman Suurkula M, Blomberg S et al (1997) Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* **78**(5): 507–14.
- Koch T, Fichtner A, Schwemmer U et al (2008) Levobupivacaine for epidural anaesthesia and postoperative analgesia in hip surgery: a multi-center efficacy and safety equivalence study with bupivacaine and ropivacaine. *Anaesthesist* **57**(5): 475–82.
- Koppert W, Likar R, Geisslinger G et al (1999) Peripheral antihyperalgesic effect of morphine to heat, but not mechanical, stimulation in healthy volunteers after ultraviolet-B irradiation. *Anesth Analg* **88**(1): 117–22.
- Kumar P, Rudra A, Pan AK et al (2005) Caudal additives in pediatrics: a comparison among midazolam, ketamine, and neostigmine coadministered with bupivacaine. *Anesth Analg* **101**(1): 69–73.
- Kumar A, Srivastava U, Saxena S et al (2007) Comparison of intrathecal morphine and pethidine for post caesarean analgesia and side effects. *Journal of Anaesthesiology Clinical Pharmacology* **23**(1): 35–39.



- Lacassie HJ, Columb MO, Lacassie HP et al (2002) The relative motor blocking potencies of epidural bupivacaine and ropivacaine in labor. *Anesth Analg* **95**(1): 204–8.
- Lacassie HJ & Columb MO (2003) The relative motor blocking potencies of bupivacaine and levobupivacaine in labor. *Anesth Analg* **97**(5): 1509–13.
- Lavand'homme PM, Roelants F, Waterloos H et al (2008) An evaluation of the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective cesarean delivery. *Anesth Analg* **107**(3): 948–55.
- Le LT, Loland VJ, Mariano ER et al (2008) Effects of local anesthetic concentration and dose on continuous interscalene nerve blocks: a dual-center, randomized, observer-masked, controlled study. *Reg Anesth Pain Med* **33**(6): 518–25.
- Lee IO, Kim WK, Kong MH et al (2002) No enhancement of sensory and motor blockade by ketamine added to ropivacaine interscalene brachial plexus blockade. *Acta Anaesthesiol Scand* **46**(7): 821–6.
- Litz RJ, Popp M, Stehr SN et al (2006) Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. *Anaesthesia* **61**(8): 800–1.
- Litz RJ, Roessel T, Heller AR et al (2008) Reversal of central nervous system and cardiac toxicity after local anesthetic intoxication by lipid emulsion injection. *Anesth Analg* **106**(5): 1575–7.
- Liu S, Carpenter RL, Mulroy MF et al (1995) Intravenous versus epidural administration of hydromorphone. Effects on analgesia and recovery after radical retropubic prostatectomy. *Anesthesiology* **82**(3): 682–8.
- Loffinia I, Khallaghi E, Meshkini A et al (2007) Intraoperative use of epidural methylprednisolone or bupivacaine for postsurgical lumbar discectomy pain relief: a randomized, placebo-controlled trial. *Annals of Saudi Medicine* **27**(4): 279–83.
- Lurie SD, Reuben SS, Gibson CS et al (2000) Effect of clonidine on upper extremity tourniquet pain in healthy volunteers. *Reg Anesth Pain Med* **25**(5): 502–5.
- Lyons G, Columb M, Wilson RC et al (1998) Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth* **81**(6): 899–901.
- Macias A, Monedero P, Adame M et al (2002) A randomized, double-blinded comparison of thoracic epidural ropivacaine, ropivacaine/fentanyl, or bupivacaine/fentanyl for postthoracotomy analgesia. *Anesth Analg* **95**(5): 1344–50.
- Marchal JM, Delgado-Martinez AD, Poncela M et al (2003) Does the type of arthroscopic surgery modify the analgesic effect of intraarticular morphine and bupivacaine? A preliminary study. *Clin J Pain* **19**(4): 240–6.
- Markham A & Faulds D (1996) Ropivacaine. A review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs* **52**(3): 429–49.
- Martin G, Hartmannsgruber M, Riley E et al (2006) Single-dose extended-release epidural morphine for pain after hip arthroplasty. *J Opioid Manag* **2**(4): 209–18.
- Marwick PC, Levin AI & Coetzee AR (2009) Recurrence of cardiotoxicity after lipid rescue from bupivacaine-induced cardiac arrest. *Anesth Analg* **108**(4): 1344–6.
- Mason L, Moore RA, Edwards JE et al (2004) Topical NSAIDs for acute pain: a meta-analysis. *BMC Family Practice* **5**: 10.
- Mather LE & Chang DH (2001) Cardiotoxicity with modern local anaesthetics: is there a safer choice? *Drugs* **61**(3): 333–42.
- Mather LE, Copeland SE & Ladd LA (2005) Acute toxicity of local anesthetics: underlying pharmacokinetic and pharmacodynamic concepts. *Reg Anesth Pain Med* **30**(6): 553–66.
- Mazieres B, Rouanet S, Guillon Y et al (2005) Topical ketoprofen patch in the treatment of tendinitis: a randomized, double blind, placebo controlled study. *J Rheumato* **32**(8): 1563–70.
- Mazieres B, Rouanet S, Velicy J et al (2005) Topical ketoprofen patch (100 mg) for the treatment of ankle sprain: a randomized, double-blind, placebo-controlled study. *Am J Sports Med* **33**(4): 515–23.
- McCartney CJ, Duggan E & Apatu E (2007) Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Reg Anesth Pain Med* **32**(4): 330–8.



- McGlade DP, Kalpokas MV, Mooney PH et al (1998) A comparison of 0.5% ropivacaine and 0.5% bupivacaine for axillary brachial plexus anaesthesia. *Anaesth Intensive Care* **26**(5): 515–20.
- McLauchlan GJ & Handoll HHG (2001) Interventions for treating acute and chronic Achilles tendinitis. *Cochrane Database of Systematic Reviews*(2): CD000232.
- McLeod GA & Burke D (2001) Levobupivacaine. *Anaesthesia* **56**(4): 331–41.
- McLeod GA, Munishankar B & Columb MO (2005) Is the clinical efficacy of epidural diamorphine concentration-dependent when used as analgesia for labour? *Br J Anaesth* **94**(2): 229–33.
- Memis D, Turan A, Karamanlioglu B et al (2004) Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. *Anesth Analg* **98**(3): 835–40.
- Mendola C, Ferrante D, Oldani E et al (2009) Thoracic epidural analgesia in post-thoracotomy patients: comparison of three different concentrations of levobupivacaine and sufentanil. *Br J Anaesth* **102**(3): 418–23.
- Merson N (2001) A comparison of motor block between ropivacaine and bupivacaine for continuous labor epidural analgesia. *AANA J* **69**(1): 54–8.
- Meylan N, Elia N, Lysakowski C et al (2009) Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth* **102**(2): 156–67.
- Milligan KR, Convery PN, Weir P et al (2000) The efficacy and safety of epidural infusions of levobupivacaine with and without clonidine for postoperative pain relief in patients undergoing total hip replacement. *Anesth Analg* **91**(2): 393–7.
- Mirzai H, Tekin I & Alincak H (2002) Perioperative use of corticosteroid and bupivacaine combination in lumbar disc surgery: a randomized controlled trial. *Spine* **27**(4): 343–6.
- Miyoshi RH & Lackband SG (2001) Systemic opioid analgesics. In: *Bonica's Management of Pain* 3rd edn. Loeser J (eds). Lippincott Williams & Wilkins.
- Mogensen T (1995) Tachyphylaxis to epidural local anaesthetics. *Dan Med Bull* **42**(2): 141–6.
- Molnar RR, Davies MJ, Scott DA et al (1997) Comparison of clonidine and epinephrine in lidocaine for cervical plexus block. *Reg Anesth* **22**(2): 137–42.
- Moore JM, Liu SS, Pollock JE et al (1998) The effect of epinephrine on small-dose hyperbaric bupivacaine spinal anesthesia: clinical implications for ambulatory surgery. *Anesth Analg* **86**(5): 973–7.
- Moore RA, Tramer MR, Carroll D et al (1998) Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ* **316**(7128): 333–8.
- Mousa SA, Straub RH, Schafer M et al (2007) Beta-endorphin, Met-enkephalin and corresponding opioid receptors within synovium of patients with joint trauma, osteoarthritis and rheumatoid arthritis. *Ann Rheum Dis* **66**(7): 871–9.
- Movafegh A, Razazian M, Hajimaohamadi F et al (2006) Dexamethasone added to lidocaine prolongs axillary brachial plexus blockade. *Anesth Analg* **102**(1): 263–7.
- Muldoon T, Milligan K, Quinn P et al (1998) Comparison between extradural infusion of ropivacaine or bupivacaine for the prevention of postoperative pain after total knee arthroplasty. *Br J Anaesth* **80**(5): 680–1.
- Murali Krishna T, Panda NB, Batra YK et al (2008) Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves postoperative analgesia in orthopaedic surgery. *Eur J Anaesthesiol* **25**(4): 299–306.
- Murphy DB, McCartney CJ & Chan VW (2000) Novel analgesic adjuncts for brachial plexus block: a systematic review. *Anesth Analg* **90**(5): 1122–8.
- Murphy PM, Stack D, Kinirons B et al (2003) Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. *Anesth Analg* **97**(6): 1709–15.
- Nader ND, Li CM, Dosluoglu HH et al (2009) Adjuvant therapy with intrathecal clonidine improves postoperative pain in patients undergoing coronary artery bypass graft. *Clin J Pain* **25**(2): 101–6.
- Ngan Kee WD (1998) Epidural pethidine: pharmacology and clinical experience. *Anaesth Intensive Care* **26**(3): 247–55.

- Niemi G & Breivik H (1998) Adrenaline markedly improves thoracic epidural analgesia produced by a low-dose infusion of bupivacaine, fentanyl and adrenaline after major surgery. A randomised, double-blind, cross-over study with and without adrenaline. *Acta Anaesthesiol Scand* **42**(8): 897–909.
- Niemi G & Breivik H (2002) Epinephrine markedly improves thoracic epidural analgesia produced by a small-dose infusion of ropivacaine, fentanyl, and epinephrine after major thoracic or abdominal surgery: a randomized, double-blinded crossover study with and without epinephrine. *Anesth Analg* **94**(6): 1598–605.
- Niemi G & Breivik H (2003) The minimally effective concentration of adrenaline in a low-concentration thoracic epidural analgesic infusion of bupivacaine, fentanyl and adrenaline after major surgery. A randomized, double-blind, dose-finding study. *Acta Anaesthesiol Scand* **47**(4): 439–50.
- Nishiyama T, Matsukawa T & Hanaoka K (2002) Effects of adding midazolam on the postoperative epidural analgesia with two different doses of bupivacaine. *J Clin Anesth* **14**(2): 92–7.
- Ohmura S, Kawada M, Ohta T et al (2001) Systemic toxicity and resuscitation in bupivacaine-, levobupivacaine-, or ropivacaine-infused rats. *Anesth Analg* **93**(3): 743–8.
- Paech MJ, Moore JS & Evans SF (1994) Meperidine for patient-controlled analgesia after cesarean section. Intravenous versus epidural administration. *Anesthesiology* **80**(6): 1268–76.
- Paech MJ, Pavy TJ, Orlikowski CE et al (2000) Postoperative intraspinal opioid analgesia after caesarean section; a randomised comparison of subarachnoid morphine and epidural pethidine. *Int J Obstet Anesth* **9**(4): 238–45.
- Paech MJ, Pavy TJ, Orlikowski CE et al (2004) Postcesarean analgesia with spinal morphine, clonidine, or their combination. *Anesth Analg* **98**(5): 1460–6.
- Peloso P, Gross A, Haines T et al (2007) Medicinal and injection therapies for mechanical neck disorders. *Cochrane Database Syst Rev*(3): CD000319.
- Pert CB, Kuhar MJ & Snyder SH (1976) Opiate receptor: autoradiographic localization in rat brain. *Proc Natl Acad Sci U S A* **73**(10): 3729–33.
- Pham-Dang C, Beaumont S, Floch H et al (2000) [Acute toxic accident following lumbar plexus block with bupivacaine]. *Ann Fr Anesth Reanim* **19**(5): 356–9.
- Pham Dang C, Delecrcin J, Pereon Y et al (2008) Epidural analgesia after scoliosis surgery: electrophysiologic and clinical assessment of the effects of bupivacaine 0.125% plus morphine versus ropivacaine 0.2% plus morphine. *J Clin Anesth* **20**(1): 17–24.
- Picard PR, Tramer MR, McQuay HJ et al (1997) Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomised controlled trials. *Pain* **72**(3): 309–18.
- Pitimana-aree S, Visalyaputra S, Komoltri C et al (2005) An economic evaluation of bupivacaine plus fentanyl versus ropivacaine alone for patient-controlled epidural analgesia after total-knee replacement procedure: a double-blinded randomized study. *Reg Anesth Pain Med* **30**(5): 446–51.
- Polley LS, Columb MO, Naughton NN et al (1999) Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: implications for therapeutic indexes. *Anesthesiology* **90**(4): 944–50.
- Polley LS, Columb MO, Naughton NN et al (2003) Relative analgesic potencies of levobupivacaine and ropivacaine for epidural analgesia in labor. *Anesthesiology* **99**(6): 1354–8.
- Popping DM, Elia N, Marret E et al (2009) Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. *Anesthesiology* **111**(2): 406–15.
- Poyhia R & Vainio A (2006) Topically administered ketamine reduces capsaicin-evoked mechanical hyperalgesia. *Clin J Pain* **22**(1): 32–6.
- Prakash S, Joshi N, Gogia AR et al (2006) Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing cesarean delivery. *Reg Anesth Pain Med* **31**(3): 221–6.
- Rasmussen S, Lorentzen JS, Larsen AS et al (2002) Combined intra-articular glucocorticoid, bupivacaine and morphine reduces pain and convalescence after diagnostic knee arthroscopy. *Acta Orthop Scand*. **73**(2): 175–78.
- Rathmell JP, Pino CA, Taylor R et al (2003) Intrathecal morphine for postoperative analgesia: a randomized, controlled, dose-ranging study after hip and knee arthroplasty. *Anesth Analg* **97**(5): 1452–7.

- Rigler ML, Drasner K, Krejcie TC et al (1991) Cauda equina syndrome after continuous spinal anesthesia. *Anesth Analg* **72**(3): 275–81.
- Roelants F (2006) The use of neuraxial adjuvant drugs (neostigmine, clonidine) in obstetrics. *Current Opinion in Anaesthesiology* **19**(3): 233–7.
- Roelofs P, Deyo RA, Koes BW et al (2008) Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database of Systematic Reviews*(1): CD000396.
- Rosenblatt MA, Abel M, Fischer GW et al (2006) Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. *Anesthesiology* **105**(1): 217–8.
- Ross VH, Pan PH, Owen MD et al (2009) Neostigmine decreases bupivacaine use by patient-controlled epidural analgesia during labor: a randomized controlled study. *Anesth Analg* **109**(2): 524–31.
- Rosseland LA, Stubhaug A, Sandberg L et al (2003) Intra-articular (IA) catheter administration of postoperative analgesics. A new trial design allows evaluation of baseline pain, demonstrates large variation in need of analgesics, and finds no analgesic effect of IA ketamine compared with IA saline. *Pain* **104**(1-2): 25–34.
- Rosseland LA (2005) No evidence for analgesic effect of intra-articular morphine after knee arthroscopy: a qualitative systematic review. *Reg Anesth Pain Med* **30**(1): 83–98.
- Royse CE, Royse AG & Deelen DA (2005) An audit of morphine versus fentanyl as an adjunct to ropivacaine 0.2% for high thoracic epidural analgesia. *Anaesth Intensive Care* **33**(5): 639–44.
- Sakaguchi Y, Sakura S, Shinzawa M et al (2000) Does adrenaline improve epidural bupivacaine and fentanyl analgesia after abdominal surgery? *Anaesth Intensive Care* **28**(5): 522–6.
- Saryazdi H, Kashefi P, Heydari M et al (2006) Analgesic effects of intra-articular fentanyl, pethidine and dexamethasone after knee arthroscopic surgery. *JRMS* **11**(3): 156–59.
- Schafer M (1999) Peripheral opioid analgesia: from experimental to clinical studies. *Curr Opin Anaesthesiol* **12**(5): 603–7.
- Schell RM, Brauer FS, Cole DJ et al (1991) Persistent sacral nerve root deficits after continuous spinal anaesthesia. *Can J Anaesth* **38**(7): 908–11.
- Schug SA, Scott DA, Payne J et al (1996) Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery. *Br J Anaesth* **76**(4): 487–91.
- Schug SA (2001) Correction factor for comparisons between levobupivacaine and racemic bupivacaine. *Reg Anesth Pain Med* **26**(1): 91.
- Scott DA, Chamley DM, Mooney PH et al (1995) Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery—a dose finding study. *Anesth Analg* **81**(5): 982–6.
- Scott DA, Emanuelsson BM, Mooney PH et al (1997) Pharmacokinetics and efficacy of long-term epidural ropivacaine infusion for postoperative analgesia. *Anesth Analg* **85**(6): 1322–30.
- Scott DA, Blake D, Buckland M et al (1999) A comparison of epidural ropivacaine infusion alone and in combination with 1, 2, and 4 microg/mL fentanyl for seventy-two hours of postoperative analgesia after major abdominal surgery. *Anesth Analg* **88**(4): 857–64.
- Scott DB, Lee A, Fagan D et al (1989) Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* **69**(5): 563–9.
- Senard M, Joris JL, Ledoux D et al (2002) A comparison of 0.1% and 0.2% ropivacaine and bupivacaine combined with morphine for postoperative patient-controlled epidural analgesia after major abdominal surgery. *Anesth Analg* **95**(2): 444–9.
- Shakespeare DT, Boggild M & Young C (2003) Anti-spasticity agents for multiple sclerosis. *Cochrane Database Syst Rev*(4): CD001332.
- Simpson DM, Blitzer A, Brashear A et al (2008) Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **70**(19): 1699–706.
- Sitsen E, van Poorten F, van Alphen W et al (2007) Postoperative epidural analgesia after total knee arthroplasty with sufentanil 1 microg/ml combined with ropivacaine 0.2%, ropivacaine 0.125%, or levobupivacaine 0.125%: a randomized, double-blind comparison. *Reg Anesth Pain Med* **32**(6): 475–80.

- Slatkin NE & Rhiner M (2003) Topical ketamine in the treatment of mucositis pain. *Pain Med* **4**(3): 298–303.
- Smet I, Vlamincx E & Vercauteren M (2008) Randomized controlled trial of patient-controlled epidural analgesia after orthopaedic surgery with sufentanil and ropivacaine 0.165% or levobupivacaine 0.125%. *Br J Anaesth* **100**(1): 99–103.
- Smith HS (2008) Peripherally-acting opioids. *Pain Physician* **11**(2 Suppl): S121–32.
- Soltész EG, van Pelt F & Byrne JG (2003) Emergent cardiopulmonary bypass for bupivacaine cardiotoxicity. *J Cardiothorac Vasc Anesth* **17**(3): 357–8.
- Staal JB, de Bie RA, de Vet HC et al (2009) Injection therapy for subacute and chronic low back pain: an updated Cochrane review. *Spine* **34**(1): 49–59.
- Stein C, Hassan AH, Przewlocki R et al (1990) Opioids from immunocytes interact with receptors on sensory nerves to inhibit nociception in inflammation. *Proc Natl Acad Sci U S A* **87**(15): 5935–9.
- Stein C (1995) The control of pain in peripheral tissue by opioids. *N Engl J Med* **332**(25): 1685–90.
- Stewart J, Kellett N & Castro D (2003) The central nervous system and cardiovascular effects of levobupivacaine and ropivacaine in healthy volunteers. *Anesth Analg* **97**(2): 412–6.
- Subramaniam K, Subramaniam B & Steinbrook RA (2004) Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg* **99**(2): 482–95.
- Tan PH, Cheng JT, Kuo CH et al (2007) Preincisional subcutaneous infiltration of ketamine suppresses postoperative pain after circumcision surgery. *Clin J Pain* **23**(3): 214–8.
- Thomas S & Beevi S (2006) Epidural dexamethasone reduces postoperative pain and analgesic requirements. *Canadian Journal of Anaesthesia* **53**(9): 899–905.
- Treman J & Bonica J (2001) Spinal mechanisms and their mechanisms. In: *Bonica's Management of Pain* 3rd edn. Loesser J (eds). Philadelphia USA, Lippincott Williams and Wilkins. 101.
- Tsui BC & Berde CB (2005) Caudal analgesia and anesthesia techniques in children. *Curr Opin Anaesthesiol* **18**(3): 283–8.
- Tucker AP, Lai C, Nadeson R et al (2004) Intrathecal midazolam I: a cohort study investigating safety. *Anesth Analg* **98**(6): 1512–20.
- Tucker AP, Mezzatesta J, Nadeson R et al (2004) Intrathecal midazolam II: combination with intrathecal fentanyl for labor pain. *Anesth Analg* **98**(6): 1521–7.
- Turan A, Memis D, Karamanlioglu B et al (2005) Intravenous regional anesthesia using lidocaine and magnesium. *Anesth Analg* **100**(4): 1189–92.
- Unlugenc H, Ozalevli M, Gunes Y et al (2006) A double-blind comparison of intrathecal S(+) ketamine and fentanyl combined with bupivacaine 0.5% for Caesarean delivery. *Eur J Anaesthesiol* **23**(12): 1018–24.
- Vernassiere C, Cornet C, Trechot P et al (2005) Study to determine the efficacy of topical morphine on painful chronic skin ulcers. *J Wound Care* **14**(6): 289–93.
- Viscomi CM, Friend A, Parker C et al (2009) Ketamine as an adjuvant in lidocaine intravenous regional anesthesia: a randomized, double-blind, systemic control trial. *Reg Anesth Pain Med* **34**(2): 130–3.
- Viscusi ER, Gambling DR, Hughes TL et al (2009) Pharmacokinetics of extended-release epidural morphine sulfate: pooled analysis of six clinical studies. *Am J Health Syst Pharm* **66**(11): 1020–30.
- Viscusi ER, Martin G, Hartrick CT et al (2005) Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. *Anesthesiology* **102**(5): 1014–22.
- Viscusi ER, Kopacz D, Hartrick C et al (2006) Single-dose extended-release epidural morphine for pain following hip arthroplasty. *Am J Ther* **13**(5): 423–31.
- Walker SM, Goudas LC, Cousins MJ et al (2002) Combination spinal analgesic chemotherapy: a systematic review. *Anesth Analg* **95**(3): 674–715.
- Wang JJ, Ho ST, Lee SC et al (1998) Intraarticular triamcinolone acetonide for pain control after arthroscopic knee surgery. *Anesth Analg* **87**(5): 1113–6.
- Wang JK, Nauss LA & Thomas JE (1979) Pain relief by intrathecally applied morphine in man. *Anesthesiology* **50**(2): 149–51.

- Wang X, Xie H & Wang G (2006) Improved postoperative analgesia with coadministration of preoperative epidural ketamine and midazolam. *J Clin Anesth* **18**(8): 563–9.
- Warren JA, Thoma RB, Georgescu A et al (2008) Intravenous lipid infusion in the successful resuscitation of local anesthetic-induced cardiovascular collapse after supraclavicular brachial plexus block. *Anesth Analg* **106**(5): 1578–80.
- Weinberg G, Ripper R, Feinstein DL et al (2003) Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. *Reg Anesth Pain Med* **28**(3): 198–202.
- Weinberg G (2006) Lipid rescue resuscitation from local anaesthetic cardiac toxicity. *Toxicol Rev* **25**(3): 139–45.
- Weinberg GL, VadeBoncouer T, Ramaraju GA et al (1998) Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology* **88**(4): 1071–5.
- Weinberg GL, Palmer JW, VadeBoncouer TR et al (2000) Bupivacaine inhibits acylcarnitine exchange in cardiac mitochondria. *Anesthesiology* **92**(2): 523–8.
- Welling A (2007) A randomised controlled trial to test the analgesic efficacy of topical morphine on minor superficial and partial thickness burns in accident and emergency departments. *Emerg Med J* **24**(6): 408–12.
- Wheatley RG, Schug SA & Watson D (2001) Safety and efficacy of postoperative epidural analgesia. *Br J Anaesth* **87**(1): 47–61.
- Wilson JA, Nimmo AF, Fleetwood-Walker SM et al (2008) A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. *Pain* **135**(1-2): 108–18.
- YaDeau JT, LaSala VR, Paroli L et al (2008) Clonidine and analgesic duration after popliteal fossa nerve blockade: randomized, double-blind, placebo-controlled study. *Anesth Analg* **106**(6): 1916–20.
- Yaksh TL & Rudy TA (1976) Analgesia mediated by a direct spinal action of narcotics. *Science* **192**(4246): 1357–8.
- Yaksh TL (1981) Spinal opiate analgesia: characteristics and principles of action. *Pain* **11**(3): 293–346.
- Yaksh TL & Allen JW (2004) Preclinical insights into the implementation of intrathecal midazolam: a cautionary tale. *Anesth Analg* **98**(6): 1509–11.
- Yildiz TS, Korkmaz F, Solak M et al (2006) Clonidine addition prolongs the duration of caudal analgesia. *Acta Anaesthesiol Scand* **50**(4): 501–4.
- Zacher J, Altman R, Bellamy N et al (2008) Topical diclofenac and its role in pain and inflammation: an evidence-based review. *Current Medical Research & Opinion* **24**(4): 925–50.
- Zaric D, Nydahl PA, Adel SO et al (1996) The effect of continuous epidural infusion of ropivacaine (0.1%, 0.2% and 0.3%) on nerve conduction velocity and postural control in volunteers. *Acta Anaesthesiol Scand* **40**(3): 342–9.
- Zaric D, Pace NL. (2009) Transient neurologic symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics. *Cochrane Database of Syst Rev.* (2): CD003006
- Zeidan A, Kassem R, Nahleh N et al (2008) Intraarticular tramadol-bupivacaine combination prolongs the duration of postoperative analgesia after outpatient arthroscopic knee surgery. *Anesth Analg* **107**(1): 292–9.
- Zohar E, Luban I, Zunser I et al (2002) Patient-controlled bupivacaine wound instillation following cesarean section: the lack of efficacy of adjuvant ketamine. *J Clin Anesth* **14**(7): 505–11.
- Zollner C, Mousa S, Klinger A et al (2008) Topical fentanyl in a randomized, double-blind study in patients with corneal damage. *Clin J Pain* **24**(8): 690–6.

## 6. ADMINISTRATION OF SYSTEMIC ANALGESIC DRUGS

Opioid and non-opioid analgesic drugs can be administered systemically by a number of different routes. The choice of route may be determined by various factors, including the aetiology, severity, location and type of pain, the patient's overall condition and the characteristics of the chosen administration technique. Additional factors to consider with any route of administration are ease of use, accessibility, speed of analgesic onset, reliability of effect, duration of action, patient acceptability, cost, staff education and supervision available. The principles of individualisation of dose and dosing intervals apply to the administration of all analgesic agents, particularly opioids, by any route. A lack of flexibility in dose schedules has often meant that intermittent and 'prn' (as needed) methods of pain relief have been ineffective when the routes of administration discussed below have been used (Bandolier, 2003). Frequent assessment of the patient's pain and their response to treatment (including the occurrence of any side effects) rather than strict adherence to a given dosing regimen is required if adequate analgesia is to be obtained.

The text in Sections 6.1 to 6.4 below relates to opioids, non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) and coxibs. For information about oral and parenteral routes of administration of systemically administered adjuvant drugs, refer to Section 4.3.

### 6.1 ORAL ROUTE

Oral administration of analgesic agents is simple, non-invasive, has good efficacy in most settings and high patient acceptability. Other than in the treatment of severe acute pain and providing there are no contraindications to its use, it is the route of choice for the administration of most analgesic drugs.

Limitations to the oral route include vomiting or delayed gastric emptying, when absorption is likely to be impaired. If multiple doses of an oral analgesic drug are given before return of normal gastric motility, accumulated doses may enter the small intestine at the same time once emptying resumes ('dumping effect'). This could result in an unexpectedly large systemic uptake of the drug and an increased risk of adverse effects.

Rates of absorption will vary according to the formulation of the oral analgesic agent (eg tablet, suspension, controlled-release [CR] preparation). Bioavailability will also vary between drugs because of the effects of first-pass hepatic metabolism following uptake into the portal circulation. Titration of pain relief with oral analgesic drugs is slower compared with some of the other routes of administration discussed below.

Direct comparisons between oral opioid and non-opioid analgesics, or between oral and other routes of administration, are limited. Indirect comparisons, where the individual drugs have been compared with a placebo, have been used to generate a 'league table' of analgesic efficacy (see Table 6.1). This table is based on randomised, double-blind, single-dose studies in patients with moderate to severe pain and shows the number of patients that need to be given the active drug (NNT) to achieve at least 50% pain relief in one patient compared with a placebo over a 4 to 6 hour treatment period (Moore et al, 2003).

The validity of this approach as a true method of comparison of drugs may be questioned as there is no standardisation of the acute pain model or patient and only single doses of the



analgesic agents are used. The effects of the analgesics may vary with different pain models (Gray et al, 2005 **Level I**; Oscier & Milner, 2009). However, it may be reasonable, in some circumstances, to extrapolate estimates of analgesic efficacy from one pain model to another (Barden, Edwards, McQuay et al, 2004 **Level I**).

**Table 6.1** The 2007 Oxford league table of analgesic efficacy (commonly used analgesic doses)

Analgesic	Number of patients in comparison	At least 50% pain relief (%)	NNT	Lower confidence interval	Higher confidence interval
Etoricoxib 180/240	248	77	1.5	1.3	1.7
Etoricoxib 100/120	500	70	1.6	1.5	1.8
Valdecoxib 40	473	73	1.6	1.4	1.8
Dipyron 1000	113	79	1.6	1.3	2.2
Ibuprofen 600/800	165	86	1.7	1.4	2.3
Valdecoxib 20	204	68	1.7	1.4	2.0
Ketorolac 20	69	57	1.8	1.4	2.5
Ketorolac 60 (intramuscular)	116	56	1.8	1.5	2.3
Diclofenac 100	545	69	1.8	1.6	2.1
Piroxicam 40	30	80	1.9	1.2	4.3
Celecoxib 400	298	52	2.1	1.8	2.5
Paracetamol 1000 + Codeine 60	197	57	2.2	1.7	2.9
Oxycodone IR 5 + Paracetamol 500	150	60	2.2	1.7	3.2
Bromfenac 25	370	51	2.2	1.9	2.6
Rofecoxib 50	675	54	2.3	2.0	2.6
Oxycodone IR 15	60	73	2.3	1.5	4.9
Aspirin 1200	279	61	2.4	1.9	3.2
Bromfenac 50	247	53	2.4	2.0	3.3
Dipyron 500	288	73	2.4	1.9	3.2
Ibuprofen 400	5456	55	2.5	2.4	2.7
Bromfenac 100	95	62	2.6	1.8	4.9
Oxycodone IR 10 + Paracetamol 650	315	66	2.6	2.0	3.5
Diclofenac 25	502	53	2.6	2.2	3.3
Ketorolac 10	790	50	2.6	2.3	3.1
Paracetamol 650 + tramadol 75	679	43	2.6	2.3	3.0
Oxycodone IR 10 + Paracetamol 1000	83	67	2.7	1.7	5.6



Analgesic	Number of patients in comparison	At least 50% pain relief (%)	NNT	Lower confidence interval	Higher confidence interval
Naproxen 400/440	197	51	2.7	2.1	4.0
Piroxicam 20	280	63	2.7	2.1	3.8
Lumiracoxib 400	370	48	2.7	2.2	3.5
Naproxen 500/550	784	52	2.7	2.3	3.3
Diclofenac 50	1296	57	2.7	2.4	3.1
Ibuprofen 200	3248	48	2.7	2.5	2.9
Dextropropoxyphene 130	50	40	2.8	1.8	6.5
Paracetamol 650 + tramadol 112	201	60	2.8	2.1	4.4
Bromfenac 10	223	39	2.9	2.3	4.0
Pethidine 100 (intramuscular)	364	54	2.9	2.3	3.9
Tramadol 150	561	48	2.9	2.4	3.6
Morphine 10 (intramuscular)	946	50	2.9	2.6	3.6
Naproxen 200/220	202	45	3.4	2.4	5.8
Ketorolac 30 (intramuscular)	359	53	3.4	2.5	4.9
Paracetamol 500	561	61	3.5	2.2	13.3
Celecoxib 200	805	40	3.5	2.9	4.4
Paracetamol 1500	138	65	3.7	2.3	9.5
Ibuprofen 100	495	36	3.7	2.9	4.9
Oxycodone IR 5 + Paracetamol 1000	78	55	3.8	2.1	20.0
Paracetamol 1000	2759	46	3.8	3.4	4.4
Paracetamol 600/650 + Codeine 60	1123	42	4.2	3.4	5.3
Paracetamol 650 + Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate)	963	38	4.4	3.5	5.6
Aspirin 600/650	5061	38	4.4	4.0	4.9
Paracetamol 600/650	1886	38	4.6	3.9	5.5
Ibuprofen 50	316	32	4.7	3.3	8.0
Tramadol 100	882	30	4.8	3.8	6.1
Tramadol 75	563	32	5.3	3.9	8.2

Analgesic	Number of patients in comparison	At least 50% pain relief (%)	NNT	Lower confidence interval	Higher confidence interval
Aspirin 650 + Codeine 60	598	25	5.3	4.1	7.4
Oxycodone IR 5 + Paracetamol 325	149	24	5.5	3.4	14.0
Ketorolac 10 (intramuscular)	142	48	5.7	3.0	53.0
Paracetamol 300 + Codeine 30	379	26	5.7	4.0	9.8
Bromfenac 5	138	20	7.1	3.9	28.0
Tramadol 50	770	19	8.3	6.0	13.0
Codeine 60	1305	15	16.7	11.0	48.0
Placebo	>10,000	18	N/A	N/A	N/A

Source: Bandolier ([www.medicine.ox.ac.uk/bandolier](http://www.medicine.ox.ac.uk/bandolier)). Reproduced with permission.

### 6.1.1 Opioids and tramadol

Oral opioids can be as effective in the treatment of acute pain as opioids given by other more invasive routes if equianalgesic doses are administered. Both immediate-release (IR) and CR formulations have been used. When opioids are prescribed for the treatment of acute pain, consideration should be given to duration of therapy. In most cases short-term use only of these drugs is warranted. Discharge planning must take into account the duration of use of opioids prescribed for the short-term management of acute pain and the weaning of those drugs and, in a small minority of patients, the potential for prescribed opioids to be abused or misused.

#### **Immediate-release formulations**

The NNTs of various IR opioids is listed in Table 6.1.

The effectiveness of the different opioids and tramadol increases with the addition of paracetamol.

- Codeine in a single dose of 60 mg is not an effective analgesic agent (Moore & McQuay, 1997 **Level I**). Combined with paracetamol a significant dose response was seen with NNTs of 2.2 for 800 to 1000 mg paracetamol plus 60 mg codeine, 3.9 for 600 to 650 mg paracetamol plus 60 mg codeine, and 6.9 for 300 mg paracetamol plus 30 mg codeine, and the combination extended the duration of analgesia by 1 hour compared with paracetamol alone (Toms et al, 2009 **Level I**).
- Dextropropoxyphene 65 mg is not an effective analgesic agent; it was effective when combined with 650 mg paracetamol (Collins, Edwards et al, 2000 **Level I**).
- Oxycodone (IR), in a single dose of 5 mg showed no benefit over placebo for the treatment of moderate to severe acute pain; doses of 15 mg alone, 10 mg plus paracetamol and 5 mg plus paracetamol are effective (Gaskell et al, 2009 **Level I**).
- Tramadol is an effective analgesic agent (Moore & McQuay, 1997 **Level I**). The combination of tramadol 75 mg or 112.5 mg with paracetamol (acetaminophen) 560 mg or 975 mg was more effective than either of its two components administered alone (McQuay & Edwards, 2003 **Level I**).

Morphine (IR, oral) is effective in the treatment of acute pain. Following preloading with IV morphine, morphine liquid 20 mg (initial dose 20 mg; subsequent doses increased by 5 mg if breakthrough doses needed) every 4 hours with additional 10 mg doses as needed has been shown to provide better pain relief after hip surgery than IM morphine 5 to 10 mg prn (McCormack et al, 1993 **Level II**).

In comparison with IV morphine patient-controlled analgesia (PCA) alone, regular 4-hourly administration of 20 mg but not 10 mg oral morphine reduced PCA morphine consumption but there were no differences in pain relief or side effects (Manoir et al, 2006 **Level II**).

IR oral opioids such as oxycodone, morphine and tramadol have also been used as 'step-down' analgesia after PCA, with doses based on prior PCA requirements (Macintyre & Schug, 2007) and after epidural analgesia (Lim & Schug, 2001 **Level II**).

### **Controlled-release formulations**

CR formulations also referred to as slow-release (SR) or prolonged-release, may take 3 to 4 hours or more to reach peak effect. In contrast and in most cases, the analgesic effect of the IR opioid preparations will be seen within about 45 to 60 minutes. This means that rapid titration to effect is easier and safer with IR formulations.

In general the use of CR opioid preparations as the sole agents for the early management of acute pain is discouraged because of difficulties in short-term dose adjustments needed for titration. CR opioid preparations should only be used at set time intervals and IR opioids should be used for acute and breakthrough pain, and for titration of CR opioids.

CR oral oxycodone comprises an IR component as well as the delayed-release compound and therefore has a more rapid onset of action than other CR agents. CR oxycodone may be effective in the immediate management of acute pain (Sunshine et al, 1996 **Level II**; Kampe et al, 2004 **Level II**). However, IR oxycodone 5 mg and paracetamol 325 mg given 6-hourly led to better pain relief than 10 mg CR oxycodone given 12-hourly (Kogan et al, 2007 **Level II**). In comparison with IV morphine PCA alone, CR oxycodone in addition to morphine PCA resulted in improved pain relief and patient satisfaction after lumbar discectomy and a lower incidence of nausea and vomiting, as well as earlier return of bowel function (Blumenthal et al, 2007 **Level II**). CR oral oxycodone was found to be effective as 'step-down' analgesia after 12 to 24 hours of PCA morphine (Ginsberg et al, 2003 **Level IV**).

More recently, a combined formulation of CR oxycodone and naloxone has been studied. Compared with CR oxycodone alone in patients with chronic non-malignant back pain, the combination formulation resulted in similar analgesic efficacy but less bowel dysfunction (Vondrackova et al, 2008 **Level II**). The addition of naloxone may also discourage unauthorised injection of the drug (see Suboxone in Section 11.8).

### **6.1.2 Non-selective non-steroidal anti-inflammatory drugs and coxibs**

A number of nsNSAIDs and coxibs have been shown to be effective as sole therapy in a variety of acute pain settings (see Table 6.1). Those for which there is Level I evidence of efficacy include: aspirin 600 to 1200 mg (Edwards, Oldman et al, 2000 **Level I**), ibuprofen 200 to 400 mg (Derry et al 2009a **Level I**), piroxicam 20 to 40 mg (Edwards, Loke et al, 2000 **Level I**), valdecoxib 20 to 40 mg (Lloyd et al, 2009 **Level I**), naproxen (Derry et al, 2009b **Level I**), ketorolac (Smith et al, 2000 **Level I**), lumiracoxib 400mg (Roy et al, 2007 **Level I**), celecoxib 200 to 400 mg (Derry et al, 2008 **Level I**) and diclofenac 50 to 100 mg (Derry et al, 2009c **Level I**).

The NNTs of each of these drugs is listed in Table 6.1.

In general, there is no good evidence that nsNSAIDs given parenterally or rectally are more effective, or result in fewer side effects, than the same drug given orally for the treatment of postoperative pain (Tramer et al, 1998 **Level I**). Only in the treatment of renal colic do IV nsNSAIDs result in more rapid analgesia (Tramer et al, 1998 **Level I**).

### 6.1.3 Paracetamol

Paracetamol is an effective analgesic for acute pain (Toms et al 2008 **Level I**; Toms et al, 2009 **Level I**; Weil et al, 2007 **Level I**). However, as noted above, the effects of different analgesics may vary with different pain models (Oscier & Milner, 2009). In a re-analysis of data available for paracetamol, it was found to be significantly less effective for pain relief after orthopaedic than after dental procedures (Gray et al, 2005 **Level I**).

The oral bioavailability of paracetamol is good at between 63% and 89% (Oscier & Milner, 2009). However, early postoperative oral administration can result in plasma concentrations that can vary enormously after the same dose and may remain subtherapeutic in some patients (Holmer Pettersson et al, 2004 **Level II**).

In the same doses, orally administered paracetamol was less effective and of slower onset than paracetamol given by IV injection, but more effective and of faster onset than paracetamol administered by the rectal route (see below).

Paracetamol effervescent tablets were absorbed significantly faster than ordinary paracetamol (Rygnestad et al, 2000 **Level II**).

## 6.2 INTRAVENOUS ROUTE

Analgesic drugs given by the IV route have a more rapid onset of action compared with most other routes of administration.

### 6.2.1 Opioids and tramadol

#### *Intermittent intravenous bolus doses*

Titration of opioids for severe acute pain is best achieved using intermittent IV bolus doses as it allows more rapid titration of effect and avoids the uncertainty of drug absorption by other routes. The optimal doses and dose intervals for this technique have not yet been established.

In a postoperative care unit, 2 mg or 3 mg bolus doses of morphine given at 5-minute dose intervals as needed and with no limitation on the number of bolus doses administered, was more effective and resulted in no greater incidence of side effects than the same doses given at 10-minute intervals or when a maximum of 5 doses only was allowed (Aubrun et al, 2001 **Level III-3**). In a comparison of IV fentanyl and morphine bolus doses every 5 minutes as needed for prehospital analgesia over a period of just 30 minutes, no difference was found in pain relief or incidence of side effects (Galinski et al, 2005 **Level II**).

Titration of IV bolus doses of an opioid is frequently accomplished using a treatment algorithm to guide management, which includes age-based bolus doses of opioid given at 3- or 5-minute intervals as needed (Macintyre & Schug, 2007).

IV tramadol was found to be more effective than the same dose given orally after dental surgery; however it was recognised that the difference in bioavailability of a single dose of tramadol may be up to 30% (Ong et al, 2005 **Level II**).

Large IV bolus doses of tramadol can result in a high incidence of emetic symptoms. This effect can be reduced by slowing delivery of the drug or, in the surgical setting, by giving it before the patient emerges from general anaesthesia (Pang et al, 2000 **Level II**).

### **Continuous infusions**

A continuous infusion of opioids results in constant blood levels after approximately 4 half-lives of the opioid used. The aim of an infusion is to avoid the problems associated with the peaks and troughs of intermittent administration techniques. However, the variation in patient response, the changing intensity of acute pain with time and the delay between any alteration of the infusion rate and its subsequent effect, may result in inadequate treatment of incident pain or delayed onset of side effects, such as respiratory depression. Very close monitoring is therefore essential with continuous infusions of opioids.

Compared with PCA, continuous IV opioid infusions in a general ward setting resulted in a 5-fold increase in the incidence of respiratory depression (Schug & Torrie, 1993 **Level IV**).

## **6.2.2 Non-selective non-steroidal anti-inflammatory drugs and coxibs**

There are only a limited number of nsNSAIDs or coxibs available for IV injection at present and fewer still where Level I evidence for individual efficacy is available. In single doses as the sole analgesic agent, the coxib parecoxib IV 20 to 40 mg has been shown to be effective (Lloyd et al, 2009 **Level I**).

The formulation of drug used may affect efficacy. Comparison of a polyethylene glycol and benzyl alcohol (PG-BA) diclofenac solution with one that used hydroxypropyl beta-cyclodextrin (HP $\beta$ CD) to solubilise diclofenac in a small volume showed that IV HP $\beta$ CD diclofenac resulted in more rapid onset of analgesia (Leeson et al, 2007 **Level II**). The incidence of moderate to severe, but not mild thrombophlebitis may be less with IV diclofenac (Colucci et al, 2009).

In most cases the route of administration does not seem to alter efficacy. IV nsNSAIDs or coxibs are more expensive than oral or rectal nsNSAIDs although their efficacy and likelihood of side effects is similar (Tramer et al, 1998 **Level I**). A more recent comparison of rectal diclofenac and IV parecoxib showed no difference in pain relief, side effects or rescue analgesic requirements (Ng et al, 2008 **Level II**). Efficacy and times to onset of analgesia were similar with IV and IM parecoxib (Daniels et al, 2001 **Level II**).

For renal colic, the onset of action of NSAIDs was faster when given IV compared with IM, oral or rectal administration (Tramer et al, 1998 **Level I**).

## **6.2.3 Paracetamol**

IV paracetamol was an effective analgesic after surgery (Sinatra et al, 2005 **Level II**). It was of faster onset than the same dose given orally (Moller, Sindet-Pedersen et al, 2005 **Level II**) but, as with IV NSAIDs, it is more expensive.

While of equal analgesic efficacy, the incidence of local pain at the infusion site was significantly less after IV paracetamol compared with the prodrug propacetamol (Moller, Juhl et al, 2005 **Level II**).

Due to the good bioavailability and tolerability of oral paracetamol, the use of the IV form should be limited to clinical circumstances where use of the enteral route is not appropriate.

## 6.3 INTRAMUSCULAR AND SUBCUTANEOUS ROUTES

IM and SC injections of analgesic agents (usually opioids) are still commonly employed for the treatment of moderate or severe pain. Absorption may be impaired in conditions of poor perfusion (eg in hypovolaemia, shock, hypothermia or immobility), leading to inadequate early analgesia and late absorption of the drug depot when perfusion is restored.

### 6.3.1 Opioids and tramadol

IM injection of opioids has been the traditional mainstay of postoperative pain management, despite the fact that surveys have repeatedly shown that pain relief with prn IM opioids is frequently inadequate. Although IM opioids are often perceived to be safer than opioids given by other parenteral routes, the incidence of respiratory depression reported in a review ranged from 0.8 (0.2 to 2.5)% to 37.0 (22.6 to 45.9)% using respiratory rate and oxygen saturation, respectively, as indicators (for comparisons with PCA and epidural analgesia, see Section 7; for comments on respiratory rate as an unreliable indicator of respiratory depression, see Section 4.1.3) (Cashman & Dolin, 2004 **Level IV**).

Single doses of IM morphine 10 mg (McQuay et al, 1999 **Level I**) and IM pethidine (meperidine) 100 mg (Smith et al, 2000 **Level I**) have been shown to be effective in the initial treatment of moderate to severe postoperative pain.

The use of an algorithm allowing administration of IM morphine or pethidine hourly prn and requiring frequent assessments of pain and sedation, led to significant improvements in pain relief compared with longer dose interval prn regimens (Gould et al, 1992 **Level III-3**).

The quality of pain relief was less with intermittent IM regimens compared with IV PCA (Hudcova et al, 2005 **Level I**).

The placement of SC plastic cannulae or 'butterfly' needles allows the use of intermittent injections without repeated skin punctures. In healthy volunteers, median time to reach maximum serum concentration ( $T_{max}$ ) after SC injection of morphine was 15 mins (Stuart-Harris et al, 2000). In elderly adults, mean  $T_{max}$  after a single SC injection of morphine was 15.9 minutes and the rate of absorption and the variability in the rate of absorption were similar to those reported after IM injection (Semple et al, 1997 **Level IV**). In patients given a second and same dose of SC morphine 5 hours after the first, it was shown that there can also be significant within-patient variations in absorption (Upton et al, 2006).

In children, there was no difference in rate of onset, analgesic effect and side effects when SC injections of morphine were compared with IM morphine injections, and there was a significantly higher patient preference for the SC route (Cooper, 1996 **Level II**; Lamacraft et al, 1997 **Level IV**). A comparison of IM and SC morphine in patients after Caesarean section reported no significant differences in side effects, patient satisfaction or pain relief at rest, but lower pain scores after SC administration at 12, 16 and 20 hours after surgery (Safavi & Honarmand, 2007 **Level II**).

A comparison of the same dose of morphine given as either a single SC or IV injection, showed that use of the IV route resulted in more rapid onset of analgesia (5 minutes IV; 20 minutes SC) and better pain relief between 5 minutes and 25 minutes after injection, but also led to higher sedation scores up to 30 minutes after injection, and higher  $PCO_2$  levels (Tveita et al, 2008 **Level II**). However, a comparison of intermittent IV and SC doses of hydromorphone (the doses adjusted in a similar manner according to the patients' pain scores and given at intervals of no less than 3 hours) showed no differences in pain relief or side effects over a 48-hour

period after surgery; pain relief was the same but the incidence of pruritus was lower compared with PCA hydromorphone (Bell et al, 2007 **Level II**).

Treatment algorithms for intermittent SC morphine using age-based dosing are available (Macintyre & Schug, 2007).

Continuous infusions of opioids via the SC route were as effective as continuous IV infusions (Semple et al, 1996 **Level II**).

### **6.3.2 Non-selective non-steroidal anti-inflammatory drugs and coxibs**

There are only a limited number of nsNSAIDs or coxibs available for IM injection at present and fewer still where Level I evidence for individual efficacy is available. Ketorolac and parecoxib IM are effective analgesic agents (Smith et al, 2000 **Level I**; Lloyd et al, 2009 **Level I**).

## **6.4 RECTAL ROUTE**

Rectal administration of drugs is useful when other routes are unavailable. It results in uptake into the submucosal venous plexus of the rectum, which drains into the inferior, middle and superior rectal veins. Drug absorbed from the lower half of the rectum will pass into the inferior and middle rectal veins and then the inferior vena cava, bypassing the portal system. Any portion of the drug absorbed into the superior rectal vein enters the portal system, subjecting it to hepatic first-pass metabolism.

Potential problems with the rectal route of drug administration relate to the variability of absorption, possible rectal irritation and cultural factors. Some suppositories should not be divided as the drug may not be evenly distributed in the preparation. Contraindications to the use of this route include pre-existing rectal lesions, recent colorectal surgery and immune suppression. Whether the drug is administered to a patient who is awake or under anaesthesia, it is important to obtain prior consent from the patient or guardian.

### **6.4.1 Opioids**

In most instances similar doses of rectal and oral opioids are administered, although there may be differences in bioavailability and the time to peak analgesic effect for the reasons outlined above.

In cancer patients no differences in either pain relief or adverse effects were found in a comparison of oral and rectally administered tramadol (Mercadante et al, 2005 **Level II**).

### **6.4.2 Non-selective non-steroidal anti-inflammatory drugs**

Rectal administration of nsNSAIDs provides effective analgesia (Tramer et al, 1998 **Level I**). Local effects such as rectal irritation and diarrhoea were reported following use of the rectal route, but other commonly reported adverse effects such as nausea, vomiting, dizziness and indigestion were independent of the route of administration (Tramer et al, 1998 **Level I**). In a study comparing oral and rectal indomethacin (indometacin) given over a period of 2 weeks, the degree of gastric erosion at endoscopy was the same (Hansen et al, 1984 **Level II**). Consequently, there appears to be no advantage in using nsNSAID suppositories if the oral route is available (Tramer et al, 1998 **Level I**).



### 6.4.3 Paracetamol

Paracetamol is effective when given by the rectal route (Romsing et al, 2002 **Level I**) although rectal absorption of paracetamol was slower and less predictable than after oral administration, with a bioavailability of between 24% and 98% (Oscier & Milner, 2009). It was also less effective than the same dose administered by the oral route (Anderson et al, 1996 **Level II**; Anderson et al, 1999 **Level IV**). Doses of 1 g rectally after cardiac surgery (Holmer Pettersson et al, 2006 **Level II**) and hysterectomy (Kvalsvik et al, 2003 **Level II**) as well as 2 g given rectally to patients undergoing laparoscopic gynaecological surgery (Hahn, Mogensen et al, 2000 **Level II**) also resulted in subtherapeutic blood levels, although levels may increase to within the therapeutic range after repeat administration (Holmer Pettersson et al, 2006 **Level II**).

In children, similar results have been noted. Initial administration of doses of 25 mg/kg achieved average blood concentrations at the lower end of the therapeutic range and large variations in absorption were reported (Hahn, Henneberg et al, 2000 **Level IV**).

Higher doses may be more effective. Blood concentrations in the therapeutic range have been reported in adults after doses of 40 mg/kg but not 20 mg/kg (Beck et al, 2000 **Level IV**) and sustained therapeutic levels followed the use of 35 mg/kg and 45 mg/kg but not 15 mg/kg and 25 mg/kg (Stocker & Montgomery, 2001 **Level IV**). In children, initial doses of 40 mg/kg followed by 20 mg/kg also provided therapeutic blood levels without evidence of accumulation (Birmingham et al, 2001 **Level IV**).

When available, the oral route is therefore preferable.

## 6.5 TRANSDERMAL ROUTE

Not all medications applied topically have a local, peripheral action. The term ‘transdermal’ will be used to describe drugs that while applied to the skin, have predominantly central effects that are the result of systemic absorption of the drug. The term ‘topical’ will be used in the discussion of drugs — primarily NSAIDs — that are applied topically (including to skin) but have a predominantly peripheral effect.

### 6.5.1 Opioids

The stratum corneum of the epidermis forms a major barrier to the entry of drugs. However, drugs such as fentanyl (Sathyan et al, 2005) and buprenorphine (Skaer, 2006) are available as transdermal preparations. The analgesic effects are a result of systemic effects rather than local peripheral opioid analgesia (Worrich et al, 2007 **Level IV**). The original transdermal fentanyl patches consisted of a reservoir system and rate-controlling membrane. In the newer system, which has the same bioequivalence, the fentanyl is dissolved in the adhesive matrix; the patient’s stratum corneum and the characteristics of the drug-in-adhesive matrix control the rate of systemic delivery (Sathyan et al, 2005).

Transdermal fentanyl is commonly used in the management of cancer and chronic pain. Due to the formation of a significant intradermal ‘reservoir’, onset and offset times of this preparation are slow and this makes short-term titration impossible. The time to peak blood concentration is generally between 24 and 72 hours after initial patch application and after the patch is removed, serum fentanyl concentrations decline gradually, with a mean terminal half-life ranging from 22 to 25 hours (MIMS, 2008).

Transdermal fentanyl patches are currently specifically contraindicated for the management of acute or postoperative pain in many countries (FDA, 2007; eCompendium, 2008; MIMS, 2008) and

their use cannot be recommended. Specific safety alerts have been issued warning against use in opioid-naive patients, and highlighting the risk that increased body temperature, exposure of patches to external heat sources, and concomitant use of CYP3A4 inhibitors may lead to potentially dangerous rises in serum fentanyl levels (FDA, 2005).

However, transdermal fentanyl patches have been trialled in the management of postoperative pain. For example, after hip arthroplasty (Minville et al, 2008 **Level II**) and hysterectomy (Sandler et al, 1994 **Level II**), preoperative use significantly reduced postoperative pain scores and PCA morphine requirements. However, the wide variability of clinical effect (Peng & Sandler, 1999) and the high incidence of respiratory depression that can occur in the postoperative setting (Sandler et al, 1994 **Level II**; Bulow et al, 1995 **Level II**), make transdermal fentanyl preparations unsuitable for acute pain management.

Iontophoretic patient-controlled transdermal delivery systems for fentanyl were introduced for the management of acute pain, but marketing authority was later withdrawn after discovery of a fault that could lead to triggering of the self-activation of the system (see Section 7.1.4).

Transdermal buprenorphine patches are available for the management of chronic and cancer pain (Skaer, 2006). After application of the patch, steady state is achieved by day 3; after removal of the patch, buprenorphine concentrations decrease by about 50% in 12 hours (range 10 to 24 hours) (MIMS, 2008). Given the slow onset and offset of the drug, it is unlikely to be of much use in the management of acute pain.

### 6.5.2 Other drugs

The results from studies looking at the use of transdermal nicotine patches for the management of postoperative pain have been inconclusive with both a reduction (Hong et al, 2008 **Level II**) and no reduction in pain scores (Habib et al, 2008 **Level II**; Turan et al, 2008 **Level II**), and opioid-sparing (Habib et al, 2008 **Level II**) and no opioid-sparing (Hong et al, 2008 **Level II**; Turan et al, 2008 **Level II**) reported.

Topical administration might result in effective systemic plasma concentrations, as a transdermal ketamine patch delivering 25 mg over 24 hours reduced rescue analgesic consumption after gynaecological surgery (Azevedo et al, 2000 **Level II**) and, in an experimental pain study, use of a ketamine gel reduced capsaicin-induced hyperalgesia (Poyhia & Vainio, 2006).

## 6.6 TRANSMUCOSAL ROUTES

Drugs administered by transmucosal routes (IN, sublingual, buccal, and pulmonary) are rapidly absorbed directly into the systemic circulation, thus bypassing hepatic first-pass metabolism. The drugs most commonly administered by transmucosal routes in acute pain management are the more lipid-soluble opioids.

### 6.6.1 Intranasal route

A variety of drugs can be administered by the IN route, including analgesic drugs. The human nasal mucosa contains drug-metabolising enzymes but the extent and clinical significance of human nasal first-pass metabolism is unknown (Dale et al, 2002). It is suggested that the volume of a dose of any drug given intranasally should not exceed 150 microlitres (0.150 mL) in order to avoid run-off into the pharynx (Dale et al, 2002). Absorption through the nasal mucosa depends on both the lipid solubility and degree of ionisation of the drug (Shelley & Paech, 2008).

## Opioids

Single-dose pharmacokinetic data in healthy volunteers for a number of opioids administered by the IN route have been summarised by Dale et al (Dale et al, 2002). The mean bioavailabilities and  $T_{max}$  reported were fentanyl 71% and 5 minutes; sufentanil 78% and 10 minutes; alfentanil 65% and 9 minutes; butorphanol 71% and 49 minutes; oxycodone 46% and 25 minutes; and buprenorphine 48% and 30 minutes. A later comparison of IN and IV fentanyl showed mean  $T_{max}$  values of 12.8 and 6.0 minutes and times to onset of analgesia of 7 and 2 minutes respectively; the bioavailability of IN fentanyl was 89% (Foster et al, 2008 **Level II**).

Hydromorphone, when given to volunteers in doses of 1 mg or 2 mg IN and compared with 2 mg IV, had median times to peak blood concentration after the 1 mg and 2 mg IN doses of 20 minutes and 25 minutes respectively and an overall bioavailability of only 55% (Coda et al, 2003).

Clinical data also exist for the effectiveness of several opioids administered via the IN route, including fentanyl (Toussaint et al, 2000 **Level II**; Manjushree et al, 2002 **Level II**; Paech et al, 2003 **Level II**; Christrup et al, 2008 **Level II**; Foster et al, 2008 **Level II**), butorphanol (Abboud et al, 1991 **Level II**; Wermeling et al, 2005), pethidine (Striebel et al, 1993 **Level II**; Striebel et al, 1995 **Level II**) and morphine (Stoker et al, 2008 **Level II**).

Fentanyl had similar analgesic efficacy when given by the IN or IV routes (Toussaint et al, 2000 **Level II**; Manjushree et al, 2002 **Level II**; Paech et al, 2003 **Level II**) as did butorphanol (Abboud et al, 1991 **Level II**) and morphine (Christensen et al, 2008 **Level II**). IN pethidine was more effective than SC injections of pethidine (Striebel et al, 1995 **Level II**).

In patients undergoing third molar extraction, mean  $T_{max}$  values were 12.8 and 6.0 minutes ( $P < 0.001$ ), times to onset of analgesia were 7 and 2 minutes ( $P < 0.001$ ), and durations of effect were 56 and 59 minutes ( $P = NS$ ) after IN and IV fentanyl administration respectively (Christrup et al, 2008 **Level II**). Also after third molar extraction, mean times to onset of analgesia were 11 minutes for both 15 mg IN and 7.5 mg IV morphine and efficacy profiles were similar (Christensen et al, 2008 **Level II**).

When fentanyl was used in the prehospital setting, there was no difference in effectiveness between IN fentanyl (180 mcg +/- 2 doses of 60 mcg at  $>$  or  $=$  5 minute intervals) and IV morphine (2.5 to 5 mg +/- 2 doses of 2.5 to 5 mg at  $>$  or  $=$  5-minute intervals) (Rickard et al, 2007 **Level II**).

Patient-controlled intranasal analgesia (PCINA) using diamorphine (bolus doses of 0.5mg) was less effective than PCA IV morphine (1 mg bolus doses) after joint replacement surgery (Ward et al, 2002 **Level II**) but provided better pain relief in doses of 0.1 mg/kg compared with 0.2 mg/kg IM morphine in children with fractures (Kendall et al, 2001 **Level II**). In children, IN fentanyl at a dose of 1.7 mcg/kg was shown to be as effective as IV morphine 0.1 mg/kg in children presenting to an emergency department with an acute fracture (Borland et al, 2007 **Level II**) and equivalent to oral morphine for pain relief during burn wound dressing changes (Borland et al, 2005 **Level II**) (see Sections 9.3 and 10.4.2).

A comparison of two different doses of IN sufentanil (0.025 and 0.05 mcg/mL), given as often as every 5 minutes in order to obtain a verbal pain score of less than 4 after inguinal hernia repair or haemorrhoidectomy, confirmed the effectiveness of the nasal route for postoperative analgesia, although the larger doses enabled effective pain relief to be achieved more rapidly (Mathieu et al, 2006 **Level II**).

Adverse effects can be related to the drug itself or to the route of administration. Systemic effects appear to be no higher for IN administration than for other routes with equivalent

efficacy; nasal irritation, congestion and bad taste have been reported with the short-term use of butorphanol and pethidine (Dale et al, 2002).

Technical problems with pumps have been reported in up to 10% of cases and dispensing issues for techniques such as PCINA, which could allow ready and unauthorised access to the drugs, have not been addressed (Dale et al, 2002).

### **Other analgesic drugs**

IN ketamine has been shown to provide relatively rapid onset of effective pain relief (within 15 minutes); any adverse effects were mild and transient (Christensen et al, 2007 **Level II**).

IN ketorolac has also been shown to be effective; after major surgery 30 mg but not 10 mg IN ketorolac resulted in significant opioid-sparing over 20 hours and better pain relief in the first 6 hours after surgery (Moodie et al, 2008 **Level II**).

## **6.6.2 Sublingual and buccal routes**

When analgesic drugs are administered by the sublingual or buccal routes, their efficacy will in part depend on the proportion of drug swallowed.

### **Opioids**

Sublingual buprenorphine, given as a tablet, has an overall bioavailability of 30% to 50% (Mendelson et al, 1997; Kuhlman et al, 1996) and a long duration of action (mean half-life 28 hours) (Kuhlman et al, 1996). Sublingual buprenorphine 0.4 mg was found to be as effective as 10 mg morphine IM (Cuschieri et al, 1984 **Level II**) and 75 mg pethidine IM after abdominal surgery (Moa & Zetterstrom, 1990 **Level II**).

Oral transmucosal fentanyl citrate (OTFC) incorporates fentanyl into a flavoured solid lozenge on a stick and is available in a range of doses from 200 to 1600 mcg. Overall, the bioavailability of OTFC is about 52% compared with IV fentanyl, with peak blood levels achieved in  $22 \pm 2.5$  minutes (Streisand et al, 1991 **Level IV**). The median time to onset of analgesia was about 5 minutes and the relative potency compared with IV morphine was 8–14:1. (Lichter et al, 1999 **Level II**).

In many countries, regulatory authorities have specifically noted that OTFC must not be used in opioid-naïve patients or in the management of acute and postoperative pain: approval is limited to the management of break-through pain in patients who are opioid-tolerant (FDA, 2007; MIMS, 2008; eCompendium, 2008).

Only a few studies have investigated the postoperative use of OTFC. It was found to be an effective analgesic after orthopaedic (Ashburn et al, 1993 **Level II**) and abdominal surgery (Lichter et al, 1999 **Level II**) and during burns wound care (Sharar et al, 1998 **Level II**; Sharar et al, 2002 **Level II**). Pain relief at 15 minutes in children with lower extremity injuries was the same with IV bolus doses of morphine and OTFC, but lower with OTFC after that until the end of the 75 minute study period (Mahar et al, 2007 **Level II**).

However, because of the risk of achieving high peak plasma levels with unsupervised administration, the limited data available, and the specific lack of approval for use in opioid-naïve patients, OTFC cannot be recommended for the management of acute pain.

Fentanyl buccal tablets (FBT) use an effervescent drug delivery technology that enables more rapid absorption and delivery of a larger proportion of the fentanyl dose compared with OTFC (Darwish et al, 2006; Darwish et al, 2007). They were effective in opioid-tolerant patients for the treatment of breakthrough cancer pain (Portenoy et al, 2006 **Level II**; Slatkin et al, 2007 **Level II**), chronic low back pain (Portenoy et al, 2007 **Level II**) and chronic neuropathic pain (Simpson et al, 2007 **Level II**). At present, this formulation is also not approved for use in the acute pain setting.

## Other analgesic drugs

A pharmacokinetic study in healthy volunteers calculated the bioavailability of oral ketamine as 20%, sublingual 30% and IN 45%: the pharmacodynamic effects of the active metabolite norketamine were thought to be of potential significance (Yanagihara et al, 2003). The bioavailability of a 25 mg ketamine lozenge was 24% when given by both sublingual and oral routes; peak plasma levels were seen at 30 minutes and 120 minutes respectively and terminal half-lives were similar at around 5 hours. For both routes, norketamine concentrations exceeded the concentrations of ketamine, and given its pharmacological activity profile, norketamine is therefore likely to be a major contributor to the overall analgesic effect (Chong et al, 2009).

### 6.6.3 Inhaled

#### Opioids

Opioids are rapidly absorbed after nebulised inhalation, reflecting the high blood flow, surface area, and permeability of the lungs.

Clinical data exist for the effectiveness of several opioids administered via the pulmonary route including morphine (Masood & Thomas, 1996 **Level II**; Ward et al, 1997 **Level II**; Dershwitz et al, 2000 **Level IV**; Thippawong et al, 2003 **Level II**) and fentanyl (Worsley et al, 1990 **Level II**; Miner et al, 2007 **Level II**). In a small study of 44 patients with post-traumatic thoracic pain, there was no difference in the pain relief obtained from nebulised morphine and PCA morphine (Fulda et al, 2005 **Level II**). In another study of only 28 patients in an emergency department, no patient experienced pain relief 10 minutes after inhalation of morphine (Bounes et al, 2009 **Level III-3**). In children requiring pain relief in an emergency department, nebulised fentanyl was also as effective as IV fentanyl (Miner et al, 2007 **Level II**) (see Sections 9.3 and 10.4.4).

Peak plasma concentrations following administration of morphine via a standard nebuliser occurred within 10 minutes but bioavailability was low with a mean of only 5% (Masood & Thomas, 1996 **Level II**). Bioavailability may be improved (up to 59 to 100%) with peak plasma concentrations occurring at 2 minutes using pulmonary drug delivery systems (Ward et al, 1997 **Level II**; Dershwitz et al, 2000 **Level IV**). Similarly, bioavailability of inhaled fentanyl may approach 100% (Mather et al, 1998 **Level IV**).

These systems await further development and thus these data are insufficient to support the routine use of inhaled opioids in acute pain management.

#### Other analgesic drugs

See Section 4.3.1 for inhaled nitrous oxide and methoxyflurane.

#### Key messages

1. Paracetamol combined with codeine is more effective than either drug alone and shows a dose-response effect (**N**) (**Level I** [Cochrane Review]).
2. NSAIDs (both nsNSAIDs and coxibs) given parenterally or rectally are not more effective and do not result in fewer side effects than the same drug given orally (**U**) (**Level I** [Cochrane Review]).
3. Paracetamol combined with tramadol is more effective than either drug alone and shows a dose-response effect (**N**) (**Level I**).
4. Early postoperative oral administration of paracetamol results in highly variable plasma concentrations that may remain subtherapeutic in some patients (**N**) (**Level II**).

5. Rectal administration of single doses of paracetamol results in highly variable plasma concentrations that often remain subtherapeutic **(N)** **(Level II)**.
6. Intermittent subcutaneous morphine injections are as effective as intramuscular injections and have better patient acceptance **(U)** **(Level II)**.
7. Intranasal opioids, in particular the more lipid-soluble drugs such as fentanyl, are effective for the management of acute pain **(N)** **(Level II)**.
8. Continuous intravenous infusion of opioids in the general ward setting is associated with an increased risk of respiratory depression compared with other methods of parenteral opioid administration **(U)** **(Level IV)**.
9. Transdermal fentanyl should not be used in the management of acute pain because of safety concerns and difficulties in short-term dose adjustments needed for titration; furthermore, in most countries, it lacks regulatory approval for use in other than opioid-tolerant patients **(S)** **(Level IV)**.

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Other than in the treatment of severe acute pain, and providing there are no contraindications to its use, the oral route is the route of choice for the administration of most analgesic drugs **(U)**.
- Titration of opioids for severe acute pain is best achieved using intermittent intravenous bolus doses as it allows more rapid titration of effect and avoids the uncertainty of drug absorption by other routes **(U)**.
- Controlled-release opioid preparations should only be given at set time intervals **(U)**.
- Immediate-release opioids should be used for breakthrough pain and for titration of controlled-release opioids **(U)**.
- The use of controlled-release opioid preparations as the sole agents for the early management of acute pain is discouraged because of difficulties in short-term dose adjustments needed for titration **(U)**.
- Neither oral transmucosal fentanyl citrate nor fentanyl buccal tablets should be used in the management of acute pain because of safety concerns and, in most countries, lack of regulatory approval for use in other than opioid-tolerant patients **(N)**.

## REFERENCES

- Abboud TK, Zhu J, Gangolly J et al (1991) Transnasal butorphanol: a new method for pain relief in post-caesarean section pain. *Acta Anaesthesiol Scand* **35**(1): 14–8.
- Anderson B, Kanagasundaram S & Woollard G (1996) Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. *Anaesth Intensive Care* **24**(6): 669–73.
- Anderson BJ, Holford NH, Woollard GA et al (1999) Perioperative pharmacodynamics of acetaminophen analgesia in children. *Anesthesiology* **90**(2): 411–21.
- Ashburn MA, Lind GH, Gillie MH et al (1993) Oral transmucosal fentanyl citrate (OTFC) for the treatment of postoperative pain. *Anesth Analg* **76**(2): 377–81.
- Aubrun F, Monseil S, Langeron O et al (2001) Postoperative titration of intravenous morphine. *Eur J Anaesthesiol* **18**(3): 159–65.

- Azevedo VM, Lauretti GR, Pereira NL et al (2000) Transdermal ketamine as an adjuvant for postoperative analgesia after abdominal gynecological surgery using lidocaine epidural blockade. *Anesth Analg* **91**(6): 1479–82.
- Bandolier (2003) *Acute Pain*. www.ebandolier.com. Accessed January 2009.
- Barden J, Edwards JE, McQuay HJ et al (2004) Pain and analgesic response after third molar extraction and other postsurgical pain. *Pain* **107**(1-2): 86–90.
- Beck DH, Schenk MR, Hagemann K et al (2000) The pharmacokinetics and analgesic efficacy of larger dose rectal acetaminophen (40 mg/kg) in adults: a double-blinded, randomized study. *Anesth Analg* **90**(2): 431–6.
- Bell JG, Shaffer LE & Schrickel-Feller T (2007) Randomized trial comparing 3 methods of postoperative analgesia in gynecology patients: patient-controlled intravenous, scheduled intravenous, and scheduled subcutaneous. *Am J Obstet Gynecol* **197**(5): 472 e1–7.
- Birmingham PK, Tobin MJ, Fisher DM et al (2001) Initial and subsequent dosing of rectal acetaminophen in children: a 24-hour pharmacokinetic study of new dose recommendations. *Anesthesiology* **94**(3): 385–9.
- Blumenthal S, Min K, Marquardt M et al (2007) Postoperative intravenous morphine consumption, pain scores, and side effects with perioperative oral controlled-release oxycodone after lumbar discectomy. *Anesth Analg* **105**(1): 233–7.
- Borland ML, Bergesio R, Pascoe EM et al (2005) Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns* **31**(7): 831–7.
- Borland M, Jacobs I, King B et al (2007) A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* **49**(3): 335–40.
- Bounes V, Ducasse JL, Bona AM et al (2009) Nebulized morphine for analgesia in an emergency setting. *J Opioid Manag* **5**(1): 23–6.
- Bulow HH, Linnemann M, Berg H et al (1995) Respiratory changes during treatment of postoperative pain with high dose transdermal fentanyl. *Acta Anaesthesiol Scand* **39**(6): 835–9.
- Cashman JN & Dolin SJ (2004) Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. *Br J Anaesth* **93**(2): 212–23.
- Chong C, Schug SA, Page-Sharp M et al (2009) Development of a sublingual/oral formulation of ketamine for use in neuropathic pain: preliminary findings from a three-way randomized, crossover study. *Clin Drug Investig* **29**(5): 317–24.
- Christensen KS, Rogers E, Green GA et al (2007) Safety and efficacy of intranasal ketamine for acute postoperative pain. *Acute Pain* **9**: 183–92.
- Christensen KS, Cohen AE, Mermelstein FH et al (2008) The analgesic efficacy and safety of a novel intranasal morphine formulation (morphine plus chitosan), immediate release oral morphine, intravenous morphine, and placebo in a postsurgical dental pain model. *Anesth Analg* **107**(6): 2018–24.
- Christrup LL, Foster D, Popper LD et al (2008) Pharmacokinetics, efficacy, and tolerability of fentanyl following intranasal versus intravenous administration in adults undergoing third-molar extraction: a randomized, double-blind, double-dummy, two-way, crossover study. *Clin Ther* **30**(3): 469–81.
- Coda BA, Rudy AC, Archer SM et al (2003) Pharmacokinetics and bioavailability of single-dose intranasal hydromorphone hydrochloride in healthy volunteers. *Anesth Analg* **97**(1): 117–23.
- Collins SL, Edwards JE, Moore RA et al (2000) Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database Syst Rev*(2): CD001440.
- Collins SL, Moore RA, McQuay HJ et al (2000) Single dose oral ibuprofen and diclofenac for postoperative pain. *Cochrane Database Syst Rev*(2): CD001548.
- Colucci RD, Wright C, Mermelstein FH et al (2009) Dyloject®, a novel injectable diclofenac solubilised with cyclodextrin: reduced incidence of thrombophlebitis compared to injectable diclofenac solubilised with polyethylene glycol and benzyl alcohol. *Acute Pain* **11**: 15–21.



- Cooper IM (1996) Morphine for postoperative analgesia. A comparison of intramuscular and subcutaneous routes of administration. *Anaesth Intensive Care* **24**(5): 574–8.
- Cuschieri RJ, Morran CG & McArdle CS (1984) Comparison of morphine and sublingual buprenorphine following abdominal surgery. *Br J Anaesth* **56**(8): 855–9.
- Dale O, Hjortkjaer R & Kharasch ED (2002) Nasal administration of opioids for pain management in adults. *Acta Anaesthesiol Scand* **46**(7): 759–70.
- Daniels SE, Grossman EH, Kuss ME et al (2001) A double-blind, randomized comparison of intramuscularly and intravenously administered parecoxib sodium versus ketorolac and placebo in a post-oral surgery pain model. *Clin Ther* **23**(7): 1018–31.
- Darwish M, Tempero K, Kirby M et al (2006) Relative bioavailability of the fentanyl effervescent buccal tablet (FEFT) 1,080 pg versus oral transmucosal fentanyl citrate 1,600 pg and dose proportionality of FEFT 270 to 1,300 microg: a single-dose, randomized, open-label, three-period study in healthy adult volunteers. *Clin Ther* **28**(5): 715–24.
- Darwish M, Kirby M, Robertson P, Jr. et al (2007) Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol* **47**(3): 343–50.
- Derry S, Barden J, McQuay HJ et al (2008) Single dose oral celecoxib for acute postoperative pain in adults. *Cochrane Database Syst Rev*(4): CD004233.
- Derry C, Derry S, Moore RA et al (2009a) Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database Syst Rev*(3): CD001548.
- Derry C, Derry S, Moore RA et al (2009b) Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. *Cochrane Database Syst Rev* (1) CD004234.
- Derry P, Derry S, Moore RA et al (2009c) Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database Syst Rev*(2): CD004768.
- Dershwitz M, Walsh JL, Morishige RJ et al (2000) Pharmacokinetics and pharmacodynamics of inhaled versus intravenous morphine in healthy volunteers. *Anesthesiology* **93**(3): 619–28.
- eCompendium (2008) *Medicines Compendium*. <http://www.emc.medicines.org.uk/>. Accessed October 2008.
- Edwards JE, Loke YK, Moore RA et al (2000) Single dose piroxicam for acute postoperative pain. *Cochrane Database Syst Rev*(4): CD002762.
- Edwards JE, Oldman A, Smith L et al (2000) Single dose oral aspirin for acute pain. *Cochrane Database Syst Rev*(2): CD002067.
- FDA (2005) *Fentanyl Transdermal System (marketed as Duragesic and generics) Healthcare Professional Sheet*. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125840.htm>. Accessed July 2009.
- FDA (2007) *Prescribing information for Actiq*. <http://www.fda.gov/cder/foi/label/2007/020747s027lbl.pdf>. Accessed October 2008.
- Foster D, Upton R, Christrup L et al (2008) Pharmacokinetics and pharmacodynamics of intranasal versus intravenous fentanyl in patients with pain after oral surgery. *Ann Pharmacother* **42**(10): 1380–7.
- Fulda GJ, Giberson F & Fagraeus L (2005) A prospective randomized trial of nebulized morphine compared with patient-controlled analgesia morphine in the management of acute thoracic pain. *J Trauma* **59**(2): 383–8.
- Galinski M, Dolveck F, Borron SW et al (2005) A randomized, double-blind study comparing morphine with fentanyl in prehospital analgesia. *Am J Emerg Med* **23**(2): 114–9.
- Gaskell H, Derry S, Moore RA et al (2009) Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. *Cochrane Database Syst Rev*(3): CD002763.
- Ginsberg B, Sinatra RS, Adler LJ et al (2003) Conversion to oral controlled-release oxycodone from intravenous opioid analgesic in the postoperative setting. *Pain Med* **4**(1): 31–8.
- Gould TH, Crosby DL, Harmer M et al (1992) Policy for controlling pain after surgery: effect of sequential changes in management. *BMJ* **305**(6863): 1187–93.

- Gray A, Kehlet H, Bonnet F et al (2005) Predicting postoperative analgesia outcomes: NNT league tables or procedure-specific evidence? *Br J Anaesth* **94**(6): 710–4.
- Habib AS, White WD, El Gasim MA et al (2008) Transdermal nicotine for analgesia after radical retropubic prostatectomy. *Anesth Analg* **107**(3): 999–1004.
- Hahn TW, Henneberg SW, Holm-Knudsen RJ et al (2000) Pharmacokinetics of rectal paracetamol after repeated dosing in children. *Br J Anaesth* **85**(4): 512–9.
- Hahn TW, Mogensen T, Lund C et al (2000) High-dose rectal and oral acetaminophen in postoperative patients—serum and saliva concentrations. *Acta Anaesthesiol Scand* **44**(3): 302–6.
- Hansen TM, Matzen P & Madsen P (1984) Endoscopic evaluation of the effect of indomethacin capsules and suppositories on the gastric mucosa in rheumatic patients. *J Rheumatol* **11**(4): 484–7.
- Holmer Pettersson P, Owall A & Jakobsson J (2004) Early bioavailability of paracetamol after oral or intravenous administration. *Acta Anaesthesiol Scand* **48**(7): 867–70.
- Holmer Pettersson P, Jakobsson J & Owall A (2006) Plasma concentrations following repeated rectal or intravenous administration of paracetamol after heart surgery. *Acta Anaesthesiol Scand* **50**(6): 673–7.
- Hong D, Conell-Price J, Cheng S et al (2008) Transdermal nicotine patch for postoperative pain management: a pilot dose-ranging study. *Anesth Analg* **107**(3): 1005–10.
- Hudcova J, McNicol E, Quah C et al (2005) Patient controlled intravenous opioid analgesia versus conventional opioid analgesia for postoperative pain control; a quantitative systematic review. *Acute Pain* **7**: 115–32.
- Kampe S, Warm M, Kaufmann J et al (2004) Clinical efficacy of controlled-release oxycodone 20 mg administered on a 12-h dosing schedule on the management of postoperative pain after breast surgery for cancer. *Curr Med Res Opin* **20**(2): 199–202.
- Kendall JM, Reeves BC & Latter VS (2001) Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical fractures. *BMJ* **322**(7281): 261–5.
- Kogan A, Medalion B, Raanani E et al (2007) Early oral analgesia after fast-track cardiac anesthesia. *Can J Anaesth* **54**(4): 254–61.
- Kuhlman JJ, Jr., Lalani S, Maglulilo J, Jr. et al (1996) Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Anal Toxicol* **20**(6): 369–78.
- Kvalsvik O, Borchgrevink PC, Hagen L et al (2003) Randomized, double-blind, placebo-controlled study of the effect of rectal paracetamol on morphine consumption after abdominal hysterectomy. *Acta Anaesthesiol Scand* **47**(4): 451–6.
- Lamacraft G, Cooper MG & Cavalletto BP (1997) Subcutaneous cannulae for morphine boluses in children: assessment of a technique. *J Pain Symptom Manage* **13**(1): 43–9.
- Leeson RM, Harrison S, Ernst CC et al (2007) Dyloject, a novel injectable diclofenac formulation, offers greater safety and efficacy than voltarol for postoperative dental pain. *Reg Anesth Pain Med* **32**(4): 303–10.
- Lichtor JL, Sevarino FB, Joshi GP et al (1999) The relative potency of oral transmucosal fentanyl citrate compared with intravenous morphine in the treatment of moderate to severe postoperative pain. *Anesth Analg* **89**(3): 732–8.
- Lim AW & Schug SA (2001) Tramadol versus morphine as oral step-down analgesia after postoperative epidural analgesia. *Reg Anesth Pain Med* **26**: S133.
- Lloyd R, Derry S, Moore RA et al (2009) Intravenous or intramuscular parecoxib for acute postoperative pain in adults. *Cochrane Database Syst Rev* (2): CD004771.
- Macintyre PE & Schug SA (2007) *Acute Pain Management: A Practical Guide*. London, Saunders Elsevier.
- Mahar PJ, Rana JA, Kennedy CS et al (2007) A randomized clinical trial of oral transmucosal fentanyl citrate versus intravenous morphine sulfate for initial control of pain in children with extremity injuries. *Pediatr Emerg Care* **23**(8): 544–8.
- Manjushree R, Lahiri A, Ghosh BR et al (2002) Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients. *Can J Anaesth* **49**(2): 190–3.
- Manoir BD, Bourget P, Langlois M et al (2006) Evaluation of the pharmacokinetic profile and analgesic efficacy of oral morphine after total hip arthroplasty. *Eur J Anaesthesiol* **23**(9): 748–54.

- Masood AR & Thomas SH (1996) Systemic absorption of nebulized morphine compared with oral morphine in healthy subjects. *Br J Clin Pharmacol* **41**(3): 250–2.
- Mather LE, Woodhouse A, Ward ME et al (1998) Pulmonary administration of aerosolised fentanyl: pharmacokinetic analysis of systemic delivery. *Br J Clin Pharmacol* **46**(1): 37–43.
- Mathieu N, Cnudde N, Engelman E et al (2006) Intranasal sufentanil is effective for postoperative analgesia in adults. *Can J Anaesth* **53**(1): 60–6.
- McCormack JP, Warriner CB, Levine M et al (1993) A comparison of regularly dosed oral morphine and on-demand intramuscular morphine in the treatment of postsurgical pain. *Can J Anaesth* **40**(9): 819–24.
- McQuay HJ, Carroll D & Moore RA (1999) Injected morphine in postoperative pain: a quantitative systematic review. *J Pain Symptom Manage* **17**(3): 164–74.
- McQuay H & Edwards J (2003) Meta-analysis of single dose oral tramadol plus acetaminophen in acute postoperative pain. *Eur J Anaesthesiol Suppl* **28**: 19–22.
- Mendelson J, Upton RA, Everhart ET et al (1997) Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* **37**(1): 31–7.
- Mercadante S, Arcuri E, Fusco F et al (2005) Randomized double-blind, double-dummy crossover clinical trial of oral tramadol versus rectal tramadol administration in opioid-naïve cancer patients with pain. *Support Care Cancer* **13**(9): 702–7.
- MIMS (2008) *MIMS Annual 2008*, MediMedia Australia Pty Ltd.
- Miner JR, Kletti C, Herold M et al (2007) Randomized clinical trial of nebulized fentanyl citrate versus i.v. fentanyl citrate in children presenting to the emergency department with acute pain. *Acad Emerg Med* **14**(10): 895–8.
- Minville V, Lubrano V, Bounes V et al (2008) Postoperative analgesia after total hip arthroplasty: patient-controlled analgesia versus transdermal fentanyl patch. *J Clin Anesth* **20**(4): 280–3.
- Moa G & Zetterstrom H (1990) Sublingual buprenorphine as postoperative analgesic: a double-blind comparison with pethidine. *Acta Anaesthesiol Scand* **34**(1): 68–71.
- Moller PL, Juhl GI, Payen-Champenois C et al (2005) Intravenous acetaminophen (paracetamol): comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. *Anesth Analg* **101**(1): 90–6.
- Moller PL, Sindet-Pedersen S, Petersen CT et al (2005) Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery. *Br J Anaesth* **94**(5): 642–8.
- Moodie JE, Brown CR, Bisley EJ et al (2008) The safety and analgesic efficacy of intranasal ketorolac in patients with postoperative pain. *Anesth Analg* **107**(6): 2025–31.
- Moore A, Edwards J, Barden J et al (2003) *Banholier's Little Book of Pain*. In: edn. (eds). Oxford, Oxford University Press.
- Moore RA & McQuay HJ (1997) Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain* **69**(3): 287–94.
- Ng A, Swami A, Smith G et al (2008) Early analgesic effects of intravenous parecoxib and rectal diclofenac following laparoscopic sterilization: a double-blind, double-dummy randomized controlled trial. *J Opioid Manag* **4**(1): 49–53.
- Ong CK, Lirk P, Tan JM et al (2005) The analgesic efficacy of intravenous versus oral tramadol for preventing postoperative pain after third molar surgery. *J Oral Maxillofac Surg* **63**(8): 1162–8.
- Oscier CD & Milner QJ (2009) Peri-operative use of paracetamol. *Anaesthesia* **64**(1): 65–72.
- Paech MJ, Lim CB, Banks SL et al (2003) A new formulation of nasal fentanyl spray for postoperative analgesia: a pilot study. *Anaesthesia* **58**(8): 740–4.
- Pang WW, Mok MS, Huang S et al (2000) Intraoperative loading attenuates nausea and vomiting of tramadol patient-controlled analgesia. *Can J Anaesth* **47**(10): 968–73.
- Peng PW & Sandler AN (1999) A review of the use of fentanyl analgesia in the management of acute pain in adults. *Anesthesiology* **90**(2): 576–99.
- Portenoy RK, Taylor D, Messina J et al (2006) A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain* **22**(9): 805–11.

- Portenoy RK, Messina J, Xie F et al (2007) Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. *Curr Med Res Opin* **23**(1): 223–33.
- Poyhia R & Vainio A (2006) Topically administered ketamine reduces capsaicin-evoked mechanical hyperalgesia. *Clin J Pain* **22**(1): 32–6.
- Rickard C, O'Meara P, McGrail M et al (2007) A randomized controlled trial of intranasal fentanyl vs intravenous morphine for analgesia in the prehospital setting. *Am J Emerg Med* **25**(8): 911–7.
- Romsing J, Moiniche S & Dahl JB (2002) Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. *Br J Anaesth* **88**(2): 215–26.
- Roy YM, Derry S & Moore RA (2007) Single dose oral lumiracoxib for postoperative pain. *Cochrane Database Syst Rev*(4): CD006865.
- Rygnestad T, Zahlsten K & Samdal FA (2000) Absorption of effervescent paracetamol tablets relative to ordinary paracetamol tablets in healthy volunteers. *Eur J Clin Pharmacol* **56**(2): 141–3.
- Safavi M & Honarmand A (2007) Postoperative analgesia after caesarean section: intermittent intramuscular versus subcutaneous morphine boluses. *Acute Pain* **9**: 215–9.
- Sandler AN, Baxter AD, Katz J et al (1994) A double-blind, placebo-controlled trial of transdermal fentanyl after abdominal hysterectomy. Analgesic, respiratory, and pharmacokinetic effects. *Anesthesiology* **81**(5): 1169–80.
- Sathyan G, Guo C, Sivakumar K et al (2005) Evaluation of the bioequivalence of two transdermal fentanyl systems following single and repeat applications. *Curr Med Res Opin* **21**(12): 1961–8.
- Schug SA & Torrie JJ (1993) Safety assessment of postoperative pain management by an acute pain service. *Pain* **55**(3): 387–91.
- Semple D, Aldridge LA & Doyle E (1996) Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children. *Br J Anaesth* **76**(2): 310–2.
- Semple TJ, Upton RN, Macintyre PE et al (1997) Morphine blood concentrations in elderly postoperative patients following administration via an indwelling subcutaneous cannula. *Anaesthesia* **52**(4): 318–23.
- Sharar SR, Bratton SL, Carrougher GJ et al (1998) A comparison of oral transmucosal fentanyl citrate and oral hydromorphone for inpatient pediatric burn wound care analgesia. *J Burn Care Rehabil* **19**(6): 516–21.
- Sharar SR, Carrougher GJ, Selzer K et al (2002) A comparison of oral transmucosal fentanyl citrate and oral oxycodone for pediatric outpatient wound care. *J Burn Care Rehabil* **23**(1): 27–31.
- Shelley K & Paech MJ (2008) The clinical applications of intranasal opioids. *Curr Drug Deliv* **5**(1): 55–8.
- Simpson DM, Messina J, Xie F et al (2007) Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* **29**(4): 588–601.
- Sinatra RS, Jahr JS, Reynolds LW et al (2005) Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology* **102**(4): 822–31.
- Skaer TL (2006) Transdermal opioids for cancer pain. *Health Qual Life Outcomes* **4**: 24.
- Slatkin NE, Xie F, Messina J et al (2007) Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol* **5**(7): 327–34.
- Smith LA, Carroll D, Edwards JE et al (2000) Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis. *Br J Anaesth* **84**(1): 48–58.
- Stocker ME & Montgomery JE (2001) Serum paracetamol concentrations in adult volunteers following rectal administration. *Br J Anaesth* **87**(4): 638–40.
- Stoker DG, Reber KR, Waltzman LS et al (2008) Analgesic efficacy and safety of morphine-chitosan nasal solution in patients with moderate to severe pain following orthopedic surgery. *Pain Med* **9**(1): 3–12.
- Streisand JB, Varvel JR, Stanski DR et al (1991) Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology* **75**(2): 223–9.
- Striebel WH, Malewicz J, Hermanns K et al (1993) Intranasal meperidine titration for postoperative pain relief. *Anesth Analg* **76**(5): 1047–51.

- Striebel HW, Bonillo B, Schwagmeier R et al (1995) Self-administered intranasal meperidine for postoperative pain management. *Can J Anaesth* **42**(4): 287–91.
- Stuart-Harris R, Joel SP, McDonald P et al (2000) The pharmacokinetics of morphine and morphine glucuronide metabolites after subcutaneous bolus injection and subcutaneous infusion of morphine. *Br J Clin Pharmacol* **49**(3): 207–14.
- Sunshine A, Olson NZ, Colon A et al (1996) Analgesic efficacy of controlled-release oxycodone in postoperative pain. *J Clin Pharmacol* **36**(7): 595–603.
- Thippawong JB, Babul N, Morishige RJ et al (2003) Analgesic efficacy of inhaled morphine in patients after bunionectomy surgery. *Anesthesiology* **99**(3): 693–700.
- Toms L, Derry S, Moore RA et al (2009) Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev*(1): CD001547.
- Toms L, McQuay HJ, Derry S et al (2008) Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database Syst Rev*(4): CD004602.
- Toussaint S, Mavid J, Schwagmeier R et al (2000) Patient-controlled intranasal analgesia: effective alternative to intravenous PCA for postoperative pain relief. *Can J Anaesth* **47**(4): 299–302.
- Tramèr MR, Williams JE, Carroll D et al (1998) Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiol Scand* **42**(1): 71–9.
- Turan A, White PF, Koyuncu O et al (2008) Transdermal nicotine patch failed to improve postoperative pain management. *Anesth Analg* **107**(3): 1011–7.
- Tveita T, Thoner J, Klepstad P et al (2008) A controlled comparison between single doses of intravenous and intramuscular morphine with respect to analgesic effects and patient safety. *Acta Anaesthesiol Scand* **52**(7): 920–5.
- Upton RN, Semple TJ, Macintyre PE et al (2006) Population pharmacokinetic modelling of subcutaneous morphine in the elderly. *Acute Pain* **8**: 109–16.
- Vondrackova D, Leyendecker P, Meissner W et al (2008) Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *J Pain* **9**(12): 1144–54.
- Ward M, Minto G & Alexander-Williams JM (2002) A comparison of patient-controlled analgesia administered by the intravenous or intranasal route during the early postoperative period. *Anaesthesia* **57**(1): 48–52.
- Ward ME, Woodhouse A, Mather LE et al (1997) Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. *Clin Pharmacol Ther* **62**(6): 596–609.
- Weil K, Hooper L, Afzal Z et al (2007) Paracetamol for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database Syst Rev*(3): CD004487.
- Wermeling DP, Grant GM, Lee A et al (2005) Analgesic effects of intranasal butorphanol tartrate administered via a unit-dose device in the dental impaction pain model: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* **27**(4): 430–40.
- Worrish S, Schuler G & Janicki PK (2007) Effect of local administration of transdermal fentanyl on peripheral opioid analgesia. *Pain Med* **8**(1): 41–7.
- Worsley MH, MacLeod AD, Brodie MJ et al (1990) Inhaled fentanyl as a method of analgesia. *Anaesthesia* **45**(6): 449–51.
- Yanagihara Y, Ohtani M, Kariya S et al (2003) Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharm Drug Dispos* **24**(1): 37–43.

# 7. PCA, REGIONAL AND OTHER LOCAL ANALGESIA TECHNIQUES

## 7.1 PATIENT-CONTROLLED ANALGESIA

Patient-controlled analgesia (PCA) refers to methods of pain relief that allow a patient to self-administer small doses of an analgesic agent as required. Most often, however, the term PCA is associated with programmable infusion pumps that deliver opioid medications intravenously, although a variety of other methods and routes of delivery (systemic and regional) using opioids as well as other analgesic agents have been described. For epidural PCA see Section 7.2.3; for regional PCA techniques see Section 7.5.1.

### 7.1.1 Efficacy of intravenous PCA

#### ***Analgesia, patient preference and outcomes***

IV opioid PCA provides better analgesia than conventional (IM, SC) opioid regimens, although the magnitude of the difference in analgesia is small (8.012 on a pain scale of 0 to 100); opioid consumption is greater; there are no differences in duration of hospital stay or opioid-related adverse effects other than pruritus, which is increased, and patient satisfaction is higher (Hudcova et al, 2006 **Level I**).

**Note: reversal of conclusions**

This partly reverses the Level I conclusion in the previous edition of this document; earlier meta-analyses had reported no difference in opioid consumption or opioid-related adverse effects

Other information obtained from published cohort studies, case-controlled studies and audit reports only (ie not RCTs) (Dolin & Cashman, 2002 **Level IV**) suggests that IV PCA may be appreciably more effective than intermittent IM opioid analgesia in a 'real life' clinical setting; patients given IM opioid analgesia were more than twice as likely to experience moderate-to-severe pain and severe pain as those given PCA.

In settings where there are high nurse:patient ratios and where it might be easier to provide analgesia truly on-demand, conventional forms of opioid administration may be as effective as IV PCA. A comparison of PCA versus nurse-administered analgesia following cardiac surgery found no difference in analgesia at 24 hours (a period when nursing attention is likely to be higher) but significantly better pain relief with PCA at 48 hours (Bainbridge et al, 2006 **Level I**). In an emergency department setting, IV PCA was as effective as nurse-administered IV bolus doses of opioid (Evans et al, 2005 **Level II**).

The enormous variability in PCA parameters (bolus doses, lockout intervals and maximum permitted cumulative doses) used in many studies indicates uncertainty as to the ideal PCA program and may limit the flexibility, and thus the efficacy, of the technique. Individual PCA prescriptions may need to be adjusted if patients are to receive maximal benefit (Macintyre, 2005; Macintyre & Schug, 2007; Macintyre & Coldrey, 2008).

A number of studies have shown that PCA provides less effective pain relief compared with epidural analgesia (see Section 7.2).



## Cost of PCA

The use of any analgesic technique, even if it is known to provide more effective pain relief, also requires consideration of the cost involved. There are no good, consistent data on the cost-effectiveness of PCA compared with conventional opioid analgesic techniques; information that is available often does not include the full scope of costs (eg cost of adverse events or failure of an analgesic technique as well as the more obvious costs of pumps, disposables and nursing time). However, in general, PCA comes at a higher cost because of the equipment, consumables and drugs required; nursing time needed is much less (Jacox et al, 1997; Choiniere et al, 1998 **Level II**; Rittenhouse & Choiniere, 1999; Chang et al, 2004 **Level II**). PCA was more cost-effective than epidural analgesia after major abdominal surgery (Bartha et al, 2006).

### 7.1.2 Drugs used for parenteral PCA

#### Opioids

In general there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of side effects between morphine and other opioids commonly used in PCA, although the results of individual studies are inconsistent.

##### *Pethidine*

Compared with morphine, pethidine (meperidine) may lead to less effective pain relief on movement (Bahar et al, 1985 **Level II**; Sinatra et al, 1989 **Level II**; Plummer et al, 1997 **Level II**); no difference in nausea and vomiting (Bahar et al, 1985 **Level II**; Stanley et al, 1996 **Level II**; Woodhouse et al, 1996 **Level II**; Plummer et al, 1997 **Level II**); and less sedation (Sinatra et al, 1989 **Level II**) and pruritus (Sinatra et al, 1989 **Level II**; Woodhouse et al, 1996 **Level II**).

##### *Fentanyl*

There was no difference between morphine and fentanyl in terms of pain relief (Howell et al, 1995 **Level II**; Woodhouse et al, 1996 **Level II**) or the incidence of most side effects (Howell et al, 1995 **Level II**; Woodhouse et al, 1996 **Level II**); pruritus was more common with morphine (Woodhouse et al, 1996 **Level II**).

##### *Tramadol*

Tramadol by PCA had a similar analgesic effect compared with morphine (Erolcay & Yuceyar, 2003 **Level II**; Unlugenc, Vardar et al, 2008 **Level II**), pethidine (Unlugenc, Vardar et al, 2008 **Level II**) and oxycodone (Silvasti et al, 1999 **Level II**). The majority of studies showed that the incidence of nausea and vomiting was no higher than with pure agonist opioids (Silvasti et al, 1999 **Level II**; Erolcay & Yuceyar, 2003 **Level II**; Unlugenc, Vardar et al, 2008 **Level II**). Tramadol also had a lower risk of respiratory depression and less effect on gastrointestinal motor function compared with other opioids (see Section 4.1.2).

##### *Other comparisons*

Other comparisons with morphine include hydromorphone (no difference in pain relief or side effects) (Rapp et al, 1996 **Level II**; Hong et al, 2008 **Level II**), oxycodone (no difference in pain relief or side effects) (Silvasti et al, 1998 **Level II**) and piritramide (equally effective and similar side effects) (Dopfmer et al, 2001 **Level II**).

Remifentanyl provided at least equivalent analgesia compared with morphine (Kucukemre et al, 2005 **Level II**; Gurbet et al, 2004 **Level II**) and fentanyl PCA (Gurbet et al, 2004 **Level II**) and may be associated with less nausea and vomiting (Kucukemre et al, 2005 **Level II**; Gurbet et al, 2004 **Level II**).



The combination of two opioids in the PCA syringe has also been investigated. There was no difference in pain scores and side effects between fentanyl-morphine and fentanyl PCA (Friedman et al, 2008 **Level II**). Beneficial effects on pain relief and the incidence of pruritus in a comparison of morphine, nalbuphine and varying combinations of the two drugs were dependent on the ratio of drugs used (Yeh et al, 2008 **Level II**). The addition of alfentanil to morphine resulted in no differences in pain relief or adverse effects compared with morphine alone, although patients who received the alfentanil-morphine mixture rated speed of onset and effectiveness of analgesia as better (Ngan Kee et al, 1999 **Level II**). In contrast, compared with tramadol alone, remifentanil added to tramadol improved pain relief, but increased total opioid dose (Unlugenc, Tetiker et al, 2008 **Level II**).

On an individual patient basis, one opioid may be better tolerated than another and a change to an alternative opioid may be beneficial if the patient is experiencing intolerable side effects (Woodhouse et al, 1999 **Level II**).

### **Adverse effects of PCA opioids**

As noted above and in Section 7.1.1, meta-analyses and individual studies have shown that the risk of side effects is similar for opioids administered by PCA or more traditional routes, regardless of the opioid used.

A review of published cohort studies, case-controlled studies and audit reports only (ie not RCTs), reported the following incidences associated with the use of PCA: respiratory depression 1.2% to 11.5% (depending whether respiratory rate or oxygen saturation were used as indicators), nausea 32%, vomiting 20.7%, and pruritus 13.8% (Cashman & Dolin, 2004 **Level IV**; Dolin & Cashman, 2005 **Level IV**). Excessive sedation was not used as an indicator of respiratory depression in any of the studies included in these reviews (see importance of sedation score in Section 4.1).

In an audit of 700 patients who received PCA for postoperative pain relief, respiratory depression was defined as a respiratory rate of <10 breaths/min and/or a sedation score of 2 (defined as 'asleep but easily roused'); of the 13 patients (1.86%) reported with respiratory depression, all had respiratory rates of <10 breaths/min and 11 also had sedation scores of 2 (Shapiro et al, 2005 **Level IV**).

The incidence of PCA-related sedation was reduced significantly in patients given concurrent non-steroidal anti-inflammatory drugs (NSAIDs) (Marret et al, 2005 **Level I**).

### **Adjuvant drugs**

Discussion of adjuvant drugs in this section will be confined to those added to the PCA opioid solution. For additional information see Section 4.3.

#### **Antiemetics**

Droperidol added to the PCA morphine solution was an effective antiemetic with an NNT of 2.7 for nausea and 3.1 for vomiting (Tramèr & Walder, 1999 **Level I**). Tramèr's group noted no dose-responsiveness with droperidol (Tramèr & Walder, 1999 **Level I**). However, in a comparison of the effects of the addition of 0.5 mg, 1.5 mg and 5 mg droperidol to 100 mg PCA morphine, the smallest dose had no significant antiemetic effect and the 1.5 mg dose was effective against nausea but not vomiting (Culebras et al, 2003 **Level II**). The 5 mg dose significantly reduced both nausea and vomiting, but at the cost of unacceptable sedation, which was not seen at the other doses. In contrast to the NNTs reported by Tramèr et al (Tramèr & Walder, 1999 **Level I**), these results translate to NNTs of 3.7 for nausea and 8.3 for vomiting; as noted, the higher dose increased the risk of sedation (Culebras et al, 2003 **Level II**).

In another study, coadministration of droperidol and morphine via PCA resulted in morphine-sparing and reduced the frequency of postoperative nausea and vomiting (Lo et al, 2005 **Level II**).

Droperidol given separately was as effective as adding droperidol to PCA morphine (Gan et al, 1995 **Level II**). The cost-benefit and risk-benefit of the routine addition of droperidol to PCA opioids must therefore be considered because all patients receive the drug when not all will need it and some patients might receive inappropriately high doses of droperidol.

Evidence of benefit from the addition of 5HT3 antagonists to PCA is unclear. Ondansetron, given both as a bolus at the end of surgery and mixed with morphine in the PCA solution, reduced the incidence of nausea and the need for antiemetics, but not the patients' perception of this or their satisfaction (Cherian & Smith, 2001 **Level II**). However Tramèr's group (Tramèr & Walder, 1999 **Level I**) concluded that 5HT3 receptor antagonist drugs (eg ondansetron) showed no evidence of worthwhile antinauseant effect, although they may be effective for vomiting with an NNT of approximately 5. A more recent study showed that ondansetron given as an initial dose of 4 mg followed by 0.2 mg/1 mg morphine PCA morphine can reduce nausea and vomiting – although pain scores were higher (Boonmak et al, 2007 **Level II**). Another study reported a reduction in vomiting with the addition of ondansetron alone to morphine PCA and a lower incidence of nausea with the addition of a combination of ondansetron plus prochlorperazine (Jellish et al, 2009 **Level II**).

### **Ketamine**

In general, concurrent administration of ketamine reduced PCA opioid requirements and the incidence of nausea and vomiting (Bell et al, 2006 **Level I**). However, the same benefit may not be derived from adding ketamine to the PCA opioid solution, although the evidence is conflicting. In the meta-analyses by Bell et al (Bell et al, 2006 **Level I**), six studies are listed where ketamine was added to the PCA opioid and results were mixed; pain was reduced in four of these studies and morphine consumption in three. A more recent study of 352 patients also showed a lack of benefit (Sveticic et al, 2008 **Level II**), but in another, the addition of ketamine to morphine PCA reduced pain scores and the incidence of nausea and vomiting, was opioid-sparing, and led to shorter duration of use of PCA compared with PCA morphine alone (Kollender et al, 2008 **Level II**). In patients after thoracotomy, although the addition of ketamine to PCA morphine did not improve pain relief it was opioid-sparing, and patients in the ketamine group spent less time with oxygen saturation levels <90% and had better forced expiratory volumes (Michelet et al, 2007 **Level II**).

### **Naloxone**

There was no analgesic benefit of adding naloxone to the PCA morphine solution (Sartain et al, 2003 **Level II**; Cepeda et al, 2002 **Level II**; Cepeda et al, 2004 **Level II**); in 'ultra low doses' but not in the higher dose studies, the incidence of nausea and pruritus was decreased (Cepeda et al, 2004 **Level II**).

### **Other adjuvants**

Ketorolac added to morphine (Chen, Wu et al, 2005 **Level II**; Chen et al, 2009 **Level II**) or tramadol (Lepri et al, 2006 **Level II**) PCA did not improve pain relief or alter the incidence of side effects, however it was opioid-sparing and led to earlier return of bowel function after colorectal surgery (Chen et al, 2009 **Level II**).

The addition of lignocaine (lidocaine) to morphine conferred no benefit in terms of pain relief or side effects (Cepeda et al, 1996 **Level II**).

The addition of clonidine to IV PCA morphine resulted in significantly better pain relief for the first 12 hours only and less nausea and vomiting compared with morphine alone; there was no

reduction in morphine requirements (Jefferies et al, 2002 **Level II**). A combination of dexmedetomidine and morphine resulted in significantly better pain relief, a lower incidence of nausea but not vomiting, and significant opioid-sparing compared with morphine alone (Lin et al, 2009 **Level II**).

Magnesium added to morphine was opioid-sparing and led to better pain relief (Unlugenc et al, 2003 **Level II**); added to tramadol it was opioid-sparing but only provided better pain relief for the first 2 hours (Unlugenc et al, 2002 **Level II**).

### 7.1.3 Program parameters for intravenous PCA

#### **Bolus dose**

While the optimal sized bolus dose should provide good pain relief with minimal side effects, there are only limited data available concerning the effects of various dose sizes. In patients prescribed 0.5 mg, 1 mg and 2 mg bolus doses of morphine, most of those who were prescribed 0.5 mg were unable to achieve adequate analgesia, while a high incidence of respiratory depression was reported in those who received 2 mg (Owen, Plummer et al, 1989 **Level II**). It was concluded that the optimal PCA bolus dose for morphine was therefore 1 mg.

Similarly, in patients prescribed 20, 40 or 60 mcg bolus doses of fentanyl, the larger dose was associated with an increased risk of respiratory depression and a conclusion was made that the optimal dose of fentanyl for use in PCA was 40 mcg (Camu et al, 1998 **Level II**). However in this study, each dose was infused over 10 minutes, which could alter the effect of that dose.

Four different demand doses of fentanyl (10, 20, 30 and 40 mcg) were assessed for the management of pain during changes of burns dressings. Pain relief was significantly better with the 30 mcg and 40 mcg doses; no patient became sedated or experienced nausea and vomiting (Prakash et al, 2004 **Level II**).

Rigid adherence to an 'optimal' dose may not, however, lead to the best pain relief for all patients. If the prescribed dose is not 'optimal' and not too small, the patient will be able to compensate to some degree by changing their demand rate. However, they will only compensate to a certain degree. Even if uncomfortable, patients may only average four demands per hour, even though they could press the PCA button more frequently (Owen, Plummer et al, 1989 **Level II**).

Initial orders for bolus doses should take into account factors such as a history of prior opioid use (see Section 11.7) and patient age (Macintyre & Schug, 2007; Macintyre & Coldrey, 2008); PCA morphine requirements are known to decrease as patient age increases (Macintyre & Jarvis, 1996 **Level IV**; Gagliese et al, 2008 **Level IV**). Subsequent bolus doses may require adjustment according to patient pain reports or the onset of any side effects. Even though the length of the lockout interval could allow it, patients may not increase their demand rate enough to compensate for bolus doses that are too small (Owen, Plummer et al, 1989 **Level II**).

The number of demands a patient makes, including the number of 'unsuccessful' demands, is often used as an indication that the patient is in pain and as a guide to adjusting the size of the bolus dose. However, there may be a number of reasons for a high demand rate other than pain. For example, excessive PCA demands may correlate with anxiety, poor perioperative adaptation to surgery involving avoidance behaviour and intrusive thoughts, as well as high pain scores (Katz et al, 2008 **Level IV**). See also Section 1.2.4 for additional information on the relationship between pain relief and psychological factors in PCA.

#### **Lockout interval**

The lockout interval is a safety mechanism that limits the frequency of demands made by the patient. For maximum safety it should be long enough to allow the patient to feel the full

effect of one opioid dose before another dose can be delivered. However, if it is too long the effectiveness of PCA could be reduced. There were no differences in pain relief, side effects or anxiety when lockout intervals of 7 or 11 minutes for morphine and 5 or 8 minutes for fentanyl were used (Ginsberg et al, 1995 **Level II**).

### **Concurrent background (continuous) infusions**

There is no good evidence to show that the addition of a background infusion to IV PCA improves pain relief or sleep, or reduces the number of demands (Owen, Szekely et al, 1989 **Level II**; Parker et al, 1991 **Level II**; Parker et al, 1992 **Level II**; Dal et al, 2003 **Level II**). Large audits of adult patients have also shown that the risk of respiratory depression is increased when a background infusion is added (Notcutt & Morgan, 1990 **Level IV**; Fleming & Coombs, 1992 **Level IV**; Schug & Torrie, 1993 **Level III-2**; Sidebotham et al, 1997 **Level IV**). In adults, the routine use of a background infusion is therefore not recommended, although it may be useful in opioid-tolerant patients (see Section 11.7).

### **Dose limits**

Limits to the maximum amount of opioid that can be delivered over a certain period (commonly 1 or 4 hours) can be programmed into most PCA machines. There is no good evidence of any benefit that can be attributed to these limits.

### **Loading dose**

There is enormous variation in the amount of opioid a patient may need as a 'loading dose' and there is no good evidence of any benefit that can be attributed to the use of the loading dose feature that can be programmed into PCA machines. PCA is essentially a maintenance therapy, therefore a patient's pain should be controlled before PCA is started by administration of individually titrated loading doses (Macintyre & Schug, 2007; Macintyre & Coldrey, 2008). IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy in the treatment of acute sickle cell pain (Rees et al, 2003 **Level II**).

## **7.1.4 Efficacy of PCA using other systemic routes of administration**

### **Subcutaneous PCA**

Data on the effectiveness of SC PCA compared with IV PCA are variable and inconsistent. Both similar (Urquhart et al, 1988 **Level II**; White, 1990 **Level II**; Munro et al, 1998 **Level II**; Bell et al, 2007 **Level II**) and significantly better (Dawson et al, 1999 **Level II**; Keita et al, 2003 **Level II**) pain relief has been reported, as well as the same (Urquhart et al, 1988 **Level II**; Munro et al, 1998 **Level II**; Dawson et al, 1999 **Level II**; Keita et al, 2003 **Level II**) and a higher incidence of nausea and vomiting (White, 1990 **Level II**) or pruritus (Bell et al, 2007 **Level II**). Compared with IV PCA, SC PCA may (Urquhart et al, 1988 **Level II**; White, 1990 **Level II**; Dawson et al, 1999 **Level II**; Bell et al, 2007 **Level II**) or may not (Munro et al, 1998 **Level II**) result in higher opioid use.

### **Oral PCA**

Oral PCA, using a modified IV PCA system, is as effective as IV PCA (Striebel et al, 1998 **Level II**). An oral PCA device has been developed that uses radiofrequency identification technology to allow patients in an oncology ward access (subject to a lockout interval) to a medication-dispensing system at the bedside (Rosati et al, 2007 **Level IV**).

### **Intranasal PCA**

Patient-controlled intranasal analgesia (PCINA) fentanyl can be as effective as IV PCA (Striebel et al, 1996 **Level II**; Toussaint et al, 2000 **Level II**; Manjushree et al, 2002 **Level II**; Paech et al, 2003 **Level II**), as is butorphanol (Abboud et al, 1991 **Level II**). As would be expected from the data on IN bioavailability of opioids (see Section 6.6.1), higher doses are needed via the IN route

(Manjushree et al, 2002 **Level II**). PCINA pethidine is as effective as IV pethidine, although larger doses are needed (Striebel, Malewicz et al, 1993 **Level II**), and more effective than SC injections of pethidine (Striebel et al, 1995 **Level II**). Diamorphine PCINA (bolus doses of 0.5mg) was less effective than PCA IV morphine (higher bolus doses of 1 mg were used) after joint replacement surgery (Ward et al, 2002 **Level II**) but provided better pain relief in doses of 0.1 mg/kg compared with 0.2 mg/kg IM morphine in children with fractures (Kendall & Latter, 2003).

### **Transdermal PCA**

A number of studies have reported that the iontophoretic fentanyl patient-controlled transdermal system (PCTS) is comparable with standard IV PCA morphine regimens in terms of pain relief and incidence of side effects (Viscusi et al, 2004 **Level II**; Hartrick et al, 2006 **Level II**; Ahmad et al, 2007 **Level II**; Grond et al, 2007 **Level II**; Minkowitz et al, 2007 **Level II**; Viscusi et al, 2007 **Level II**). However, a meta-analysis showed that while fentanyl PCTS provided good pain relief, it may not be as effective as IV morphine PCA. While there was no difference in Patient Global Assessment, significantly more patients in the PCTS group withdrew because of inadequate analgesia (Poon et al, 2009 **Level I**).

Comparison of ease-of-care and satisfaction measures of the two techniques showed that patients, nurses and physiotherapists found the iontophoretic fentanyl PCTS system easier to use than IV PCA and they were more satisfied with PCTS (Hartrick et al, 2006 **Level II**; Gan et al, 2007 **Level IV**; Grond et al, 2007 **Level II**; Minkowitz et al, 2007 **Level II**).

Maximum blood concentrations of fentanyl were the same if the fentanyl PCTS patch was placed on the chest, or upper outer arm, but less if placed on the lower inner arm; the pharmacokinetics were not affected by gender, ethnicity, age or weight (Gupta et al, 2005 **Level II**).

## **7.1.5 Complications related to PCA**

Complications related to the use of PCA can be divided into operator or patient-related errors, and problems due to the equipment or the opioid used.

An early prospective study of 4000 patients given PCA postoperatively found nine cases of respiratory depression. These were associated with drug interactions, continuous (background) infusions, nurse- or physician-controlled analgesia, and inappropriate use of PCA by patients (Looi-Lyons et al, 1996 **Level IV**). A similar sized prospective survey of 3785 patients showed that use of PCA was associated with 14 critical events: 8 programming errors (all associated with the setting of a continuous infusion); 3 family members activating PCA; 1 patient tampering; and 3 errors in clinical judgment (Ashburn et al, 1994 **Level IV**).

The most common of the 5377 PCA-related errors reported from September 1998 to August 2003 and examined by the United States Pharmacopeia (USP) were improper dose/quantity 38.9%, unauthorised drug 18.4%, omission error 17.6% and prescribing error 9.2%. Other errors included wrong administration technique, wrong drug preparation, wrong patient and wrong route (US Pharmacopeia, 2004 **Level IV**).

A much later retrospective analysis of information (from July 2000 to June 2005) reported to a national voluntary medication error-reporting database, showed that PCA-related medication errors continue. Of 919 241 medication errors reported, 9571 (only 1%) were associated with PCA and of these, just 624 were associated with patient harm; the majority of errors occurred during drug administration (Hicks et al, 2008). Of these, 38% were errors in dose or quantity, 17.4% involved an omission, and 17.3% were related to an unauthorised or wrong drug; human factors were the main cause of errors; distractions (37.8%) and inexperienced staff (26.3%) were the leading contributing factors (Hicks et al, 2008).

For more detail on adverse effects due to the opioid administered, equipment used, or operator and patient-related factors, see Sections 7.1.2, 7.1.6 and 7.1.7 respectively.

### **7.1.6 Equipment**

Both programmable PCA pumps and disposable PCA devices are available.

#### ***Programmable PCA pumps***

These types of pumps allow significant flexibility of use. Adjustments can be made to the dose delivered and lockout intervals, background infusions can be added, and accurate assessments can be made of the total dose of drug delivered. In addition, access to the syringe (or other drug reservoir) and the microprocessor program is only possible using a key or access code.

All require disposable items, eg generic or dedicated syringes or cartridges, antisiphon valves to prevent siphoning of drug from the drug reservoir, and antireflux valves to prevent backflow of drug into the IV infusion line (see later).

#### ***Disposable PCA devices***

There is a variety of disposable PCA devices.

##### ***Parenteral PCA devices***

Disposable PCA devices are often based on the same physical principle; the volume of pressurised fluid delivered (dependent upon spring or elastomer technology) is determined by mechanical restrictions within the flow path and the speed of filling of the bolus dose reservoir determines the 'lockout' interval (Skryabina & Dunn, 2006). Advantages include small size and weight, freedom from an external power source, elimination of programming errors, and simplicity of use. Disadvantages include an inability to alter the volume of the bolus dose delivered or add a background infusion, difficulties determining the amount of drug the patient has received accurately, the possibility of inaccurate flow rates, and long-term costs (Skryabina & Dunn, 2006). There may also be security issues as the drug reservoirs for these devices are more readily accessible.

##### ***Transmucosal PCA devices***

Metered-dose PCINA devices are available. The drugs must be administered in small volumes to avoid significant run-off into the pharynx.

Initial PCINA devices delivered sprays of a reasonable dose but large volume (eg 25 mcg fentanyl/0.5 mL (Striebel, Pommerening et al, 1993) or smaller volume but with smaller doses than commonly used with IV PCA (eg 9 mcg fentanyl/0.18 mL (O'Neil et al, 1997). A specially formulated solution of 300 mcg/mL fentanyl has been used in a device that enables fentanyl doses of 54 mcg to be delivered in just 0.18 mL (Paech et al, 2003).

##### ***Transdermal PCA devices***

The fentanyl PCTS uses a low-intensity electric current to drive the drug from the reservoir through the skin and into the systemic circulation (Banga, 2005). The IONSYS™ device, which is applied to the chest or upper outer arm, delivers a fixed dose of 40 mcg fentanyl over a 10-minute period following a patient demand and allows delivery of up to 6 doses each hour, up to a maximum of 80 doses in 24 hours (Banga, 2005; Koo, 2005). This device must be replaced every 24 hours, was not available in all countries, and was designed for in-hospital use only.

Despite the potential advantages noted under Section 7.1.4, the marketing authority for the fentanyl PCTS was suspended by the European Medicines Agency in November 2008, after corrosion of a component of the system in one batch was detected (European Medicines Agency, 2008). This fault carries the risk of triggering the self-activation of the system, which could lead

to fentanyl overdose; as this problem could not yet be resolved, the system is currently not available.

### **Equipment-related complications**

In general, modern PCA pumps have a high degree of reliability. However, problems continue to be reported as well as problems related to the disposable items required. Information regarding complications due to equipment problems is mainly case-based; examples from a range of the cases reported are given.

While the number of reports of ‘run-away’ pumps, where the PCA pump unexpectedly delivers an unprescribed dose of drug (Notcutt & Morgan, 1990), has decreased following changes made to pump design, they continue to occur, including a report of spontaneous triggering (Christie & Cranfield, 1998) and of a frayed wire in the demand apparatus leading to triggering as a result of an electrical short circuit (Doyle & Vicente, 2001).

Uncontrolled syphoning of syringe contents when the PCA machine was above patient level has been reported following cracked glass PCA syringes (Thomas & Owen, 1988; ECRI, 1996), failure of a damaged drive mechanism to retain the syringe plunger (Kwan, 1995), improperly secured PCA cassettes (ECRI, 1995) and broken drug cartridge syringe (Doyle & Keebler, 2008). To minimise the risk of syphoning, the use of antisiphon valves is recommended (ECRI, 1996). Antireflux (one-way) valves are essential if the PCA infusion is not connected to a dedicated IV line. The non-PCA infusion tubing should have an antireflux valve upstream from the connection with the PCA line to prevent back-flow up the non-PCA line should distal obstruction occur; otherwise, inappropriate dosing can occur (Paterson, 1998; Rutherford & Patri, 2004).

## **7.1.7 Patient and staff factors**

### **Patient factors**

Patient factors play a role in the effectiveness of PCA as well as complications that can arise from its use: much of the information regarding complications due to patient factors is case-based — examples from a range of the cases reported are given below. Psychological factors that may affect PCA use and efficacy are discussed in Section 1.2.

### **Education**

Few controlled studies have evaluated the influence of information on PCA use. Of 200 patients surveyed who used PCA, approximately 20% were worried that they may become addicted, and 20% and 30% respectively felt that the machine could give them too much drug or that they could self-administer too much opioid (Chumbley et al, 1998 **Level IV**). In a follow-up study, the same authors conducted focus groups with previous PCA users, developed a new information leaflet and then undertook a randomised study comparing the old and new leaflet. They found that patients wanted more information on the medication in the PCA, the possible side effects and assurance that they would not become addicted (Chumbley et al, 2002 **Level II**).

Comparisons have been made between different forms of education given to patients about PCA and results are inconsistent. In an assessment of patient information delivered using structured preoperative interviews or leaflets compared with routine preoperative education, patients given leaflets were better informed and less confused about PCA and became familiar with using PCA more quickly, but there were no effects on pain relief, worries about addiction and safety, or knowledge of side effects; the structured preoperative interview resulted in no benefits (Chumbley et al, 2004 **Level III-2**). Another comparison of structured education versus routine information showed that overall analgesic efficacy, side effects, and recovery times



were not affected by the education program (Lam et al, 2001 **Level II**). Patients who were shown a video on PCA prior to surgery had better knowledge about the technique and reported better pain control after surgery (Knoerl et al, 1999 **Level III-2**; Chen, Yeh et al, 2005 **Level III-2**).

### ***Inappropriate use of PCA***

The safety of PCA depends on an adequate understanding of the technique by the patient and the fact that unauthorised persons do not press the demand button.

Oversedation with PCA has followed the patient mistaking the PCA handset for the nurse-call button and family or unauthorised nurse-activated demands ('PCA by proxy') (Wakerlin & Larson, 1990; Fleming & Coombs, 1992; Chisakuta, 1993; Ashburn et al, 1994; Sidebotham et al, 1997; Tsui et al, 1997).

There have been case reports expressing concerns that patients can use PCA to treat increasing pain and therefore mask problems such as compartment syndrome (Harrington et al, 2000; Richards et al, 2004), urinary retention (Hodsman et al, 1988), pulmonary embolism (Meyer & Eagle, 1992) and myocardial infarction (Finger & McLeod, 1995). However, appropriate routine patient monitoring should detect changes in pain scores and analgesic consumption enabling identification of such complications.

### ***Nursing and medical staff***

Much of the information regarding complications due to nursing and medical staff factors is case-based — examples from a range of the cases reported are given.

As noted above in Section 7.1.5, operator error is a common safety problem related to PCA use (Ashburn et al, 1994; Looi-Lyons et al, 1996; US Pharmacopeia, 2004). Misprogramming of PCA pumps is thought to account for around 30% of PCA errors, be twice as likely to result in injury or death than errors involving general-purpose infusion pumps, and lead to more harm than errors in other types of medication administration (ECRI, 2006). Mortality from programming errors has been estimated to range from 1 in 33 000 to 1 in 338 800 patients prescribed PCA (Vicente et al, 2003).

A number of reports involve the programming of drug concentrations that were lower than the concentration ordered, with the resultant delivery of an excessive amount of opioid leading to respiratory depression and sometimes death (ECRI, 1997; ECRI, 2002). The use of an incorrect prefilled 'standard syringe' for PCA (morphine 5 mg/mL instead of the prescribed 1 mg/mL) also had a fatal outcome (Vicente et al, 2003). It has been suggested that drug concentrations should be standardised within institutions to reduce the chance of administration and programming errors (ECRI, 2002).

Some PCA pumps now incorporate dose-error reduction systems that use internal software to guide manual programming by checking programmed doses against preset limits and alerting the programmer to inappropriate dose or continuous infusion settings; preset dosing protocols can also be used, so that 'standard' settings can be programmed for each of the opioids administered (ECRI, 2006).

Inappropriate prescriptions of supplementary opioids (by other routes) and sedative drugs (including some antihistamines) can lead to oversedation and respiratory depression (Ashburn et al, 1994; Tsui et al, 1997; Lotsch et al, 2002).

## **7.1.8 PCA in specific patient groups**

For PCA in the paediatric patient, the elderly patient, the patient with obstructive sleep apnoea and the opioid-tolerant patient, see Sections 10.6, 11.2, 11.5 and 11.7 respectively.

**Key messages**

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens **(S)** (**Level I** [Cochrane review]).
2. Opioid administration by intravenous PCA leads to higher opioid consumption **(R)**, a higher incidence of pruritus **(R)**, and no difference in other opioid-related adverse effects **(S)** or hospital stay **(S)** compared with traditional methods of intermittent parenteral opioid administration (**Level I** [Cochrane review]).
3. In settings where there are high nurse-patient ratios there may be no difference in effectiveness of PCA and conventional parenteral opioid regimens **(N)** (**Level I**).
4. Patient preference for intravenous PCA is higher when compared with conventional regimens **(U)** (**Level I**).
5. The addition of ketamine to PCA morphine does not improve analgesia or reduce the incidence of opioid-related side effects **(U)** (**Level I**).
6. Iontophoretic fentanyl PCA may not be as effective as intravenous morphine PCA, with more patients withdrawing from studies because of inadequate pain relief (**Level I**).
7. There is little evidence that one opioid via PCA is superior to another with regards to analgesic or adverse effects in general; although on an individual patient basis, one opioid may be better tolerated than another **(U)** (**Level II**).
8. There is no analgesic benefit in adding naloxone to the PCA morphine solution; however in ultra-low doses the incidence of nausea and pruritus may be decreased **(U)** (**Level II**).
9. The addition of a background infusion to intravenous PCA does not improve pain relief or sleep, or reduce the number of PCA demands **(U)** (**Level II**).
10. Subcutaneous PCA opioids can be as effective as intravenous PCA **(U)** (**Level II**).
11. Intranasal PCA opioids can be as effective as intravenous PCA **(U)** (**Level II**).
12. The risk of respiratory depression with PCA is increased when a background infusion is used **(U)** (**Level IV**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Adequate analgesia needs to be obtained prior to commencement of PCA. Initial orders for bolus doses should take into account individual patient factors such as a history of prior opioid use and patient age. Individual PCA prescriptions may need to be adjusted **(U)**.
- The routine addition of antiemetics to PCA opioids is not encouraged, as it is of no benefit compared with selective administration **(U)**.
- PCA infusion systems must incorporate antisiphon valves and in non-dedicated lines, antireflux valves **(U)**.
- Drug concentrations should be standardised within institutions to reduce the chance of programming errors **(U)**.
- Operator error remains a common safety problem **(N)**.

## 7.2 EPIDURAL ANALGESIA

Epidural analgesia (ie the provision of pain relief by continuous administration of pharmacological agents into the epidural space via an indwelling catheter) has become a widely used technique for the management of acute pain in adults and children, particularly after surgery and sometimes trauma, and in parturients.

### 7.2.1 Efficacy

The difficulty with interpretation of available data is that epidural analgesia is not a single entity but can be provided by a number of pharmacological agents administered into different levels of the epidural space for a wide variety of operations.

However, the consistent efficacy of epidural analgesia has been well demonstrated. Regardless of analgesic agent used, location of catheter, type of surgery and type or time of pain assessment, it provided better pain relief than parenteral opioid administration (Werawatganon & Charuluxanun, 2005 **Level I**; Wu et al, 2005 **Level I**; Guay, 2006 **Level I**; Nishimori et al, 2006 **Level I**; Marret et al, 2007 **Level I**).

One meta-analysis of systemic opioids via PCA versus epidural analgesia concluded that epidural analgesia provides better pain relief at rest and with movement after all types of surgery — with the exception of epidural analgesia using hydrophilic opioids only. The epidural group had a lower incidence of nausea/vomiting and sedation, but a higher incidence of pruritus, urinary retention and motor block (Wu et al, 2005 **Level I**). Another meta-analysis reviewed studies looking at the benefits of epidural analgesia in addition to general anaesthesia (Guay, 2006 **Level I**). It included a wide variety of surgical procedures and epidural regimens and reported a reduction in a range of adverse outcomes with epidural analgesia including reduced rate of arrhythmias, earlier extubation, reduced intensive care unit (ICU) stay, reduced stress hormone, cortisol and glucose concentrations as well as reduced incidence of renal failure, when local anaesthetics were used.

Improved pain relief with epidural local anaesthetic drugs led to increased PaO<sub>2</sub> levels and a decreased incidence of pulmonary infections and pulmonary complications overall when compared with systemic opioids (Ballantyne et al, 1998 **Level I**). Similar results were confirmed in a subsequent meta-analysis; however, it is of note that from 1971 to 2006 the baseline risk of pneumonia decreased from 34% to 12% in the opioid group, but remained at 8% in the epidural group, suggesting a decrease in relative benefit of epidural analgesia over time (Popping et al, 2008 **Level I**).

The benefits of epidural analgesia were confirmed when used in patients undergoing abdominal surgery. After a variety of different types of intra-abdominal surgery, pain relief was better but pruritus was also noted to be more likely with epidural analgesia than with PCA opioids (Werawatganon & Charuluxanun, 2005 **Level I**). The majority of trials included in the latter two reviews used thoracic epidural analgesia (TEA) with a local anaesthetic/opioid infusion.

After abdominal aortic surgery and in comparison with systemic opioid administration, epidural analgesia resulted in significantly lower pain scores in the first 3 postoperative days, and reduced duration of intubation and ventilation, rates of cardiovascular (CV) complications, myocardial infarction, acute respiratory failure, gastrointestinal (GI) complications and renal insufficiency (Nishimori et al, 2006 **Level I**). Benefits were found in particular when thoracic epidural catheters were used, but these did not translate into reduced mortality.

After colorectal surgery, epidural analgesia in comparison to systemic opioid analgesia reduced pain scores and duration of ileus, but had no effect on hospital stay; rates of pruritus,

urinary retention and hypotension were increased (Marret et al, 2007 **Level I**). A large retrospective cohort study of 12 817 patients after elective colectomy reported that postoperative epidural analgesia significantly reduced 7-day (OR 0.35) and 30-day (OR 0.54) mortality (Wu, Rowlingson et al, 2006 **Level III-2**).

After lung resection, postoperative epidural analgesia reduced 7-day (OR 0.39) and 30-day (OR 0.53) mortality significantly in a retrospective cohort study of 3500 patients (Wu, Sapirstein et al, 2006 **Level III-2**). TEA in patients after lobectomy resulted in better pain relief and pulmonary function compared with IV morphine (Bauer et al, 2007 **Level II**). When started preoperatively in comparison to postoperatively, TEA reduced the severity of acute post-thoracotomy pain, but not the incidence of chronic pain (Bong et al, 2005 **Level I**).

High TEA used for coronary artery bypass graft (CABG) surgery, resulted in reduced postoperative pain (both at rest and with activity), risk of dysrhythmias, pulmonary complications and time to extubation when compared with IV opioid analgesia; there were no differences in mortality or the rate of myocardial infarction (Liu et al, 2004 **Level I**). A later study confirmed better pain relief using TEA (continuous infusion) in CABG patients compared with IV morphine PCA, with improved pulmonary function for the first 2 days and decreased atelectasis (Tenenbein et al, 2008 **Level II**); another reported no difference in analgesia, morbidity or pulmonary function when patient-controlled TEA was compared with IV PCA (Hansdottir et al, 2006 **Level II**). High TEA also improved left ventricular function (Schmidt et al, 2005 **Level III-3**; Jakobsen et al, 2009 **Level III-3**) and myocardial oxygen availability (Lagunilla et al, 2006 **Level II**) in patients with ischaemic heart disease prior to CABG surgery, and partly normalised myocardial blood flow in response to sympathetic stimulation (Nygard et al, 2005 **Level III-3**). However, epidural analgesia in patients undergoing CABG surgery has not been shown to improve ischaemic outcome (Barrington, Kluger et al, 2005 **Level II**).

Continuous TEA compared with continuous intrathecal thoracic analgesia after abdominal cancer surgery resulted in similar efficacy and adverse effects (Mercadante et al, 2008 **Level II**).

Thoracic epidural analgesia in combination with NSAIDs and IV nutritional support after major abdominal surgery has been shown to prevent protein loss compared with epidural analgesia alone, or PCA with or without nutritional support (Barratt et al, 2002 **Level II**). Similarly, after colonic surgery, TEA increased the anabolic effect of amino acid infusions in diabetic patients (Lugli et al, 2008 **Level II**) and reduced whole body protein breakdown (Lattermann et al, 2007 **Level II**). However, although epidural anaesthesia/analgesia reduced insulin resistance in comparison to general anaesthesia/systemic analgesia in patients who were insulin resistant preoperatively, it did not affect insulin resistance in those who had no preoperative insulin resistance (Donatelli et al, 2007 **Level II**).

Lumbar epidural analgesia is widely used to provide analgesia after orthopaedic and vascular operations to the lower limbs and urological and other pelvic surgery.

After hip or knee replacement, epidural analgesia provides better pain relief than parenteral opioids, in particular with movement (Choi et al, 2003 **Level I**). Although epidural infusions of local anaesthetics alone or combined with opioids are better than opioids alone, there is insufficient evidence to make conclusions about other outcomes. Used in vascular surgery, lumbar epidural analgesia improves outcome by reducing incidence of graft occlusion (Tuman et al, 1991 **Level II**; Christopherson et al, 1993 **Level II**). However, these findings have not been confirmed by other investigators in retrospective reviews (Pierce et al, 1997 **Level IV**; Schunn et al, 1998 **Level IV**).

### **Level of administration**

Thoracic epidural analgesia is widely used for the treatment of pain after major abdominal and thoracic surgery. Administration of local anaesthetics into the thoracic epidural space resulted

in improved bowel recovery after abdominal surgery, while these benefits were not consistent with lumbar administration (Steinbrook, 1998; Jorgensen et al, 2000 **Level I**). If epidural analgesia was extended for more than 24 hours, a further benefit was a significant reduction in the incidence of postoperative myocardial infarction (Beattie et al, 2001 **Level I**). Benefits of epidural analgesia after abdominal aortic surgery were found in particular with TEA (Nishimori et al, 2006 **Level I**). A comparison of TEA and lumbar epidural administration in patients undergoing gynaecological surgery showed that TEA provided better pain relief only when the incision extended above the umbilicus and led to less motor block but more pruritus (Richman et al, 2007 **Level II**).

In patients with multiple traumatic rib fractures, provision of TEA with local anaesthetics has been shown to reduce the duration of ventilation compared with other forms of analgesia (including lumbar epidural analgesia); although mortality and length of ICU stay was not different in pooled analysis of all routes of epidural administration versus parenteral opioids, and hypotension was more frequent in the epidural groups when TEA with local anaesthetics was used (Carrier et al, 2009 **Level I**). In one study, the risk of nosocomial pneumonia was reduced by TEA compared with parenteral opioids (Bulger et al, 2004 **Level II**).

## 7.2.2 Drug used for epidural analgesia

Differences in effects and adverse effects can be found with the local anaesthetics, opioids and various adjuvant drugs used in epidural analgesia.

### **Local anaesthetics**

For epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Scott et al, 1995 **Level II**; Schug et al, 1996 **Level II**). Therefore, most investigators compare infusions of bupivacaine or levobupivacaine at 0.1% or 0.125% with ropivacaine 0.2%, which removes any imbalance in comparative potency.

For more information on differences in efficacy and adverse effects between the local anaesthetics used for epidural analgesia see Section 5.1.2.

### **Opioids**

Opioids alone via the epidural route seem to be of limited benefit. In particular, when administered via a thoracic approach, opioids failed to demonstrate any advantage over parenteral opioids except for a slight reduction in the rate of atelectasis (Ballantyne et al, 1998 **Level I**); there is no benefit on bowel recovery (Steinbrook, 1998; Jorgensen et al, 2000 **Level I**). On the basis of the available studies, the benefits of administering lipophilic opioids alone by the epidural route would appear to be marginal, or unproven in the case of upper abdominal surgery, and in many situations will not outweigh the risks of the more invasive route of administration (for detailed discussion see Wheatley et al, 2001 and Section 5.2.1).

For information on the epidural use of morphine, extended-release morphine, pethidine, fentanyl, alfentanil, sufentanil, diamorphine and hydromorphone see Section 5.2.1.

### **Local anaesthetic-opioid combinations**

Combinations of low concentrations of local anaesthetic agents and opioids have been shown to provide consistently superior pain relief compared with either of the drugs alone (Curatolo et al, 1998 **Level I**). Addition of fentanyl to a continuous epidural infusion of ropivacaine reduced the rate of regression of sensory block (Kanai et al, 2007 **Level II**) and decreased the discontinuation of postoperative epidural infusion due to lack of efficacy (Scott et al, 1999 **Level II**).

For more information on the epidural use of different local anaesthetic-opioid drug combinations see Section 5.2.1.

## Adjuvant drugs

The efficacy of adding of adjuvant drugs such as adrenaline (epinephrine), clonidine, ketamine, midazolam, neostigmine and magnesium to solutions used for epidural analgesia has also been investigated (see Section 5.3).

### 7.2.3 Patient-controlled epidural analgesia

The use of patient-controlled epidural analgesia (PCEA) has become increasingly popular; it is based on similar concepts as for other patient-controlled techniques.

#### Comparison with continuous epidural infusions

A meta-analysis comparing PCEA, continuous epidural infusions and IV PCA opioids after surgery showed that both forms of epidural analgesia (with the exception of hydrophilic opioid-only epidural regimens) provided better pain relief with rest and with activity than PCA opioids, but that analgesia with a continuous epidural infusion was superior to PCEA, although the incidence of nausea, vomiting and motor block was higher (Wu et al, 2005 **Level I**).

However, results from other more recent studies are conflicting. In a large study looking specifically at patients after colonic resection, PCEA was superior to continuous epidural infusion with regard to pain control, requirements for top-ups and systemic analgesia as well as patient satisfaction (Nightingale et al, 2007 **Level II**). In contrast, comparisons of PCEA and continuous epidural infusions for pain relief after thoracotomy using both high (5 mg/mL) and low (1.5 mg/mL) concentrations of levobupivacaine showed no differences in quality of analgesia, morphine consumption or satisfaction; more patients in the high concentration continuous epidural infusion group had significant motor blockade (Dernedde et al, 2006 **Level II**).

For pain relief during labour, a comparison of demand dose-only PCEA, PCEA with a continuous infusion, and a continuous epidural infusion only during labour, showed that dose-only PCEA resulted in less total epidural dose compared with the other modalities; no differences were noted with respect to pain scores, motor block, duration of labour, number of staff interventions, delivery outcome, and maternal satisfaction score (Vallejo et al, 2007 **Level II**).

#### Concurrent background (continuous) infusions

The addition of a continuous background infusion to PCEA using bupivacaine and fentanyl following gastrectomy resulted in significantly better dynamic pain scores, higher total doses and a greater incidence of pruritus than PCEA-bolus dose only (Komatsu et al, 1998 **Level II**). The use of a night-time-only infusion with PCEA bupivacaine-fentanyl, also in postgastrectomy patients, resulted in better sleep, but total cumulative doses were similar and pain scores were only better in the morning of the second postoperative day (Komatsu et al, 2001 **Level II**).

However, pain relief is not always improved. After lower abdominal surgery there was no difference in pain scores, but higher total cumulative doses and incidence of side effects when a background infusion was added to PCEA with ropivacaine and fentanyl (Wong et al, 2000 **Level II**). The addition of a background infusion to bupivacaine-fentanyl PCEA did not improve pain relief after pelvic reconstruction (Nolan et al, 1992 **Level II**).

In a systematic review of PCEA in labour analgesia, the use of a continuous background epidural infusion combined with PCEA resulted in improved maternal analgesia and reduced unscheduled clinician interventions (Halpern & Carvalho 2009, **Level I**).

## **Drugs used in postoperative patient-controlled epidural analgesia**

The drugs used for PCEA are the same as those used for continuous epidural infusions (see also Section 5). Generalisations about the efficacy of different drugs and drug combinations administered via PCEA are difficult because of the wide variety of analgesic agents and concentrations used in the various studies.

### **7.2.4 Adverse effects**

#### **Neurological injury**

Permanent neurological damage is the most feared complication of epidural analgesia.

A retrospective survey from Sweden put the risk of a severe neurological complication after obstetric epidural analgesia at 1:25 000 and for all other patients at 1:3600; 67% of events resulted in permanent neurological deficit (Moen et al, 2004 **Level IV**). It also identified osteoporosis as a previously neglected risk factor. A review of data from publications reporting adverse events after obstetric epidural analgesia reported a risk estimate of 1: 240 000 for persistent neurological injury and 1:6700 for transient (resolved within one year) neurological symptoms (Ruppen et al, 2006a **Level IV**).

A review of data from published studies of the risk of neurological injury associated with epidural and other regional anaesthesia and analgesia differentiated between the risk of permanent (neurological deficit lasting more than 12 months) neurological injury and transient neuropathy (Brull et al, 2007 **Level IV**). This review focussed on adverse neurological sequelae associated with the technique and did not address the overall risk of epidural haematoma or abscess, nor did it differentiate between obstetric and non-obstetric neuraxial block outcomes. The incidence of transient neuropathy (radiculopathy) after epidural anaesthesia was estimated to be 2.19:10 000. The risk of permanent neurological injury was less and the incidences reported in the studies included in this review ranged from 0 to 7.6:10 000. The rates of paraplegia and cauda equina syndrome associated with epidural anaesthesia were estimated to be 0.09:10 000 and 0.23:10 000 respectively (Brull et al, 2007 **Level IV**).

A project in the United Kingdom assessed the incidence of neurological complications in an estimated 97 925 adult patients with perioperative epidural catheters (Cook et al, 2009 **Level IV**). Depending on the inclusion or exclusion of cases with unlikely causation, pessimistic and optimistic data were published. The incidence of permanent injury was pessimistically assessed as 17.4 per 100,000 (95% CI 7.2 to 27.8; 1 in 5800) and optimistically as 8.2 per 100,000 (95% CI 3.5 to 16.1; 1 in 12 200). Laminectomy was performed with an incidence of 12.3 per 100 000 cases (95% CI 6.3 to 21.4, 1 in 8100). Paraplegia was caused in 6.1 per 100 000 (95% CI 2.2 to 13.3; 1 in 16,400) in the pessimistic and in 1.0 per 100,000 (95% CI 1.0 to 5.7; 1 in 100,000) in the optimistic model.

The worst-case estimate for persistent neurological injury after epidural anaesthesia for vascular and cardiothoracic surgery is 1 in 4600 based on a meta-analysis of case series with an event rate of zero in 14 105 patients; the risk of transient neurological injury was 1 in 1 700 (Ruppen et al, 2006b **Level IV**).

Audit data from a single (non-obstetric) tertiary institution showed that 8210 epidural catheters were inserted over a 16-year period for postoperative pain relief and that two spinal haematomas and six epidural abscesses were diagnosed during this time; only one patient (with an epidural abscess) required surgical decompression and no patient suffered any long-term neurological loss (Cameron et al, 2007 **Level IV**).



The incidence of transient neuropathy after epidural analgesia in large case series was in the range of 0.013 to 0.023% (Xie & Liu, 1991 **Level IV**; Tanaka et al, 1993 **Level IV**; Auroy et al, 1997 **Level IV**).

### **Epidural haematoma**

A major concern is the development of an epidural haematoma with subsequent, potentially permanent, spinal cord injury. A review including case series involving over 1 335 000 patients with epidural analgesia reported seven cases of haematoma (0.0005%) (Wulf, 1996 **Level IV**). On the basis of this case series the possible incidence is in the order of 1 in 100 000 at the upper limit of the 95% confidence interval. The Swedish case series quoted above puts the overall risk of epidural haematoma after epidural blockade at 1 in 10 300 (Moen et al, 2004 **Level IV**). An even higher incidence of epidural haematoma (1:3100) has been estimated for epidural analgesia in association with inappropriate low molecular weight heparin (LMWH) dose regimens (Horlocker et al, 2003) (see Section 7.4).

A review of data from publications reporting adverse events after obstetric epidural analgesia reported a risk estimate of 1:168 000 for epidural haematoma (Ruppen et al, 2006a **Level IV**).

A meta-analysis of the risks of epidural haematoma associated with epidural anaesthesia/analgesia in cardiac, vascular and thoracic surgery patients concluded that the maximum risks of epidural haematoma were 1:1700, 1:1700 and 1:1400 respectively (Ruppen et al, 2006b **Level IV**). However, this was a calculated risk only; there were actually no cases of epidural haematoma reported in the studies (14 105 patients) used in this analysis.

In another analysis of a case series after cardiac surgery, the risk of epidural haematoma was calculated at 1:12 000 (95% CI 1:2100 to 1:68 000) — comparable to an obstetric population. It was described as being in the same risk range as receiving a wrong blood product (or the yearly risk of having a fatal traffic accident in a Western country) (Bracco & Hemmerling, 2007 **Level IV**).

Early diagnosis and, if indicated, immediate decompression (less than 8 hours after the onset of neurological signs) increases the likelihood of partial or good neurological recovery (Horlocker et al, 2010 **Level IV**).

### **Epidural abscess**

Serious neuraxial infections following epidural anaesthesia have previously been reported as rare. However, prospective studies have found rates in the range of 0.015% to 0.05% (Kindler et al, 1996 **Level IV**; Rygnestad et al, 1997 **Level IV**; Wang et al, 1999 **Level IV**). It is of note that in the studies with these high incidences, patients had long durations of epidural catheterisation; the mean duration in patients with an epidural space infection was 11 days; no infection occurred in any patient whose catheter was in situ for less than 2 days and the majority of patients were immunocompromised (Wang et al, 1999 **Level IV**).

Only 5.5% of 915 cases of epidural abscess published between 1954 and 1997 developed following epidural anaesthesia and analgesia; 71% of all patients had back pain as the initial presenting symptom and only 66% were febrile (Reihnsaus et al, 2000 **Level IV**). The classic triad of symptoms (back pain, fever and neurological changes) was present in only 13% of patients with an epidural abscess (in a study unrelated to epidural catheterisation); diagnostic delays occurred in 75% of these patients and such delays led to a significantly higher incidence of residual motor weakness (Davis et al, 2004 **Level IV**).

Audit data from the study referred to above (Cameron et al, 2007 **Level IV**) showed that of the 8210 patients with epidural catheters over the period of 16 years, six developed epidural abscesses. Only one of these required surgical decompression and they did not suffer any long-term neurological loss. The authors stress the importance of appropriate patient

monitoring and early diagnosis using MRI. In five of their six patients diagnosed with an epidural abscess, both fever and epidural insertion site infection were present. They therefore suggested that MRI investigation may be warranted if this combination is present and that urgent investigation is especially indicated if there is a third sign that could indicate an abscess, such as back pain or neurological change. If the diagnosis of epidural abscess can be made before the onset of any neurological deficit, conservative treatment (antibiotics only) may be effective (Cameron et al, 2007). The presence of severe or increasing back pain, even in the absence of a fever, may indicate epidural space infection and should be investigated promptly.

A review of data from publications reporting adverse events after obstetric epidural analgesia reported a risk estimate of 1: 145 000 for epidural space infection (Ruppen et al, 2006a **Level IV**). Bacterial colonisation of epidural catheter tips is reported to occur in 0% to 28% of patients. (Simpson et al, 2000 **Level IV**; Steffen et al, 2004 **Level IV**; Mishra et al, 2006 **Level IV**; Yuan et al, 2008 **Level IV**). The most common organism cultured from the catheter tips was coagulase-negative staphylococcus.

Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo or povidone-iodine-impregnated dressings reduced the incidence of catheter colonisation (Ho & Litton, 2006 **Level I**).

An *in vitro* comparison of the antibacterial activity of drugs used in epidural solutions showed that the minimal inhibitory concentration of bupivacaine for *Staphylococcus aureus*, *Enterococcus faecalis* and *Escherichia coli* (growth of *Pseudomonas aeruginosa* was not affected at any of the concentrations investigated) was at concentrations between 0.125% and 0.25%; levobupivacaine and ropivacaine showed no activity against *Staphylococcus aureus*, *Enterococcus faecalis* and *Pseudomonas aeruginosa*, even at the highest concentrations tested, and minimal activity against *Escherichia coli* (minimum inhibitory concentrations 0.5% and 1% respectively); and the addition of fentanyl, clonidine and adrenaline did not improve antibacterial activity (Coghlan et al, 2009 **Level III-2**).

A comprehensive review of infectious complications associated with central neuraxial and peripheral nerve blockade, including epidemiology, factors affecting bacterial colonisation of the epidural catheter as well as use in febrile, infected and immunocompromised patients was published by Horlocker and Wedel (Horlocker & Wedel, 2008).

### **Respiratory depression**

The incidence of respiratory depression with epidural analgesia depends on the criteria used to define respiratory depression. In a review of published case series and audit data, the reported incidence of respiratory depression ranged from 1.1 (0.6% to 1.9%) to 15.1 (5.6% to 34.8%) using respiratory rate and oxygen saturation, respectively, as indicators (see Section 4.1.3 for comments on respiratory rate as an unreliable indicator of respiratory depression); this was very similar to the incidence reported for PCA (Cashman & Dolin, 2004 **Level IV**).

### **Hypotension**

The incidence of hypotension depends on the dose of local anaesthetic and criteria used to define hypotension. In the same review as above, the reported incidence of hypotension was 5.6 (3.0% to 10.2%) (Cashman & Dolin, 2004 **Level IV**). It is often the result of hypovolaemia (Wheatley et al, 2001).

### **Postdural puncture headache**

Headache following dural puncture may occur with an incidence of 0.4% to 24%. Postdural puncture headache (PDPH) is classically postural in nature and is more common in patients

under 50 years of age and in the parturient. Up to 90% of cases improve spontaneously within 10 days (Candido & Stevens, 2003).

For discussion of possible prevention and treatment see Section 9.6.5.

### **Treatment failure**

Epidural analgesia may not always be successful due to a number of factors including catheter malposition or displacement, or technical and patient factors resulting in an inability to achieve effective analgesia. Intolerable side effects may also be an indication for premature discontinuation. In a large prospective audit, 22% of patients had premature termination of postoperative epidural infusions: the most common causes were dislodgement (10%) and inadequate analgesia (3.5%), sensory or motor deficit (2.2%). Most of these failures occurred on or after postoperative day 2 (Ballantyne et al, 2003 **Level IV**). These outcomes supported similar findings by Burstal et al (Burstal et al, 1998 **Level IV**) and reinforce the need for strategies to support epidural analgesia as part of a multimodal approach to acute pain management.

### **Other**

There has been concern among surgeons about increased risk of anastomotic leakage after bowel surgery due to the stimulating effects of epidural administration of local anaesthetics; so far there is no evidence to support these claims (Holte & Kehlet, 2001 **Level I**).

#### **Key messages**

1. Thoracic epidural analgesia for open abdominal aortic surgery reduces the duration of tracheal intubation and mechanical ventilation, as well as the incidence of myocardial infarction, acute respiratory failure, gastrointestinal complications and renal insufficiency (**N**) (**Level I** [Cochrane]).
2. For all types of surgery, epidural analgesia provides better postoperative pain relief compared with parenteral (including PCA) opioid administration (**S**) (**Level I** [Cochrane review]); except epidural analgesia using a hydrophilic opioid only (**N**) (**Level I**).
3. High thoracic epidural analgesia used for coronary artery bypass graft surgery reduces postoperative pain, risk of dysrhythmias, pulmonary complications and time to extubation when compared with IV opioid analgesia (**N**) (**Level I**).
4. Epidural local anaesthetics improve oxygenation and reduce pulmonary infections and other pulmonary complications compared with parenteral opioids (**S**) (**Level I**).
5. Thoracic epidural analgesia improves bowel recovery after abdominal surgery (including colorectal surgery) (**S**) (**Level I**).
6. Thoracic epidural analgesia extended for more than 24 hours reduces the incidence of postoperative myocardial infarction (**U**) (**Level I**).
7. Epidural analgesia is not associated with increased risk of anastomotic leakage after bowel surgery (**U**) (**Level I**).
8. Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo- or povidone-iodine-impregnated dressings reduce the incidence of catheter colonisation (**N**) (**Level I**).
9. The use of continuous background epidural infusion combined with PCEA results in improved maternal analgesia and reduced unscheduled clinician interventions (**N**) (**Level I**).
10. Thoracic epidural analgesia reduces need for ventilation in patients with multiple rib fractures (**S**) (**Level I**) and reduces incidence of pneumonia (**U**) (**Level II**).

11. The combination of thoracic epidural analgesia with local anaesthetics and nutritional support leads to preservation of total body protein after upper abdominal surgery (**U**) (**Level II**).
12. The risk of permanent neurological damage in association with epidural analgesia is very low; the incidence is higher where there have been delays in diagnosing an epidural haematoma or abscess (**S**) (**Level IV**).
13. Immediate decompression (within 8 hours of the onset of neurological signs) increases the likelihood of partial or good neurological recovery (**U**) (**Level IV**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- The provision of epidural analgesia by continuous infusion or patient-controlled administration of local anaesthetic-opioid mixtures is safe on general hospital wards, as long as supervised by an anaesthesia-based pain service with 24-hour medical staff cover and monitored by well-trained nursing staff (**U**).
- Magnetic resonance imaging investigation may be warranted if patients who have had an epidural catheter inserted develop a fever and infection at the catheter insertion site; urgent investigation is especially indicated if other signs are present that could indicate an abscess, such as back pain or neurological change (**N**).

## 7.3 INTRATHECAL ANALGESIA

### 7.3.1 Drugs used for intrathecal analgesia

#### **Local anaesthetics**

Local anaesthetics given intrathecally provide only short-term postoperative analgesia. The use of spinal microcatheters (<24 gauge) for postoperative infusions of local anaesthetics became controversial when multiple cases of cauda equina syndrome were reported (Bevacqua, 2003). See also Section 5.1.3.

#### **Opioids**

Intrathecal opioids have been used for surgical procedures ranging from lower limb orthopaedic surgery to CABG because of their ability to provide prolonged postoperative analgesia following a single dose. Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal intrathecal doses (Hodgson et al, 1999 **Level IV**).

Intrathecal morphine produces analgesia lasting 12 hours or more. Side effects include respiratory depression, nausea, vomiting and pruritus. Early clinical studies used very high intrathecal morphine doses (ie 0.5 mg or more), however adequate postoperative analgesia with fewer adverse effects may be obtained with significantly less morphine — although at lower doses there is not a clear dose-response relationship for some side effects or analgesia (Meylan et al, 2009 **Level I**). A meta-analysis comparing intrathecal morphine doses of less than 300 mcg, equal to or greater than 300 mcg, and placebo reported a greater risk of respiratory depression with the higher doses of morphine (there was no increased risk with lower morphine doses) and while the incidence of pruritus was increased for all doses, the risk of nausea and vomiting was increased only in those patients given less than 300 mcg morphine (Gehling & Tryba, 2009 **Level I**).

A prospective study of 5969 patients given intrathecal morphine (200 to 800 mcg) for pain relief following a range of surgical procedures reported a high degree of patient satisfaction and effective analgesia in the first 24 hours. The incidence of pruritus was 37%, nausea and vomiting 25% and respiratory depression 3% ( $\text{PaCO}_2 > 50$  mmHg and/or respiratory rate  $< 8$ ) (Gwartz et al, 1999 **Level IV**).

In patients having abdominal, cardiothoracic or spinal surgery, intrathecal morphine (100 to 500 mcg) reduced pain scores by 1 to 2 cm (using a 10 cm visual analogue scale) for at least 24 hours following the procedure, with morphine-sparing being more pronounced after abdominal than cardiothoracic surgery (Meylan et al, 2009 **Level I**). Intrathecal morphine 50 to 200 mcg  $\pm$  clonidine after prostatic surgery (Brown et al, 2004 **Level II**), 300 mcg after colorectal surgery (Beaussier et al, 2006 **Level II**), and 500 mcg plus fentanyl 150 mcg after liver resection (Roy et al, 2006 **Level II**) also resulted in better analgesia and lower opioid requirements than morphine PCA during the first 24 hours postoperatively. After CABG surgery, intrathecal morphine reduced systemic morphine use and global pain scores, but increased pruritus; there were no significant effects on mortality, myocardial infarction, dysrhythmias, nausea and vomiting, or time to tracheal extubation (Liu et al, 2004 **Level I**).

Compared with a continuous epidural infusion of ropivacaine after liver resection, patients given intrathecal morphine 200 mcg had higher IV PCA opioid requirements in the postoperative period and more nausea and pruritus; there was no difference in pain relief (De Pietri et al, 2006 **Level II**).

For comparisons of different opioids and doses used for intrathecal analgesia see Section 5.2.1.

### **Side effects**

Typical side effects of intrathecal opioids include nausea and vomiting, pruritus and delayed respiratory depression. The definition of 'respiratory depression' in different investigations often lacks uniformity with a quarter of the studies cited in a review using respiratory rate as the primary marker (Ko et al, 2003). Patients may be hypoxic or hypercapnic with a normal respiratory rate (Bailey et al, 1993 **Level IV**), while others may be able to maintain normocarbida with a lower respiratory rate (Boezaart et al, 1999 **Level II**). In a volunteer study, clinical signs or symptoms including respiratory rate, sedation and pupil size, did not reliably indicate hypoventilation or hypoxaemia, unlike peripheral pulse oximetry (Bailey et al, 1993 **Level IV**); although desaturation itself is a late indicator when supplemental oxygen is being administered (Shapiro et al, 2005 **Level IV**). See Section 4.1 for the use of sedation as a better clinical early indicator of respiratory depression.

Respiratory depression occurs in up to 1.2% to 7.6% of patients (Meylan et al, 2009 **Level I**) given intrathecal morphine. When measured in opioid-naive volunteers, respiratory depression peaked at 3.5 to 7.5 hours following intrathecal morphine at 200 to 600 mcg doses (Bailey et al, 1993 **Level IV**). Volunteers given 600 mcg had significant depression of the ventilatory response to carbon dioxide up to 19.5 hours later.

When combined with local anaesthetic for analgesia following Caesarean section, the rate of respiratory depression with intrathecal opioids (all opioids and all doses) was low and not significantly different from controls, with a NNH of 476 for respiratory depression (Dahl et al, 1999 **Level I**). In patients following major surgery, the incidence of respiratory depression was increased with intrathecal morphine over control treatment (IV PCA morphine) (OR 7.86; 95% CI 1.54 to 40.3) (Meylan et al, 2009 **Level I**). Clinically detected respiratory depression in the 24 hours following 0.15 mg intrathecal morphine for Caesarean section was noted in 0.26% of a large sample (Kato et al, 2008 **Level IV**).

Pruritus is common after intrathecal morphine, being reported in up to 37% of patients (Gwirtz et al, 1999 **Level IV**), although the number requiring treatment was lower (5.1%). This rate was significantly higher than that for patients receiving IV PCA morphine (OR 3.85; 95% CI 2.40 to 6.15) (Meylan et al, 2009 **Level I**). Pruritus can be difficult to treat and a variety of agents have been used including low dose naloxone, nalbuphine, ondansetron, propofol and antihistamines. The itch is thought to be caused by stimulation of spinal and supraspinal mu-opioid receptors. Nalbuphine (Charuluxananan et al, 2003 **Level II**) and ondansetron (Charuluxananan et al, 2003 **Level II**; Tzeng et al, 2003 **Level II**; Pirat et al, 2005 **Level II**) were effective in reducing spinal opioid-induced pruritus, although this has not been consistently reported (Sarvela et al, 2006 **Level II**; Siddik-Sayyid et al, 2007 **Level II**).

Postoperative nausea and vomiting (PONV) is also common after intrathecal morphine with incidences reported at 30% and 24% respectively, although this rate was similar to IV PCA morphine (Meylan et al, 2009 **Level I**). Ondansetron or scopolamine was equally effective in reducing emesis with intrathecal morphine analgesia for Caesarean section, although scopolamine use was associated with more anticholinergic side effects (Harnett et al, 2007 **Level II**). The combination of ondansetron with either dexamethasone or droperidol had a better antiemetic effect after gynaecological surgery compared with droperidol plus dexamethasone (Sanchez-Ledesma et al, 2002 **Level II**); although dexamethasone plus droperidol was superior to either alone (Wu et al, 2007 **Level II**).

In parturients, reactivation of oral herpes simplex labialis was more frequent (38%) following intrathecal morphine for labour analgesia than IV PCA morphine (16.6%) (Davies et al, 2005 **Level II**).

### **Adjuvant drugs**

A variety of adjuvant drugs has been used with intrathecal analgesia, including clonidine, ketamine, neostigmine and midazolam. Many drugs are not licensed for use as spinal analgesic agents; however adequate evidence from the literature may make their use acceptable. For more detail see Section 5.3.

## **7.3.2 Combined spinal-epidural versus epidural analgesia in labour**

Combined spinal epidural (CSE) analgesia provided faster onset of analgesia compared with epidural analgesia. However, as CSE did not improve satisfaction or mobilisation, and increased the risk of pruritus, clinical advantages over epidural analgesia (either traditional or low dose) are limited (Simmons et al, 2007 **Level I**) (see Section 11.1). Traditional (higher-dose) epidural analgesia, unlike low-dose epidurals, was associated with increased urinary retention compared with CSE (Simmons et al, 2007 **Level I**).

### **Key messages**

1. Intrathecal morphine offers improved analgesia and opioid-sparing for up to 24 hours especially following abdominal surgery (**S**) (**Level I**).
2. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**N**) (**Level I**).
3. After major surgery, the incidence of respiratory depression and pruritus is higher with intrathecal morphine compared with IV PCA opioids, but there is no difference in the incidence of nausea and vomiting (**N**) (**Level I**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (**U**).
- The absence of consistent dose-responsiveness to the efficacy of intrathecal opioids or the adverse event rate, suggests that the lowest effective dose should be used in all circumstances (**N**).

## 7.4 REGIONAL ANALGESIA AND CONCURRENT ANTICOAGULANT MEDICATIONS

### 7.4.1 Neuraxial blockade

The low event rate of epidural haematoma makes RCTs and subsequent evidence-based statements impossible. Information comes only from case reports and case series. An American Society of Regional Anesthesia and Pain Medicine (ASRA&PM) Practice Advisory publication provides a good overview of and guidance on neurological complications in regional anaesthesia (Neal et al, 2008 **Level IV**). The ASRA&PM guidelines on regional anaesthesia in patients receiving antithrombotic or thrombolytic therapy have also been updated (Horlocker et al, 2010).

Such information suggests that the incidence is possibly smaller than that of spontaneous epidural haematoma. Between 1962 and 1992, 326 case reports of spontaneous epidural haematoma were published (Schmidt & Nolte, 1992), while between 1966 and 1996 only 51 cases of epidural haematoma following epidural anaesthesia or analgesia were reported (Wulf, 1996).

Anticoagulation (48% of cases) was the most important risk factor for epidural haematoma following insertion of an epidural needle/catheter, followed by coagulopathy (38% of cases) (Wulf, 1996 **Level IV**). This was confirmed by the series of epidural haematomas that followed epidural anaesthesia/analgesia in combination with inappropriate low molecular weight heparin (LMWH) regimens in the USA, where the incidence was reported to be 1 in 3,000 (Horlocker et al, 2003).

In view of the increased risk of epidural haematoma associated with the concurrent use of epidural analgesia and anticoagulants, ASRA&PM published updated evidence-based guidelines on regional anaesthesia in patients receiving antithrombotic or thrombolytic therapy (Horlocker et al, 2010). These statements have to be seen as 'a panel of experts' best faith efforts to offer reasonable pathways for patient management' (Bergqvist et al, 2003) to provide safe and quality patient care while allowing for clinical differences based on individual situations. It is recognised that variances from recommendations outlined in the ASRA&APM guidelines 'may be acceptable based on the judgement of the responsible anesthesiologist' (Horlocker et al, 2010). That is, they will not substitute for an individual risk/benefit assessment of every patient by the individual anaesthetist.

The most relevant statements are summarised as follows (Horlocker et al, 2010):

*Antiplatelet medications* — NSAIDs alone do not significantly increase the risk of spinal haematoma, but should be regarded as a risk factor if combined with other classes of anticoagulants. In such situations COX-2 inhibitors should be considered. Recommended time intervals between discontinuation of other antiplatelet medications and neuraxial blockade



are 4 to 8 hours for eptifibatide and tirofiban, 24 to 48 hours for abciximab, 7 days for clopidogrel and 14 days for ticlopidine.

*Unfractionated SC heparin* — thromboprophylaxis with SC heparin given *twice-daily* is not a contraindication to neuraxial blockade. To identify heparin-induced thrombocytopenia, a platelet count should be done prior to removal of an epidural catheter in patients who have had more than 4 days of heparin therapy. Epidural catheters should be removed a minimum of 6 hours after the last heparin dose and not less than 2 hours before the next dose.

Safety in patients receiving total daily doses of greater than 10 000 units, or if doses are given more often than twice a day, has not yet been established.

*Unfractionated IV heparin* — intraoperative anticoagulation with IV heparin should start no sooner than 1 hour after placement of the epidural or spinal needle. Epidural catheters should be removed 2–4 hours after the last heparin dose. A bloody tap may increase the risk, but there are insufficient data to support cancellation of a case. Careful patient monitoring should be continued postoperatively.

*Low molecular weight heparin* — Epidural catheter placement should occur at least 10–12 hours after standard prophylactic *once-daily* LMWH doses. The first postoperative dose of LMWH dose should be given 6 to 8 hours after surgery and subsequent doses every 24 hours after that. The epidural catheter should be removed at least 10–12 hours after the last dose of LMWH and the next dose should not be given until at least 2 hours after removal. Concurrent administration of other drugs that may affect haemostasis (eg antiplatelet drugs) should be avoided.

Epidural catheters should be removed at least 2 hours before *twice-daily* LMWH dose regimens are started.

*Oral anticoagulants (warfarin)* — Established warfarin therapy should be discontinued at least 4 to 5 days prior to neuraxial blockade and the INR normalised. Preoperative initiation of warfarin therapy requires an INR check prior to neuraxial blockade if a single dose of warfarin 5 mg was given more than 24 hours preoperatively or a second dose was given. INR should also be checked prior to removal of indwelling epidural catheters if warfarin was administered more than 36 hours preoperatively. An INR < 1.5 is a value estimated to be a safe level for removal, while an INR > 3 requires withholding or reducing warfarin therapy before the catheter is removed.

*Fibrinolysis and thrombolysis* — Patients receiving fibrinolytic or thrombolytic drugs should not undergo neuraxial blockade except in exceptional circumstances; no data are available on a safe time interval after use of such drugs. No definite recommendations are given for the removal of neuraxial catheters after initiation of such therapy, although determination of fibrinogen level might be a useful guide in such situations.

*Herbal therapy* — Although garlic, ginkgo and ginseng have effects on haemostasis, there are currently no specific concerns about their use with neuraxial blockade.

*New anticoagulants* — The situation with regard to the newer anticoagulants remains unclear. Recommendations are to avoid neuraxial techniques with thrombin inhibitors present and to use extreme caution in association with fondaparinux, avoiding indwelling catheters.

Recommendations for newer anticoagulants and antiplatelet drugs are also discussed in other reviews (Vitin et al, 2008; Rosencher et al, 2007; Kopp & Horlocker, 2008).

## 7.4.2 Plexus and other peripheral regional blockade

Significant blood loss rather than neurological deficit seems to be the main risk when plexus or other regional blocks are performed in patients taking anticoagulant medications (Horlocker et al 2003). However, a case series of bleeding complications associated with lumbar plexus blocks and, femoral and sciatic catheters and perioperative anticoagulants suggests that caution is appropriate (Bickler et al, 2006 **Level IV**; Horlocker et al, 2003). The previously quoted evidence-based ASRA&PM guidelines conclude that recommendations for neuraxial block be followed for patients receiving deep plexus or peripheral blocks (Horlocker et al, 2010)

### Key messages

1. Anticoagulation is the most important risk factor for the development of epidural haematoma after neuraxial blockade (**U**) (**Level IV**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Consensus statements of experts guide the timing and choice of regional anaesthesia and analgesia in the context of anticoagulation, but do not represent a standard of care and will not substitute the risk/benefit assessment of the individual patient by the individual anaesthetist (**U**).

## 7.5 OTHER REGIONAL AND LOCAL ANALGESIC TECHNIQUES

### 7.5.1 Continuous peripheral nerve blockade

Continuous peripheral nerve blockade (CPNB) extends the duration of postoperative analgesia beyond the finite period that single injection techniques provide. Important technical issues include the technique used for nerve location, the type of continuous catheter equipment, and local anaesthetic infusion choice and management.

Compared with opioid analgesia, CPNB (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as the incidence of nausea, vomiting, pruritus and sedation (Richman et al, 2006 **Level I**).

Compared with general anaesthesia, peripheral nerve block (PNB) was associated with increased induction time, improved analgesia, a decreased requirement for opioids in the postanesthesia care unit (PACU); but there was no significant reduction in PACU discharge time (Liu et al, 2005 **Level I**). However, it is not clear what proportion of patients received single-shot versus CPNB.

#### Upper limb

##### Interscalene

Continuous interscalene analgesia improved pain relief and patient satisfaction and reduced opioid-related side effects compared with IV PCA (Borgeat et al, 1997 **Level II**; Borgeat et al, 1998 **Level II**; Borgeat et al, 2000 **Level II**). Continuous interscalene analgesia also provided better analgesia and reduced opioid requirements following shoulder surgery compared with single injection interscalene blockade (Klein, Grant et al, 2000 **Level II**; Ilfeld et al, 2003 **Level II**; Kean et al, 2006 **Level II**) with higher patient satisfaction (Kean et al, 2006 **Level II**). Compared with a single-injection interscalene block, a 2-day interscalene infusion at home after shoulder surgery was

opioid-sparing and improved pain relief, sleep and patient satisfaction (Mariano et al, 2009 **Level II**). Continuous interscalene nerve blockade compared with placebo following shoulder arthroplasty also reduced time to discharge readiness and was associated with a greater degree of shoulder movement (Ilfeld et al, 2006 **Level II**).

### **Axillary**

There is no consistent evidence that continuous axillary analgesia is better than a single axillary brachial plexus injection of a long-acting local anaesthetic. After elective hand surgery continuous axillary infusions of 0.1%, 0.2% ropivacaine or saline were not sufficient to adequately treat pain without the addition of adjunct agents (Salonen et al, 2000 **Level II**).

### **Infraclavicular**

Use of an infraclavicular brachial plexus catheter in patients at home after upper limb surgery led to better pain relief, patient satisfaction and sleep compared with oral opioid analgesia (Ilfeld, Morey & Enneking, 2002 **Level II**).

The incidence of insensate limb was higher when smaller volumes of 0.4% ropivacaine were used compared with higher volumes of 0.2%, despite no difference in the total amount of local anaesthetic (mg) used; there was no difference in analgesia but satisfaction scores were higher in patients who received the 0.2% infusion (Ilfeld, Le et al, 2009 **Level II**).

### **Lower limb**

Peripheral nerve blocks, including CPNB, after major knee surgery, provided postoperative analgesia that was comparable with that obtained with epidural techniques but with an improved side-effect profile (Fowler et al, 2008 **Level I**).

### **Femoral nerve and fascia iliaca blocks**

Continuous femoral nerve blockade (often called a '3 in 1' block as a catheter placed in the femoral nerve sheath may allow local anaesthetic to reach both the lateral femoral cutaneous and obturator nerves as well as the femoral nerve) provided postoperative analgesia and functional recovery that was better than IV PCA morphine and comparable with epidural analgesia following total knee arthroplasty (Singelyn et al, 1998 **Level II**; Capdevila et al, 1999 **Level II**; Barrington, Olive et al, 2005 **Level II**). It decreased nausea and vomiting compared with morphine and decreased hypotension and urinary retention compared with epidural analgesia (Capdevila et al, 1999 **Level II**; Singelyn et al, 1998 **Level II**). Similar results were reported in a later study. Although continuous femoral nerve blockade provided pain relief that was comparable to both IV morphine and epidural analgesia, the incidence of nausea, vomiting, pruritus and sedation was also reduced compared with morphine and there was again a lower incidence of urinary retention and hypotension compared with epidural analgesia (Singelyn et al, 2005 **Level II**).

Femoral nerve block (either continuous or single shot) combined with spinal or general anaesthesia for total knee arthroplasty led to better analgesia (lower pain intensity scores especially on movement, reduction in supplemental analgesia use) for up to 48 hours compared with parenteral opioid-based techniques (Fischer et al, 2008 **Level I**). In a later study, continuous femoral nerve block also led to better pain relief and opioid-sparing, however there was a reduction in opioid-related side effects and patients were able to achieve better knee flexion in the postoperative period; no functional benefit was seen at 3 months (Kadic et al, 2009 **Level II**).

Femoral nerve block (either single shot or continuous) was more effective than intra-articular local anaesthesia following arthroscopic anterior cruciate ligament reconstruction (Dauri et al, 2003 **Level II**; Iskandar et al, 2003 **Level II**; Dauri et al, 2009 **Level II**). In day case surgical patients,

continuous femoral nerve block (via elastomeric device; mean duration 50 hours) provided more effective analgesia for up to 4 days following anterior cruciate ligament reconstruction than either single-shot femoral nerve block or placebo (saline) block (Williams et al, 2006 **Level II**).

Continuous fascia iliaca block provided similar analgesia to a '3-in-1' block following anterior cruciate ligament repair and the catheter was considered technically easier to insert (Morau et al, 2003 **Level II**). It is likely that many catheters placed as a classic '3-in-1' block were in fact relying on local anaesthetic spread along the plane of the fascia iliaca (Capdevila et al, 1998 **Level II**). Fascia iliaca block is also of benefit in some paediatric procedures (see Section 10.7.1). For more information on any differences between the local anaesthetics used for femoral nerve blocks see Section 5.1.2.

### **Sciatic nerve**

Following total knee arthroplasty, combined sciatic and femoral nerve blockade did not improve analgesia compared with femoral block alone (Allen et al, 1998 **Level II**). However, after lower extremity surgery (Ilfeld, Morey, Wang et al, 2002 **Level II**) and foot surgery (White et al, 2003 **Level II**), continuous popliteal sciatic nerve analgesia resulted in better pain relief, lower opioid requirements and fewer side effects compared with opioids alone.

A comparison of epidural analgesia and combined sciatic-femoral nerve blockade after total knee arthroplasty showed no differences in pain relief (rest and with movement), side effects (apart from urinary retention, which was greater in the epidural group), rehabilitation or length of hospital stay (Zaric et al, 2006 **Level II**).

For more information on any differences between the local anaesthetics used for sciatic nerve blocks see Section 5.1.2.

### **Lumbar plexus**

Continuous psoas compartment blockade can be used for postoperative analgesia following total hip replacement (Capdevila et al, 2002 **Level IV**) and surgical repair of hip fractures (Chudinov et al, 1999 **Level II**).

Femoral and posterior lumbar plexus blocks compared with placebo for knee and hip arthroplasty respectively reduced the time to discharge readiness (criteria included adequate analgesia, independence from IV analgesia and ambulatory targets) (Ilfeld, Le et al, 2008 **Level II**; Ilfeld, Ball et al, 2008 **Level II**). However, there was no significant reduction in ambulation distance achieved. There was no evidence that either a 4-day continuous lumbar plexus block after hip arthroplasty (Ilfeld, Ball et al 2009 **Level II**) or 4-day continuous femoral nerve block after knee arthroplasty (Ilfeld, Meyer et al 2009 **Level II**) improved health-related quality of life between 7 days and 12 months.

Both continuous posterior lumbar plexus and femoral analgesia significantly reduced 48-hour opioid requirements and pain scores following total knee joint replacement surgery compared with IV PCA morphine (Kaloul et al, 2004 **Level II**). There were no differences in pain scores or morphine consumption between the two regional analgesia groups.

A study comparing continuous femoral nerve, femoral/sciatic nerve and lumbar plexus infusions found that the combination of femoral and sciatic nerve infusion reduced postoperative opioid requirements after total knee replacement, however there were no differences in pain scores or function (Morin, Kratz et al, 2005 **Level II**). Also after knee arthroplasty surgery, epidural analgesia provided better analgesia at 6 hours than a lumbar plexus infusion, but there were no differences in pain at rest or with movement at 24 hours, or in range of movement or mobility (Campbell et al, 2008 **Level II**).

## Thoracic

### *Paravertebral blocks*

Following cosmetic breast surgery thoracic paravertebral blockade resulted in modest benefits only; reduced nausea (at 24 hours) and opioid requirements compared with general anaesthesia (Klein, Bergh et al, 2000 **Level II**). After breast cancer surgery, no difference in opioid requirements or pain scores was found (Moller et al, 2007 **Level II**).

Continuous thoracic paravertebral blockade was as effective as thoracic epidural analgesia for pain relief after thoracotomy (Davies et al, 2006 **Level I**), with a better side-effect profile (less urinary retention, hypotension and nausea and vomiting) than epidural analgesia and resulted in a lower incidence of postoperative pulmonary complications (Davies et al, 2006 **Level I**). Similarly, in a comparison of different modes of analgesia for thoracotomy, paravertebral and epidural techniques provided superior analgesia to intrathecal, interpleural, intercostal and systemic opioid techniques; paravertebral blocks resulted in less hypotension than epidural analgesia with local anaesthetic and paravertebral blocks reduced the incidence of pulmonary complications compared with systemic analgesia (Joshi et al, 2008 **Level I**).

Continuous thoracic paravertebral blockade was also effective for pain relief in patients with multiple unilateral rib fractures (Shukula et al, 2008 **Level IV**).

### *Intercostal and interpleural blocks*

There was no evidence that continuous interpleural analgesia provided superior analgesia compared with thoracic epidural analgesia following thoracotomy for minimally invasive direct coronary artery bypass surgery (Mehta et al, 1998 **Level II**). However, after thoracotomy for correction of aortic coarctation or patient ductus arteriosus, thoracic epidural analgesia resulted in better pain relief and pulmonary function than continuous interpleural analgesia (Yildirim et al, 2007 **Level II**).

Continuous epidural analgesia was superior to continuous intercostal analgesia following thoracotomy (Debreceni et al, 2003 **Level II**).

### *Needle and catheter localising techniques*

Stimulating catheters have been compared with non-stimulating catheter techniques in establishing continuous femoral nerve blockade for postoperative analgesia following total knee arthroplasty. There was no difference in quality of postoperative analgesia between these two insertion techniques (Morin, Eberhart et al, 2005 **Level II**; Barrington et al, 2008 **Level II**). Stimulating catheters have also been compared with non-stimulating catheter techniques at other anatomical locations with inconclusive results (Rodriguez et al, 2006 **Level II**; Dauri et al, 2007 **Level II**; Stevens et al, 2007 **Level II**).

Ultrasound guidance has been compared with stimulating and non-stimulating techniques for continuous infraclavicular brachial plexus blockade. The combination of ultrasound and nerve stimulator guidance (with stimulating catheters) resulted in the highest primary success and reduced secondary catheter failure (Dhir & Ganapathy, 2008 **Level II**). In comparison with a peripheral nerve stimulator (PNS), blocks performed using ultrasound guidance were found to be more likely to be successful (RR for block failure 0.41; 95% CI 0.26 to 0.66), faster to perform (mean 1 minute less to perform with ultrasound), and have faster onset (29% shorter onset time; 95% CI 45% to 12%), and longer duration (mean difference 25% longer; 95% CI 12% to 38%) than those performed with PNS guidance (Abrahams et al, 2009 **Level I**). In one RCT comparing blocks performed using PNS or ultrasound guidance, there was no difference in block performance time (but this was only 5 minutes for both techniques), block failure rate, or incidence of postoperative neurological symptoms, however there was enhanced motor block at 5 minutes when ultrasound was used (Liu et al, 2009 **Level II**).

## **Patient-controlled regional analgesia**

Continuous regional analgesia techniques can be provided with continuous infusion alone, a combination of continuous infusion and patient-controlled bolus doses or patient-controlled bolus doses alone. In a comparison with continuous infusions for '3 in 1' nerve blockade, patient-controlled regional analgesia (PCRA) was associated with similar pain scores and patient satisfaction but reduced consumption of local anaesthetic (Singelyn & Gouverneur, 2000 **Level II**). A study in patients having open shoulder surgery concluded that a baseline infusion, with PCRA added to reinforce the block before physiotherapy, was the best choice (Singelyn et al, 1999 **Level II**).

The addition of a background infusion to '3 in 1' PCRA (Singelyn & Gouverneur, 2000 **Level II**) or femoral nerve PCRA (Singelyn et al, 2001 **Level II**) did not improve pain relief or alter the incidence of side effects but could increase total local anaesthetic consumption. The addition of a background infusion to interscalene brachial plexus PCRA did result in better analgesia (Singelyn et al, 1999 **Level II**).

For more information on any differences between the local anaesthetics used for PCRA see Section 5.1.2.

### **7.5.2 Intra-articular analgesia**

Continuous ropivacaine infusion via interscalene or intra-articular catheters were compared following rotator cuff surgery in an outpatient setting. Both study groups had logistical problems and relatively high pain scores following resolution of the surgical block (Klein et al, 2003 **Level II**).

Intra-articular infusions of bupivacaine with adrenaline following shoulder arthroscopy have been associated with gleno-humoral chondrolysis in cases series, and their use has been cautioned against (Hansen et al 2007 **Level IV**; Bailie & Ellenbecker, 2009 **Level IV**). The chondrotoxicity of bupivacaine has been supported by animal experiments (Gomoll et al, 2006).

There is evidence of a small benefit only of intra-articular local anaesthesia for postoperative pain relief after anterior cruciate ligament repair (Moiniche et al, 1999 **Level I**). Femoral nerve block (either single shot or continuous) was more effective than intra-articular local anaesthesia following arthroscopic repair (Dauri et al, 2003 **Level II**; Iskandar et al, 2003 **Level II**).

Following knee arthroplasty, the use of periarticular and intra-articular local anaesthetics in large volumes (eg 170 mL 0.2% ropivacaine) with supplemental doses over 24 hours via an intra-articular catheter resulted in lower opioid requirements for up to 24 hours and less nausea over 5 days compared with systemic morphine (Vendittoli et al, 2006 **Level II**), improved analgesia and earlier ambulation compared with femoral nerve block (Toftdahl et al, 2007 **Level II**), and reduced pain over 32 hours compared with saline (Andersen et al, 2008 **Level II**). The technique has been recently been reviewed (Otte et al, 2008).

Following hip arthroplasty, the use of periarticular and intra-articular local anaesthetics in large volumes with supplemental doses over 24 hours via an intra-articular catheter resulted in improved analgesia for 2 weeks postoperatively and lower opioid requirements for up to 4 days compared with saline (Andersen, Poulsen et al, 2007 **Level II**) and reduced opioid consumption and length of hospital stay compared with epidural analgesia (Andersen, Pfeiffer-Jensen et al, 2007 **Level II**). Plasma levels of ropivacaine after this technique have been reported to be below the toxic range (Vendittoli et al, 2006 **Level IV**; Bianconi et al, 2003 **Level IV**).

In clinical practice, morphine injected as a single dose into the knee intra-articular space produced analgesia that lasted up to 24 hours, but evidence for a peripheral rather than a systemic effect was not conclusive (Gupta et al, 2001 **Level I**; Kalso et al, 2002 **Level I**). Confounding

variables that hinder analysis included the pre-existing degree of inflammation, type of surgery, the baseline pain severity and the overall relatively weak clinical effect (Gupta et al, 2001 **Level I**). When published trials were analysed taking these confounding factors into consideration, including the intensity of early postoperative pain, the data did not support an analgesic effect for intra-articular morphine following arthroscopy compared with placebo (Rosseland, 2005 **Level I**).

**Note: reversal of conclusions**

This reverses the Level 1 conclusion in the previous edition of this document; the earlier meta-analyses performed without taking confounding factors into consideration had reported improved pain relief with intra-articular morphine.

### 7.5.3 Wound infiltration including wound catheters

A meta-analysis reviewed outcomes following postoperative analgesia using continuous local anaesthetic wound infusions (Liu et al, 2006 **Level I**). Analyses were performed for all surgical groups combined and for the four subgroups (cardiothoracic, general, gynaecology-urology and orthopaedics). While there were some minor variations between the subgroups, the results overall (ie for all surgical groups combined) showed that this technique led to reductions in pain scores (at rest and with activity), opioid consumption, PONV and length of hospital stay; patient satisfaction was higher and there was no difference in the incidence of wound infections (Liu et al, 2006 **Level I**).

Continuous infusion of ropivacaine into the wound after appendicectomy was superior to a saline infusion (Ansaloni et al, 2007 **Level II**) as was a continuous wound infusion of bupivacaine after open nephrectomy (Forastiere et al, 2008 **Level II**). Infusion of ropivacaine into the site of iliac crest bone graft harvest resulted in better pain relief in the postoperative period compared with IV PCA alone and significantly less pain in the iliac crest during movement at 3 months (Blumenthal et al, 2005 **Level II**).

Continuous infusion of bupivacaine below the superficial abdominal fascia resulted in more effective analgesia than an infusion sited above the fascia after abdominal hysterectomy (Hafizoglu et al, 2008 **Level II**).

Continuous wound infusion of diclofenac after Caesarean section was as effective as a ropivacaine infusion with systemic diclofenac (Lavand'homme et al, 2007 **Level II**).

Early postoperative abdominal pain was improved after laparoscopic cholecystectomy by the use of intraperitoneal local anaesthetic; the effect was better when given at the start of the operation compared with instillation at the end of surgery (Boddy et al, 2006 **Level I**). There were no differences in pain relief found between systemic pethidine and intraperitoneal administration of pethidine and ropivacaine, alone or in combination (Paech et al, 2008 **Level II**). Preperitoneal infusion of ropivacaine after colorectal surgery resulted in improved pain relief, opioid-sparing and earlier recovery of bowel function (Beaussier et al, 2007 **Level II**).

### 7.5.4 Topical application of local anaesthetics

Topical EMLA<sup>®</sup> cream (eutectic mixture of lignocaine and prilocaine) was effective in reducing the pain associated with venous ulcer debridement (Briggs & Nelson, 2003 **Level I**). When compared with EMLA<sup>®</sup> cream, topical amethocaine provided superior analgesia for superficial procedures in children, especially IV cannulation. (Lander et al, 2006 **Level I**).



Topical tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lignocaine were as effective as EMLA® cream for dermal instrumentation analgesia in the emergency department (Eidelman et al, 2005 **Level I**). See Section 10.4.2 for use in children and Section 9.9.2 for use in the emergency department.

Topical local anaesthetic provided no analgesic benefit when performing flexible diagnostic nasoendoscopy, either alone or in combination with a vasoconstrictor (Conlin & McLean, 2008 **Level I**; Nankivell & Pothier, 2008 **Level I**).

Intraurethral instillation of lidocaine gel provides superior analgesia to lubricating gel during flexible cystoscopy (Aaronson et al, 2009 **Level I**).

Following tonsillectomy, local anaesthetics provided a modest reduction in post-tonsillectomy pain; administering the local anaesthetic on swabs appeared to provide a similar level of analgesia to that of infiltration (Grainger & Saravanappa, 2008 **Level I**).

A meta-analysis concludes that there is insufficient evidence to recommend topical lignocaine as a first-line agent in the treatment of postherpetic neuralgia with allodynia (Khaliq et al, 2007 **Level I**).

### 7.5.5 Safety

#### **Anticoagulation**

Caution should be applied in the use of some peripheral nerve or plexus blocks in patients with impaired coagulation (see Section 7.4.2)

#### **Nerve injury**

An ASRA&PM Practice Advisory publication (Neal et al, 2008 **Level IV**) provides a good overview of and guidance on neurological complications in regional anaesthesia, importantly noting that most symptoms resolve within days to weeks and that many factors unrelated to the block itself may contribute perioperative nerve injury (Welch et al, 2009 **Level IV**; Neal et al, 2008 **Level IV**).

Most nerve injury after these techniques presents as residual paraesthesia and rarely as permanent paralysis (persisting for more than 6 to 12 months). A review of data from published studies of the risk of neurological injury associated with epidural and other regional anaesthesia and analgesia differentiated between the risk of permanent neurological injury and transient neuropathy (Brull et al, 2007 **Level IV**). The incidence of transient neuropathy (radiculopathy) after three common forms of peripheral nerve blockade — interscalene brachial plexus block, axillary brachial plexus block and femoral nerve block — was estimated to be 2.84%, 1.48% and 0.34% respectively.

A review of 1416 patients after CPNB for orthopaedic surgery reported three patients with nerve lesions (all after femoral nerve CPNB); full recovery was seen within 10 weeks (Capdeville et al, 2005 **Level IV**). Another prospective audit of 1065 patients after CPNB reported a similar block-related neuropathy rate of 0.22% (Watts & Sharma, 2007 **Level IV**).

The risk of permanent neurological injury (lasting over 12 months) after peripheral neural blockade was much lower. In all the studies included in this review, only one case was reported (out of 22 414 cases with follow-up data recorded), making it a very rare event (Brull et al, 2007 **Level IV**). The Australasian Regional Anaesthesia Collaboration (ARAC) followed up 6069 patients who received 7156 peripheral nerve blocks for neurological and other complications. The incidence of late neurological deficit was 0.4:1000 procedures (Barrington et al, 2009 **Level IV**).

The overall incidence of long-term injury following brachial plexus block ranged between 0.02% and 0.4% depending on the definition of injury and length of follow-up (Borgeat et al, 2001 **Level IV**; Klein et al, 2002 **Level IV**; Neal et al, 2002 **Level IV**; Watts & Sharma, 2007 **Level IV**).

Borgeat et al studied continuous popliteal nerve blockade in 1001 patients with no incidence of neuropathy (Borgeat et al, 2006 **Level IV**) while Compere et al (Compere, Rey et al, 2009 **Level IV**) reported an infection incidence a 0.5% risk of severe neuropathy — 2 patients of the 400 included in the study.

Ultrasound guidance has been shown to reduce the likelihood of intravascular injection (RR 0.16; 95% CI 0.05 to 0.47;  $P < 0.001$ ) but insufficient data are available to determine whether neurological injury is less likely (Abrahams et al, 2009 **Level I**). A review of 1010 consecutive peripheral nerve blocks performed under ultrasound guidance concluded that the incidence of neurological symptoms, most thought to be due to causes others than the block, was similar to that reported for blocks performed using traditional techniques (Fredrickson & Kilfoyle, 2009 **Level IV**).

Permanent neurological injury has been reported following injection of local anaesthetic into the cervical spinal cord when an interscalene block was performed under general anaesthesia (Benumof, 2000).

### **Toxicity**

Local anaesthetic toxicity due to accidental intravascular injection or rapid absorption is a known complication of all peripheral nerve blocks, and was associated with cardiac arrest (1.4 per 10 000) or seizures (7.5 per 10 000) in a prospective survey of over 21 000 cases (Auroy et al, 1997 **Level IV**). The incidence of acute systemic toxicity reported by ARAC was 0.98:1000 procedures (Barrington et al, 2009 **Level IV**). Surveys specifically investigating brachial plexus blocks have reported a higher rate of seizures (0.2%) (Brown et al, 1995 **Level IV**; Borgeat et al, 2001 **Level IV**) (see Section 5.1.3).

### **Infection**

Despite a structured literature search regarding infection in regional analgesia, insufficient prospective trials were found to conduct a meta-analysis (Schulz-Stubner et al, 2008). In a follow-up of 1416 patients with CPNB catheters only one patient had a serious complication (psoas abscess), although a relatively high rate of catheter colonisation (28.7%) occurred (Capdevila et al, 2005 **Level IV**). Unfortunately, the infection control practices were not fully disclosed. In another series, 16% of all CPNB catheters were colonised and the risk factors for colonisation were catheter placement in the groin and repeated changes of the catheter dressing (Morin, Kerwat et al, 2005 **Level IV**). In perineural catheters that were tunnelled, the rate of contamination was just 6% (Compere, Legrand et al, 2009 **Level IV**).

After 48 hours, 57% of femoral nerve catheters were colonised (Cuvillon et al, 2001 **Level IV**).

Wiege et al (Wiegel et al, 2007 **Level IV**) documented an incidence of local inflammation at the catheter site (0.6%) and local infection (0.2%) in femoral and sciatic blocks. The incidence of local inflammation and infection in a study of 2285 patients with CPNB (axillary, interscalene, psoas compartment, femoral, sciatic and popliteal) was 4.2% and 3.2% respectively (Neuburger et al, 2007 **Level IV**). Borgeat et al studied continuous popliteal nerve blockade in 1001 patients with no incidence of infection (Borgeat et al, 2006 **Level IV**) while Compere et al reported an infection incidence of 0.25% — 1 patient of the 400 included in the study — for the same block (Compere, Rey et al, 2009 **Level IV**).

The strongest recommendations for preventive measures are hand hygiene and effective skin preparation, preferably with alcohol-based chlorhexidine solution — as found in the epic2 National Guidelines in the United Kingdom (Pratt et al, 2007). These guidelines recommend full

barrier precautions for central venous catheter placement (cap, mask, sterile gown and gloves; and large drape). Specific trial data for aseptic technique in CPNB is lacking, however in a review of infections associated with CPNB as reported in 12 case series, Capdevila et al (Capdevila et al, 2009 **Level IV**) supported the use of full surgical-type aseptic technique for CPNB procedures.

Identified risk factors for local CPNB catheter inflammation include intensive care unit stay, duration of catheter use greater than 48 hours, lack of antibiotic prophylaxis, axillary or femoral location and frequent dressing changes (Capdevila et al, 2009 **Level IV**). The implications of catheter-related sepsis in patients with implanted prosthetic devices (eg joint arthroplasty) are significant and therefore all reasonable measures should be taken to minimise this risk.

### Key messages

1. Topical EMLA® cream (eutectic mixture of lignocaine [lidocaine] and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (**U**) (**Level I** [Cochrane Review]).
2. Compared with opioid analgesia, continuous peripheral nerve blockade (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as nausea, vomiting, pruritus and sedation (**N**) (**Level I**).
3. Femoral nerve block provides better analgesia compared with parenteral opioid-based techniques after total knee arthroplasty (**S**) (**Level I**).
4. Compared with thoracic epidural analgesia, continuous thoracic paravertebral analgesia results in comparable analgesia but has a better side effect profile (less urinary retention, hypotension, nausea, and vomiting) than epidural analgesia and leads to a lower incidence of postoperative pulmonary complications (**N**) (**Level I**).
5. Blocks performed using ultrasound guidance are more likely to be successful, faster to perform, with faster onset and longer duration compared with localisation using a peripheral nerve stimulator (**N**) (**Level I**).
6. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo (**R**) (**Level I**).
7. Intra-articular local anaesthetics reduce postoperative pain to a limited extent only (**U**) (**Level I**).
8. Continuous local anaesthetic wound infusions lead to reductions in pain scores (at rest and with activity), opioid consumption, postoperative nausea and vomiting, and length of hospital stay; patient satisfaction is higher and there is no difference in the incidence of wound infections (**S**) (**Level I**).
9. Intraperitoneal local anaesthetic after laparoscopic cholecystectomy improves early postoperative pain relief (**N**) (**Level I**).
10. Intraurethral instillation of lignocaine gel provides analgesia during flexible cystoscopy (**N**) (**Level I**).
11. Continuous interscalene analgesia provides better analgesia, reduced opioid-related side effects and improved patient satisfaction compared with IV PCA after open shoulder surgery (**U**) (**Level II**).
12. Continuous femoral nerve blockade provides postoperative analgesia that is as effective as epidural analgesia but with fewer side effects following total knee joint replacement surgery (**U**) (**Level II**).

13. Continuous posterior lumbar plexus analgesia is as effective as continuous femoral analgesia following total knee joint replacement surgery (**U**) (**Level II**).
14. Intra-articular bupivacaine infusions have been associated with chondrolysis and their use has been cautioned against (**N**) (**Level IV**).

## REFERENCES

- Aaronson DS, Walsh TJ, Smith JF (2009) Meta-analysis: does lidocaine gel before flexible cystoscopy provide pain relief? *BJU Int* **104**(4): 506–9
- Abboud TK, Zhu J, Gangolly J et al (1991) Transnasal butorphanol: a new method for pain relief in post-cesarean section pain. *Acta Anaesthesiol Scand* **35**(1): 14–8.
- Abrahams MS, Aziz MF, Fu RF et al (2009) Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: a systematic review and meta-analysis of randomized controlled trials. *Br J Anaesth* **102**(3): 408–17.
- Ahmad S, Hewitt DJ & Damaraju CV (2007) Fentanyl HCl iontophoretic transdermal system versus intravenous morphine pump after gynecologic surgery. *Arch Gynecol Obstet* **276**(3): 251–8.
- Allen HW, Liu SS, Ware PD et al (1998) Peripheral nerve blocks improve analgesia after total knee replacement surgery. *Anesth Analg* **87**(1): 93–7.
- Andersen KV, Pfeiffer-Jensen M, Haraldsted V et al (2007) Reduced hospital stay and narcotic consumption, and improved mobilization with local and intraarticular infiltration after hip arthroplasty: a randomized clinical trial of an intraarticular technique versus epidural infusion in 80 patients. *Acta Orthop* **78**(2): 180–6.
- Andersen LJ, Poulsen T, Krogh B et al (2007) Postoperative analgesia in total hip arthroplasty: a randomized double-blinded, placebo-controlled study on preoperative and postoperative ropivacaine, ketorolac, and adrenaline wound infiltration. *Acta Orthop* **78**(2): 187–92.
- Andersen LO, Husted H, Otte KS et al (2008) High-volume infiltration analgesia in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. *Acta Anaesthesiol Scand* **52**(10): 1331–5.
- Ansaloni L, Agnoletti V, Bettini D et al (2007) The analgesic efficacy of continuous elastomeric pump ropivacaine wound instillation after appendectomy. *J Clin Anesth* **19**(4): 256–63.
- Ashburn MA, Love G & Pace NL (1994) Respiratory-related critical events with intravenous patient-controlled analgesia. *Clin J Pain* **10**(1): 52–6.
- Auroy Y, Narchi P, Messiah A et al (1997) Serious complications related to regional anesthesia: results of a prospective survey in France. *Anesthesiology* **87**(3): 479–86.
- Bahar M, Rosen M & Vickers MD (1985) Self-administered nalbuphine, morphine and pethidine. Comparison, by intravenous route, following cholecystectomy. *Anaesthesia* **40**(6): 529–32.
- Bailey PL, Rhondeau S, Schafer PG et al (1993) Dose-response pharmacology of intrathecal morphine in human volunteers. *Anesthesiology* **79**(1): 49–59.
- Bailie DS & Ellenbecker TS (2009) Severe chondrolysis after shoulder arthroscopy: a case series. *J Shoulder Elbow Surg* **18**(5): 742–7.
- Bainbridge D, Martin JE & Cheng DC (2006) Patient-controlled versus nurse-controlled analgesia after cardiac surgery--a meta-analysis. *Can J Anaesth* **53**(5): 492–9.
- Ballantyne JC, Carr DB, deFerranti S et al (1998) The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. *Anesth Analg* **86**(3): 598–612.
- Ballantyne JC, McKenna JM & Ryder E (2003) Epidural analgesia - experience of 5628 patients in a large teaching hospital derived audit. *Acute Pain* **4**: 89–97.
- Banga AK (2005) Iontophoretic topical and transdermal drug delivery. *Drug Delivery Report Autumn/Winter*: 51–3.
- Barratt SM, Smith RC, Kee AJ et al (2002) Multimodal analgesia and intravenous nutrition preserves total body protein following major upper gastrointestinal surgery. *Reg Anesth Pain Med* **27**(1): 15–22.

- Barrington MJ, Kluger R, Watson R et al (2005) Epidural anesthesia for coronary artery bypass surgery compared with general anesthesia alone does not reduce biochemical markers of myocardial damage. *Anesth Analg* **100**(4): 921–8.
- Barrington MJ, Olive D, Low K et al (2005) Continuous femoral nerve blockade or epidural analgesia after total knee replacement: a prospective randomized controlled trial. *Anesth Analg* **101**(6): 1824–9.
- Barrington MJ, Olive DJ, McCutcheon CA et al (2008) Stimulating catheters for continuous femoral nerve blockade after total knee arthroplasty: a randomized, controlled, double-blinded trial. *Anesth Analg* **106**(4): 1316–21.
- Barrington MJ, Watts SA, Gledhill SR et al (2009) Preliminary results of the Australasian Regional Anaesthesia Collaboration: a prospective audit of over 7000 peripheral nerve and plexus blocks for neurological and other complications. *Reg Anesth Pain Med*. (accepted for publication).
- Bartha E, Carlsson P & Kalman S (2006) Evaluation of costs and effects of epidural analgesia and patient-controlled intravenous analgesia after major abdominal surgery. *Br J Anaesth* **96**(1): 111–7.
- Bauer C, Hentz JG, Ducrocq X et al (2007) Lung function after lobectomy: a randomized, double-blinded trial comparing thoracic epidural ropivacaine/sufentanil and intravenous morphine for patient-controlled analgesia. *Anesth Analg* **105**(1): 238–44.
- Beattie WS, Badner NH & Choi P (2001) Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesth Analg* **93**(4): 853–8.
- Beaussier M, Weickmans H, Parc Y et al (2006) Postoperative analgesia and recovery course after major colorectal surgery in elderly patients: a randomized comparison between intrathecal morphine and intravenous PCA morphine. *Reg Anesth Pain Med* **31**(6): 531–8.
- Beaussier M, El'Ayoubi H, Schiffer E et al (2007) Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery: a randomized, double-blind, placebo-controlled study. *Anesthesiology* **107**(3): 461–8.
- Bell RF, Dahl JB, Moore RA et al (2006) Perioperative ketamine for acute postoperative pain. *Cochrane Database Syst Rev*(1): CD004603.
- Bell JG, Shaffer LE & Schrickel-Feller T (2007) Randomized trial comparing 3 methods of postoperative analgesia in gynecology patients: patient-controlled intravenous, scheduled intravenous, and scheduled subcutaneous. *Am J Obstet Gynecol* **197**(5): 472 e1–7.
- Benumof JL (2000) Permanent loss of cervical spinal cord function associated with interscalene block performed under general anesthesia. *Anesthesiology* **93**(6): 1541–4.
- Bergqvist D, Wu CL & Neal JM (2003) Anticoagulation and neuraxial regional anesthesia: perspectives. *Reg Anesth Pain Med* **28**(3): 163–6.
- Bevacqua BK (2003) Continuous spinal anaesthesia: what's new and what's not. *Best Pract Res Clin Anaesthesiol* **17**(3): 393–406.
- Bianconi M, Ferraro L, Traina GC et al (2003) Pharmacokinetics and efficacy of ropivacaine continuous wound instillation after joint replacement surgery. *Br J Anaesth* **91**(6): 830–5.
- Bickler P, Brandes J, Lee M et al (2006) Bleeding complications from femoral and sciatic nerve catheters in patients receiving low molecular weight heparin. *Anesth Analg* **103**(4): 1036–7.
- Blumenthal S, Dullenkopf A, Rentsch K et al (2005) Continuous infusion of ropivacaine for pain relief after iliac crest bone grafting for shoulder surgery. *Anesthesiology* **102**(2): 392–7.
- Boddy AP, Mehta S & Rhodes M (2006) The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. *Anesth Analg* **103**(3): 682–8.
- Boezaart AP, Eksteen JA, Spuy GV et al (1999) Intrathecal morphine. Double-blind evaluation of optimal dosage for analgesia after major lumbar spinal surgery. *Spine* **24**(11): 1131–7.
- Bong CL, Samuel M, Ng JM et al (2005) Effects of preemptive epidural analgesia on post-thoracotomy pain. *J Cardiothorac Vasc Anesth* **19**(6): 786–93.
- Boonmak P, Boonmak S, Bunsangjaroen P et al (2007) Antiemetic effect of ondansetron 0.2 mg mL<sup>-1</sup> in PCA morphine solution. *Eur J Anaesthesiol* **24**(8): 664–7.

- Borgeat A, Schappi B, Biasca N et al (1997) Patient-controlled analgesia after major shoulder surgery: patient-controlled interscalene analgesia versus patient-controlled analgesia. *Anesthesiology* **87**(6): 1343–7.
- Borgeat A, Tewes E, Biasca N et al (1998) Patient-controlled interscalene analgesia with ropivacaine after major shoulder surgery: PCIA vs PCA. *Br J Anaesth* **81**(4): 603–5.
- Borgeat A, Perschak H, Bird P et al (2000) Patient-controlled interscalene analgesia with ropivacaine 0.2% versus patient-controlled intravenous analgesia after major shoulder surgery: effects on diaphragmatic and respiratory function. *Anesthesiology* **92**(1): 102–8.
- Borgeat A, Ekatothramis G, Kalberer F et al (2001) Acute and nonacute complications associated with interscalene block and shoulder surgery: a prospective study. *Anesthesiology* **95**(4): 875–80.
- Borgeat A, Blumenthal S, Lambert M et al (2006) The feasibility and complications of the continuous popliteal nerve block: a 1001-case survey. *Anesth Analg* **103**(1): 229–33.
- Bracco D & Hemmerling T (2007) Epidural analgesia in cardiac surgery: an updated risk assessment. *Heart Surg Forum* **10**(4): E334–7.
- Briggs M & Nelson EA (2003) Topical agents or dressings for pain in venous leg ulcers. *Cochrane Database Syst Rev*(1): CD001177.
- Brown DL, Ransom DM, Hall JA et al (1995) Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. *Anesth Analg* **81**(2): 321–8.
- Brown DR, Hofer RE, Patterson DE et al (2004) Intrathecal anesthesia and recovery from radical prostatectomy: a prospective, randomized, controlled trial. *Anesthesiology* **100**(4): 926–34.
- Brull R, McCartney CJ, Chan VW et al (2007) Neurological complications after regional anesthesia: contemporary estimates of risk. *Anesth Analg* **104**(4): 965–74.
- Bulger EM, Edwards T, Klotz P et al (2004) Epidural analgesia improves outcome after multiple rib fractures. *Surgery* **136**(2): 426–30.
- Burstal R, Wegener F, Hayes C et al (1998) Epidural analgesia: prospective audit of 1062 patients. *Anaesth Intensive Care* **26**(2): 165–72.
- Cameron CM, Scott DA, McDonald WM et al (2007) A review of neuraxial epidural morbidity: experience of more than 8,000 cases at a single teaching hospital. *Anesthesiology* **106**(5): 997–1002.
- Campbell A, McCormick M, McKinlay K et al (2008) Epidural vs. lumbar plexus infusions following total knee arthroplasty: randomized controlled trial. *Eur J Anaesthesiol* **25**(6): 502–7.
- Camu F, Van Aken H & Bovill JG (1998) Postoperative analgesic effects of three demand-dose sizes of fentanyl administered by patient-controlled analgesia. *Anesth Analg* **87**(4): 890–5.
- Candido KD & Stevens RA (2003) Post-dural puncture headache: pathophysiology, prevention and treatment. *Best Pract Res Clin Anaesthesiol* **17**(3): 451–69.
- Capdevila X, Biboulet P, Bouregba M et al (1998) Comparison of the three-in-one and fascia iliaca compartment blocks in adults: clinical and radiographic analysis. *Anesth Analg* **86**(5): 1039–44.
- Capdevila X, Barthelet Y, Biboulet P et al (1999) Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* **91**(1): 8–15.
- Capdevila X, Macaire P, Dadure C et al (2002) Continuous psoas compartment block for postoperative analgesia after total hip arthroplasty: new landmarks, technical guidelines, and clinical evaluation. *Anesth Analg* **94**(6): 1606–13.
- Capdevila X, Pirat P, Bringuier S et al (2005) Continuous peripheral nerve blocks in hospital wards after orthopedic surgery: a multicenter prospective analysis of the quality of postoperative analgesia and complications in 1,416 patients. *Anesthesiology* **103**(5): 1035–45.
- Capdevila X, Bringuier S & Borgeat A (2009) Infectious risk of continuous peripheral nerve blocks. *Anesthesiology* **110**(1): 182–8.
- Carrier FM, Turgeon AF, Nicole PC et al (2009) Effect of epidural analgesia in patients with traumatic rib fractures: a systematic review and meta-analysis of randomized controlled trials. *Can J Anaesth* **56**(3): 230–42.
- Cashman JN & Dolin SJ (2004) Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. *Br J Anaesth* **93**(2): 212–23.



- Cepeda MS, Delgado M, Ponce M et al (1996) Equivalent outcomes during postoperative patient-controlled intravenous analgesia with lidocaine plus morphine versus morphine alone. *Anesth Analg* **83**(1): 102–6.
- Cepeda MS, Africano JM, Manrique AM et al (2002) The combination of low dose of naloxone and morphine in PCA does not decrease opioid requirements in the postoperative period. *Pain* **96**(1-2): 73–9.
- Cepeda MS, Alvarez H, Morales O et al (2004) Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. *Pain* **107**(1-2): 41–6.
- Chang AM, Ip WY & Cheung TH (2004) Patient-controlled analgesia versus conventional intramuscular injection: a cost effectiveness analysis. *J Adv Nurs* **46**(5): 531–41.
- Charuluxananan S, Kyokong O, Somboonviboon W et al (2003) Nalbuphine versus ondansetron for prevention of intrathecal morphine-induced pruritus after cesarean delivery. *Anesth Analg* **96**(6): 1789–93.
- Chen HH, Yeh ML & Yang HJ (2005) Testing the impact of a multimedia video CD of patient-controlled analgesia on pain knowledge and pain relief in patients receiving surgery. *Int J Med Inform* **74**(6): 437–45.
- Chen JY, Wu GJ, Mok MS et al (2005) Effect of adding ketorolac to intravenous morphine patient-controlled analgesia on bowel function in colorectal surgery patients—a prospective, randomized, double-blind study. *Acta Anaesthesiol Scand* **49**(4): 546–51.
- Chen JY, Ko TL, Wen YR et al (2009) Opioid-sparing effects of ketorolac and its correlation with the recovery of postoperative bowel function in colorectal surgery patients: a prospective randomized double-blinded study. *Clin J Pain* **25**(6): 485–9.
- Cherian VT & Smith I (2001) Prophylactic ondansetron does not improve patient satisfaction in women using PCA after Caesarean section. *Br J Anaesth* **87**(3): 502–4.
- Chisakuta AM (1993) Nurse-call button on a patient-controlled analgesia pump? *Anaesthesia* **48**(1): 90.
- Choi PT, Bhandari M, Scott J et al (2003) Epidural analgesia for pain relief following hip or knee replacement. *Cochrane Database Syst Rev*(3): CD003071.
- Choiniere M, Rittenhouse BE, Perreault S et al (1998) Efficacy and costs of patient-controlled analgesia versus regularly administered intramuscular opioid therapy. *Anesthesiology* **89**(6): 1377–88.
- Christie L & Cranfield KA (1998) A dangerous fault with a PCA pump. *Anaesthesia* **53**(8): 827.
- Christopherson R, Beattie C, Frank SM et al (1993) Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology* **79**(3): 422–34.
- Chudinov A, Berkenstadt H, Salai M et al (1999) Continuous psoas compartment block for anesthesia and perioperative analgesia in patients with hip fractures. *Reg Anesth Pain Med* **24**(6): 563–8.
- Chumbley GM, Hall GM & Salmon P (1998) Patient-controlled analgesia: an assessment by 200 patients. *Anaesthesia* **53**(3): 216–21.
- Chumbley GM, Hall GM & Salmon P (2002) Patient-controlled analgesia: what information does the patient want? *J Adv Nurs* **39**(5): 459–71.
- Chumbley GM, Ward L, Hall GM et al (2004) Pre-operative information and patient-controlled analgesia: much ado about nothing. *Anaesthesia* **59**(4): 354–8.
- Coghlan MW, Davies MJ, Hoyt C et al (2009) Antibacterial activity of epidural infusions. *Anaesth Intensive Care* **37**(1): 66–9.
- Compere V, Legrand JF, Guitard PG et al (2009) Bacterial colonization after tunneling in 402 perineural catheters: a prospective study. *Anesth Analg* **108**(4): 1326–30.
- Compere V, Rey N, Baert O et al (2009) Major complications after 400 continuous popliteal sciatic nerve blocks for post-operative analgesia. *Acta Anaesthesiol Scand* **53**(3): 339–45.
- Conlin AE & McLean L (2008) Systematic review and meta-analysis assessing the effectiveness of local anesthetic, vasoconstrictive, and lubricating agents in flexible fibre-optic nasolaryngoscopy. *J Otolaryngol Head Neck Surg* **37**(2): 240–9.
- Cook TM, Counsell D & Wildsmith JA (2009) Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* **102**(2): 179–90.



- Culebras X, Corpataux JB, Gaggero G et al (2003) The antiemetic efficacy of droperidol added to morphine patient-controlled analgesia: a randomized, controlled, multicenter dose-finding study. *Anesth Analg* **97**(3): 816–21.
- Curatolo M, Petersen-Felix S, Scaramozzino P et al (1998) Epidural fentanyl, adrenaline and clonidine as adjuvants to local anaesthetics for surgical analgesia: meta-analyses of analgesia and side-effects. *Acta Anaesthesiol Scand* **42**(8): 910–20.
- Cuvillon P, Ripart J, Lalourcey L et al (2001) The continuous femoral nerve block catheter for postoperative analgesia: bacterial colonization, infectious rate and adverse effects. *Anesth Analg* **93**(4): 1045–9.
- Dahl JB, Jeppesen IS, Jorgensen H et al (1999) Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. *Anesthesiology* **91**(6): 1919–27.
- Dal D, Kanbak M, Caglar M et al (2003) A background infusion of morphine does not enhance postoperative analgesia after cardiac surgery. *Can J Anaesth* **50**(5): 476–9.
- Dauri M, Polzoni M, Fabbi E et al (2003) Comparison of epidural, continuous femoral block and intraarticular analgesia after anterior cruciate ligament reconstruction. *Acta Anaesthesiol Scand* **47**(1): 20–5.
- Dauri M, Sidiropoulou T, Fabbi E et al (2007) Efficacy of continuous femoral nerve block with stimulating catheters versus nonstimulating catheters for anterior cruciate ligament reconstruction. *Reg Anesth Pain Med* **32**(4): 282–7.
- Dauri M, Fabbi E, Mariani P et al (2009) Continuous femoral nerve block provides superior analgesia compared with continuous intra-articular and wound infusion after anterior cruciate ligament reconstruction. *Reg Anesth Pain Med* **34**(2): 95–9.
- Davies PW, Vallejo MC, Shannon KT et al (2005) Oral herpes simplex reactivation after intrathecal morphine: a prospective randomized trial in an obstetric population. *Anesth Analg* **100**(5): 1472–6.
- Davies RG, Myles PS & Graham JM (2006) A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy--a systematic review and meta-analysis of randomized trials. *Br J Anaesth* **96**(4): 418–26.
- Davis DP, Wold RM, Patel RJ et al (2004) The clinical presentation and impact of diagnostic delays on emergency department patients with spinal epidural abscess. *J Emerg Med* **26**(3): 285–91.
- Dawson L, Brockbank K, Carr EC et al (1999) Improving patients' postoperative sleep: a randomized control study comparing subcutaneous with intravenous patient-controlled analgesia. *J Adv Nurs* **30**(4): 875–81.
- De Pietri L, Siniscalchi A, Reggiani A et al (2006) The use of intrathecal morphine for postoperative pain relief after liver resection: a comparison with epidural analgesia. *Anesth Analg* **102**(4): 1157–63.
- Debreceni G, Molnar Z, Szelig L et al (2003) Continuous epidural or intercostal analgesia following thoracotomy: a prospective randomized double-blind clinical trial. *Acta Anaesthesiol Scand* **47**(9): 1091–5.
- Dernedde M, Stadler M, Bardiau F et al (2006) Low vs. high concentration of levobupivacaine for postoperative epidural analgesia: influence of mode of delivery. *Acta Anaesthesiol Scand* **50**(5): 613–21.
- Dhir S & Ganapathy S (2008) Comparative evaluation of ultrasound-guided continuous infraclavicular brachial plexus block with stimulating catheter and traditional technique: a prospective-randomized trial. *Acta Anaesthesiol Scand* **52**(8): 1158–66.
- Dolin SJ, Cashman JN & Bland JM (2002) Effectiveness of acute postoperative pain management: I. Evidence from published data. *Br J Anaesth* **89**(3): 409–23.
- Dolin SJ & Cashman JN (2005) Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritis, and urinary retention. Evidence from published data. *Br J Anaesth* **95**(5): 584–91.
- Donatelli F, Vavassori A, Bonfanti S et al (2007) Epidural anesthesia and analgesia decrease the postoperative incidence of insulin resistance in preoperative insulin-resistant subjects only. *Anesth Analg* **104**(6): 1587–93.

- Dopfmer UR, Schenk MR, Kuscic S et al (2001) A randomized controlled double-blind trial comparing piritramide and morphine for analgesia after hysterectomy. *Eur J Anaesthesiol* **18**(6): 389–93.
- Doyle DJ & Vicente KJ (2001) Electrical short circuit as a possible cause of death in patients on PCA machines: report on an opiate overdose and a possible preventive remedy. *Anesthesiology* **94**(5): 940.
- Doyle DJ & Keebler A (2008) Another failure mechanism leading to patient-controlled analgesia overdoses. *Can J Anaesth* **55**(5): 319–20.
- ECRI (1995) Improper cassette attachment allows gravity free-flow from SIMS-Deltec CADD-series pumps. *Health Devices* **24**(2): 84–6.
- ECRI (1996) Overinfusion caused by gravity free-flow from a damaged prefilled glass syringe. *Health Devices* **25**(12): 476–7.
- ECRI (1997) Abbott PCA Plus II patient-controlled analgesic pumps prone to misprogramming resulting in narcotic overinfusions. *Health Devices* **26**(9-10): 389–91.
- ECRI (2002) Medication safety: PCA pump programming errors continue to cause fatal overinfusions. *Health Devices* **31**(9): 342–6.
- ECRI (2006) Patient-controlled analgesic infusion pumps. *Health Devices* **35**(1): 5–35.
- Eidelman A, Weiss JM, Lau J et al (2005) Topical anesthetics for dermal instrumentation: a systematic review of randomized, controlled trials. *Ann Emerg Med* **46**(4): 343–51.
- Erolcay H & Yuceyar L (2003) Intravenous patient-controlled analgesia after thoracotomy: a comparison of morphine with tramadol. *Eur J Anaesthesiol* **20**(2): 141–6.
- European Medicines Agency (2008) *PRESS RELEASE European Medicines Agency recommends the suspension of the marketing authorisation of Ionsys (fentanyl hydrochloride)*. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/ionsys/61385208en.pdf>. Accessed April 2009.
- Evans E, Turley N, Robinson N et al (2005) Randomised controlled trial of patient controlled analgesia compared with nurse delivered analgesia in an emergency department. *Emerg Med J* **22**(1): 25–9.
- Finger MJ & McLeod DG (1995) Postoperative myocardial infarction after radical cystoprostatectomy masked by patient-controlled analgesia. *Urology* **45**(1): 155–7.
- Fischer HB, Simanski CJ, Sharp C et al (2008) A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty. *Anaesthesia* **63**(10): 1105–23.
- Fleming BM & Coombs DW (1992) A survey of complications documented in a quality-control analysis of patient-controlled analgesia in the postoperative patient. *J Pain Symptom Manage* **7**(8): 463–9.
- Forastiere E, Sofra M, Giannarelli D et al (2008) Effectiveness of continuous wound infusion of 0.5% ropivacaine by On-Q pain relief system for postoperative pain management after open nephrectomy. *Br J Anaesth* **101**(6): 841–7.
- Fowler SJ, Symons J, Sabato S et al (2008) Epidural analgesia compared with peripheral nerve blockade after major knee surgery: a systematic review and meta-analysis of randomized trials. *Br J Anaesth* **100**(2): 154–64.
- Fredrickson MJ & Kilfoyle DH (2009) Neurological complication analysis of 1000 ultrasound guided peripheral nerve blocks for elective orthopaedic surgery: a prospective study. *Anaesthesia* **64**(8): 836–44.
- Friedman Z, Katznelson R, Phillips SR et al (2008) A randomized double-blind comparison of a morphine-fentanyl combination vs. morphine alone for patient-controlled analgesia following bowel surgery. *Pain Pract* **8**(4): 248–52.
- Gagliese L, Gauthier LR, Macpherson AK et al (2008) Correlates of postoperative pain and intravenous patient-controlled analgesia use in younger and older surgical patients. *Pain Med* **9**(3): 299–314.
- Gan TJ, Alexander R, Fennelly M et al (1995) Comparison of different methods of administering droperidol in patient-controlled analgesia in the prevention of postoperative nausea and vomiting. *Anesth Analg* **80**(1): 81–5.
- Gan TJ, Gordon DB, Bolge SC et al (2007) Patient-controlled analgesia: patient and nurse satisfaction with intravenous delivery systems and expected satisfaction with transdermal delivery systems. *Curr Med Res Opin* **23**(10): 2507–16.

- Gehling M & Tryba M (2009) Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia* **64**(6): 643–51.
- Ginsberg B, Gil KM, Muir M et al (1995) The influence of lockout intervals and drug selection on patient-controlled analgesia following gynecological surgery. *Pain* **62**(1): 95–100.
- Gomoll AH, Kang RW, Williams JM et al (2006) Chondrolysis after continuous intra-articular bupivacaine infusion: an experimental model investigating chondrotoxicity in the rabbit shoulder. *Arthroscopy* **22**(8): 813–9
- Grainger J & Saravanappa N (2008) Local anaesthetic for post-tonsillectomy pain: a systematic review and meta-analysis. *Clin Otolaryngol* **33**(5): 411–9.
- Grond S, Hall J, Spacek A et al (2007) Iontophoretic transdermal system using fentanyl compared with patient-controlled intravenous analgesia using morphine for postoperative pain management. *Br J Anaesth* **98**(6): 806–15.
- Guay J (2006) The benefits of adding epidural analgesia to general anesthesia: a metaanalysis. *J Anesth* **20**(4): 335–40.
- Gupta A, Bodin L, Holmstrom B et al (2001) A systematic review of the peripheral analgesic effects of intraarticular morphine. *Anesth Analg* **93**(3): 761–70.
- Gupta SK, Hwang S, Southam M et al (2005) Effects of application site and subject demographics on the pharmacokinetics of fentanyl HCl patient-controlled transdermal system (PCTS). *Clin Pharmacokinet* **44** (Suppl 1): 25–32.
- Gurbet A, Goren S, Sahin S et al (2004) Comparison of analgesic effects of morphine, fentanyl, and remifentanyl with intravenous patient-controlled analgesia after cardiac surgery. *J Cardiothorac Vasc Anesth* **18**(6): 755–8.
- Gwartz KH, Young JV, Byers RS et al (1999) The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. *Anesth Analg* **88**(3): 599–604.
- Hafizoglu MC, Katircioglu K, Ozkalkanli MY et al (2008) Bupivacaine infusion above or below the fascia for postoperative pain treatment after abdominal hysterectomy. *Anesth Analg* **107**(6): 2068–72.
- Halpern SH & Carvalho B (2009) Patient-controlled epidural analgesia for labor. *Anesth Analg* **108**(3): 921–8.
- Hansen BP, Beck CL, Beck EP et al (2007) Postarthroscopic glenohumeral chondrolysis. *Am J Sports Med* **35**(10): 1628–34.
- Hansdottir V, Philip J, Olsen MF et al (2006) Thoracic epidural versus intravenous patient-controlled analgesia after cardiac surgery: a randomized controlled trial on length of hospital stay and patient-perceived quality of recovery. *Anesthesiology* **104**(1): 142–51.
- Harnett MJ, O'Rourke N, Walsh M et al (2007) Transdermal scopolamine for prevention of intrathecal morphine-induced nausea and vomiting after cesarean delivery. *Anesth Analg* **105**(3): 764–9.
- Harrington P, Bunola J, Jennings AJ et al (2000) Acute compartment syndrome masked by intravenous morphine from a patient-controlled analgesia pump. *Injury* **31**(5): 387–9.
- Hartrick CT, Bourne MH, Gargiulo K et al (2006) Fentanyl iontophoretic transdermal system for acute-pain management after orthopedic surgery: a comparative study with morphine intravenous patient-controlled analgesia. *Reg Anesth Pain Med* **31**(6): 546–54.
- Hicks RW, Sikirica V, Nelson W et al (2008) Medication errors involving patient-controlled analgesia. *Am J Health Syst Pharm* **65**(5): 429–40.
- Ho KM & Litton E (2006) Use of chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. *J Antimicrob Chemother* **58**(2): 281–7.
- Hodgson PS, Neal JM, Pollock JE et al (1999) The neurotoxicity of drugs given intrathecally (spinal). *Anesth Analg* **88**(4): 797–809.
- Hodsman NB, Kenny GN & McArdle CS (1988) Patient controlled analgesia and urinary retention. *Br J Surg* **75**(3): 212.
- Holte K & Kehlet H (2001) Epidural analgesia and risk of anastomotic leakage. *Reg Anesth Pain Med* **26**(2): 111–7.

- Hong D, Flood P & Diaz G (2008) The side effects of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* **107**(4): 1384–9.
- Horlocker TT, Wedel DJ, Benzon H et al (2003) Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med* **28**(3): 172–97.
- Horlocker TT, Wedel DJ, Rowlingson JC et al (2010) Regional anesthesia patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (3<sup>rd</sup> edition). *Reg Anesth Pain Med* **35**(1): 64–101.
- Horlocker TT & Wedel DJ (2008) Infectious complications of regional anesthesia. *Best Pract Res Clin Anaesthesiol* **22**(3): 451–75.
- Howell PR, Gambling DR, Pavy T et al (1995) Patient-controlled analgesia following caesarean section under general anaesthesia: a comparison of fentanyl with morphine. *Can J Anaesth* **42**(1): 41–5.
- Hudcova J, McNicol E, Quah C et al (2006) Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. *Cochrane Database Syst Rev*(4): CD003348.
- Ilfeld BM, Morey TE & Enneking FK (2002) Continuous infraclavicular brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. *Anesthesiology* **96**(6): 1297–304.
- Ilfeld BM, Morey TE, Wang RD et al (2002) Continuous popliteal sciatic nerve block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. *Anesthesiology* **97**(4): 959–65.
- Ilfeld BM, Morey TE, Wright TW et al (2003) Continuous interscalene brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* **96**(4): 1089–95.
- Ilfeld BM, Vandenborne K, Duncan PW et al (2006) Ambulatory continuous interscalene nerve blocks decrease the time to discharge readiness after total shoulder arthroplasty: a randomized, triple-masked, placebo-controlled study. *Anesthesiology* **105**(5): 999–1007.
- Ilfeld BM, Ball ST, Gearen PF et al (2008) Ambulatory continuous posterior lumbar plexus nerve blocks after hip arthroplasty: a dual-center, randomized, triple-masked, placebo-controlled trial. *Anesthesiology* **109**(3): 491–501.
- Ilfeld BM, Le LT, Meyer RS et al (2008) Ambulatory continuous femoral nerve blocks decrease time to discharge readiness after tricompartment total knee arthroplasty: a randomized, triple-masked, placebo-controlled study. *Anesthesiology* **108**(4): 703–13.
- Ilfeld BM, Ball ST, Gearen PF et al (2009) Health-related quality of life after hip arthroplasty with and without an extended-duration continuous posterior lumbar plexus nerve block: a prospective, 1-year follow-up of a randomized, triple-masked, placebo-controlled study. *Anesth Analg* **109**(2): 586–91.
- Ilfeld BM, Le LT, Ramjohn J et al (2009) The effects of local anesthetic concentration and dose on continuous infraclavicular nerve blocks: a multicenter, randomized, observer-masked, controlled study. *Anesth Analg* **108**(1): 345–50.
- Ilfeld BM, Meyer RS, Le LT et al (2009) Health-related quality of life after tricompartment knee arthroplasty with and without an extended-duration continuous femoral nerve block: a prospective, 1-year follow-up of a randomized, triple-masked, placebo-controlled study. *Anesth Analg* **108**(4): 1320–5.
- Iskandar H, Benard A, Ruel-Raymond J et al (2003) Femoral block provides superior analgesia compared with intra-articular ropivacaine after anterior cruciate ligament reconstruction. *Reg Anesth Pain Med* **28**(1): 29–32.
- Jacox A, Carr DB, Mahrenholz DM et al (1997) Cost considerations in patient-controlled analgesia. *Pharmacoeconomics* **12**(2 Pt 1): 109–20.
- Jakobsen CJ, Nygaard E, Norrild K et al (2009) High thoracic epidural analgesia improves left ventricular function in patients with ischemic heart. *Acta Anaesthesiol Scand* **53**(5): 559–64.
- Jeffs SA, Hall JE & Morris S (2002) Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia. *Br J Anaesth* **89**(3): 424–7.

- Jellish WS, Owen K, Fluder E et al (2009) Patient-controlled analgesia combined with either ondansetron or ondansetron plus prochlorperazine for control of pain and nausea and vomiting in patients undergoing abdominal surgery. *J Clin Anesth* **20**: 594–600.
- Jorgensen H, Wetterslev J, Moench S et al (2000) Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev*(4): CD001893.
- Joshi GP, Bonnet F, Shah R et al (2008) A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. *Anesth Analg* **107**(3): 1026–40.
- Kadic L, Boonstra MC, MC DEWM et al (2009) Continuous femoral nerve block after total knee arthroplasty? *Acta Anaesthesiol Scand* **53**(7): 914–20.
- Kalouli I, Guay J, Cote C et al (2004) The posterior lumbar plexus (psoas compartment) block and the three-in-one femoral nerve block provide similar postoperative analgesia after total knee replacement. *Can J Anaesth* **51**(1): 45–51.
- Kalso E, Smith L, McQuay HJ et al (2002) No pain, no gain: clinical excellence and scientific rigour—lessons learned from IA morphine. *Pain* **98**(3): 269–75.
- Kanai A, Osawa S, Suzuki A et al (2007) Regression of sensory and motor blockade, and analgesia during continuous epidural infusion of ropivacaine and fentanyl in comparison with other local anesthetics. *Pain Med* **8**(7): 546–53.
- Kato R, Shimamoto H, Terui K et al (2008) Delayed respiratory depression associated with 0.15 mg intrathecal morphine for cesarean section: a review of 1915 cases. *J Anesth* **22**(2): 112–6.
- Katz J, Buis T & Cohen L (2008) Locked out and still knocking: predictors of excessive demands for postoperative intravenous patient-controlled analgesia. *Can J Anaesth* **55**(2): 88–99.
- Kean J, Wigderowitz CA & Coventry DM (2006) Continuous interscalene infusion and single injection using levobupivacaine for analgesia after surgery of the shoulder. A double-blind, randomised controlled trial. *J Bone Joint Surg Br* **88**(9): 1173–7.
- Keita H, Geachan N, Dahmani S et al (2003) Comparison between patient-controlled analgesia and subcutaneous morphine in elderly patients after total hip replacement. *Br J Anaesth* **90**(1): 53–7.
- Kendall JM & Latter VS (2003) Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* **42**(6): 501–13.
- Khalik W, Alam S & Puri N (2007) Topical lidocaine for the treatment of postherpetic neuralgia. *Cochrane Database Syst Rev*(2): CD004846.
- Kindler C, Seeberger M, Siegemund M et al (1996) Extradural abscess complicating lumbar extradural anaesthesia and analgesia in an obstetric patient. *Acta Anaesthesiol Scand* **40**(7): 858–61.
- Klein SM, Bergh A, Steele SM et al (2000) Thoracic paravertebral block for breast surgery. *Anesth Analg* **90**(6): 1402–5.
- Klein SM, Grant SA, Greengrass RA et al (2000) Interscalene brachial plexus block with a continuous catheter insertion system and a disposable infusion pump. *Anesth Analg* **91**(6): 1473–8.
- Klein SM, Nielsen KC, Greengrass RA et al (2002) Ambulatory discharge after long-acting peripheral nerve blockade: 2382 blocks with ropivacaine. *Anesth Analg* **94**(1): 65–70.
- Klein SM, Steele SM, Nielsen KC et al (2003) The difficulties of ambulatory interscalene and intra-articular infusions for rotator cuff surgery: a preliminary report. *Can J Anaesth* **50**(3): 265–9.
- Knoerl DV, Faut-Callahan M, Paice J et al (1999) Preoperative PCA teaching program to manage postoperative pain. *Medsurg Nurs* **8**(1): 25–33, 36.
- Ko S, Goldstein DH & VanDenKerkhof EG (2003) Definitions of "respiratory depression" with intrathecal morphine postoperative analgesia: a review of the literature. *Can J Anaesth* **50**(7): 679–88.
- Kollender Y, Bickels J, Stocki D et al (2008) Subanaesthetic ketamine spares postoperative morphine and controls pain better than standard morphine does alone in orthopaedic-oncological patients. *Eur J Cancer* **44**(7): 954–62.
- Komatsu H, Matsumoto S, Mitsuhashi H et al (1998) Comparison of patient-controlled epidural analgesia with and without background infusion after gastrectomy. *Anesth Analg* **87**(4): 907–10.

- Komatsu H, Matsumoto S & Mitsuhashi H (2001) Comparison of patient-controlled epidural analgesia with and without night-time infusion following gastrectomy. *Br J Anaesth* **87**(4): 633–5.
- Koo PJ (2005) Postoperative pain management with a patient-controlled transdermal delivery system for fentanyl. *Am J Health Syst Pharm* **62**(11): 1171–6.
- Kopp SL & Horlocker TT (2008) Anticoagulation in pregnancy and neuraxial blocks. *Anesthesiol Clin* **26**(1): 1–22.
- Kucukemre F, Kunt N, Kaygusuz K et al (2005) Remifentanyl compared with morphine for postoperative patient-controlled analgesia after major abdominal surgery: a randomized controlled trial. *Eur J Anaesthesiol* **22**(5): 378–85.
- Kwan A (1995) Overdose of morphine during PCA. *Anaesthesia* **50**(10): 919.
- Lagunilla J, Garcia-Bengochea JB, Fernandez AL et al (2006) High thoracic epidural blockade increases myocardial oxygen availability in coronary surgery patients. *Acta Anaesthesiol Scand* **50**(7): 780–6.
- Lam KK, Chan MT, Chen PP et al (2001) Structured preoperative patient education for patient-controlled analgesia. *J Clin Anesth* **13**(6): 465–9.
- Lander JA, Weltman BJ & So SS (2006) EMLA and amethocaine for reduction of children's pain associated with needle insertion. *Cochrane Database Syst Rev* **3**: CD004236.
- Lattermann R, Wykes L, Eberhart L et al (2007) A randomized controlled trial of the anticatabolic effect of epidural analgesia and hypocaloric glucose. *Reg Anesth Pain Med* **32**(3): 227–32.
- Lavand'homme PM, Roelants F, Waterloos H et al (2007) Postoperative analgesic effects of continuous wound infiltration with diclofenac after elective cesarean delivery. *Anesthesiology* **106**(6): 1220–5.
- Lepri A, Sia S, Catinelli S et al (2006) Patient-controlled analgesia with tramadol versus tramadol plus ketorolac. *Minerva Anestesiol* **72**(1–2): 59–67.
- Lin TF, Yeh YC, Lin FS et al (2009) Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth* **102**(1): 117–22.
- Liu SS, Block BM & Wu CL (2004) Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. *Anesthesiology* **101**(1): 153–61.
- Liu SS, Strodtbeck WM, Richman JM et al (2005) A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. *Anesth Analg* **101**(6): 1634–42.
- Liu SS, Richman JM, Thirlby RC et al (2006) Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. *J Am Coll Surg* **203**(6): 914–32.
- Liu SS, Zayas VM, Gordon MA et al (2009) A prospective, randomized, controlled trial comparing ultrasound versus nerve stimulator guidance for interscalene block for ambulatory shoulder surgery for postoperative neurological symptoms. *Anesth Analg* **109**(1): 265–71.
- Lo Y, Chia YY, Liu K et al (2005) Morphine sparing with droperidol in patient-controlled analgesia. *J Clin Anesth* **17**(4): 271–5.
- Looi-Lyons LC, Chung FF, Chan VW et al (1996) Respiratory depression: an adverse outcome during patient controlled analgesia therapy. *J Clin Anesth* **8**(2): 151–6.
- Lotsch J, Skarke C, Tegeder I et al (2002) Drug interactions with patient-controlled analgesia. *Clin Pharmacokinet* **41**(1): 31–57.
- Lugli AK, Donatelli F, Schrickler T et al (2008) Epidural analgesia enhances the postoperative anabolic effect of amino acids in diabetes mellitus type 2 patients undergoing colon surgery. *Anesthesiology* **108**(6): 1093–9.
- Macintyre PE & Jarvis DA (1996) Age is the best predictor of postoperative morphine requirements. *Pain* **64**(2): 357–64.
- Macintyre PE (2005) Intravenous patient-controlled analgesia: one size does not fit all. *Anesthesiol Clin North America* **23**(1): 109–23.
- Macintyre PE & Schug SA (2007) *Acute pain management: a practical guide*. London, Elsevier.
- Macintyre PE & Coldrey J (2008) Patient-controlled analgesia. In: *Clinical Pain Management: Acute Pain* edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.



- Manjushree R, Lahiri A, Ghosh BR et al (2002) Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients. *Can J Anaesth* **49**(2): 190–3.
- Mariano ER, Afra R, Loland VJ et al (2009) Continuous interscalene brachial plexus block via an ultrasound-guided posterior approach: a randomized, triple-masked, placebo-controlled study. *Anesth Analg* **108**(5): 1688–94.
- Marret E, Kurdi O, Zufferey P et al (2005) Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. *Anesthesiology* **102**(6): 1249–60.
- Marret E, Remy C & Bonnet F (2007) Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *Br J Surg* **94**(6): 665–73.
- Mehta Y, Swaminathan M, Mishra Y et al (1998) A comparative evaluation of intrapleural and thoracic epidural analgesia for postoperative pain relief after minimally invasive direct coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* **12**(2): 162–5.
- Mercadante S, Villari P, Casuccio A et al (2008) A randomized-controlled study of intrathecal versus epidural thoracic analgesia in patients undergoing abdominal cancer surgery. *J Clin Monit Comput* **22**(4): 293–8.
- Meyer GS & Eagle KA (1992) Patient-controlled analgesia masking pulmonary embolus in a postoperative patient. *Crit Care Med* **20**(11): 1619–21.
- Meylan N, Elia N, Lysakowski C et al (2009) Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth* **102**(2): 156–67.
- Michelet P, Guervilly C, Helaine A et al (2007) Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation. *Br J Anaesth* **99**(3): 396–403.
- Minkowitz HS, Rathmell JP, Vallow S et al (2007) Efficacy and safety of the fentanyl iontophoretic transdermal system (ITS) and intravenous patient-controlled analgesia (IV PCA) with morphine for pain management following abdominal or pelvic surgery. *Pain Med* **8**(8): 657–68.
- Mishra S, Bhatnagar S, Srikanti M et al (2006) Clinical implication of routine bacterial culture from epidural catheter tips in postoperative cancer patients: a prospective study. *Anaesthesia* **61**(9): 878–82.
- Moen V, Dahlgren N & Irestedt L (2004) Severe neurological complications after central neuraxial blockades in Sweden 1990–1999. *Anesthesiology* **101**(4): 950–9.
- Moiniche S, Mikkelsen S, Wetterslev J et al (1999) A systematic review of intra-articular local anesthesia for postoperative pain relief after arthroscopic knee surgery. *Reg Anesth Pain Med* **24**(5): 430–7.
- Moller JF, Nikolajsen L, Rodt SA et al (2007) Thoracic paravertebral block for breast cancer surgery: a randomized double-blind study. *Anesth Analg* **105**(6): 1848–51.
- Morau D, Lope S, Biboulet P et al (2003) Comparison of continuous 3-in-1 and fascia iliaca compartment blocks for postoperative analgesia: feasibility, catheter migration, distribution of sensory block, and analgesic efficacy. *Reg Anesth Pain Med* **28**(4): 309–14.
- Morin AM, Eberhart LH, Behnke HK et al (2005) Does femoral nerve catheter placement with stimulating catheters improve effective placement? A randomized, controlled, and observer-blinded trial. *Anesth Analg* **100**(5): 1503–10.
- Morin AM, Kerwat KM, Klotz M et al (2005) Risk factors for bacterial catheter colonization in regional anaesthesia. *BMC Anesthesiol* **5**(1): 1.
- Morin AM, Kratz CD, Eberhart LH et al (2005) Postoperative analgesia and functional recovery after total-knee replacement: comparison of a continuous posterior lumbar plexus (psoas compartment) block, a continuous femoral nerve block, and the combination of a continuous femoral and sciatic nerve block. *Reg Anesth Pain Med* **30**(5): 434–45.
- Munro AJ, Long GT & Sleigh JW (1998) Nurse-administered subcutaneous morphine is a satisfactory alternative to intravenous patient-controlled analgesia morphine after cardiac surgery. *Anesth Analg* **87**(1): 11–5.
- Nankivell PC & Pothier DD (2008) Nasal and instrument preparation prior to rigid and flexible nasendoscopy: a systematic review. *J Laryngol Otol* **122**(10): 1024–8.



- Neal JM, Hebl JR, Gerancher JC et al (2002) Brachial plexus anesthesia: essentials of our current understanding. *Reg Anesth Pain Med* **27**(4): 402–28.
- Neal JM, Bernardis CM, Hadzic A et al (2008) ASRA Practice Advisory on Neurologic Complications in Regional Anesthesia and Pain Medicine. *Reg Anesth Pain Med* **33**(5): 404–15.
- Neuburger M, Buttner J, Blumenthal S et al (2007) Inflammation and infection complications of 2285 perineural catheters: a prospective study. *Acta Anaesthesiol Scand* **51**(1): 108–14.
- Ngan Kee WD, Khaw KS & Wong EL (1999) Randomised double-blind comparison of morphine vs. a morphine-alfentanil combination for patient-controlled analgesia. *Anaesthesia* **54**(7): 629–33.
- Nightingale JJ, Knight MV, Higgins B et al (2007) Randomized, double-blind comparison of patient-controlled epidural infusion vs nurse-administered epidural infusion for postoperative analgesia in patients undergoing colonic resection. *Br J Anaesth* **98**(3): 380–4.
- Nishimori M, Ballantyne JC & Low JH (2006) Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. *Cochrane Database Syst Rev* **3**: CD005059.
- Nolan JP, Dow AA, Parr MJ et al (1992) Patient-controlled epidural analgesia following post-traumatic pelvic reconstruction. A comparison with continuous epidural analgesia. *Anaesthesia* **47**(12): 1037–41.
- Notcutt WG & Morgan RJ (1990) Introducing patient-controlled analgesia for postoperative pain control into a district general hospital. *Anaesthesia* **45**(5): 401–6.
- Nygaard E, Kofoed KF, Freiberg J et al (2005) Effects of high thoracic epidural analgesia on myocardial blood flow in patients with ischemic heart disease. *Circulation* **111**(17): 2165–70.
- O'Neil G, Paech M & Wood F (1997) Preliminary clinical use of a patient-controlled intranasal analgesia (PCINA) device. *Anaesth Intensive Care* **25**(4): 408–12.
- Otte KS, Husted H, Andersen LA et al (2008) Local infiltration analgesia in total knee arthroplasty and hip resurfacing: A methodological study. *Acute Pain* **10**(3): 111–16.
- Owen H, Plummer JL, Armstrong I et al (1989) Variables of patient-controlled analgesia. 1. Bolus size. *Anaesthesia* **44**(1): 7–10.
- Owen H, Szekely SM, Plummer JL et al (1989) Variables of patient-controlled analgesia. 2. Concurrent infusion. *Anaesthesia* **44**(1): 11–3.
- Paech MJ, Lim CB, Banks SL et al (2003) A new formulation of nasal fentanyl spray for postoperative analgesia: a pilot study. *Anaesthesia* **58**(8): 740–4.
- Paech MJ, Ilett KF, Hackett LP et al (2008) Disposition and clinical outcome after intraperitoneal meperidine and ropivacaine administration during laparoscopic surgery. *Anesth Analg* **106**(1): 278–86.
- Parker RK, Holtmann B & White PF (1991) Patient-controlled analgesia. Does a concurrent opioid infusion improve pain management after surgery? *JAMA* **266**(14): 1947–52.
- Parker RK, Holtmann B & White PF (1992) Effects of a nighttime opioid infusion with PCA therapy on patient comfort and analgesic requirements after abdominal hysterectomy. *Anesthesiology* **76**(3): 362–7.
- Paterson JG (1998) Intravenous obstruction and PCA machines. *Can J Anaesth* **45**(3): 284.
- Pierce ET, Pomposelli FB, Jr., Stanley GD et al (1997) Anesthesia type does not influence early graft patency or limb salvage rates of lower extremity arterial bypass. *J Vasc Surg* **25**(2): 226–32.
- Pirat A, Tuncay SF, Torgay A et al (2005) Ondansetron, orally disintegrating tablets versus intravenous injection for prevention of intrathecal morphine-induced nausea, vomiting, and pruritus in young males. *Anesth Analg* **101**(5): 1330–6.
- Plummer JL, Owen H, Ilesley AH et al (1997) Morphine patient-controlled analgesia is superior to meperidine patient-controlled analgesia for postoperative pain. *Anesth Analg* **84**(4): 794–9.
- Poon K-H, Tan K-T & Ho K-Y (2009) Efficacy of fentanyl iontophoretic transdermal system in postoperative pain - a meta-analysis. *Acute Pain* **11**: 65–74.
- Popping DM, Elia N, Marret E et al (2008) Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Arch Surg* **143**(10): 990–9.
- Prakash S, Fatima T & Pawar M (2004) Patient-controlled analgesia with fentanyl for burn dressing changes. *Anesth Analg* **99**(2): 552–5.
- Pratt RJ, Pellowe CM, Wilson JA et al (2007) epic2: National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *J Hosp Infect* **65** Suppl 1: S1–64.

- Rapp SE, Egan KJ, Ross BK et al (1996) A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* **82**(5): 1043–8.
- Rees DC, Olujuhongbe AD, Parker NE et al (2003) Guidelines for the management of the acute painful crisis in sickle cell disease. *Br J Haematol* **120**(5): 744–52.
- Reihsaus E, Waldbaur H & Seeling W (2000) Spinal epidural abscess: a meta-analysis of 915 patients. *Neurosurg Rev* **23**(4): 175–204.
- Richards H, Langston A, Kulkarni R et al (2004) Does patient controlled analgesia delay the diagnosis of compartment syndrome following intramedullary nailing of the tibia? *Injury* **35**(3): 296–8.
- Richman JM, Liu SS, Courpas G et al (2006) Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. *Anesth Analg* **102**(1): 248–57.
- Richman JM, Rowlingson AJ, Maine DN et al (2007) The effects of epidural catheter location on outcomes in women undergoing gynecologic surgery with an abdominal incision: a randomised clinical trial. *Acute Pain* **9**: 109–18.
- Rittenhouse BE & Choiniere M (1999) An economic evaluation of pain therapy after hysterectomy. Patient-controlled analgesia versus regular intramuscular opioid therapy. *Int J Technol Assess Health Care* **15**(3): 548–62.
- Rodriguez J, Taboada M, Carceller J et al (2006) Stimulating popliteal catheters for postoperative analgesia after hallux valgus repair. *Anesth Analg* **102**(1): 258–62.
- Rosati J, Gallagher M, Shook B et al (2007) Evaluation of an oral patient-controlled analgesia device for pain management in oncology inpatients. *J Support Oncol* **5**(9): 443–8.
- Rosencher N, Bonnet MP & Sessler DI (2007) Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies. *Anaesthesia* **62**(11): 1154–60.
- Rosseland LA (2005) No evidence for analgesic effect of intra-articular morphine after knee arthroscopy: a qualitative systematic review. *Reg Anesth Pain Med* **30**(1): 83–98.
- Roy JD, Massicotte L, Sassine MP et al (2006) A comparison of intrathecal morphine/fentanyl and patient-controlled analgesia with patient-controlled analgesia alone for analgesia after liver resection. *Anesth Analg* **103**(4): 990–4.
- Ruppen W, Derry S, McQuay H et al (2006a) Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anaesthesia. *Anesthesiology* **105**(2): 394–9.
- Ruppen W, Derry S, McQuay HJ et al (2006) Incidence of epidural haematoma and neurological injury in cardiovascular patients with epidural analgesia/anaesthesia: systematic review and meta-analysis. *BMC Anesthesiol* **6**: 10.
- Rutherford J & Patri M (2004) Failure of antireflux valve in a Vygon PCA set. *Anaesthesia* **59**(5): 511.
- Rygnestad T, Borchgrevink PC & Eide E (1997) Postoperative epidural infusion of morphine and bupivacaine is safe on surgical wards. Organisation of the treatment, effects and side-effects in 2000 consecutive patients. *Acta Anaesthesiol Scand* **41**(7): 868–76.
- Salonen MH, Haasio J, Bachmann M et al (2000) Evaluation of efficacy and plasma concentrations of ropivacaine in continuous axillary brachial plexus block: high dose for surgical anaesthesia and low dose for postoperative analgesia. *Reg Anesth Pain Med* **25**(1): 47–51.
- Sanchez-Ledesma MJ, Lopez-Olaondo L, Pueyo FJ et al (2002) A comparison of three antiemetic combinations for the prevention of postoperative nausea and vomiting. *Anesth Analg* **95**(6): 1590–5.
- Sartain JB, Barry JJ, Richardson CA et al (2003) Effect of combining naloxone and morphine for intravenous patient-controlled analgesia. *Anesthesiology* **99**(1): 148–51.
- Sarvela PJ, Halonen PM, Soikkeli AI et al (2006) Ondansetron and tropisetron do not prevent intraspinal morphine- and fentanyl-induced pruritus in elective cesarean delivery. *Acta Anaesthesiol Scand* **50**(2): 239–44.
- Schmidt A & Nolte H (1992) [Subdural and epidural hematomas following epidural anaesthesia. A literature review]. *Anaesthesist* **41**(5): 276–84.
- Schmidt C, Hinder F, Van Aken H et al (2005) The effect of high thoracic epidural anaesthesia on systolic and diastolic left ventricular function in patients with coronary artery disease. *Anesth Analg* **100**(6): 1561–9.

- Schug SA & Torrie JJ (1993) Safety assessment of postoperative pain management by an acute pain service. *Pain* **55**(3): 387–91.
- Schug SA, Scott DA, Payne J et al (1996) Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery. *Br J Anaesth* **76**(4): 487–91.
- Schulz-Stubner S, Pottinger JM, Coffin SA et al (2008) Nosocomial infections and infection control in regional anesthesia. *Acta Anaesthesiol Scand* **52**(8): 1144–57.
- Schunn CD, Hertzner NR, O'Hara PJ et al (1998) Epidural versus general anesthesia: does anesthetic management influence early infrainguinal graft thrombosis? *Ann Vasc Surg* **12**(1): 65–9.
- Scott DA, Chamley DM, Mooney PH et al (1995) Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery--a dose finding study. *Anesth Analg* **81**(5): 982–6.
- Scott DA, Blake D, Buckland M et al (1999) A comparison of epidural ropivacaine infusion alone and in combination with 1, 2, and 4 microg/mL fentanyl for seventy-two hours of postoperative analgesia after major abdominal surgery. *Anesth Analg* **88**(4): 857–64.
- Shapiro A, Zohar E, Zaslansky R et al (2005) The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth* **17**(7): 537–42.
- Shukula AN, Ghaffar ZBA, Auang AC et al (2008) Continuous thoracic paravertebral blockade for pain relief in unilateral multiple rib fractures: a case series. *Acute Pain* **10**: 39–44.
- Siddik-Sayyid SM, Aouad MT, Taha SK et al (2007) Does ondansetron or granisetron prevent subarachnoid morphine-induced pruritus after cesarean delivery? *Anesth Analg* **104**(2): 421–4.
- Sidebotham D, Dijkhuizen MR & Schug SA (1997) The safety and utilization of patient-controlled analgesia. *J Pain Symptom Manage* **14**(4): 202–9.
- Silvasti M, Rosenberg P, Seppala T et al (1998) Comparison of analgesic efficacy of oxycodone and morphine in postoperative intravenous patient-controlled analgesia. *Acta Anaesthesiol Scand* **42**(5): 576–80.
- Silvasti M, Tarkkila P, Tuominen M et al (1999) Efficacy and side effects of tramadol versus oxycodone for patient-controlled analgesia after maxillofacial surgery. *Eur J Anaesthesiol* **16**(12): 834–9.
- Simmons SW, Cyna AM, Dennis AT et al (2007) Combined spinal-epidural versus epidural analgesia in labour. *Cochrane Database Syst Rev*(3): CD003401.
- Simpson RS, Macintyre PE, Shaw D et al (2000) Epidural catheter tip cultures: results of a 4-year audit and implications for clinical practice. *Reg Anesth Pain Med* **25**(4): 360–7.
- Sinatra RS, Lodge K, Sibert K et al (1989) A comparison of morphine, meperidine, and oxymorphone as utilized in patient-controlled analgesia following cesarean delivery. *Anesthesiology* **70**(4): 585–90.
- Singelyn FJ, Deyaert M, Joris D et al (1998) Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. *Anesth Analg* **87**(1): 88–92.
- Singelyn FJ & Gouverneur JM (2000) Extended "three-in-one" block after total knee arthroplasty: continuous versus patient-controlled techniques. *Anesth Analg* **91**(1): 176–80.
- Singelyn FJ, Seguy S & Gouverneur JM (1999) Interscalene brachial plexus analgesia after open shoulder surgery: continuous versus patient-controlled infusion. *Anesth Analg* **89**(5): 1216–20.
- Singelyn FJ, Vanderelst PE & Gouverneur JM (2001) Extended femoral nerve sheath block after total hip arthroplasty: continuous versus patient-controlled techniques. *Anesth Analg* **92**(2): 455–9.
- Singelyn FJ, Ferrant T, Malisse MF et al (2005) Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous femoral nerve sheath block on rehabilitation after unilateral total-hip arthroplasty. *Reg Anesth Pain Med* **30**(5): 452–7.
- Skryabina EA & Dunn TS (2006) Disposable infusion pumps. *Am J Health Syst Pharm* **63**(13): 1260–8.
- Stanley G, Appadu B, Mead M et al (1996) Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery. *Br J Anaesth* **76**(4): 484–6.
- Steffen P, Seeling W, Essig A et al (2004) Bacterial contamination of epidural catheters: microbiological examination of 502 epidural catheters used for postoperative analgesia. *J Clin Anesth* **16**(2): 92–7.
- Steinbrook RA (1998) Epidural anesthesia and gastrointestinal motility. *Anesth Analg* **86**(4): 837–44.

- Stevens MF, Werdehausen R, Golla E et al (2007) Does interscalene catheter placement with stimulating catheters improve postoperative pain or functional outcome after shoulder surgery? A prospective, randomized and double-blinded trial. *Anesth Analg* **104**(2): 442–7.
- Striebel HW, Pommerening J & Rieger A (1993) Intranasal fentanyl titration for postoperative pain management in an unselected population. *Anaesthesia* **48**(9): 753–7.
- Striebel HW, Malewicz J, Hermanns K et al (1993) Intranasal meperidine titration for postoperative pain relief. *Anesth Analg* **76**(5): 1047–51.
- Striebel HW, Bonillo B, Schwagmeier R et al (1995) Self-administered intranasal meperidine for postoperative pain management. *Can J Anaesth* **42**(4): 287–91.
- Striebel HW, Oelmann T, Spies C et al (1996) Patient-controlled intranasal analgesia: a method for noninvasive postoperative pain management. *Anesth Analg* **83**(3): 548–51.
- Striebel HW, Scheitza W, Philippi W et al (1998) Quantifying oral analgesic consumption using a novel method and comparison with patient-controlled intravenous analgesic consumption. *Anesth Analg* **86**(5): 1051–3.
- Sveticic G, Farzanegan F, Zmoos P et al (2008) Is the combination of morphine with ketamine better than morphine alone for postoperative intravenous patient-controlled analgesia? *Anesth Analg* **106**(1): 287–93.
- Tanaka K, Watanabe R, Harada T et al (1993) Extensive application of epidural anesthesia and analgesia in a university hospital: incidence of complications related to technique. *Reg Anesth* **18**(1): 34–8.
- Tenenbein PK, Debrouwere R, Maguire D et al (2008) Thoracic epidural analgesia improves pulmonary function in patients undergoing cardiac surgery. *Can J Anaesth* **55**(6): 344–50.
- Thomas DW & Owen H (1988) Patient-controlled analgesia—the need for caution. A case report and review of adverse incidents. *Anaesthesia* **43**(9): 770–2.
- Toftdahl K, Nikolajsen L, Haraldsted V et al (2007) Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty: a randomized clinical trial. *Acta Orthop* **78**(2): 172–9.
- Toussaint S, Mairl J, Schwagmeier R et al (2000) Patient-controlled intranasal analgesia: effective alternative to intravenous PCA for postoperative pain relief. *Can J Anaesth* **47**(4): 299–302.
- Tramèr MR & Walder B (1999) Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy: a quantitative systematic review. *Anesth Analg* **88**(6): 1354–61.
- Tsui SL, Irwin MG, Wong CM et al (1997) An audit of the safety of an acute pain service. *Anaesthesia* **52**(11): 1042–7.
- Tuman KJ, McCarthy RJ, March RJ et al (1991) Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anesth Analg* **73**(6): 696–704.
- Tzeng JI, Chu KS, Ho ST et al (2003) Prophylactic iv ondansetron reduces nausea, vomiting and pruritus following epidural morphine for postoperative pain control. *Can J Anaesth* **50**(10): 1023–6.
- Unlugenc H, Gunduz M, Ozalevli M et al (2002) A comparative study on the analgesic effect of tramadol, tramadol plus magnesium, and tramadol plus ketamine for postoperative pain management after major abdominal surgery. *Acta Anaesthesiol Scand* **46**(8): 1025–30.
- Unlugenc H, Ozalevli M, Guler T et al (2003) Postoperative pain management with intravenous patient-controlled morphine: comparison of the effect of adding magnesium or ketamine. *Eur J Anaesthesiol* **20**(5): 416–21.
- Unlugenc H, Tetiker S & Isik G (2008) Addition of remifentanyl to patient-controlled tramadol for postoperative analgesia: a double-blind, controlled, randomized trial after major abdominal surgery. *Eur J Anaesthesiol* **25**(12): 968–75.
- Unlugenc H, Vardar MA & Tetiker S (2008) A comparative study of the analgesic effect of patient-controlled morphine, pethidine, and tramadol for postoperative pain management after abdominal hysterectomy. *Anesth Analg* **106**(1): 309–12.
- Urquhart ML, Klapp K & White PF (1988) Patient-controlled analgesia: a comparison of intravenous versus subcutaneous hydromorphone. *Anesthesiology* **69**(3): 428–32.

- US Pharmacopeia (2004) *Patient-controlled analgesia pumps*. <http://www.usp.org/patientSafety/newsletters/qualityReview/qr812004-09-01.html>. Accessed November 2006.
- Vallejo MC, Ramesh V, Phelps AL et al (2007) Epidural labor analgesia: continuous infusion versus patient-controlled epidural analgesia with background infusion versus without a background infusion. *J Pain* **8**(12): 970–5.
- Vendittoli PA, Makinen P, Drolet P et al (2006) A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study. *J Bone Joint Surg Am* **88**(2): 282–9.
- Vicente KJ, Kada-Bekhaled K, Hillel G et al (2003) Programming errors contribute to death from patient-controlled analgesia: case report and estimate of probability. *Can J Anaesth* **50**(4): 328–32.
- Viscusi ER, Reynolds L, Chung F et al (2004) Patient-controlled transdermal fentanyl hydrochloride vs intravenous morphine pump for postoperative pain: a randomized controlled trial. *JAMA* **291**(11): 1333–41.
- Viscusi ER, Siccardi M, Damaraju CV et al (2007) The safety and efficacy of fentanyl iontophoretic transdermal system compared with morphine intravenous patient-controlled analgesia for postoperative pain management: an analysis of pooled data from three randomized, active-controlled clinical studies. *Anesth Analg* **105**(5): 1428–36.
- Vitin AA, Dembo G, Vater Y et al (2008) Anesthetic implications of the new anticoagulant and antiplatelet drugs. *J Clin Anesth* **20**(3): 228–37.
- Wakerlin G & Larson CP, Jr. (1990) Spouse-controlled analgesia. *Anesth Analg* **70**(1): 119.
- Wang LP, Hauerberg J & Schmidt JF (1999) Incidence of spinal epidural abscess after epidural analgesia: a national 1-year survey. *Anesthesiology* **91**(6): 1928–36.
- Ward M, Minto G & Alexander-Williams JM (2002) A comparison of patient-controlled analgesia administered by the intravenous or intranasal route during the early postoperative period. *Anaesthesia* **57**(1): 48–52.
- Watts SA & Sharma DJ (2007) Long-term neurological complications associated with surgery and peripheral nerve blockade: outcomes after 1065 consecutive blocks. *Anaesth Intensive Care* **35**(1): 24–31.
- Welch MB, Brummett CM, Welch TD et al (2009) Perioperative peripheral nerve injuries: a retrospective study of 380,680 cases during a 10-year period at a single institution. *Anesthesiology* **111**(3): 490–7.
- Werawatganon T & Charuluxanun S (2005) Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. *Cochrane Database Syst Rev*(1): CD004088.
- Wheatley RG, Schug SA & Watson D (2001) Safety and efficacy of postoperative epidural analgesia. *Br J Anaesth* **87**(1): 47–61.
- White PF (1990) Subcutaneous-PCA: an alternative to IV-PCA for postoperative pain management. *Clin J Pain* **6**(4): 297–300.
- White PF, Issioui T, Skrivanek GD et al (2003) The use of a continuous popliteal sciatic nerve block after surgery involving the foot and ankle: does it improve the quality of recovery? *Anesth Analg* **97**(5): 1303–9.
- Wiegel M, Gottschaldt U, Hennebach R et al (2007) Complications and adverse effects associated with continuous peripheral nerve blocks in orthopedic patients. *Anesth Analg* **104**(6): 1578–82.
- Williams BA, Kentor ML, Vogt MT et al (2006) Reduction of verbal pain scores after anterior cruciate ligament reconstruction with 2-day continuous femoral nerve block: a randomized clinical trial. *Anesthesiology* **104**(2): 315–27.
- Wong K, Chong JL, Lo WK et al (2000) A comparison of patient-controlled epidural analgesia following gynaecological surgery with and without a background infusion. *Anaesthesia* **55**(3): 212–6.
- Woodhouse A, Hobbes AF, Mather LE et al (1996) A comparison of morphine, pethidine and fentanyl in the postsurgical patient-controlled analgesia environment. *Pain* **64**(1): 115–21.
- Woodhouse A, Ward ME & Mather LE (1999) Intra-subject variability in post-operative patient-controlled analgesia (PCA): is the patient equally satisfied with morphine, pethidine and fentanyl? *Pain* **80**(3): 545–53.

- Wu CL, Cohen SR, Richman JM et al (2005) Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: a meta-analysis. *Anesthesiology* **103**(5): 1079–88.
- Wu CL, Rowlingson AJ, Herbert R et al (2006) Correlation of postoperative epidural analgesia on morbidity and mortality after colectomy in Medicare patients. *J Clin Anesth* **18**(8): 594–9.
- Wu CL, Sapirstein A, Herbert R et al (2006) Effect of postoperative epidural analgesia on morbidity and mortality after lung resection in Medicare patients. *J Clin Anesth* **18**(7): 515–20.
- Wu JI, Lo Y, Chia YY et al (2007) Prevention of postoperative nausea and vomiting after intrathecal morphine for Cesarean section: a randomized comparison of dexamethasone, droperidol, and a combination. *Int J Obstet Anesth* **16**(2): 122–7.
- Wulf H (1996) Epidural anaesthesia and spinal haematoma. *Can J Anaesth* **43**(12): 1260–71.
- Xie R & Liu YP (1991) Survey of the use of epidural analgesia in China. *Chin Med J (Engl)* **104**(6): 510–5.
- Yeh YC, Lin TF, Lin FS et al (2008) Combination of opioid agonist and agonist-antagonist: patient-controlled analgesia requirement and adverse events among different-ratio morphine and nalbuphine admixtures for postoperative pain. *Br J Anaesth* **101**(4): 542–8.
- Yildirim V, Akay HT, Bingol H et al (2007) Interpleural versus epidural analgesia with ropivacaine for postthoracotomy pain and respiratory function. *J Clin Anesth* **19**(7): 506–11.
- Yuan HB, Zuo Z, Yu KW et al (2008) Bacterial colonization of epidural catheters used for short-term postoperative analgesia: microbiological examination and risk factor analysis. *Anesthesiology* **108**(1): 130–7.
- Zaric D, Boysen K, Christiansen C et al (2006) A comparison of epidural analgesia with combined continuous femoral-sciatic nerve blocks after total knee replacement. *Anesth Analg* **102**(4): 1240–6.

## 8. NON-PHARMACOLOGICAL TECHNIQUES

---

### 8.1 PSYCHOLOGICAL INTERVENTIONS

The role of psychological interventions in the management of acute pain is generally seen as adjunctive to somatic modalities, but evidence for the value of their contribution is strengthening.

Psychological interventions can be grouped under a number of headings, but, by their very nature, they share some common features. Some of these features may also apply to effective pharmacological and physical interventions. Typically, the treatment provider is encouraged to firstly establish a degree of rapport or acceptance with the patient as well as give some information about the purpose and nature of the intervention and reasonable expectations the patient should hold for their outcome. These aspects may be seen as necessary to gain both the informed consent of the patient for treatment, as well as their active cooperation. Interestingly, one of the conclusions that can be drawn from the available studies is that good psychological preparation for surgical interventions can enhance the outcome of such procedures, including length of hospital stay. Thus, skilled combination of psychological and medical/surgical modalities may lead to better outcomes than either alone.

Psychological interventions may be divided into four broad categories: information provision (procedural or sensory); stress/tension reduction (relaxation and hypnotic strategies); attentional strategies; and cognitive-behavioural interventions. It should be emphasised that these are rarely 'stand-alone' interventions and elements of each may form a single intervention.

#### 8.1.1 Provision of information

*Procedural information* is information given to a patient before any treatment that summarises what will happen during that treatment. Preparatory information has been found to be effective in improving postoperative recovery and reducing pain reports, pain medication use, and length of hospital stay (Johnston & Vogeles, 1993) (see also Section 3.1.1).

*Sensory information* is information that describes the sensory experiences the patient may expect during treatment. Sensory information given alone has some positive, albeit inconsistent, effects compared with no instruction (Suls & Wan, 1989 **Level I**). This review also found that sensory information reduced self-rated pain more than procedural information; however, the effect sizes were variable. Sensory information had no significant effect on postoperative pain perception in patients who underwent two types of elective surgery (Campbell et al, 1999 **Level II**).

*Combined sensory-procedural preparatory information* yielded the strongest and most consistent benefits in reducing negative affect, pain reports and other related distress (Suls & Wan, 1989 **Level I**). This finding was replicated in a controlled study of ear-piercing in children. In this case, those children whose parents were provided with accurate information about the procedure and sensory (pain) expectations reported significantly less pain and more accurate expectations than controls (Spafford et al, 2002 **Level II**).

However, a recent meta-analysis of 28 trials of different psychological interventions for procedure-related pain in children concluded the evidence for the efficacy of information/preparation is only tentatively supportive; the evidence is not sufficient to make firm recommendations (Uman et al, 2006 **Level I**).



In some patients, especially those with an avoidant coping style, giving too much information or asking them to make too many decisions may exacerbate anxiety and pain (Wilson, 1981 **Level II**). However, later evidence suggested that this may not be a strong effect (Miro and Raich 1999 **Level II**). Nevertheless, it may be useful to assess a patient's normal approach to managing stress to identify the best option for that patient. A more recent study with over 3000 surgical patients identified four information factors that were each associated with global evaluations — surgical information, recovery information, general information and sensory information (Krupat et al, 2000 **Level III-3**).

## 8.1.2 Stress and tension reduction

### **Relaxation**

Relaxation training usually involves teaching a patient ways of reducing their feelings of stress/tension by various techniques. The techniques may be taught by recorded audiotape, written or spoken instructions. The use of audiotapes often includes the use of suitable (calming) music. The use of relevant imagery (mental pictures of relaxing scenes) is also often encouraged as an element of relaxation techniques. Typically, all methods require the patient to practise the technique regularly, especially when feeling stressed. Some methods focus on altering muscle tension, often sequentially, while others focus on altering breathing patterns (eg emphasising releasing tension with exhalation). Relaxation techniques are closely related to, and often indistinguishable from, forms of meditation and self-hypnosis.

A systematic review of relaxation techniques, when used alone for the management of pain after surgery and during procedures, concluded that there was some (weak) evidence to support the use of relaxation in these settings — three of the seven studies reported significant reductions in pain and distress (Seers & Carroll, 1998 **Level IV**). Methodological shortcomings in the studies included in the review meant that a meta-analysis was not possible, limiting the strength of the findings. Similar conclusions were made in another systematic review which found that eight of fifteen studies (again, most had weaknesses in methodology) demonstrated reductions in pain; the most supported methods were progressive muscle relaxation for arthritis pain and a systematic relaxation technique for postoperative pain, little evidence was found for autogenic training, and no support for rhythmic breathing or other relaxation techniques (Kwekkeboom & Gretarsdottir, 2006 **Level IV**). Another review of studies using relaxation techniques for burns pain also found insufficient high quality evidence to draw any conclusions, but did recommend further research into the use of a technique that combined focusing on breathing and jaw muscle relaxation (de Jong & Gamel, 2006 **Level IV**). There was no difference found in pain scores after surgery in patients given either relaxation training or routine information prior to spinal surgery; however morphine use was higher in the relaxation group (Gavin et al, 2006 **Level II**).

In contrast, studies of relaxation techniques with cancer patients (with acute pain) provided moderately strong (clinical) support for its effectiveness in improving nausea, pain, pulse rate and blood pressure, as well as emotional adjustment variables (depression, anxiety and hostility) (Luebbert et al, 2001 **Level I**).

### **Hypnosis**

Hypnosis shares many features of relaxation with imagery and has a long history of use in acute pain conditions. While there are many versions of hypnosis, they share the common feature of one person responding to suggestions made by another on experiences involving changes in perception, memory and voluntary actions (Kihlstrom, 1985). The variable or unstandardised nature of hypnotic procedures has made it difficult to compare studies or

draw general conclusions (Ellis & Spanos, 1994), although some more standardised (according to a manual) procedures have been reported (Lioffi & Hatira, 2003).

Until recently much of the literature on the use of hypnosis in acute pain has been based on studies with non-RCT designs (Patterson & Jensen, 2003). However, recent papers have displayed more experimental rigour.

Studies using hypnosis for pain control in both the laboratory and clinical settings (eight of the eighteen studies included pain populations) indicated that hypnosis for pain had a moderate to large effect size and provided substantial pain relief for 75% of laboratory and clinical participants (Montgomery et al, 2000 **Level I**).

A review of hypnosis in clinical pain settings (including pain associated with invasive medical procedures, burns wound care, labour and bone marrow aspiration) provided moderate support for the use of hypnosis in the treatment of acute pain (Patterson & Jensen, 2003 **Level I**). Eight of the nineteen studies showed hypnosis to be more effective on pain reports than no treatment, standard care, or an attention control condition; three studies showed hypnosis to be no better than such control conditions, and one study showed mixed results. Eight studies compared hypnosis with other psychological interventions (cognitive-behavioural intervention, relaxation training, distraction, emotional support), and hypnosis was more effective in reducing pain scores in four of the eight studies.

In relation to acute pain in cancer patients, some individual studies have found hypnosis to be superior to other psychological interventions in reducing pain reports (eg Syrjala et al, 1992 **Level II**). In many of the hypnotic studies with cancer patients, the focus has been on acute pain associated with procedures such as bone marrow aspiration, breast biopsy, or lumbar puncture. In each case the findings have supported the use of hypnosis to reduce pain (eg Wall & Womack, 1989 **Level II**; Lioffi & Hatira, 1999 **Level II**; Montgomery et al, 2002 **Level II**). A systematic review by Wild and Espie (Wild & Espie, 2004) of hypnosis in paediatric oncology pain concluded the evidence was not consistent enough for general recommendations, but that hypnosis was potentially useful.

### 8.1.3 Attentional techniques

A range of attention-based strategies have been reported, from those involving distraction from the pain through to attention to imagined scenes/sensations or to external stimuli such as music, scenes or smells. Some techniques also involve deliberately attending to the pain, but in ways intended to modify the threat value of pain (eg Logan et al, 1995 **Level II**).

Attempting to alter the patient's emotional state, from stress or fear to comfort or peace, is also a common feature of many of these techniques. Commonly, these techniques are used in conjunction with relaxation methods and at times may be inseparable (Williams, 1996).

There is some evidence to support the benefit of some attentional techniques, often in combination with relaxation, in acute postoperative pain (Raft et al, 1986 **Level II**; Daake & Gueldner, 1989 **Level II**; Good et al, 1999 **Level II**). In children and adolescents, a systematic review concluded that distraction is effective in needle-related procedure-related pain (Uman et al, 2006 **Level I**). A more recent comparison of two interventions, guided imagery and relaxation, did not result in any difference in pain relief or analgesic use in elderly patients after colorectal surgery (Haase et al, 2005 **Level II**).

Using thermal pain stimulation in volunteers and measuring pain-related brain activity with fMRI, both opioids and immersive virtual reality (VR) distraction led to reductions in pain unpleasantness and pain-related brain activity; the combination was more effective than opioid alone (Hoffman et al, 2007 **Level III-2**). VR distraction has also been reported to provide

effective analgesia in clinical situations, for example, in burns patients (Hoffman et al, 2000 **Level III-2**; Das et al, 2005 **Level III-2**).

The use of certain music to divert attention from pain and to promote a sense of relaxation and well-being has long been a popular approach. A Cochrane review, which included studies published up to and including 2004, concluded that listening to music reduced pain intensity and opioid requirements after surgery, but that the magnitude of benefit was small (Cepeda et al, 2006 **Level I**). Later systematic reviews of studies investigating the use of music found that pain and anxiety in the perioperative period were reduced in half of the studies examined (Nilsson, 2008 **Level I**) and that anxiety and pain were reduced in children undergoing medical and dental procedures (Klassen et al, 2008 **Level I**).

There is some evidence that rather than shifting attention away from the pain, instructions to focus attention on the pain site can alter pain perception, but possibly mainly among sub-groups of patients (Baron et al, 1993 **Level II**; Logan et al, 1995 **Level II**). The study by Haythornthwaite et al (Haythornthwaite et al, 2001 **Level II**) provides further support for this approach.

The use of mindfulness meditation is a type of attentional technique that includes noting pain sensations. This approach encourages the patient to deliberately experience their pain as calmly as possible, as just another sensation (ie without judging it as good or bad), often while engaging in slowed breathing styles (Kabat-Zinn, 2003). This approach derives from ancient Buddhist methods and was initially described as a stress-reduction technique by Kabat-Zinn. While this technique has been used in people experiencing chronic pain (McCracken et al, 2007 **Level IV**), and has been shown to increase experimental pain tolerance (Kingston et al, 2007 **Level II**), there are no reports on its use in the management of acute pain.

#### **8.1.4 Cognitive-behavioural interventions**

Typically, cognitive-behavioural interventions involve the application of a range of behaviour-change principles, such as differential positive reinforcement of desired behaviours, identification and modification of unhelpful thoughts, and goal setting, in order to achieve change in targeted behaviours. In the context of acute pain this could include encouraging the appropriate use of the techniques outlined above.

Cognitive-behavioural methods focus on both overt behaviours and cognitions (thought processes) in patients, but interactions with environmental factors are often also addressed. This means that interactions between patients and others, especially medical and nursing staff as well as families, may need to be specifically changed to support the desired responses in the patient. The latter may entail displaying a calm and reassuring manner, and encouragement to persevere with a given task or procedure. Specific training in skills (eg relaxation and other coping strategies), other behavioural techniques (eg modelling and systematic desensitisation), information provision and reconceptualisation of the experiences of the patient may also be provided as part of this approach.

Cognitive-behavioural interventions are usually aimed at reducing the distressing or threat value of pain and enhancing a patient's sense of his or her ability to cope with pain. In this context, coping usually refers to acceptance of pain rather than pain control or relief. Effective coping with pain may be reflected in minimal pain-related distress or disability. If patients are able to perceive their pain as less threatening, they might also evaluate their pain as less severe. But in this context reduced severity would be seen more as a by-product rather than the primary goal.

Critically, in using cognitive-behavioural methods, the patient is necessarily an active participant in the process, rather than a passive recipient, as he or she must apply the methods taught as needed.

### ***Applying pain coping strategies within a cognitive-behavioural intervention***

Generally, while some responses by patients to their pain may be helpful, others may not. For example, those who respond with overly alarmist (or catastrophic) thoughts tended to experience more pain and distress, compared with those who did not respond in this way (eg Jensen et al, 1991; Haythornthwaite et al, 2001 **Level II**; Sullivan et al, 2001). Identifying unhelpful responses, whether they are cognitive or behavioural, and changing these responses is a key feature of cognitive-behavioural interventions. Thus, identifying and reducing catastrophic thoughts about pain has become a key intervention within this approach, whether the pain is acute or persistent (Sullivan et al, 2006). It has also been recognised that a given coping strategy may not always be useful and that this may depend upon circumstances and timing (Turk & Monarch, 2002). For example, ignoring or denying the presence of pain may be useful when first injured (to reduce distress), but if it means that appropriate help is not sought it could place the person in danger.

In preparation for surgery, painful medical procedures and postsurgical pain and distress, training in cognitive coping methods and behavioural instructions, in addition to relaxation training and procedural information, improved pain measures and reduced postoperative use of analgesics. These interventions were effective in achieving improvements in measures of negative affect, length of stay (not cognitive methods in this case) and recovery (Johnston & Voge, 1993 **Level I**).

A review of studies (randomised and non-randomised) using cognitive-behavioural interventions in the treatment of procedure-related pain in children and adolescents concluded that cognitive-behavioural interventions may be considered a well-established treatment in this setting. Treatments included breathing exercises and other forms of relaxation and distraction, imagery and other forms of cognitive coping skills, filmed modelling, reinforcement/incentive, behavioural rehearsal and active coaching by a psychologist, parents, and /or medical staff member (Powers, 1999 **Level IV**).

Another review included studies (all non-randomised) that used behavioural interventions in the care of children and adolescents with cancer pain undergoing a wide range of cancer-related diagnostic and treatment procedures including bone marrow aspiration, lumbar puncture, venipuncture, and chemotherapy. The behavioural interventions included hypnosis, relaxation, procedural information, distraction techniques, modifications of children's fears, anxiety and pain, contingency management, systematic desensitisation and behavioural rehearsal. Experience of pain during diagnostic and treatment procedures was included as an outcome measure in nine of the twenty-three included studies; all nine studies found a clinically significant reduction in pain following behavioural intervention (DuHamel et al, 1999 **Level IV**).

A further review examined the effectiveness of behavioural intervention methods in studies (randomised and non-randomised) looking at the control of aversive side effects of cancer treatment, including pain (Redd et al, 2001 **Level IV**). The most commonly used behavioural interventions included hypnosis, relaxation and distraction via guided imagery. Of the twelve studies investigating the impact of behavioural interventions on cancer treatment-related pain, five were randomised clinical trials with either no treatment or attention control conditions; four of these five supported the efficacy of behavioural intervention and all of the remaining seven studies, incorporating a variety of designs, found a reduction in pain following

behavioural intervention. These authors concluded that although a variety of behavioural methods have been shown to reduce acute treatment-related pain, the methods are not equally effective, and hypnotic-like methods, involving relaxation, suggestion and distracting imagery, hold the greatest promise for pain management in acute treatment-related pain (Redd et al, 2001 **Level IV**).

Reports of benefit after surgery are less common. A study of three cognitive-behavioural interventions for reducing postoperative anxiety and pain following spinal fusion surgery for scoliosis in adolescent patients showed that information plus training in coping strategies achieved the greatest pain reduction (35%) compared with information only, coping strategies only, and a control condition; the effect was most evident in those subjects aged 11 to 13 years, compared to those in the 14 to 18 year age range, where no differences between interventions were found (LaMontagne et al, 2003 **Level II**).

### Key messages

1. Listening to music produces a small reduction in postoperative pain and opioid requirement (**N**) (**Level I** [Cochrane Review]).
2. The evidence that information is effective in reducing procedure-related pain is tentatively supportive and not sufficient to make recommendations (**Q**) (**Level I**).
3. Distraction is effective in procedure-related pain in children (**N**) (**Level I**).
4. Training in coping methods or behavioural instruction prior to surgery reduces pain, negative affect and analgesic use (**U**) (**Level I**).
5. Evidence of benefit of hypnosis in the management of acute pain is inconsistent (**W**) (**Level I**).
6. Immersive virtual reality distraction is effective in reducing pain in some clinical situations (**N**) (**Level III-2**).
7. Evidence for any benefit of relaxation techniques in the treatment of acute pain is weak and inconsistent (**N**) (**Level IV**).

## 8.2 TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

A systematic review published in 1996 concluded that transcutaneous electrical nerve stimulation (TENS) was not effective for the relief of postoperative pain (Carroll et al 1996). The authors noted that non-randomised studies overestimated the beneficial effects of TENS. A later Cochrane review included only RCTs looking at the benefit of TENS in the management of acute pain generally and concluded that there were inadequate data on which to perform a meta-analysis (Walsh et al, 2009). However, these authors excluded studies where TENS was used in combination with other treatments such as analgesic drugs. Hence, only one of the 12 included studies, but 62 of the 116 excluded studies related to postoperative pain.

It had been argued by Bjordal et al (Bjordal et al, 2003 **Level I**) that some of the studies reporting no benefit from TENS may have used ineffective treatment doses — low and possibly ineffective current intensities or sensory threshold intensity. They performed a systematic review of publications using TENS after surgery where ‘assumed optimal TENS parameters’ were used; that is, if TENS was administered at an intensity described by the patients as ‘strong and/or definite subnoxious, and/or maximal non-painful, and/or maximal tolerable’, or at a current amplitude of greater than 15 mA. They concluded that strong, subnoxious intensity TENS significantly reduced postoperative analgesic requirements.

The superiority of high-intensity TENS compared with low-frequency TENS, regardless of frequency used, has been demonstrated in further clinical (Olsen et al, 2007 **Level II**) and experimental (Aarskog et al, 2007 **Level II**; Claydon et al, 2008 **Level II**) pain studies.

Use of high-intensity (strong but comfortable) TENS improved pain relief after inguinal herniorrhaphy (DeSantana et al, 2008 **Level II**), laparoscopic tubal ligation (Desantana et al, 2009 **Level II**) and thoracotomy (Erdogan et al, 2005 **Level II**).

TENS was of value in the treatment of primary dysmenorrhoea (Proctor et al, 2002 **Level I**).

Overall, there appeared to be no good evidence for any analgesic effect of TENS during labour although severe pain was less likely to be reported in women receiving TENS to acupuncture points (Dowswell et al, 2009 **Level I**).

#### Key messages

1. Overall, there is no evidence that TENS is effective for the treatment of pain during labour (**N**) (**Level I** [Cochrane Review]).
2. Certain stimulation patterns of TENS are effective in some acute pain settings (**S**) (**Level I**).

## 8.3 ACUPUNCTURE

Acupuncture compared with sham controls reduced postoperative pain (at 8 hours and 72 hours) and opioid consumption as well as nausea (not vomiting), sedation, pruritus and urinary retention (Sun et al, 2008 **Level I**). There was wide variability in the types of surgery and acupuncture regimens (including type of acupuncture, time of application, and type and duration of stimulation) in the studies included in this review and the magnitude of benefit was small. Another review looking specifically at auricular acupuncture for postoperative pain control concluded that a meta-analysis was not possible because of the heterogeneity of the primary studies (Usichenko, Lehmann et al, 2008).

Reviews of the effectiveness of acupuncture in other acute pain settings suggest that it may be useful for managing pain during childbirth (analgesic requirements were reduced) (Smith et al, 2006 **Level I**) and dental pain (Ernst & Pittler, 1998 **Level I**).

A meta-analysis of trials comparing acupuncture (traditional- and electro-acupuncture) with placebo acupuncture for the treatment of pain in general concluded that it does result in a small analgesic effect (4 mm on a 100 mm VAS), but that this seemed to lack clinical relevance and could not clearly be distinguished from bias resulting from incomplete blinding (Madsen et al, 2009 **Level I**). The analgesic effect of placebo acupuncture compared with placebo was moderate but very variable, and considerable heterogeneity in the included trials was noted.

### Acupressure

Acupressure is a technique derived from acupuncture, where physical pressure is applied to acupuncture points.

Acupressure performed during prehospital transport using 'true points' led to better pain relief than acupressure using 'sham points' (Kober et al, 2002 **Level II**; Barker et al, 2006 **Level II**; Lang et al, 2007 **Level II**) or no acupressure (Kober et al, 2002 **Level II**).

#### Key messages

1. Acupuncture reduces postoperative pain as well as opioid-related adverse effects (**N**) (**Level I**).
2. Acupuncture may be effective in some other acute pain settings (**U**) (**Level I**).

## 8.4 OTHER PHYSICAL THERAPIES

### 8.4.1 Manual and massage therapies

Most publications relating to manual (eg physiotherapy, osteopathy and chiropractic) and massage therapies involve the use of these treatments in low back pain and other musculoskeletal pain. The evidence for these therapies is covered in detail in *Evidence-based Management of Musculoskeletal Pain*, published by the Australian Acute Musculoskeletal Pain Guidelines Group (2003) and endorsed by the NHMRC. For a summary of some of the key messages from this document see Sections 9.4 and 9.5.

There is little consistent evidence of any benefit for the use of massage in the treatment of postoperative pain. Foot massage and guided relaxation did not lower pain scores after cardiac surgery (Hattan et al, 2002 **Level II**). Similarly, massage after abdominal or thoracic (via a sternotomy) surgery did not reduce pain scores or analgesic use, although a significant reduction in the unpleasantness of pain (the affective component of pain) was reported (Piotrowski et al, 2003 **Level II**). However, after a variety of major operations, massage therapy reduced postoperative pain intensity and unpleasantness (Mitchinson et al, 2007 **Level II**). In patients after abdominal surgery, the use of a mechanical massage device which leads to intermittent negative pressure on the abdominal wall resulted in significantly lower pain scores and analgesic use on the second and third days after surgery as well as reduced time to first flatus (Le Blanc-Louvry et al, 2002 **Level II**).

### 8.4.2 Heat and cold

Evidence for any benefits from postoperative local cooling is mixed. Significant reductions in opioid consumption and pain scores after a variety of orthopaedic operations have been reported (Brandner et al, 1996 **Level II**; Barber et al, 1998 **Level II**; Saito et al, 2004 **Level II**); other studies have shown no such reductions (Leutz & Harris, 1995 **Level II**; Edwards et al, 1996 **Level II**; Konrath et al, 1996 **Level II**). Similarly, no benefit in terms of pain relief or opioid requirements was seen after total abdominal hysterectomy (Finan et al, 1993 **Level II**) or Caesarean section (Amin-Hanjani et al, 1992 **Level II**).

There was limited evidence to support the use of local cooling for pain relief from perineal trauma after childbirth (East et al, 2007 **Level I**) and no good quality evidence for its use in the treatment in low back pain (French et al, 2006 **Level I**).

There is moderate evidence from four trials that heat wrap therapy results in a small short-term reduction in pain in patients with acute or sub-acute low-back pain (French et al, 2006 **Level I**).

### 8.4.3 Other therapies

There is no evidence to support the use of static magnet therapy for the treatment of pain generally (Pittler et al, 2007 **Level I**) and the use of this therapy had no effect on postoperative pain or analgesic requirements (Cepeda et al, 2007 **Level II**).

Postoperative transcranial magnetic stimulation used in patients after gastric bypass surgery led to significant lower PCA opioid requirements (Borckardt et al, 2006 **Level II**).

There was no difference in postoperative analgesic requirements following use of millimetre wave therapy after total knee arthroplasty (Usichenko, Edinger et al, 2008 **Level II**) or healing touch after coronary artery bypass surgery (MacIntyre et al, 2008 **Level II**), although postoperative anxiety was significantly reduced in the latter study.



## REFERENCES

- Aarskog R, Johnson MI, Demmink JH et al (2007) Is mechanical pain threshold after transcutaneous electrical nerve stimulation (TENS) increased locally and unilaterally? A randomized placebo-controlled trial in healthy subjects. *Physiother Res Int* **12**(4): 251–63.
- Amin-Hanjani S, Corcoran J & Chatwani A (1992) Cold therapy in the management of postoperative cesarean section pain. *Am J Obstet Gynecol* **167**(1): 108–9.
- Barber FA, McGuire DA & Click S (1998) Continuous-flow cold therapy for outpatient anterior cruciate ligament reconstruction. *Arthroscopy* **14**(2): 130–5.
- Barker R, Kober A, Hoerauf K et al (2006) Out-of-hospital auricular acupuncture in elder patients with hip fracture: a randomized double-blinded trial. *Acad Emerg Med* **13**(1): 19–23.
- Baron RS, Logan H & Hoppe S (1993) Emotional and sensory focus as mediators of dental pain among patients differing in desired and felt dental control. *Health Psychol* **12**(5): 381–9.
- Bjordal JM, Johnson MI & Ljunggreen AE (2003) Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur J Pain* **7**(2): 181–8.
- Borckardt JJ, Weinstein M, Reeves ST et al (2006) Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. *Anesthesiology* **105**(3): 557–62.
- Brandner B, Munro B, Bromby LM et al (1996) Evaluation of the contribution to postoperative analgesia by local cooling of the wound. *Anaesthesia* **51**(11): 1021–5.
- Campbell C, Guy A & Banim M (1999) Assessing surgical patients' expectations and subsequent perceptions of pain in the context of exploring the effects of preparatory information: raising issues of gender and status. *Eur J Pain* **3**(3): 211–19.
- Cepeda MS, Carr DB, Lau J et al (2006) Music for pain relief. *Cochrane Database Syst Rev*(2): CD004843.
- Cepeda MS, Carr DB, Sarquis T et al (2007) Static magnetic therapy does not decrease pain or opioid requirements: a randomized double-blind trial. *Anesth Analg* **104**(2): 290–4.
- Claydon LS, Chesterton LS, Barlas P et al (2008) Effects of simultaneous dual-site TENS stimulation on experimental pain. *Eur J Pain* **12**(6): 696–704.
- Daake DR & Gueldner SH (1989) Imagery instruction and the control of postsurgical pain. *Appl Nurs Res* **2**(3): 114–20.
- Das DA, Grimmer KA, Sparnon AL et al (2005) The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: a randomized controlled trial [ISRCTN87413556]. *BMC Pediatr* **5**(1): 1.
- de Jong AE & Gamel C (2006) Use of a simple relaxation technique in burn care: literature review. *J Adv Nurs* **54**(6): 710–21.
- DeSantana JM, Santana-Filho VJ, Guerra DR et al (2008) Hypoalgesic effect of the transcutaneous electrical nerve stimulation following inguinal herniorrhaphy: a randomized, controlled trial. *J Pain* **9**(7): 623–9.
- Desantana JM, Sluka KA & Lauretti GR (2009) High and low frequency TENS reduce postoperative pain intensity after laparoscopic tubal ligation: a randomized controlled trial. *Clin J Pain* **25**(1): 12–9.
- Dowswell T, Bedwell C, Lavender T et al (2009) Transcutaneous electrical nerve stimulation (TENS) for pain relief in labour. *Cochrane Database Syst Rev*(2): CD007214.
- DuHamel KN, Redd WH & Vickberg SM (1999) Behavioral interventions in the diagnosis, treatment and rehabilitation of children with cancer. *Acta Oncol* **38**(6): 719–34.
- East CE, Begg L, Henshall NE et al (2007) Local cooling for relieving pain from perineal trauma sustained during childbirth. *Cochrane Database Syst Rev*(4): CD006304.
- Edwards DJ, Rimmer M & Keene GC (1996) The use of cold therapy in the postoperative management of patients undergoing arthroscopic anterior cruciate ligament reconstruction. *Am J Sports Med* **24**(2): 193–5.
- Ellis JA & Spanos NP (1994) Cognitive-behavioral interventions for children's distress during bone marrow aspirations and lumbar punctures: a critical review. *J Pain Symptom Manage* **9**(2): 96–108.

- Erdogan M, Erdogan A, Erbil N et al (2005) Prospective, Randomized, Placebo-controlled Study of the Effect of TENS on postthoracotomy pain and pulmonary function. *World J Surg* **29**(12): 1563–70.
- Ernst E & Pittler MH (1998) The effectiveness of acupuncture in treating acute dental pain: a systematic review. *Br Dent J* **184**(9): 443–7.
- Finan MA, Roberts WS, Hoffman MS et al (1993) The effects of cold therapy on postoperative pain in gynecologic patients: a prospective, randomized study. *Am J Obstet Gynecol* **168**(2): 542–4.
- French SD, Cameron M, Walker BF et al (2006) Superficial heat or cold for low back pain. *Cochrane Database Syst Rev*(1): CD004750.
- Gavin M, Litt M, Khan A et al (2006) A prospective, randomized trial of cognitive intervention for postoperative pain. *Am Surg* **72**(5): 414–8.
- Good M, Stanton-Hicks M, Grass JA et al (1999) Relief of postoperative pain with jaw relaxation, music and their combination. *Pain* **81**(1–2): 163–72.
- Haase O, Schwenk W, Hermann C et al (2005) Guided imagery and relaxation in conventional colorectal resections: a randomized, controlled, partially blinded trial. *Dis Colon Rectum* **48**(10): 1955–63.
- Hattan J, King L & Griffiths P (2002) The impact of foot massage and guided relaxation following cardiac surgery: a randomized controlled trial. *J Adv Nurs* **37**(2): 199–207.
- Haythornthwaite JA, Lawrence JW & Fauerbach JA (2001) Brief cognitive interventions for burn pain. *Ann Behav Med* **23**(1): 42–9.
- Hoffman HG, Patterson DR & Carrougher GJ (2000) Use of virtual reality for adjunctive treatment of adult burn pain during physical therapy: a controlled study. *Clin J Pain* **16**(3): 244–50.
- Hoffman HG, Richards TL, Van Oostrom T et al (2007) The analgesic effects of opioids and immersive virtual reality distraction: evidence from subjective and functional brain imaging assessments. *Anesth Analg* **105**(6): 1776–83.
- Jensen MP, Turner JA, Romano JM et al (1991) Coping with chronic pain: a critical review of the literature. *Pain* **47**(3): 249–83.
- Johnston M & Vogege C (1993) Benefits of psychological preparation for surgery: a meta analysis. *Annals of Behavioral Medicine* **15**: 245–56.
- Kabat-Zinn J (2003) Mindfulness-based interventions in context: past, present and future. *Clin Psychol: Sci Pract* **10**: 144–56.
- Kihlstrom JF (1985) Hypnosis. *Annu Rev Psychol* **36**: 385–418.
- Kingston J, Chadwick P, Meron D et al (2007) A pilot randomized control trial investigating the effect of mindfulness practice on pain tolerance, psychological well-being, and physiological activity. *J Psychosom Res* **62**(3): 297–300.
- Klassen JA, Liang Y, Tjosvold L et al (2008) Music for pain and anxiety in children undergoing medical procedures: a systematic review of randomized controlled trials. *Ambul Pediatr* **8**(2): 117–28.
- Kober A, Scheck T, Greher M et al (2002) Prehospital analgesia with acupressure in victims of minor trauma: a prospective, randomized, double-blinded trial. *Anesth Analg* **95**(3): 723–7, table of contents.
- Konrath GA, Lock T, Goitz HT et al (1996) The use of cold therapy after anterior cruciate ligament reconstruction. A prospective, randomized study and literature review. *Am J Sports Med* **24**(5): 629–33.
- Krupat E, Fancey M & Cleary PD (2000) Information and its impact on satisfaction among surgical patients. *Soc Sci Med* **51**(12): 1817–25.
- Kwekkeboom KL & Gretarsdottir E (2006) Systematic review of relaxation interventions for pain. *J Nurs Scholarsh* **38**(3): 269–77.
- LaMontagne LL, Hepworth JT, Cohen F et al (2003) Cognitive-behavioral intervention effects on adolescents' anxiety and pain following spinal fusion surgery. *Nurs Res* **52**(3): 183–90.
- Lang T, Hager H, Funovits V et al (2007) Prehospital analgesia with acupressure at the Baihui and Hegu points in patients with radial fractures: a prospective, randomized, double-blind trial. *Am J Emerg Med* **25**(8): 887–93.
- Le Blanc-Louvry I, Costaglioli B, Boulon C et al (2002) Does mechanical massage of the abdominal wall after colectomy reduce postoperative pain and shorten the duration of ileus? Results of a randomized study. *J Gastrointest Surg* **6**(1): 43–9.

- Leutz DW & Harris H (1995) Continuous cold therapy in total knee arthroplasty. *Am J Knee Surg* **8**(4): 121–3.
- Lioffi C & Hatira P (1999) Clinical hypnosis versus cognitive behavioral training for pain management with pediatric cancer patients undergoing bone marrow aspirations. *Int J Clin Exp Hypn* **47**(2): 104–16.
- Lioffi C & Hatira P (2003) Clinical hypnosis in the alleviation of procedure-related pain in pediatric oncology patients. *Int J Clin Exp Hypn* **51**(1): 4–28.
- Logan HL, Baron RS & Kohout F (1995) Sensory focus as therapeutic treatments for acute pain. *Psychosom Med* **57**(5): 475–84.
- Luebbert K, Dahme B & Hasenbring M (2001) The effectiveness of relaxation training in reducing treatment-related symptoms and improving emotional adjustment in acute non-surgical cancer treatment: a meta-analytical review. *Psychooncology* **10**(6): 490–502.
- MacIntyre B, Hamilton J, Fricke T et al (2008) The efficacy of healing touch in coronary artery bypass surgery recovery: a randomized clinical trial. *Altern Ther Health Med* **14**(4): 24–32.
- Madsen MV, Gotzsche PC & Hrobjartsson A (2009) Acupuncture treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. *BMJ* **338**: a3115.
- McCracken LM, Gauntlett-Gilbert J & Vowles KE (2007) The role of mindfulness in a contextual cognitive-behavioral analysis of chronic pain-related suffering and disability. *Pain* **131**(1-2): 63–9.
- Mitchinson AR, Kim HM, Rosenberg JM et al (2007) Acute postoperative pain management using massage as an adjuvant therapy: a randomized trial. *Arch Surg* **142**(12): 1158–67.
- Montgomery GH, DuHamel KN & Redd WH (2000) A meta-analysis of hypnotically induced analgesia: how effective is hypnosis? *Int J Clin Exp Hypn* **48**(2): 138–53.
- Montgomery GH, Weltz CR, Seltz M et al (2002) Brief presurgery hypnosis reduces distress and pain in excisional breast biopsy patients. *Int J Clin Exp Hypn* **50**(1): 17–32.
- Nilsson U (2008) The anxiety- and pain-reducing effects of music interventions: a systematic review. *AORN J* **87**(4): 780–807.
- Olsen MF, Elden H, Janson ED et al (2007) A comparison of high- versus low-intensity, high-frequency transcutaneous electric nerve stimulation for painful postpartum uterine contractions. *Acta Obstet Gynecol Scand* **86**(3): 310–4.
- Patterson DR & Jensen MP (2003) Hypnosis and clinical pain. *Psychol Bull* **129**(4): 495–521.
- Piotrowski MM, Paterson C, Mitchinson A et al (2003) Massage as adjuvant therapy in the management of acute postoperative pain: a preliminary study in men. *J Am Coll Surg* **197**(6): 1037–46.
- Pittler MH, Brown EM & Ernst E (2007) Static magnets for reducing pain: systematic review and meta-analysis of randomized trials. *CMAJ* **177**(7): 736–42.
- Powers SW (1999) Empirically supported treatments in pediatric psychology: procedure-related pain. *J Pediatr Psychol* **24**(2): 131–45.
- Proctor ML, Smith CA, Farquhar CM et al (2002) Transcutaneous electrical nerve stimulation and acupuncture for primary dysmenorrhoea. *Cochrane Database Syst Rev*(1): CD002123.
- Raft D, Smith RH & Warren N (1986) Selection of imagery in the relief of chronic and acute clinical pain. *J Psychosom Res* **30**(4): 481–8.
- Redd WH, Montgomery GH & DuHamel KN (2001) Behavioral intervention for cancer treatment side effects. *J Natl Cancer Inst* **93**(11): 810–23.
- Saito N, Horiuchi H, Kobayashi S et al (2004) Continuous local cooling for pain relief following total hip arthroplasty. *J Arthroplasty* **19**(3): 334–7.
- Seers K & Carroll D (1998) Relaxation techniques for acute pain management: a systematic review. *J Adv Nurs* **27**(3): 466–75.
- Smith CA, Collins CT, Cyna AM et al (2006) Complementary and alternative therapies for pain management in labour. *Cochrane Database Syst Rev*(4): CD003521.
- Spafford PA, von Baeyer CL & Hicks CL (2002) Expected and reported pain in children undergoing ear piercing: a randomized trial of preparation by parents. *Behav Res Ther* **40**(3): 253–66.

- Sullivan MJ, Thorn B, Haythornthwaite JA et al (2001) Theoretical perspectives on the relation between catastrophizing and pain. *Clin J Pain* **17**(1): 52–64.
- Sullivan MJ, Adams H, Rhodenizer T et al (2006) A psychosocial risk factor--targeted intervention for the prevention of chronic pain and disability following whiplash injury. *Phys Ther* **86**(1): 8–18.
- Suls J & Wan CK (1989) Effects of sensory and procedural information on coping with stressful medical procedures and pain: a meta-analysis. *J Consult Clin Psychol* **57**(3): 372–9.
- Sun Y, Gan TJ, Dubose JW et al (2008) Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. *Br J Anaesth* **101**(2): 151–60.
- Syrjala KL, Cummings C & Donaldson GW (1992) Hypnosis or cognitive behavioral training for the reduction of pain and nausea during cancer treatment: a controlled clinical trial. *Pain* **48**(2): 137–46.
- Turk DC & Monarch ES (2002) Biopsychosocial perspective on chronic pain. In: *Psychological Approaches to Pain Management* 2nd edn. Turk DC and Gatchel RJ (eds). New York, Guildford Press.
- Uman LS, Chambers CT, McGrath PJ et al (2006) Psychological interventions for needle-related procedural pain and distress in children and adolescents. *Cochrane Database Syst Rev*(4): CD005179.
- Usichenko TI, Edinger H, Witstruck T et al (2008) Millimetre wave therapy for pain relief after total knee arthroplasty: a randomised controlled trial. *Eur J Pain* **12**(5): 617–23.
- Usichenko TI, Lehmann C & Ernst E (2008) Auricular acupuncture for postoperative pain control: a systematic review of randomised clinical trials. *Anaesthesia* **63**(12): 1343–8.
- Wall VJ & Womack W (1989) Hypnotic versus active cognitive strategies for alleviation of procedural distress in pediatric oncology patients. *Am J Clin Hypn* **31**(3): 181–91.
- Walsh DM, Howe TE, Johnson MI et al (2009) Transcutaneous electrical nerve stimulation for acute pain. *Cochrane Database Syst Rev*(2): CD006142.
- Wild MR & Espie CA (2004) The efficacy of hypnosis in the reduction of procedural pain and distress in pediatric oncology: a systematic review. *J Dev Behav Pediatr* **25**(3): 207–13.
- Williams DA (1996) Acute pain management. In: *Psychological Approaches to Pain Management* 1st edn. Gatchel RJ and Turk DC (eds). New York, Guildford Press.
- Wilson JF (1981) Behavioral preparation for surgery: benefit or harm? *J Behav Med* **4**(1): 79–102.

## 9. SPECIFIC CLINICAL SITUATIONS

### 9.1 POSTOPERATIVE PAIN

One of the most common sources of pain is postoperative pain and a large amount of the evidence presented so far in this document is based on studies of pain relief in the postoperative setting. However, many of the management principles derived from these studies can be applied to the management of acute pain in general, as outlined in this and other sections that follow.

In addition to this approach, there is also a need for information on postoperative pain management that relates to the site of surgery and specific surgical procedures (Rowlingson & Rawal, 2003). The development of such procedure-specific guidelines is ongoing: they require considerable effort and resources and have not been addressed in this document. An ambitious project to develop such evidence-based guidelines for the management of postoperative pain was initiated by the PROSPECT group (Neugebauer et al, 2007; Kehlet et al, 2007). Guidelines for the treatment of pain after a number of specific operations can be found at the PROSPECT website (PROSPECT 2009).

#### 9.1.1 Risks of acute postoperative neuropathic pain

Neuropathic pain has been defined as ‘pain initiated or caused by a primary lesion or dysfunction in the nervous system’ (Merskey & Bogduk, 1994). Acute causes of neuropathic pain can be iatrogenic, traumatic, inflammatory or infective. Nerve injury is a risk in many surgical procedures and may present as acute neuropathic pain in the postoperative period. The incidence of acute neuropathic pain has been reported as 1% to 3%, based on patients referred to an acute pain service, primarily after surgery or trauma (Hayes et al, 2002 **Level IV**). The majority of these patients had persistent pain at 12 months, suggesting that acute neuropathic pain is a risk factor for chronic pain. The role of acute neuropathic pain as a component of postoperative pain is possibly underestimated; after sternotomy 50% of patients had dysaesthesia in the early postoperative period, which was closely associated with severity of postoperative pain (Alston & Pechon, 2005 **Level IV**). Similarly, a high incidence of acute neuropathic pain in lower limbs due to lumbosacral plexus injury has been reported after pelvic trauma (Chiodo, 2007 **Level IV**).

There is some evidence that specific early analgesic interventions may reduce the incidence of chronic pain (often neuropathic pain) after some operations (eg thoracotomy, amputation). For more details see Sections 1.3 and 9.1.2 and 9.1.3. The prompt diagnosis (Rasmussen et al, 2004) of acute neuropathic pain is therefore important. Management is based on extrapolation of data from the chronic pain setting (see Sections 4.3.2 to 4.3.6).

#### Key messages

1. Acute neuropathic pain occurs after trauma and surgery (**U**) (**Level IV**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Diagnosis and subsequent appropriate treatment of acute neuropathic pain might prevent development of chronic pain (**U**).

## 9.1.2 Acute postamputation pain syndromes

Following amputation of a limb, and also breast, tongue, teeth, genitalia and even inner organs such as the rectum, or a deafferentation injury such as brachial plexus avulsion (Bates & Stewart, 1991; Boas et al, 1993; Dijkstra et al, 2007), a number of phenomena can develop. These require differentiation.

- *Stump pain* is pain localised to the site of amputation. It can be acute (usually nociceptive) or chronic (usually neuropathic) and is most common in the immediate postoperative period (Jensen et al, 1985; Nikolajsen & Jensen, 2001). The overall incidence of stump pain is uncertain but the risk of early stump pain is increased by the presence of severe preamputation pain (Nikolajsen et al, 1997).
- *Phantom sensation* is defined as any sensory perception of the missing body part with the exclusion of pain. Almost all patients who have undergone amputation experience phantom sensations (Jensen et al, 1983). These sensations range from a vague awareness of the presence of the organ via associated paraesthesia, to complete sensation including size, shape, position, temperature and movement.
- *Phantom limb pain* is defined as any noxious sensory phenomenon in the missing limb or organ. The incidence of phantom limb pain is estimated to be 30% to 85% after limb amputation and occurs usually in the distal portion of the missing limb (Jensen et al, 1985; Perkins & Kehlet, 2000; Nikolajsen & Jensen, 2001). Pain can be immediate — 75% of patients will report phantom pain within the first few days after amputation (Nikolajsen et al, 1997) — or delayed in onset. The pain is typically intermittent and diminishes with time after amputation. Factors that may be predictive of postamputation phantom pain are the severity of preamputation pain, the degree of postoperative stump pain and chemotherapy (see Section 1.3). If preamputation pain was present, phantom pain may resemble that pain in character and localisation (Katz & Melzack, 1990). Intensity of preamputation pain and acute postoperative pain were strong predictors of intensity of chronic pain after amputation (Hanley et al, 2007 **Level III-3**). Preoperative passive coping strategies, in particular catastrophising, were other strong predictors of phantom limb pain 6 months later (Richardson et al, 2007 **Level III-3**).

There is a strong correlation between phantom limb and stump or site pain and they may be inter-related (Jensen et al, 1983; Kooijman et al, 2000). All three of the above phenomena can coexist (Nikolajsen et al, 1997).

A survey identified the high incidence of these pain syndromes after amputation in 537 amputees; only 14.8% were pain free, 74.5% had phantom limb pain, 45.2% stump pain and 35.5% a combination of both (Kern et al, 2009 **Level IV**).

### Prevention

Evidence for the benefit of epidural analgesia in the prevention of all phantom limb pain is inconclusive (Halbert et al, 2002 **Level I**). However, an analysis of studies on phantom limb pain prophylaxis showed that perioperative (pre, intra and postoperative) epidural analgesia reduced the incidence of severe phantom limb pain (NNT 5.8) (Gehling & Tryba, 2003 **Level III-2**).

A small observational study found that while the overall incidence of long-term phantom limb pain was similar in patients given ketamine (bolus dose followed by an infusion, started prior to skin incision and continued for 72 hours postoperatively) compared with no ketamine, the incidence of severe phantom limb pain was reduced in the ketamine group (Dertwinkel et al, 2002 **Level III-3**). Another study looking at the effects of ketamine reported a numerical but not statistically significant difference in the incidence of phantom limb pain at 6 months after amputation (47% in the ketamine group and 71% in the control group) (Hayes et al, 2004

**Level II**). No preventive effect of perioperative ketamine given by the epidural route was reported in another study (Wilson et al, 2008 **Level II**).

Perioperative gabapentin was ineffective in reducing incidence and severity of phantom limb pain (Nikolajsen et al, 2006 **Level II**).

Infusions of local anaesthetics via peripheral nerve sheath catheters, usually inserted by the surgeon at the time of amputation, are a safe method of providing excellent analgesia in the immediate postoperative period (Pinzur et al, 1996 **Level II**; Lambert et al, 2001 **Level II**). However, they are of no proven benefit in preventing phantom pain or stump pain (Halbert et al, 2002 **Level I**).

## **Therapy**

A survey in 1980 identified over 50 different therapies used for the treatment of phantom limb pain (Sherman et al, 1980), suggesting limited evidence for effective treatments. This was confirmed by a systematic review (Halbert et al, 2002).

Calcitonin by IV infusion is effective in the treatment of acute phantom limb pain (Jaeger & Maier, 1992 **Level II**). Calcitonin may also be given subcutaneously or intranasally (Wall & Heyneman, 1999). It was not effective for chronic phantom limb pain (Eichenberger et al, 2008 **Level II**).

- Ketamine, an NMDA-receptor antagonist (see Section 4.3.2), provided short-term relief of stump and phantom limb pain (Nikolajsen et al, 1996 **Level II**; Eichenberger et al, 2008 **Level II**).
- Oral controlled-release (CR) morphine (Huse et al, 2001 **Level II**) and IV infusions of morphine reduced phantom limb pain (Wu et al, 2002 **Level II**). Morphine was superior to mexiletine (53% vs 30% pain relief) in treating postamputation pain; the NNT for 50% pain relief was 5.6 (Wu et al, 2008 **Level II**).
- Gabapentin was effective in reducing phantom limb pain (Bone et al, 2002 **Level II**).
- IV lignocaine (lidocaine) significantly reduced stump pain but had no effect on phantom pain (Wu et al, 2002 **Level II**).
- Amitriptyline and tramadol provided good control of phantom limb and stump pain in amputees (Wilder-Smith et al, 2005 **Level II**).
- Injections of local anaesthetic into painful myofascial areas of the contralateral limb reduced phantom limb pain and sensations (Casale et al, 2009 **Level II**).

Non-pharmacological treatment options for phantom limb pain are also effective. These include sensory discrimination training (Flor et al, 2001 **Level II**), mental imagery of limb movement (MacIver et al, 2008 **Level IV**; Ulger et al, 2009 **Level IV**) and motor imagery, consisting of 2 weeks each of limb laterality recognition, imagined movements and mirror movements (Moseley, 2006 **Level II**).



### Key messages

1. Continuous regional blockade via nerve sheath catheters provides effective postoperative analgesia after amputation, but has no preventive effect on phantom limb pain (**U**) (**Level II**).
2. Calcitonin, morphine, ketamine, gabapentin, amitriptyline and tramadol reduce phantom limb pain (**S**) (**Level II**).
3. Sensory discrimination training and motor imagery reduce chronic phantom limb pain (**S**) (**Level II**).
4. Ketamine, lignocaine (lidocaine), tramadol and amitriptyline reduce stump pain (**S**) (**Level II**).
5. Perioperative epidural analgesia reduces the incidence of severe phantom limb pain (**U**) (**Level III-2**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Perioperative ketamine may prevent severe phantom limb pain (**U**).

### 9.1.3 Other postoperative pain syndromes

Increasing evidence for the development of postoperative chronic pain syndromes has led to more detailed study of a number of them. The information below does not discuss aspects of surgical techniques that may influence the incidence of chronic pain.

Risk factors that predispose to the development of chronic postsurgical pain include the severity of pre and postoperative pain, intraoperative nerve injury (see Section 1.3). Again, specific early analgesic interventions may reduce the incidence of chronic pain after some operations.

#### **Post-thoracotomy pain syndrome**

Post-thoracotomy pain syndrome is one of the most common chronic pain states. It is thought to be caused primarily by trauma to intercostal nerves and most patients relate their pain directly to the site of surgery (Karmakar & Ho, 2004; Wildgaard et al, 2009). However, myofascial pain syndromes as a consequence of thoracotomy have also been described (Hamada et al, 2000 **Level IV**).

Epidural analgesia initiated prior to thoracotomy and continued into the postoperative period resulted in significantly fewer patients reporting pain 6 months later compared with patients who had received IV PCA opioids for postoperative analgesia (45% vs 78% respectively) (Senturk et al, 2002 **Level II**). There was no statistically significant difference in the incidence of chronic pain between patients given pre-emptive epidural analgesia (initiated prior to surgery) and patients in whom epidural analgesia was commenced after surgery — 39.6% vs 48.6% (Bong et al, 2005 **Level I**).

The addition of low-dose IV ketamine to thoracic epidural analgesia reduced the severity and need for treatment of post-thoracotomy pain at 1 and 3 months postoperatively (Suzuki et al, 2006 **Level II**). However, another study showed that perioperative IV ketamine in addition to interpleural local anaesthetic did not prevent chronic neuropathic pain up to 4 months after thoracotomy (Duale et al, 2009 **Level II**).

Cryoanalgesia, which provides effective pain relief in the immediate postoperative period (De Cosmo et al, 2008), caused an increased incidence of chronic pain (Ju et al, 2008 **Level II**).

### **Postmastectomy pain syndrome**

Chronic pain after mastectomy is common. In one epidemiological study the incidence was 24% at 18 months (Vilholm et al, 2008a **Level IV**); another study looking at patients more than 5 years after surgery (with no recurrence of cancer) reported an incidence of 29% (Peuckmann et al, 2009 **Level IV**). Phantom breast pain has also been described, however, the incidence was low in the range of 7% at 6 weeks and 1% at 2 years (Dijkstra et al, 2007 **Level III-3**); phantom sensations are more common — reported in 19% of patients more than 5 years after surgery (Peuckmann et al, 2009 **Level IV**). Significant predictors for the development of postmastectomy chronic pain were radiotherapy and younger age (Peuckmann et al, 2009 **Level IV**). Other risk factors were higher postoperative pain scores and inclusion of major reconstructive surgery (Chang, Mehta et al, 2009 **Level IV**).

Sensory testing (thermal thresholds, cold allodynia, and temporal summation on repetitive stimulation) showed that postmastectomy pain is a neuropathic pain condition (Vilholm et al, 2009 **Level III-2**).

Preincisional paravertebral block reduced prevalence and intensity of pain 12 months after breast surgery (Kairaluoma et al, 2006 **Level II**). Perioperative use of gabapentin or mexiletine after mastectomy reduced the incidence of neuropathic pain at 6 months postoperatively, from 25% in the placebo to 5% in both treatment groups (Fassoulaki et al, 2002 **Level II**). Similar protective results were achieved by the same group by the use of a eutectic mixture of local anaesthetics alone (Fassoulaki et al, 2000 **Level II**) or in combination with gabapentin (Fassoulaki et al, 2005 **Level II**).

Levetiracetam was ineffective in the treatment of postmastectomy syndrome (Vilholm et al, 2008b **Level II**).

### **Postherniotomy pain syndrome**

This syndrome is thought to be mainly neuropathic pain as a result of nerve injury. This assumption was confirmed in a study that showed that all patients with chronic postherniotomy pain had features of neuropathic pain (Aasvang et al, 2008 **Level IV**). Ejaculatory pain is a feature of this syndrome and occurs in around 2.5% of patients (Aasvang et al, 2007 **Level IV**).

Very young age may be a protective factor as hernia repair in children under 3 months age did not lead to chronic pain in adulthood (Aasvang & Kehlet, 2007 **Level IV**).

Mesh removal and selective neurectomy of macroscopically injured nerves reduced impairment in patients with postherniorrhaphy pain syndrome (Aasvang & Kehlet, 2009 **Level III-3**).

### **Posthysterectomy pain syndrome**

Chronic pain is reported by 5% to 32% of women after hysterectomy (Brandsborg et al, 2008). In most women the pain was present preoperatively; at a 1 to 2 year follow-up, pain was reported as a new symptom in 1% to 15% of patients (Brandsborg et al, 2008). The origin and risk factors for persisting pain after hysterectomy are not clear. However, in a small prospective survey, postoperative pain intensity as well as preoperative non-pelvic pain were associated with the presence of pain 4 months after surgery (Brandsborg et al, 2009 **Level III-3**). For pain reported 1 year after surgery, risk factors were preoperative pelvic and non-pelvic pain and previous Caesarean section; there was no difference found between vaginal or abdominal hysterectomy (Brandsborg et al, 2007 **Level IV**).

Patients given perioperative gabapentin and a postoperative ropivacaine wound infusion had lower opioid requirements after surgery and less pain one month later compared with patients given placebo, although there was no difference in pain scores for the first 7 postoperative

days (Fassoulaki et al, 2007 **Level II**). Spinal anaesthesia in comparison with general anaesthesia reduced the risk of chronic postsurgical pain after hysterectomy (OR: 0.42; CI 0.21 to 0.85) (Brandsborg et al, 2007 **Level IV**).

#### Key messages

1. Perioperative epidural analgesia reduces the incidence of post-thoracotomy pain syndrome (**N**) (**Level II**).
2. Cryoanalgesia for thoracotomy relieves postoperative pain but increases the risk of post-thoracotomy pain syndrome (**N**) (**Level II**).
3. Preincisional paravertebral block and perioperative use of gabapentin, mexiletine and/or eutectic mixture of local anaesthetic reduce the incidence of postmastectomy pain (**N**) (**Level II**).
4. Post-thoracotomy, postmastectomy, postherniotomy and posthysterectomy pain syndromes occur frequently (**N**) (**Level IV**).

### 9.1.4 Day-stay or short-stay surgery

Over 60% of surgery is now performed on a day-stay basis. Adequate postoperative pain management is often the limiting factor when determining whether a patient can have surgery performed as a day procedure. Provision of analgesia after ambulatory surgery remains poor. In two Swedish nationwide surveys of ambulatory surgery, pain was the most common problem at follow-up after discharge in a general (Segerdahl et al, 2008a **Level IV**) and a paediatric population (Segerdahl et al, 2008b **Level IV**). Another survey from a single institution found that even at 3 and 4 days after day-stay surgery, 10% and 9% of patients respectively reported moderate to severe pain (Greengrass & Nielsen, 2005 **Level IV**). The best predictive factor was the presence of preoperative pain; other factors included preoperative high expectations of postoperative pain, anticipation of pain by clinicians and younger age (Gramke et al, 2009 **Level IV**).

#### Adverse effects of pain

Inadequate analgesia may delay patient discharge; pain was the most common cause of Phase 1 recovery delays affecting 24% of patients overall (Pavlin et al, 2002 **Level IV**).

Uncontrolled pain is also a major cause of nausea and vomiting, further extending the patient's stay in the recovery room (Eriksson et al, 1996; Michaloliakou et al, 1996). The most common reason for unplanned hospital admission across 14 day-surgery units in Finland was unrelieved pain (Mattila & Hynynen, 2009 **Level III-2**).

Inadequate pain management may cause sleep disturbance (Strassels et al, 2002 **Level IV**) and limit early mobilisation, which may be crucial for early return to normal function and work (Strassels et al, 2002 **Level IV**).

#### Analgesic drugs and techniques

More complex surgery continues to be performed on a day-stay or short-stay basis and therefore the analgesic drugs and techniques required are similar to those used for inpatient pain relief — see relevant sections of this document:

- systemically administered analgesic drugs (Section 4);
- regionally and locally administered analgesics drugs (Section 5); and
- regional and other local analgesia techniques (Section 7).

However, certain local and regional techniques offer specific benefits to patients after day-stay or short-stay surgery; these issues are discussed here. In particular, there has been increasing interest in the use of 'single-dose' as well as continuous peripheral nerve blockade (CPNB) in patients discharged home.

### **Local infiltration**

Infiltration of local anaesthetic reduced requirements for opioid analgesics after day surgery and leads to a lower incidence of nausea and vomiting (Eriksson et al, 1996 **Level II**; Michaloliakou et al, 1996 **Level II**).

After day-stay hernia repair, wound infiltration with levobupivacaine provided analgesia for 24 hours (Ausems et al, 2007 **Level II**). Local infiltration was superior to opioid and tenoxicam after minor laparoscopic surgery (Salman et al, 2000 **Level II**). Infiltration of the trocar site for day-case laparoscopic cholecystectomy was more effective if done prior to incision than postoperatively (Cantore et al, 2008 **Level II**). However, after day-case laparoscopic gynaecological surgery, wound infiltration did not significantly reduce pain or opioid requirements (Fong et al, 2001 **Level II**).

### **Continuous wound infusions with local anaesthetics**

There were only limited analgesic benefits for the first postoperative day with the continuous infusion of local anaesthetic after outpatient inguinal hernia repair (Schurr et al, 2004 **Level II**; Lau et al, 2003 **Level II**).

### **Single-dose peripheral nerve blockade**

Peripheral nerve blocks (PNBs) are useful in ambulatory surgery as they provide site-specific anaesthesia with prolonged analgesia and minimal haemodynamic changes. The decision to discharge ambulatory patients following PNB with long-acting local anaesthesia is controversial as there is always the potential risk of harm to an anaesthetised limb.

A prospective study including 1119 upper and 1263 lower extremity blocks demonstrated that long-acting PNBs were safe and that patients could be discharged with an insensate limb (Klein et al, 2002 **Level IV**). Provided patients are given verbal and written information regarding the risks as well as appropriate follow-up, it would seem reasonable to discharge these patients with the benefit of prolonged analgesia.

#### *Ilioinguinal and iliohypogastric nerve block*

Herniorrhaphy performed under ilioinguinal and iliohypogastric nerve block led to superior pain relief, less morbidity, less urinary retention and cost advantages (Ding & White, 1995 **Level II**). The analgesic benefit with bupivacaine lasted around 6 hours (Toivonen et al, 2001 **Level II**).

#### *Paravertebral block*

Paravertebral blocks provided better analgesia than more distal nerve blocks after inguinal herniorrhaphy with earlier discharge, high patient satisfaction and few side effects (Klein et al, 2002 **Level II**). Their successful use has also been reported after outpatient lithotripsy (Jamieson & Mariano, 2007 **Level IV**). While paravertebral blocks after major ambulatory breast surgery provided good analgesia (Weltz et al, 1995 **Level II**), after minor breast surgery in a day-care setting, the benefits were small and may not justify the risk (Terheggen et al, 2002 **Level II**).

#### *Upper and lower limb blocks*

A single-dose femoral nerve block with bupivacaine for anterior cruciate ligament reconstruction provided 20 to 24 hours of postoperative analgesia (Mulroy et al, 2001 **Level II**). There was an associated decreased requirement for recovery room stay and unplanned hospital admission, thereby having the potential to create significant hospital cost savings

(Williams et al, 2004 **Level III-3**). After complex outpatient knee surgery, femoral-sciatic nerve block provided better pain relief than femoral nerve block alone, and both techniques reduced unplanned hospital admissions to a similar extent (Williams et al, 2003 **Level IV**).

Interscalene plexus block provided safe and effective analgesia after ambulatory shoulder surgery (Bishop et al, 2006 **Level IV**; Faryniarz et al, 2006 **Level IV**). For hand and wrist surgery, infraclavicular nerve blocks with propofol sedation, compared with general anaesthesia followed by local anaesthetic wound infiltration, resulted in less postoperative pain, less nausea, earlier ambulation and earlier hospital discharge. (Hadzic et al, 2004 **Level II**).

### **Continuous peripheral nerve blockade**

Patients may suffer intense pain following resolution of a peripheral nerve block although it maximises pain relief in the first 12 to 24 hours (Chung et al, 1997 **Level IV**). CPNB using perineural catheters and continuous infusions of local anaesthetic led to sustained postoperative analgesia (Ilfeld, Morey, Wang et al, 2002 **Level II**; Ilfeld, Morey & Enneking, 2002 **Level II**; Zaric et al, 2004 **Level II**), was opioid-sparing (Ilfeld, Morey, Wang et al, 2002 **Level II**; Ilfeld, Morey & Enneking, 2002 **Level II**; Ilfeld et al, 2003 **Level II**) and resulted in less sleep disturbance (Ilfeld, Morey, Wang et al, 2002 **Level II**; Ilfeld, Morey & Enneking, 2002 **Level II**) and improved rehabilitation (Capdevila et al, 1999 **Level II**). Patients achieved discharge criteria significantly earlier in a number of ambulatory settings: after total shoulder arthroplasty with use of continuous interscalene blocks (21 vs 51 hours) (Ilfeld et al, 2006 **Level II**); after hip arthroplasty with use of continuous lumbar plexus block (29 vs 52 hours) (Ilfeld, Ball et al, 2008 **Level II**); and after total knee arthroplasty with the use of continuous femoral nerve blocks (25 vs 71 hours) (Ilfeld, Le et al, 2008 **Level II**). These benefits have the potential to reduce hospital costs (Ilfeld et al, 2007 **Level III-3**).

Compared with a single-injection interscalene block, a 2-day interscalene infusion at home after shoulder surgery was opioid-sparing and improved pain relief, sleep and patient satisfaction (Mariano et al, 2009 **Level II**).

Patient-controlled delivery of the infusion improved analgesia and function more than a continuous infusion and even more so compared with IV morphine PCA (Capdevila et al, 2006 **Level II**).

The safety and efficacy of CPNBs in an ambulatory setting has been confirmed in adult (Swenson et al, 2006 **Level IV**; Fredrickson et al, 2008 **Level IV**) and paediatric patients (Ganesh et al, 2007 **Level IV**; Ludot et al, 2008 **Level IV**).

Inadvertent intravascular catheter placement should be excluded prior to patient discharge using a test dose of local anaesthetic and adrenaline (epinephrine) (Rawal et al, 2002). Patients and their carers should be given extensive oral and written instructions about management, side effects and care of the local anaesthetic catheter, and have 24-hour a day telephone access to an anaesthesiologist during the postoperative period while CNPB is in use (Swenson et al, 2006), as 30% of patients make unscheduled phone calls regarding catheter infusions despite been given adequate written and verbal instructions (Ilfeld, Morey & Enneking, 2002 **Level II**). A review of 620 outpatients with CPNB (including popliteal fossa, fascia iliaca and interscalene) showed that 4.2% required assistance by the anaesthesiologist after discharge from hospital for problems relating to issues such as patient education, inadequate analgesia and equipment malfunction; only one patient was unable to remove their catheter (Swenson et al, 2006 **Level IV**), although patients may have significant anxiety about catheter removal at home (Ilfeld et al, 2004 **Level IV**).

Detailed reviews of the use of CPNBs for ambulatory surgery have been published (Cheng et al, 2008; Ilfeld & Enneking, 2005).

## Non-pharmacological techniques

Non-pharmacological techniques such as transcutaneous electrical nerve stimulation (TENS), acupuncture, hypnosis, ultrasound, laser and cryoanalgesia have also been used in the treatment of acute pain management after ambulatory surgery. Pressure on acupoints decreased pain following knee arthroscopy (Felhendler & Lisander, 1996 **Level II**). Continuous-flow cold therapy has been shown to be effective following outpatient anterior cruciate ligament reconstruction, also reducing analgesic requirements (Barber et al, 1998 **Level II**).

### Key messages

1. Infiltration of the wound with local anaesthetic agents provides good and long-lasting analgesia after ambulatory surgery (**U**) (**Level II**).
2. Peripheral nerve blocks with long-acting local anaesthetic agents provide long-lasting postoperative analgesia after ambulatory surgery (**U**) (**Level II**).
3. Single shot infraclavicular blocks provide effective analgesia and less nausea following hand and wrist surgery and earlier ambulation and hospital discharge compared with general anaesthesia (**N**) (**Level II**).
4. Continuous peripheral nerve blocks provide extended analgesia after ambulatory surgery (**U**) (**Level II**), leading to reduced opioid requirements, less sleep disturbance, earlier achievement of discharge criteria and improved rehabilitation (**N**) (**Level II**).
5. Continuous peripheral nerve blocks have been shown to be safe at home, if adequate resources and patient education are provided (**U**) (**Level IV**).
6. Pain relief after ambulatory surgery remains poor (**N**) (**Level IV**) and is a common cause of unplanned readmissions (**N**) (**Level III-3**).

### 9.1.5 Cranial neurosurgery

There is a widespread belief that intracranial surgery does not result in much patient discomfort and pain. However, recent surveys have shown that patients may have significant pain in the early phase after intracranial surgery. In one survey, 69% of patients reported moderate to severe pain on the first postoperative day (Gottschalk et al, 2007 **Level IV**). These findings are in line with another study that found incidences of 56% moderate and 25% severe pain (Thibault et al, 2007 **Level IV**). Similar numbers of up to 80% are confirmed in a review of the literature on this topic (Nemergut et al, 2007).

However, the pain is not as severe as, for example, after spinal surgery (Klimek et al, 2006 **Level III-2**) or other surgical procedures such as extracranial maxillary/mandibular surgery or lumbar surgery (Dunbar et al, 1999 **Level III-2**). The pain is said to be more severe after an infratentorial rather than a supratentorial approach (Gottschalk et al, 2007 **Level IV**; Thibault et al, 2007 **Level IV**). These differences are disputed only by one small study (Irefin et al, 2003 **Level III-2**). Non-craniotomy neurosurgery, for example trans-sphenoidal surgery, seems to be associated with very limited pain and minimal morphine requirements (Flynn & Nemergut, 2006 **Level IV**).

It is noteworthy that craniotomy can lead to significant chronic headache. Six months after supratentorial craniotomy for aneurysm repair, 40% of patients reported headache according to the International Headache Society classification, of whom 10.7% had acute and 29.3% chronic headache (Rocha-Filho et al, 2008 **Level IV**). There were no differences between patients with or without subarachnoid haemorrhage.

The management of postoperative pain after intracranial surgery is often poor. The problems of postcraniotomy analgesia were analysed in a survey of United Kingdom neurosurgical centres (Roberts, 2005 **Level IV**); the principal analgesic was IM codeine, only three of twenty-three centres used morphine and only one used PCA. Pain was only assessed in 57% of cases (Roberts, 2005 **Level IV**). This practice had not changed since 1995 when IM codeine was the primary analgesic used by 97% of centres (Stoneham & Walters, 1995 **Level IV**).

A number of reasons are likely to contribute to this, such as concerns about the adverse effects of opioids and their ability to interfere with recovery and neurological assessment, as well as the concern that opioid-induced respiratory depression will lead to hypercarbia and increased intracranial pressure (Nemergut et al, 2007). Similarly, there is a concern that non-steroidal anti-inflammatory drugs (NSAIDs) could interfere with haemostasis and increase intracranial bleeding. Furthermore, there is poor evidence on which to base protocols for the assessment and treatment of pain after cranial surgery (Nemergut et al, 2007); the limited number of available heterogeneous trials have many weaknesses in study design and methodology. The question remains as to whether all craniotomies are the same with regard to analgesic requirements (Nemergut et al, 2007).

### ***Treatment of acute postoperative pain after cranial neurosurgery***

#### ***Paracetamol***

A trial comparing paracetamol (acetaminophen) alone with paracetamol plus tramadol or paracetamol plus nalbuphin was stopped early as paracetamol alone gave ineffective pain relief in most patients (Verchere et al, 2002 **Level II**).

#### ***Non-selective non-steroidal anti-inflammatory drugs***

Ketoprofen was more effective than paracetamol in reducing PCA opioid requirements after craniotomy but with minimal benefits in regard to pain scores and no change in adverse effects (Tanskanen et al, 1999 **Level II**). However, a single-centre, retrospective cohort study of 6668 cases over 5 years identified an association between the development of postoperative haematoma and the use of aspirin or non-selective NSAIDs (nsNSAIDs) (Palmer et al, 1994 **Level IV**).

#### ***Coxibs***

There was some limited benefit with the use of parecoxib over placebo at 6 hours, but not at other time points in the first 24 hours postoperatively, with regard to pain scores and morphine use in one study (Jones et al, 2009 **Level II**). Another study identified better pain control and an opioid-sparing effect of rofecoxib compared with placebo (Rahimi et al, 2006 **Level II**).

#### ***Opioids***

Not surprisingly, PCA morphine or PCA morphine with ondansetron was superior to placebo after infratentorial craniotomy (Jellish et al, 2006 **Level II**). Morphine was also more effective than codeine following craniotomy; this was found for IM prn administration of both compounds (Goldsack et al, 1996 **Level II**) but also in a comparison of PCA morphine with IM codeine (Sudheer et al, 2007 **Level II**). PCA fentanyl was more effective than prn IV fentanyl and did not increase the risk of adverse effects after craniotomy (Morad et al, 2009 **Level II**).

Codeine 60 mg IM was more effective than tramadol 50 mg or 75 mg IM (Jeffrey et al, 1999 **Level II**) and morphine PCA was better than tramadol PCA (Sudheer et al, 2007 **Level II**).

The intraoperative use of remifentanyl may result in increased pain and/or increased analgesia requirements postoperatively (see Section 4.1.3). This was found when compared with both fentanyl (Gelb et al, 2003 **Level II**) and sufentanil (Gerlach et al, 2003 **Level II**).



### **Local anaesthetic scalp block**

A comparison between scalp nerve block and morphine showed no relevant differences in any analgesic parameters (Ayoub et al, 2006 **Level II**). Scalp infiltration was also no more effective than IV fentanyl (Biswas & Bithal, 2003 **Level II**).

However, comparisons of scalp blocks with bupivacaine or ropivacaine and placebo showed better analgesia with the local anaesthetic blocks in a number of trials (Bloomfield et al, 1998 **Level II**; Nguyen et al, 2001 **Level II**; Law-Koune et al, 2005 **Level II**; Bala et al, 2006 **Level II**; Gazoni et al, 2008 **Level II**; Batoz et al, 2009 **Level II**). Scalp infiltration with ropivacaine also reduced the incidence of persistent pain 2 months after craniotomy, from 56% to 8% (Batoz et al, 2009 **Level II**).

A comparison between SC local anaesthetic infiltration and occipital/supraorbital nerve block showed no difference between groups in the postoperative period, but nerve blocks were less painful than infiltration analgesia (Watson & Leslie, 2001 **Level II**).

### **Adjuvant drugs**

Clonidine did not improve analgesia after supratentorial craniotomy (Stapelfeldt et al, 2005 **Level II**).

### **Key messages**

1. Morphine is more effective than codeine and tramadol for pain relief after craniotomy (**N**) (**Level II**).
2. Local anaesthetic infiltration of the scalp provides early analgesia after craniotomy and reduces incidence of subsequent chronic pain (**N**) (**Level II**).
3. Craniotomy leads to significant pain in the early postoperative period (**N**) (**Level IV**), which is however not as severe as pain from other surgical interventions (**N**) (**Level III-2**).
4. Craniotomy can lead to significant chronic headache (**N**) (**Level IV**).

## **9.2 ACUTE PAIN FOLLOWING SPINAL CORD INJURY**

Acute pain following spinal cord injury (SCI) is common, with over 90% of patients experiencing pain in the first 2 weeks following injury (Siddall et al, 1999 **Level IV**); however the range of described prevalence varies between 26% and 96% (Dijkers et al, 2009 **Level IV**). Acute pain may also develop during the rehabilitation phase due to intercurrent disease (eg renal calculus) or exacerbation of a chronic pain syndrome.

Pain associated with SCI usually falls into two main categories: neuropathic pain, either at or below the level of the injury, and nociceptive pain, from somatic and visceral structures (Siddall et al, 2002). Neuropathic pain associated with a lesion of the central (somatosensory) nervous system is termed central pain (Loeser & Treede, 2008). Phantom pain and complex regional pain syndromes may also develop in patients with SCI.

**Table 9.1 Taxonomy of acute pain associated with spinal cord injury**

Pain type	Location relative to level of injury	Description, structures and pathology
Neuropathic pain	Above level	pain located in an area of sensory preservation peripheral nerve or plexus injury
	At level	'segmental pain' at level of the injury spinal cord lesion (central pain) nerve root lesion (cauda equina) combined cord and root lesions syringomyelia
	Below level	pain below the level of injury spinal cord lesion (eg central dysaesthesia syndrome) phantom pain
	Other	complex regional pain syndrome
Nociceptive pain	Somatic	musculoskeletal pain (eg vertebral fracture, muscle spasms, overuse syndromes) procedure-related pain (eg pressure sore dressings)
	Visceral	urinary tract (eg calculi) gastrointestinal tract
Other		dysreflexic headache

The taxonomy of acute pain associated with spinal cord injury in Table 9.1 is based on Siddall (Siddall et al, 2002).

### ***Treatment of acute neuropathic pain after spinal cord injury***

There are no studies specifically examining the treatment of acute neuropathic pain following SCI. Treatment must therefore be based on evidence from studies of chronic central pain and other neuropathic pain syndromes. An algorithm for the treatment of pain in patients with SCI has been promulgated (Siddall & Middleton, 2006).

#### ***Opioids and tramadol***

Under experimental conditions, IV alfentanil decreased central pain following SCI compared with placebo and ketamine (Eide et al, 1995 **Level II**). IV morphine decreased tactile allodynia but had no effect on other neuropathic pain components in SCI and poststroke patients (Attal et al, 2002 **Level II**). Tramadol was effective for the treatment of neuropathic pain after spinal cord injury but the incidence of side effects was high (Norrbrink & Lundeberg, 2009 **Level II**).

#### ***Ketamine***

Ketamine infusion decreased neuropathic pain in SCI patients (Eide et al, 1995 **Level II**; Kvarnstrom et al, 2004 **Level II**).

#### ***Membrane stabilisers***

Under experimental conditions, IV lignocaine reduced neuropathic pain in SCI (Finnerup, Biering-Sorensen et al, 2005 **Level II**) and reduced spontaneous pain and brush allodynia in central pain (Attal et al, 2000 **Level II**). Other trials have found that lignocaine reduced pain in only one of ten SCI patients (Kvarnstrom et al, 2004 **Level II**) and that mexiletine was ineffective (Chiou-Tan et al, 1996 **Level II**). Lignocaine was most effective in the treatment of neuropathic pain due to peripheral nerve lesions (Kalso et al, 1998 **Level I**).

**Antidepressants**

There was no significant difference in pain or disability in SCI patients with chronic pain treated with amitriptyline or placebo (Cardenas et al, 2002 **Level II**); however amitriptyline improved below-level neuropathic pain in patients with depression (Rintala et al, 2007 **Level II**). There are no studies of selective serotonin reuptake inhibitors (SSRIs) in the treatment of central pain (Finnerup, Otto et al, 2005 **Level I**).

**Anticonvulsants**

Pregabalin significantly reduced central pain and improved sleep, anxiety and global impression of change in patients with SCI, compared with placebo (Siddall et al, 2006 **Level II**). Smaller trials supported the effectiveness of gabapentin in decreasing central pain and improving quality of life (Levendoglu et al, 2004 **Level II**; Tai et al, 2002 **Level II**). Lamotrigine reduced spontaneous and evoked pain in patients with incomplete SCI (Finnerup et al, 2002 **Level II**). Valproate was ineffective in the treatment of SCI pain (Drewes et al, 1994 **Level II**).

**Intravenous anaesthetics**

An IV bolus of low-dose propofol reduced the intensity of central pain and allodynia for up to 1 hour in approximately 50% of patients (Canavero & Bonicalzi, 2004 **Level II**).

**Non-pharmacological techniques**

Self-hypnosis as well as electromyograph (EMG) biofeedback training led to reduced pain intensity in patients with SCI; in some aspects self-hypnosis was superior to EMG biofeedback (Jensen et al, 2009 **Level II**).

**Treatment of nociceptive and visceral pain after spinal cord injury**

There is no specific evidence to guide the treatment of acute nociceptive and visceral pain in SCI patients. Treatment must therefore be based on evidence from other studies of nociceptive and visceral pain.

**Key messages**

1. Gabapentinoids (gabapentin/pregabalin) (**S**), intravenous opioids, ketamine or lignocaine (lidocaine) (**U**) tramadol, self-hypnosis and electromyograph biofeedback (**N**) are effective in the treatment of neuropathic pain following spinal cord injury (**Level II**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Treatment of acute spinal cord pain is largely based on evidence from studies of other neuropathic and nociceptive pain syndromes (**U**).

**9.3 ACUTE BURN INJURY PAIN**

Acute pain following burn injury can be nociceptive and/or neuropathic in nature and may be constant (background pain), intermittent or procedure-related. There is limited evidence for the management of pain in burn injury and treatment is largely based on evidence from case reports and case series, or data extrapolated from other relevant areas of pain medicine.

Burn pain is often undertreated, particularly in the elderly (Choiniere, 2001). However, effective pain management after acute burn injury is essential, not only for humanitarian and psychological reasons, but also to facilitate procedures such as dressing changes and

physiotherapy, and possibly to minimise the development of chronic pain, which is reported in 35% to 58% of burn patients (Choiniere et al, 1989; Dauber et al, 2002).

Immediately after the injury, simple measures such as cooling (Davies, 1982), covering, elevating and immobilising the burn may provide analgesia (Kinsella & Booth, 1991; Gallagher, Rae & Kinsella, 2000). With severe burn pain, analgesia is best achieved by titration of IV opioids.

Opioid doses do not require adjustment, as the pharmacokinetics of morphine are unchanged in burns patients (Perreault et al, 2001). Absorption of IM and SC opioids may be unreliable in the presence of hypovolaemia and vasoconstriction associated with burns (Kinsella & Rae, 2008).

PCA with morphine is effective for burn pain in adults (Choiniere et al, 1992 **Level II**) and children (Gaukroger et al, 1991 **Level IV**). Conversion to oral opioids is possible once normal gastrointestinal (GI) function has returned; even severe burn injury does not affect gastric emptying or the absorption of oral paracetamol (Hu et al, 1993 **Level III-2**).

Opioids may be supplemented with non-opioid drugs. There is experimental evidence for beneficial effects of ketamine (Ilkjaer et al, 1996) and dextromethorphan (Ilkjaer et al, 1997) on hyperalgesia, and clinical evidence of an opioid-sparing effect with clonidine (Viggiano et al, 1998 **Level II**).

Gabapentin reduced pain and opioid consumption following acute burns injury (Cuignet et al, 2007 **Level III-3**) and reduced neuropathic pain descriptors in a small case series (Gray et al, 2008 **Level IV**).

Parenteral methylprednisolone or ketorolac reduced secondary hyperalgesia surrounding an experimental burn injury in human volunteers, however further clinical research is required (Stubhaug et al, 2007 **Level II**).

### 9.3.1 Management of procedural pain

Procedural pain may be difficult to manage in burn patients. Dressing changes may be associated with frequent and prolonged periods of pain with up to 84% of burn patients reporting extreme, intense pain during therapeutic procedures (Ashburn, 1995). The choice of dressing has an effect on time to healing and pain during dressing change; biosynthetic dressings have been found to be superior (Wasiak et al, 2008 **Level I**).

Opioid therapy is the mainstay of analgesia for burn procedures. However, very high doses may be required (Linneman et al, 2000 **Level IV**) and opioid-related sedation and respiratory depression may develop when the pain stimulus decreases following the procedure.

Short-acting opioids such as fentanyl (Prakash et al, 2004 **Level II**) or alfentanil (Sim et al, 1996 **Level IV**) administered via PCA or target-controlled infusions (Gallagher, Rae, Kenny et al, 2000 **Level IV**) have been used successfully to provide analgesia during burn dressing changes.

IN fentanyl was a viable alternative to oral morphine in children for burn dressings (Borland et al, 2005 **Level II**). In adults, there was no difference in pain scores or rescue analgesic requirements between IN fentanyl and oral morphine for burn dressings (total surface less than 26%) (Finn et al, 2004 **Level II**). Oral transmucosal fentanyl provided similar analgesia to oral oxycodone (Sharar et al, 2002 **Level II**) and hydromorphone (Sharar et al, 1998 **Level II**) with a similar side-effect profile, for daily burn care in children and adolescents (see Section 10.4.1).

Nitrous oxide (N<sub>2</sub>O), ketamine and IV lignocaine infusions (Jonsson et al, 1991 **Level IV**) have also been used to provide analgesia for burn procedures (see Sections 4.3.1, 4.3.2 and 4.3.5), however a Cochrane review reported that more trials were required to determine the efficacy of lignocaine (Wasiak & Cleland, 2007 **Level I**).

PCA with a ketamine and midazolam mixture was effective and well-tolerated when used for analgesia and sedation during burn dressings (MacPherson et al, 2008 **Level IV**).

Sedation, as an adjunct to analgesia, can improve pain relief. This has been shown for lorazepam combined with morphine (Patterson et al, 1997 **Level II**); patient-controlled sedation with propofol may also be effective (Coimbra et al, 2003 **Level IV**). A propofol/ketamine combination resulted in less 'restlessness' during burn dressing changes compared with a propofol/fentanyl combination, with no difference in emergence phenomena (Tosun et al, 2008 **Level II**). Dexmedetomidine may be effective for sedation in the intensive care unit for paediatric burn patients but further trials are required (Walker et al, 2006 **Level IV**).

Topical analgesic techniques, such as lignocaine (Brofeldt et al, 1989 **Level IV**) or morphine-infused silver sulfadiazine cream (Long et al, 2001 **Level IV**) may be effective, however a topical gel dressing containing morphine was no more effective than other gel dressing in reducing burn injury pain in the emergency department (Welling, 2007 **Level II**).

### 9.3.2 Non-pharmacological pain management

Hypnosis, distraction, auricular electrical stimulation, therapeutic touch techniques and massage therapy have been used for the treatment of burn pain, including procedural pain. A lack of prospective randomised trials makes comparisons with conventional therapies difficult (Kinsella & Rae, 2008) (see Section 8.1.3). A study comparing two psychological support interventions, hypnosis and stress-reducing strategies, found that visual analogue scale (VAS) anxiety scores were significantly better after hypnosis although there was no significant difference in pain reports (Frenay et al, 2001 **Level II**).

Distraction by virtual reality (VR) techniques reduced pain scores in children during burn dressings (Das et al, 2005 **Level III-3**) including in a hydrobath (Hoffman et al, 2008 **Level III-3**) and following burn physical rehabilitation (Sharar et al, 2007 **Level III-3**). Simply watching television during burn care may be as effective as VR in reducing pain scores (van Twillert et al, 2007 **Level III-3**).

Augmented reality techniques (interactive computer programme) produced a statistically significant reduction in pain compared with usual care during paediatric burn dressings lasting longer than 30 minutes, however further research is required to determine the clinical utility of these methods (Mott et al, 2008 **Level II**).

#### Key messages

1. The use of biosynthetic dressings is associated with a decrease in time to healing and a reduction in pain during burn dressings changes (**N**) (**Level I** [Cochrane Review]).
2. Opioids, particularly via PCA, are effective in burn pain, including procedural pain (**S**) (**Level II**).
3. Augmented reality techniques (**N**) (**Level II**), virtual reality or distraction techniques (**N**) (**Level III-3**) reduce pain during burn dressings.
4. Gabapentin reduces pain and opioid consumption following acute burn injury (**N**) (**Level III-3**).
5. PCA with ketamine and midazolam mixture provides effective analgesia and sedation for burn dressings (**N**) (**Level IV**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Acute pain following burn injury can be nociceptive and/or neuropathic in nature and may be constant (background pain), intermittent or procedure-related.
- Acute pain following burn injury requires aggressive multimodal and multidisciplinary treatment.

## 9.4 ACUTE BACK PAIN

Acute back pain in the cervical, thoracic, or, in particular, lumbar and sacral regions, is a common problem affecting most adults at some stage of their lives. The causes are rarely serious, most often non-specific and the pain is usually self-limiting.

Appropriate investigations are indicated in patients who have signs or symptoms that might indicate the presence of a more serious condition ('red flags'). Such 'red flags' include symptoms and signs of infection (eg fever), risk factors for infection (eg underlying disease process, immunosuppression, penetrating wound, drug abuse by injection), history of trauma or minor trauma, history of osteoporosis and taking corticosteroids, past history of malignancy, age greater than 50 years, failure to improve with treatment, unexplained weight loss, pain at multiple sites or at rest and absence of aggravating features (Australian Acute Musculoskeletal Pain Guidelines Group, 2003). A full neurological examination is warranted in the presence of lower limb pain and other neurological symptoms (eg weakness, foot drop, cauda equina syndrome, loss of bladder and/or bowel control).

Psychosocial and occupational factors ('yellow flags') appear to be associated with an increased risk of progression from acute to chronic pain; such factors should be assessed early in order to facilitate appropriate interventions (Australian Acute Musculoskeletal Pain Guidelines Group, 2003).

NHMRC guidelines for the evidence-based management of acute musculoskeletal pain include chapters on acute neck, thoracic spinal and low back pain (Australian Acute Musculoskeletal Pain Guidelines Group, 2003). In view of the high quality and extensiveness of these guidelines, no further assessment of these topics has been undertaken for this document. The following key messages are an abbreviated summary of key messages from these guidelines; the practice points recommended for musculoskeletal pain in general are listed in Section 9.5 and represent the consensus of the Steering Committee of these guidelines. These guidelines can be found on the NHMRC website (Australian Acute Musculoskeletal Pain Guidelines Group, 2003).

Since their publication, a number of further guidelines have been published that are worth considering. These include:

- *The Health Care Guideline: Adult Low Back Pain of the Institute for Clinical Systems Improvement* (ICSI, 2008).
- *The Guideline on Management of Acute Low Back pain by the Michigan Quality Improvement Consortium* (Michigan Quality Improvement Consortium, 2008).
- *Clinical Guidelines for Best Practice Management of Acute and Chronic Whiplash-Associated Disorders* (South Australian Centre for Trauma and Injury Recovery and endorsed by NHMRC) (TRACsa, 2008).
- *American Pain Society and American College of Physicians clinical practice guidelines*. These cover both acute and chronic low back pain (Chou & Huffman, 2007a; Chou & Huffman 2007b; Chou et al 2007).

The relevant key messages of these guidelines are very similar to the ones presented here.

#### Key messages

1. Acute low back pain is non-specific in about 95% of cases and serious causes are rare; common examination and investigation findings also occur in asymptomatic controls and may not be the cause of pain (U) (Level I).
2. Advice to stay active, 'activity-focused' printed and verbal information, and behavioural therapy interventions are beneficial in acute low back pain (U) (Level I).
3. Advice to stay active, exercises, multimodal therapy and pulsed electromagnetic therapy (in the short term) are effective in acute neck pain (U) (Level I).
4. Soft collars are not effective for acute neck pain (U) (Level I).
5. Appropriate investigations are indicated in cases of acute low back pain when alerting features ('red flags') of serious conditions are present (U) (Level III-2).
6. Psychosocial and occupational factors ('yellow flags') appear to be associated with progression from acute to chronic back pain; such factors should be assessed early to facilitate intervention (U) (Level III-2).

## 9.5 ACUTE MUSCULOSKELETAL PAIN

Other than acute back pain, acute shoulder and anterior knee pain are two common painful musculoskeletal conditions.

A summary of findings relating to acute musculoskeletal pain can be found in *Evidence-based Management of Acute Musculoskeletal Pain*, published by the Australian Acute Musculoskeletal Pain Guidelines Group and endorsed by the NHMRC (Australian Acute Musculoskeletal Pain Guidelines Group, 2003). In view of the high quality and extensiveness of these guidelines, no further assessment of these topics has been undertaken for this document.

The following is an abbreviated summary of key messages from these guidelines and represent the consensus of the Steering Committee of these guidelines.

These guidelines can be found on the NHMRC website (Australian Acute Musculoskeletal Pain Guidelines Group, 2003).

#### Key messages

1. Topical and oral NSAIDs improve acute shoulder pain (U) (Level I).
2. Subacromial corticosteroid injection relieves acute shoulder pain in the early stages (U) (Level I).
3. Exercises improve acute shoulder pain in patients with rotator cuff disease (U) (Level I).
4. Therapeutic ultrasound may improve acute shoulder pain in calcific tendonitis (U) (Level I).
5. Advice to stay active, exercises, injection therapy and foot orthoses are effective in acute patellofemoral pain (U) (Level I).
6. Low-level laser therapy is ineffective in the management of patellofemoral pain (U) (Level I).



The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- A management plan for acute musculoskeletal pain should comprise the elements of assessment (history and physical examination, but ancillary investigations are not generally indicated), management (information, assurance, advice to resume normal activity, pain management) and review to reassess pain and revise management plan (**U**).
- Information should be provided to patients in correct but neutral terms with the avoidance of alarming diagnostic labels to overcome inappropriate expectations, fears or mistaken beliefs (**U**).
- Regular paracetamol, then if ineffective, NSAIDs, may be used for acute musculoskeletal pain (**U**).
- Oral opioids, preferably short-acting agents at regular intervals, may be necessary to relieve severe acute musculoskeletal pain; ongoing need for such treatment requires reassessment (**U**).
- Adjuvant agents such as anticonvulsants, antidepressants and muscle relaxants are not recommended for the routine treatment of acute musculoskeletal pain (**U**).

## 9.6 ACUTE MEDICAL PAIN

### 9.6.1 Acute abdominal pain

Acute abdominal pain may originate from visceral or somatic structures or may be referred; neuropathic pain states should also be considered. Recurrent acute abdominal pain may be a manifestation of a chronic visceral pain disorder such as chronic pancreatitis or irritable bowel syndrome and may require a multidisciplinary pain management approach.

#### ***Analgesia and the diagnosis of acute abdominal pain.***

A common misconception is that analgesia masks the signs and symptoms of abdominal pathology and should be withheld until a diagnosis is established. Pain relief (usually in the form of opioids), does not interfere with the diagnostic process in acute abdominal pain in adults (Manterola et al, 2007 **Level I**) or in children (Kim et al, 2002 **Level II**; Green et al, 2005 **Level II**), or lead to increased errors in clinical management (Ranji et al, 2006 **Level I**).

#### ***Renal colic***

NSAIDs, opioids (Holdgate & Pollock, 2005 **Level I**) and metamizole (dipyrone) (Edwards, Meseguer et al, 2002 **Level I**) provided effective analgesia for renal colic. NSAIDs reduced requirements for rescue analgesia, produced less vomiting than opioids (particularly pethidine [meperidine] (Holdgate & Pollock, 2005 **Level I**) and reduced the number of episodes of renal colic experienced before passage of the renal calculi (Kapoor et al, 1989 **Level II**; Laerum et al, 1995 **Level II**).

Onset of analgesia was fastest when NSAIDs were administered intravenously (Tramer et al, 1998 **Level I**) although suppositories were also effective (Lee et al, 2005 **Level II**). A combination of IV ketorolac and morphine provided a greater reduction in pain scores, earlier onset of complete pain relief and a reduced need for rescue analgesia, compared with using either analgesic alone (Safdar et al, 2006 **Level II**).

Pethidine has commonly been used in the treatment of renal colic in the belief that it causes less smooth muscle spasm. However, there was no difference in analgesia when IV morphine and pethidine were compared in the treatment of renal colic (O'Connor et al, 2000 **Level II**).

The smooth muscle relaxant buscopan failed to improve analgesia when combined with nsNSAIDs (Jones et al, 2001 **Level II**), opioids (Holdgate & Oh, 2005 **Level II**) or metamizole (Edwards, Meseguer et al, 2002 **Level I**). Papaverine was as effective as IV diclofenac in the initial treatment of renal colic, but required increased use of rescue analgesia (Snir et al, 2008 **Level II**). However, as a rescue analgesic, papaverine was of similar efficacy to pethidine and superior to hyoscine in patients who failed to respond to initial treatment with a diclofenac-hyoscine combination (Yencilek et al, 2008 **Level II**).

IV ondansetron produced analgesia in 42% of patients with renal colic but was less effective than IM diclofenac (Ergene et al, 2001 **Level II**). IN desmopressin was also an effective analgesic, either alone, or in combination with IM diclofenac (Lopes et al, 2001 **Level II**).

Renal calculus expulsive therapy using the specific alpha-blocker tamsulosin was superior to comparative smooth muscle relaxants such as phloroglucinol or nifedipine in terms of increased stone expulsion and a reduction in analgesia requirements, surgical interventions, duration of hospital stay and days off work (Dellabella et al, 2005 **Level II**).

TENS applied over the painful flank during prehospital transport, reduced pain scores, anxiety and nausea in patients with renal colic (Mora et al, 2006 **Level II**).

IV fluid therapy had no effect on pain outcomes or stone transition in renal colic (Worster & Richards, 2005 **Level I**).

### ***Biliary colic and acute pancreatitis***

All opioids increase sphincter of Oddi tone and bile duct pressures in animal and human experimental models (Thompson, 2001). Morphine increased sphincter of Oddi contractions more than pethidine during cholecystectomy (Thune et al, 1990 **Level IV**).

There are no clinical studies comparing opioids in the treatment of pain associated with biliary spasm or acute pancreatitis (Thompson, 2001). Butorphanol, which is presumed to cause less biliary spasm than other opioids, and ketorolac produced a clinically significant and similar reduction in acute biliary colic within 30 minutes in patients in the emergency department (Olsen et al, 2008 **Level II**).

Parenteral nsNSAIDs such as ketorolac, tenoxicam or diclofenac were at least as effective as parenteral opioids and more effective than buscopan in providing analgesia for biliary colic (Goldman et al, 1989 **Level II**; Al-Waili & Saloom, 1998 **Level II**; Dula et al, 2001 **Level II**; Henderson et al, 2002 **Level II**; Kumar, Deed et al, 2004 **Level II**) and may also prevent progression to cholecystitis (Goldman et al, 1989 **Level II**; Akriviadis et al, 1997 **Level II**; Al-Waili & Saloom, 1998 **Level II**; Kumar, Deed et al, 2004 **Level II**).

IM atropine was no more effective than saline in the treatment of acute biliary colic (Rothrock et al, 1993 **Level II**).

### ***Irritable bowel syndrome and colic***

There was weak evidence that antispasmodics (smooth muscle relaxants) reduced pain in irritable bowel syndrome, but no evidence of an analgesic effect with antidepressants or bulking agents (Quartero et al, 2005 **Level I**). Peppermint oil may also reduce pain (Pittler & Ernst, 1998 **Level I**) and was as effective as buscopan in reducing upper (Hiki et al, 2003 **Level II**) and lower GI spasm (Asao et al, 2003 **Level II**).

## Primary dysmenorrhoea

NsNSAIDs are highly effective analgesics in dysmenorrhoea. While no difference was found between the different nsNSAIDs included in an analysis in terms of efficacy, ibuprofen had the least adverse effects (Marjoribanks et al, 2003 **Level I**). Paracetamol was less effective than naproxen, ibuprofen, mefenamic acid and aspirin; again, ibuprofen had the most favourable risk-benefit ratio (Zhang & Li Wan Po, 1998 **Level I**). NsNSAIDs also reduced bleeding and pain associated with the use of an intrauterine-device (Grimes et al, 2006 **Level I**).

Vitamin B1 (Proctor & Murphy, 2001 **Level I**), vitamin E (Ziaei et al, 2005 **Level II**) chinese herbal medicine (Zhu et al, 2007 **Level I**), rose tea (Tseng et al, 2005 **Level II**), guava leaf extract (*Psidium guajavae*) (Doubova et al, 2007 **Level II**), aromatherapy (Han et al, 2006 **Level II**) and fennel (*Foeniculum vulgare*) (Namavar Jahromi et al, 2003 **Level III-2**) are also effective.

High frequency TENS was effective in primary dysmenorrhoea (Proctor et al, 2002 **Level I**). The effectiveness of acupuncture in primary dysmenorrhoea is undetermined due to methodological problems in available studies (Yang et al, 2008 **Level I**).

## Abdominal migraine

Abdominal migraine is a neurogastrointestinal disorder, usually of male children, characterised by recurrent attacks of acute abdominal pain, nausea, vomiting and often headaches. Pizotifen was found to be effective for prophylaxis and treatment (Symon & Russell, 1995 **Level II**) (see Section 9.6.5).

### Key messages

1. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain (**S**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs, opioids and intravenous metamizole (dipyrone) provide effective analgesia for renal colic (**N**) (**Level I** [Cochrane Review]).
3. Non-selective NSAIDs given for renal colic reduce requirements for rescue analgesia and produce less vomiting compared with opioids, particularly pethidine (meperidine) (**U**) (**Level I** [Cochrane Review]).
4. High frequency TENS is effective in primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
5. The onset of analgesia is faster when non-selective NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
6. Antispasmodics and peppermint oil are effective for the treatment of acute pain in irritable bowel syndrome (**U**) and gastrointestinal spasm (**N**) (**Level I**).
7. Non-selective NSAIDs and vitamin B1 are effective in the treatment of primary dysmenorrhoea (**U**) (**Level I**).
8. There is no difference between pethidine and morphine in the treatment of renal colic (**U**) (**Level II**).
9. Parenteral non-selective NSAIDs are as effective as parenteral opioids in the treatment of biliary colic (**U**) (**Level II**).

## 9.6.2 Herpes zoster-associated pain

Herpes zoster (HZ) (shingles) is caused by reactivation of the varicella-zoster virus (VZV), which lies dormant in dorsal root and cranial nerve ganglia following primary infection with chickenpox (varicella), usually in childhood (Schmader & Dworkin, 2008). There is a marked increase in the risk of shingles with increasing age and with diseases and drugs that impair immunity: the lifetime risk is estimated at 20% to 30%, and up to 50% in those who reach 85 years of age (Schmader & Dworkin, 2008).

HZ-associated pain occurs in up to 80% of those affected and may occur before onset of the characteristic rash (during the prodrome), with onset of the rash, or following its resolution (postherpetic neuralgia). The pain varies in intensity and is described as 'burning', 'throbbing' or 'shooting'; itching, dysaesthesias, and allodynia may also be present (Dworkin et al, 2008). In the majority of cases, HZ is an acute self-limiting disease, although not infrequently, it may progress to postherpetic neuralgia (PHN) (pain that persists for more than 3 months after the onset of HZ). The incidence of PHN increases with age (over 50 years), occurring in up to 75% of patients aged 70 years or over who had shingles (Johnson & Whitton, 2004). Early, aggressive treatment of HZ infection and pain may reduce the incidence of PHN, although data on preventive strategies are limited.

### **Prevention of herpes zoster**

A live attenuated VZV vaccine (Zostavax®) is available for the prevention of HZ (and PHN) in individuals over 60 years of age. A large, multicentre, randomised placebo-controlled trial (The Shingles Prevention Study) demonstrated its efficacy, with a reduction in the incidence of HZ by 51.3%, PHN by 66.5 % and HZ-associated 'burden of illness' by 61.1% (Oxman et al, 2005). The estimated number-needed-to-vaccinate to prevent a case of HZ was 11 (CI: 10-13) and for PHN 43 (CI: 33-53) (Brisson, 2008 **Level III-3**). The Advisory Committee for Immunization Practices of the US Centres for Disease Control and Prevention recommends vaccination with live, attenuated VZV for all persons aged 60 years or over, even if they have had a previous episode of HZ (Harpaz et al, 2008) as has the Pharmaceutical Benefits Advisory Committee of the Australian Government Department of Health and Ageing (PBAC, 2008).

### **Treatment of herpes zoster-associated pain**

#### **Antiviral agents**

Acyclovir, valaciclovir or famciclovir, given within 72 hours of onset of the rash accelerated the resolution of HZ pain (Beutner et al, 1995 **Level II**; Wood et al, 1996 **Level I**; Jackson et al, 1997 **Level I**; Tyring et al, 2000 **Level II**). Famciclovir, in various doses and frequencies, was as effective as acyclovir for HZ-related outcomes, including pain (Shafran et al, 2004 **Level II**; Shen et al, 2004 **Level II**). Famciclovir or valaciclovir have replaced acyclovir as the drugs of choice in the treatment of HZ, because of more favourable pharmacokinetics and simpler dosing profiles (Cunningham et al, 2008).

#### **Opioids, tramadol and paracetamol**

HZ-associated pain may be severe and early and effective treatment is essential. Multimodal analgesia, with regular paracetamol in addition to an opioid such as oxycodone (Dworkin et al, 2007; Cunningham et al, 2008; Dwyer & Cunningham, 2002) or tramadol as required, has been recommended.

Oxycodone CR but not gabapentin was effective in significantly reducing the average worst pain during the first 14 days of HZ compared with placebo, although the group of patients taking oxycodone had a much higher rate of withdrawal from the trial, primarily because of constipation (Dworkin et al, 2009 **Level II**).

### **Corticosteroids**

Prednisolone added to acyclovir during HZ resulted in a modest reduction in pain intensity and improved the rate of skin lesion healing for up to 14 days, with no effect on the overall recovery rate at 3 weeks (Wood et al, 1994 **Level II**). Prednisolone, either as monotherapy or in combination with acyclovir, increased the likelihood of being 'pain-free' at 1 month by a factor of 2.3 (95% CI: 1.4 to 3.5), however there was no difference in the rate of skin healing, compared with placebo (Whitley et al, 1996 **Level II**).

### **Anticonvulsants**

Administration of a single dose of gabapentin (900 mg) during HZ reduced acute pain intensity by 66% (33% for placebo) and also reduced the area and severity of allodynia, for up to 6 hours (Berry & Petersen, 2005 **Level II**), however no analgesic benefit was found when gabapentin was administered for 28 days (Dworkin et al, 2009 **Level II**).

### **Topical lignocaine**

Topical lignocaine patches (5%) applied for 12 hours twice daily (on intact skin) during HZ, significantly reduced pain intensity and improved patient's global impression of pain relief, compared with a control vehicle patch: the incidence and severity of adverse events was low with both treatments (Lin et al, 2008 **Level II**).

### **Aspirin**

Topical aspirin, in either moisturiser or diethyl ether, was an effective analgesic in HZ, compared with similar preparations containing indomethacin, diclofenac or placebo (De Benedittis et al, 1992 **Level II**) or oral aspirin (Balakrishnan et al, 2001 **Level II**).

### **Neuraxial or sympathetic blockade**

A review of neuraxial (including sympathetic) blockade for the treatment of HZ-associated pain found that 71% (12/15) of studies (Kumar, Krone et al, 2004), only one of which was an RCT (Pasqualucci et al, 2000 **Level II**), reported a reduction in either the incidence or severity of HZ-associated pain to 1 month. In a subsequent RCT, there was a significant difference in the incidence (and to a lesser extent the intensity) of HZ pain in patients who received a single epidural methylprednisolone and bupivacaine injection, compared with those who received antiviral therapy and analgesia as 'standard care'; the NNT for complete resolution of HZ pain at 1 month with the epidural injection was 10 (van Wijck et al, 2006 **Level II**). However, given the modest clinical effects on acute pain and no effect on the incidence of PHN, the routine use of epidural local anaesthetic and steroid injection during HZ was not supported. Evidence of benefit for sympathetic blockade in the treatment of HZ-associated pain was conflicting (Kumar, Krone et al, 2004).

### **Prevention of postherpetic neuralgia**

Immunisation of persons aged 60 years or older with live attenuated VZV vaccine, reduces the incidence of PHN (Oxman et al, 2005) and is now recommended as the standard of care, including for those who have experienced a previous episode of HZ (Harpaz et al, 2008).

During HZ, the early administration amitriptyline (for 90 days) (Bowsher, 1997 **Level II**) significantly reduced the incidence of PHN. However, contrary to the previous literature (Wood et al, 1996 **Level I**; Jackson et al, 1997 **Level I**; Beutner et al, 1995 **Level II**; Tyring et al, 2000 **Level II**), the use of the antiviral agent acyclovir or famcyclovir did not significantly reduce the incidence of PHN (Li et al, 2009 **Level I**).

**Note: reversal of conclusion**

This reverses the Level 1 conclusion in the previous edition of this document; earlier meta-analyses reported a reduced incidence of PHN.

Similarly, systemic corticosteroids (He et al, 2008 **Level I**) or an epidural injection with methylprednisolone and bupivacaine (van Wijck et al, 2006 **Level II**) were ineffective preventive strategies.

In the review by Kumar et al (Kumar, Krone et al, 2004) five of eight studies (63%) looked at prevention of PHN (one RCT only) and suggested that neuraxial blockade during HZ reduced the incidence of PHN at 6 months. The RCT found that local anaesthetic and steroid injections via an epidural catheter, for up to 21 days during HZ, significantly reduced the incidence (but not the intensity) of pain for 1 to 6 months, compared with systemic antiviral therapy plus prednisolone; however such an approach has limited practical application (Pasqualucci et al, 2000 **Level II**).

**Key messages**

1. Antiviral agents started within 72 hours of onset of the herpes zoster rash accelerate the resolution of acute pain (**U**) (**Level I**), but do not reduce the incidence of postherpetic neuralgia (**R**) (**Level I**) [Cochrane Review].
2. Immunisation of persons aged 60 years or older with varicella-zoster virus vaccine reduces the incidence of herpes zoster and postherpetic neuralgia (**N**) (**Level II**).
3. Amitriptyline (used in low doses for 90 days from onset of the herpes zoster rash) reduces the incidence of postherpetic neuralgia (**U**) (**Level II**).
4. Topical aspirin, topical lignocaine patch or oxycodone controlled release, provide analgesia in herpes zoster (**N**) (**Level II**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Provision of early and appropriate analgesia is an important component of the management of herpes zoster and may have benefits in reducing the incidence of postherpetic neuralgia.

### 9.6.3 Acute cardiac pain

Acute coronary syndrome refers to a range of acute myocardial ischaemic states including unstable angina and myocardial infarction. Typically, myocardial ischaemia causes central chest pain, which may radiate into the arm, neck or jaw; non-typical presentations can occur, particularly in the elderly patient (see Section 11.2). Reducing ischaemia by optimising myocardial oxygen delivery, reducing myocardial oxygen consumption and restoring coronary blood flow will reduce ischaemic pain and limit myocardial tissue damage. The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation as outlined above, including the use of supplemental oxygen (Pollack & Braunwald, 2008; Cannon, 2008).

Nitroglycerine was effective in relieving acute ischaemic chest pain; however, the analgesic response did not predict the diagnosis of coronary artery disease (Henrikson et al, 2003 **Level IV**).

In patients with suspected acute coronary syndrome, IV morphine significantly reduced pain within 20 minutes of administration; morphine doses were low (average of 7 mg over 3 days)

and 52% of patients required no morphine at all. Independent predictors of increased morphine requirements included suspicion or confirmation of infarction, ST-segment changes on the admission ECG, male sex and a history of angina or cardiac failure (Everts et al, 1998 **Level IV**).

Morphine provided better analgesia than IV metoprolol (Everts et al, 1999 **Level II**) and was associated with better cardiovascular outcomes during acute hospital admission and later follow-up, when compared with a fentanyl-droperidol mixture administered early in the treatment of patients with acute ischaemic chest pain (Burduk et al, 2000 **Level II**). However a large retrospective audit reported increased mortality in patients treated with morphine, either alone or in combination with nitroglycerine (independent of other confounders), in non-ST segment elevation acute coronary syndrome (Meine et al, 2005 **Level III-2**). IV bolus doses of morphine and alfentanil were equally effective in relieving acute ischaemic chest pain but the onset of analgesia was faster with alfentanil (Silfvast & Saarnivaara, 2001 **Level II**). Morphine was similar to buprenorphine (Weiss & Ritz, 1988 **Level II**) and pethidine (Nielsen et al, 1984 **Level II**) in terms of analgesia and adverse effects. IN fentanyl and IV morphine were equally effective in reducing acute cardiac chest pain during prehospital transfer (Rickard et al, 2007 **Level II**).

In patients with chest pain due to cocaine-induced acute coronary syndrome, the addition of IV diazepam or lorazepam to treatment with sublingual nitroglycerine provided superior analgesia (Baumann et al, 2000 **Level II**; Honderick et al, 2003 **Level II**).

In acute coronary syndrome, hyperbaric oxygen therapy reduced time to relief of ischaemic pain, although insufficient evidence exists to recommend its routine use (Bennett et al, 2005 **Level I**).

N<sub>2</sub>O in oxygen was effective in relieving acute ischaemic chest pain, with a significant reduction in beta-endorphin levels (O'Leary et al, 1987 **Level II**).

TENS reduced the number and duration of ischaemic events during unstable angina, however without a significant effect on pain (Borjesson et al, 1997 **Level II**).

NSAIDs may be useful in the treatment of acute pain in pericarditis (Schifferdecker & Spodick, 2003).

### Key messages

1. Morphine is an effective and appropriate analgesic for acute cardiac pain (**U**) (**Level II**).
2. Nitroglycerine is an effective and appropriate agent in the treatment of acute ischaemic chest pain (**U**) (**Level IV**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, including the use of supplemental oxygen, nitroglycerine, beta blockers and strategies to improve coronary vascular perfusion (**U**).

## 9.6.4 Acute pain associated with haematological disorders

### Sickle cell disease

Sickle cell disease includes a group of inherited disorders of haemoglobin production. Haemoglobin S polymerises when deoxygenated, causing rigidity of the erythrocytes, blood hyperviscosity and occlusion of the microcirculation with resultant tissue ischaemia and infarction (Niscola et al, 2009).



Sickle cell disease is a systemic multiorgan disease that most commonly presents with painful vaso-occlusive crises, occurring either spontaneously or due to factors such as dehydration, infection, hypothermia and low oxygen tension. There is great interindividual variability in the frequency and severity of crises. Pain during an acute crisis is typically severe and most frequently reported in the back, legs, knees, arms, chest and abdomen and may last from hours to weeks. Sickle cell crises involving abdominal organs can mimic an acute surgical abdomen. Acute chest syndrome secondary to sickle cell disease may present with chest pain, cough, dyspnoea and fever (Niscola et al, 2009).

### **Treatment of pain**

Biopsychosocial assessment and multidisciplinary pain management may be required when treating patients with frequent, painful sickle cell crises. A pain management plan in the form of a letter, card or portfolio carried by the patient is also recommended (Rees et al, 2003). Detailed clinical guidelines for managing acute painful crises in sickle cell disease are listed in Rees et al (Rees et al, 2003). The implementation of clinical practice guidelines for acute pain treatment in sickle cell crisis leads to more timely and more effective analgesia (Morrissey et al, 2009 **Level III-3**).

Overall, there is only very limited evidence for analgesic interventions in acute pain crises of sickle cell disease and meaningful meta-analyses cannot be performed (Dunlop & Bennett, 2006 **Level I**).

#### *Oxygen*

Although oxygen supplementation is often prescribed during acute sickle cell crises, there was no difference in pain duration, number of pain sites or opioid consumption in patients treated with either air or oxygen (Robieux et al, 1992 **Level II**; Zipursky et al, 1992 **Level II**). However, nocturnal oxygen desaturation was associated with a significantly higher rate of painful sickle cell crises in children (Hargrave et al, 2003 **Level IV**).

#### *Rehydration*

There was insufficient evidence to suggest any benefit from fluid replacement therapy in reducing pain associated with sickle cell crises (Okomo & Meremikwu, 2007 **Level I**).

#### *NsNSAIDs*

Single-dose parenteral ketorolac did not reduce opioid requirements in painful vaso-occlusive crisis (Wright et al, 1992 **Level II**; Hardwick et al, 1999 **Level II**).

#### *Opioids*

In treating acute pain during a sickle cell crisis, IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy (Rees et al, 2003 **Level II**). A continuous IV morphine infusion shortened the duration of severe pain compared with intermittent parenteral opioids (Robieux et al, 1992 **Level II**) and PCA with morphine reduced opioid dose and related side effects (with a tendency to reduced length of hospital stay) compared with continuous infusion (van Beers et al, 2007 **Level II**). The use of inpatient morphine PCA, rapidly converted to oral CR morphine for use at home reduced the length of hospital stay by 23% and subsequent emergency department visits and readmissions by approximately 50%, compared with IM pethidine (Brookoff & Polomano, 1992 **Level III-3**).

Although IV opioid PCA is widely accepted in the management of acute pain in sickle cell disease, oral opioids are also effective. One trial in paediatric patients showed that oral sustained-release morphine for acute pain was just as effective as a continuous IV morphine infusion (Jacobson et al, 1997 **Level II**). The use of oral opioids at home reduced the number of emergency department visits and hospital admissions for sickle cell pain (Conti et al, 1996

**Level III-3;** Friedman et al, 1986 **Level III-3**). However in children, the incidence of acute sickle chest syndrome, and plasma levels of morphine and M6G, was significantly higher with oral morphine compared with IV infusion (Kopecky et al, 2004 **Level II**).

Care must be taken when using opioids in the treatment of pain in sickle cell disease. In a review of 35 patients who died in hospital following an exacerbation of sickle cell disease, 9 of the 35 patients received excessive opioids and 'overdose' directly contributed to death in 5 out of the 35 (NCEPOD, 2008). In two-thirds of patients, there were inadequate observations of sedation and respiratory rates after opioid administration and IM pethidine administration was prevalent.

#### *Inhaled nitrous oxide*

Inhaled N<sub>2</sub>O in 50% oxygen used for limited periods may provide analgesia for acute sickle cell pain in the primary care setting (Rees et al, 2003).

#### *Inhaled nitric oxide*

Nitric oxide (NO) deficiency or defective NO-dependent mechanisms may underlie many of the processes leading to vaso-occlusion. Inhaled NO may be of benefit in painful acute vaso-occlusive crises in children; however, further studies are required (Weiner et al, 2003 **Level II**).

#### *Corticosteroids*

Parenteral corticosteroids appear to reduce the duration of analgesia requirements and length of hospital stay, without major side effects, during sickle cell crises (Dunlop & Bennett, 2006 **Level I**). In children, a short course of high-dose IV methylprednisolone decreased the duration of severe pain associated with acute sickle cell crises but patients who received methylprednisolone had more rebound attacks after therapy was discontinued (Griffin et al, 1994 **Level II**).

#### *Epidural analgesia*

In severe crises, where pain is unresponsive to other measures, epidural analgesia has been used effectively (Yaster et al, 1994 **Level IV**).

#### **Prevention of painful sickle cell crises**

Hydroxyurea increases fetal haemoglobin levels, thereby reducing the frequency of acute crises, blood transfusions and life-threatening complications (including acute chest syndrome) in adults with severe disease who are homozygous for the sickle cell gene (Davies & Olujuhunge, 2001 **Level I**).

Niprisan (an antisickling agent), zinc and piracetam (which prevent red blood cell dehydration) may reduce the incidence of painful sickle cell crises (Wambebe et al, 2001, **Level II**; Riddington & De Franceschi, 2002 **Level II**). The evidence for pircetam, however, is insufficient to support its use (Al Hajeri et al, 2007 **Level I**).

#### **Haemophilia**

Deficiency of Factor VIII (haemophilia A) and deficiency of Factor IX (haemophilia B) are inherited disorders of coagulation characterised by spontaneous and post-traumatic haemorrhages, the frequency and severity of which are proportional to the degree of clotting factor deficiency. Bleeding into joints and muscle is common, although other sites such as abdominal organs may also be involved. In haemophilic arthropathy the most frequent sites of pain are the ankle joints (45%), knee joints (39%), spine (14%) and elbow joints (7%) (Wallny et al, 2001 **Level IV**). Haemophilia patients may also have pain syndromes associated with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) (see Section 9.6.8). Recurrent acute pain may have a significant adverse impact on mood, mobility and quality of

life in haemophilia patients; biopsychosocial assessment and treatment should be considered (Wallny et al, 2001 **Level IV**).

Many haemophilia patients use Factor VIII to decrease pain associated with a bleeding episode (Wallny et al, 2001 **Level IV**). Higher-dose Factor VIII replacement reduced the number of patients with restricted joint movement after an acute haemarthrosis (Aronstam et al, 1983, **Level II**). Joint aspiration may reduce pain and improve joint function (Baker, 1992).

Although there is no good evidence available, opioids, simple analgesics, cold therapy and bandaging have been used in treating acute pain associated with haemophilia. NsNSAIDs have been used to provide analgesia in haemophilic arthropathy, but there are no data on their use in acute haemarthrosis. Coxibs may be of benefit due to a lack of platelet inhibitory effects (see Section 4.2). IM analgesics should be avoided due to the risk of bleeding.

### **The porphyrias**

The acute porphyrias are a group of inherited disorders of haem biosynthesis. The most common autosomal dominant forms are acute intermittent porphyria, variegate porphyria and hereditary coproporphyria. The disorder of haem biosynthesis leads to accumulation of neurotoxic aminolaevulinic acid (ALA) and porphyrin metabolites, which can result in peripheral, visceral and autonomic neuropathies (eg clinical features might include motor weakness, abdominal pain and tachycardia) as well as central nervous system (CNS) toxicity (neuropsychiatric symptoms, seizures, brainstem and pituitary dysfunction); some patients may have a cutaneous photosensitivity (Visser & Goucke, 2008).

Pain management in acute porphyria is based on treatment of the disease, including resuscitation and supportive care, ceasing 'triggers', the early administration of hem arginate (Herrick et al, 1989 **Level II**), and possibly high-dose IV dextrose or cimetidine administration ('disease modifying agents') (Rogers, 1997).

Specific evidence for pain management in acute porphyria is limited. Analgesia is based largely on the use of IV and (later) oral opioids (Anderson et al, 2005; Herrick & McColl, 2005). Opioids such as pethidine (Deeg & Rajamani, 1990) or tramadol, and other 'analgesics' (such as tricyclic antidepressants [TCAs]) that lower seizure threshold should be avoided in acute porphyria, because of increased seizure risk.

The safety of nsNSAIDs or coxibs in acute porphyria has not been established; paracetamol, buscopan (for colic) or N<sub>2</sub>O in oxygen, are considered safe (Anderson et al, 2005; Stoelting & Dierdorf, 1993).

There may be a place for IV low-dose ketamine or regional analgesia, although the safety of these approaches has not been established in acute porphyria. Ketamine does not induce ALA synthetase in rats (Harrison et al, 1985) and has been used for anaesthesia in porphyria patients without apparent problems (Capouet et al, 1987). However one case report noted increased porphyrin levels in a patient after induction with ketamine (Kanbak, 1997).

As metoclopramide is contraindicated and the safety of 5HT<sub>3</sub> antagonists is as yet unclear, droperidol has been suggested as the antiemetic of choice in acute porphyria (Anderson et al, 2005).

### Key messages

1. Parenteral corticosteroids appear to reduce the duration of analgesia requirements and length of hospital stay, without major side effects, during sickle cell crises (**S**) (**Level I** [Cochrane Review]).
2. There is insufficient evidence to suggest that fluid replacement therapy reduces pain associated with sickle cell crises (**N**) (**Level I** [Cochrane Review]).
3. Hydroxyurea is effective in decreasing the frequency of acute crises, life-threatening complications and transfusion requirements in sickle cell disease (**U**) (**Level I**).
4. Intravenous opioid loading optimises analgesia in the early stages of an acute sickle cell crisis. Effective analgesia may be continued with intravenous opioid therapy, optimally as PCA (**U**) (**Level II**).
5. Oxygen supplementation does not decrease pain during a sickle cell crisis (**U**) (**Level II**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Pethidine should be avoided for the treatment of acute pain in sickle cell disease or acute porphyria, with increased seizure risk being a potential problem (**U**).

### 9.6.5 Acute headache

Headaches are a common cause of acute pain. There are many causes of acute headache, some of which involve structures other than the head (eg the neck). Before treating acute headache, it is vital to rule out serious cranial pathologies such as tumour, infection, cerebrovascular abnormalities, acute glaucoma and temporal arteritis (Silberstein, 2000; Steiner & Fontebasso, 2002).

The most frequent causes of acute headache are episodic tension-type headache (TTH) and migraine (Headache Classification Subcommittee of the IHS, 2004). Less frequent causes include trigeminal autonomic cephalalgias (episodic cluster headache, episodic paroxysmal hemicrania and Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing [SUNCT]) or 'secondary headaches', such as acute post-traumatic headache, postdural puncture headache (PDPH), headache attributed to substance use or its withdrawal and cervicogenic headache (Headache Classification Subcommittee of the IHS, 2004).

Comprehensive guidelines for the evaluation and treatment of acute headaches including migraine have been promulgated (Edlow et al, 2008; Steiner et al, 2007; Evers et al, 2006), including for children and adolescents (Lewis et al, 2004).

#### **Episodic tension-type headache**

TTHs may be episodic (frequent or infrequent) or chronic in nature. The lifetime prevalence of TTH in the general population is between 30% and 78%. Episodic TTH is usually bilateral and is often described as a mild to moderate 'pressing' or 'tight pain' (sometimes with pericranial tenderness), not worsened by movement and not associated with nausea. Photophobia or phonophobia may occasionally be present (Headache Classification Subcommittee of the IHS, 2004).

The symptoms and pathogenesis of TTH may overlap with migraine, chronic daily headache, medication overuse headache and cervicogenic headache (Goadsby, 2003). Psychological, physical and environmental factors are important in TTH and should be addressed during assessment and treatment (Holroyd, 2002).

### **Treatment**

Simple analgesics such as nsNSAIDs, paracetamol (Prior et al, 2002 **Level II**; Steiner et al, 2003 **Level II**) or aspirin (Steiner et al, 2003 **Level II**), either alone or in combination, provided effective analgesia in TTH. Ketoprofen, ibuprofen and naproxen were equally effective and superior to paracetamol (Lange & Lentz, 1995 **Level I**; Dahlof & Jacobs, 1996 **Level II**).

The addition of caffeine to paracetamol, aspirin (Migliardi et al, 1994 **Level I**) or ibuprofen (Diamond et al, 2000 **Level II**) significantly improved analgesia and a paracetamol-aspirin-caffeine combination was more effective than placebo and all three component drugs alone, in terms of analgesia outcomes and time to effect (Diener et al, 2005 **Level II**). IV magnesium was ineffective in treating acute TTH in the emergency department (Frank et al, 2004 **Level II**).

Acupuncture is an effective non-pharmacological intervention in TTH (Linde et al, 2009 **Level I**).

### **Migraine**

Migraine is common, with a prevalence of 6% to 8% in males and 12% to 14% in females (Evers et al, 2006). Migraine headache is usually unilateral and is often severe, disabling and worsened by movement. Nausea, vomiting, photophobia and phonophobia are common and 20% of migraineurs experience an aura.

Most migraines are successfully managed by the patient and his or her family doctor, with up to 57% of patients not seeking medical attention for significant attacks (Mitchell et al, 1998). However a small number of patients fail to respond and present for treatment at emergency departments; approximately 80% of patients have tried their usual medications including simple analgesics or triptans before presentation (Larkin & Prescott, 1992; Shrestha et al, 1996) (see Section 9.9.2).

### **Treatment**

The management of migraine includes avoidance of triggers such as sleep deprivation, stress, sensory stimulation such as bright lights, exercise, alcohol, foods etc. Management of associated symptoms, particularly nausea and vomiting is important, as is the prevention of acute recurrence. Environmental modification (quiet dark room) and particularly sleep, is integral to the successful treatment of migraine (Steiner et al, 2007).

Analgesia outcomes in migraine trials are usually listed as the proportion of patients who are either:

- pain free at 2 hours;
- report significant pain relief at 2 hours (no headache or mild headache); or
- report a sustained response over 24 hours (migraine stays away for at least a day).

Many trials fail to document associated outcomes such as improvement in nausea, vomiting or disability (Moore et al, 2003).

### **Strategies for the use of migraine medications**

There are three major strategies for the use of analgesics in the treatment of acute migraine (Lipton, Stewart et al, 2000):

- *Stratified care* — where for each attack, the severity and disability caused by the migraine is assessed. The patient uses simple analgesia for a mild attack and a triptan for a severe attack;
- *Step-up during an attack* — for each attack a simple analgesic is always tried first, but the patient ‘steps up’ to a triptan if there is no relief in 2 hours; and

- *Step-up across attacks* — a patient tries simple analgesics exclusively for the first three attacks: if there has been no benefit from simple analgesia over the trial period, then a triptan is used for all further attacks.

The US Headache Consortium (Silberstein, 2000) and European Federation of Neurological Societies (Evers et al, 2006) have recommended a ‘stratified care’ approach; later British guidelines promote the use of ‘step-up’ regimens during each attack (Steiner et al, 2007).

### Simple analgesics

Patients who experience mild migraine-related headache and disability may be effectively treated with simple analgesics, either alone or in combination with an antiemetic. European consensus guidelines recommend the routine, early use of metoclopramide (or domperidone in children) (Evers et al, 2006).

Combined soluble aspirin 900 mg and metoclopramide 10 mg was of similar analgesic efficacy to sumatriptan in mild acute migraine (Oldman et al, 2002 **Level I**) and may be considered first-line treatment. Effervescent aspirin 1000 mg was as effective as sumatriptan 50 mg orally, with fewer side effects (Lampl et al, 2007 **Level I**). Ibuprofen (200 to 400 mg) was effective in achieving pain-free status within 2 hours, but was no different to placebo for pain outcomes at 24 hours (Suthising et al, 2007 **Level I**). Paracetamol 1000 mg was effective, usually for mild-to-moderate migraine (Lipton, Baggish et al, 2000 **Level II**).

A paracetamol-aspirin-caffeine combination was superior to placebo and each component drug alone in terms of analgesia and time to effect (Diener et al, 2005 **Level II**). It was also more effective than oral sumatriptan 50 mg in the early treatment of migraine headache (without associated nausea, vomiting or disability) (Goldstein et al, 2005 **Level II**) and was better than ibuprofen in terms of analgesic endpoints and speed of onset (Goldstein et al, 2006 **Level II**). Combined tramadol and paracetamol was superior to placebo for improved migraine headache outcomes to 24 hours and reduced photo/phonophobia (but not nausea) at 2 hours (Silberstein et al, 2005 **Level II**).

Dipyrone was also effective for the treatment of migraine and episodic TTHs (Ramacciotti et al, 2007 **Level I**).

**Table 9.2 Simple analgesics for the treatment of migraine**

Analgesic regimen	NNT*	Source
Aspirin 600 to 900 mg +metoclopramide 10 mg	3.2	Oldman et al, 2002 <b>Level I</b>
Paracetamol 1000 mg	5.2	Lipton, Baggish et al, 2000 <b>Level II</b>
Ibuprofen 200 to 400 mg	8.0	Suthising et al, 2007 <b>Level I</b>

\* Simple analgesics for the treatment of migraine: 2-hour pain response (nil or mild residual headache at 2 hours).

### Over-the-counter analgesics

Sixty percent of patients treat their migraines exclusively with over-the-counter (OTC) analgesics; however most trials of OTC medications excluded patients with severe headaches and related symptoms (nausea and vomiting) or disability.

When data from 11 trials of adequate study design were combined, OTC analgesics such as paracetamol (alone or in combination with caffeine), aspirin (alone or in combination with either caffeine and/or paracetamol) and ibuprofen, were more effective than placebo at reducing moderate-to-severe headache (mild or no pain) within 2 hours, with a significant minority of patients achieving pain-free status within 2 hours (Wenzel et al, 2003 **Level I**). Up to 76% of patients returned to normal functioning after 2 hours, especially if their migraine

symptoms and disability were mild-to-moderate. No OTC agent was found to be superior. However, OTC medications are only indicated in migraineurs with mild-to-moderate symptoms (Wenzel et al, 2003 **Level I**).

### ***Triptans***

Triptans are effective in the treatment of acute migraine, particularly in the presence of severe pain and disability, where simple analgesia has failed to provide adequate relief in the past. As there is considerable interindividual response to the different triptans, patients should trial a variety of drugs and doses until the most suitable regimen is found (Silberstein, 2000; Oldman et al, 2002 **Level I**).

The route of administration of a triptan may affect its efficacy, speed of onset and tolerability. SC injections and nasal sprays provide fast onset of symptom relief and higher efficacy, however injections are less well tolerated by patients. In contrast, oral triptans are well tolerated but have a slower onset of action and lower reliability due to gastric stasis associated with migraine. Therefore, if the oral route is used, the triptan should preferably be given early in an attack (Dahlof, 2002). Suppositories are well tolerated and avoid problems with oral absorption.

Table 9.3 lists commonly prescribed triptans with NNT for pain-free response at 2 hours.

**Table 9.3 Table of triptans**

<b>Drug</b>	<b>Route</b>	<b>NNT (95% Confidence intervals) *</b>
Sumatriptan 6 mg	SC	2.1 (1.9–2.4)
Rizatriptan 10 mg	oral	3.1 (2.9–3.5)
Eletriptan 80 mg	oral	3.7 (3.2–4.2)
Zolmitriptan 5 mg	oral	3.9 (3.4–4.6)
Eletriptan 40 mg	oral	4.5 (3.9–5.1)
Sumatriptan 20 mg	IN	4.6 (3.6–6.1)
Sumatriptan 100 mg	oral	4.7 (4.1–5.7)
Rizatriptan 2.5 mg	oral	4.7 (4.0–5.7)
Zolmitriptan 2.5 mg	oral	5.9 (4.5–8.7)
Sumatriptan 50 mg	oral	7.8 (6.1–11)
Naratriptan 2.5 mg	oral	8.2 (5.1–21)
Eletriptan 20 mg	oral	10 (7–17)
Aspirin 900 mg plus metoclopramide 10 mg	oral	8.6 (6.2–14)

\* NNTs to provide 2-hour pain-free response in migraine patient.

Source: Bandolier (at <http://www.medicine.ox.ac.uk/bandolier>); reproduced with permission.

Comparative randomised trials of triptans and other antimigrainals do not give a clear picture of relative efficacy. Oral triptans were found to be superior to oral ergotamine — most likely because the bioavailability oral of ergotamine is extremely low (<1%). Of the nine trials that met the inclusion criteria for review, six compared sumatriptan (two zolmitriptan and one eletriptan) with other migraine treatments. In seven of the nine studies reviewed, differences between triptan and other drugs for migraine endpoints were not dramatic. Triptans were no more effective than nsNSAIDs (and in most cases aspirin) and in several RCTs they produced



more side-effects than an aspirin-metoclopramide combination (Tfelt-Hansen, 2008; Lipton et al, 2004).

A combination of sumatriptan-naproxen as a single tablet for acute migraine, was superior to monotherapy with each component drug alone or placebo, in terms of pain-free outcome from 2 to 24 hours, with an adverse effects profile no worse than sumatriptan alone (Brandes et al, 2007 **Level II**).

The most frequent adverse events associated with triptans are dizziness, fatigue, sleepiness, nausea, chest tightness and paraesthesiae. The average incidence of any adverse events reported using various triptans ranged from approximately 18% to 50%. Sumatriptan has the greatest incidence and range of reported adverse events in placebo-controlled trials (Dahlof, 2002). Triptans may have significant sensory side effects, particularly an increase in light touch-evoked allodynia and thermal sensitivity (Linde, 2004).

Concern about adverse cardiac events is the main reason why only 10% of patients with migraine receive a triptan for acute therapy (Dahlof, 2002). A sensation of chest tightness occurred in 0.1 to 0.2% of patients who received almotriptan compared with 3 to 5% of patients on sumatriptan (Dahlof, 2002). There is no association between a lifetime history of migraine, with or without aura, and coronary artery disease related angina (Rose et al, 2004). However, chest tightness may not always be due to a cardiac cause (Dahlof, 2002). In a positron emission tomography study, sumatriptan did not affect myocardial perfusion or the ECG in migraine patients who had no history of ischaemic heart disease (Lewis et al, 1997).

Frequent use of triptans may lead to triptan-induced rebound headaches (Silberstein & Welch, 2002; Limmroth et al, 2002).

### ***Ergot derivatives***

Ergotamine and dihydroergotamine preparations have been used for many years to treat migraine, although they are rapidly being superseded by the triptans.

Intranasal (IN) dihydroergotamine (2 mg) has a NNT of 2.5 for 2-hour headache response in migraine (Oldman et al, 2002 **Level I**). As a single agent, parenteral dihydroergotamine may not be as effective as other migraine treatments (Colman et al, 2005 **Level I**). It was less effective than chlorpromazine (Bell et al, 1990 **Level II**) or sumatriptan (Winner et al, 1996 **Level II**), with increased side effects (Bell et al, 1990 **Level II**). However, when dihydroergotamine was combined with an antiemetic such as metoclopramide, the efficacy of this combination was similar to valproate, ketorolac and opioids (Colman et al, 2005 **Level I**).

### ***Opioids and tramadol***

Opioids are of limited benefit in the treatment of migraine. Morphine without an antiemetic was no more effective than placebo (Nicolodi, 1996 **Level II**). Butorphanol was effective when given by the IN or IM route (Elenbaas et al, 1991 **Level II**; Diamond et al, 1992 **Level II**; Hoffert et al, 1995 **Level II**).

Pethidine in particular, is not recommended for the treatment of migraine, due to lack of evidence of efficacy and the risk of developing dependency. Pethidine was less effective than dihydroergotamine or antiemetics for the treatment of migraine; however, it was of similar efficacy to ketorolac (Friedman et al, 2008 **Level I**). Pethidine was no more effective than dihydroergotamine, chlorpromazine, dimenhydrinate, metoclopramide, promethazine or NSAIDs (Lane et al, 1989 **Level II**; Stiell et al, 1991 **Level II**; Davis et al, 1995 **Level II**; Scherl & Wilson, 1995 **Level II**).

IM tramadol was similar to diclofenac for pain response at 2 hours in migraine (approximately 80% of patients) (Engindeniz et al, 2005 **Level II**).

### **Antiemetics and major tranquilisers**

Metoclopramide, as monotherapy or in combination, was effective for the treatment of headache and nausea, in mild-to-moderate migraine, and is considered first-line therapy in the emergency department (Colman et al, 2004 **Level I**). IV prochlorperazine was also more effective than metoclopramide for initial emergency department treatment of migraine (Coppola et al, 1995 **Level II**); buccal prochlorperazine was superior to an oral ergotamine-caffeine combination or placebo (Sharma et al, 2002 **Level II**). A combination of indomethacin, prochlorperazine and caffeine was more effective than sumatriptan (Di Monda et al, 2003 **Level II**). Parenteral chlorpromazine (Bigal, Bordini & Speciali, 2002 **Level II**) or low-dose IM droperidol were also effective (Richman et al, 2002 **Level II**); the latter was associated with a 13% incidence of akathisia.

### **Other drug treatments**

Dexamethasone was similar to placebo in the treatment of migraine, however a single dose was associated with a 26% reduction in recurrence rate (NNT 9) within 25 hours and offered a degree of migraine prophylaxis (Colman et al, 2008 **Level I**; Singh et al, 2008 **Level I**).

The efficacy of lignocaine in the treatment of migraine is unclear. Analgesia provided by IV lignocaine was similar to dihydroergotamine, but not as effective as chlorpromazine (Bell et al, 1990 **Level II**) and in one trial no better than placebo (Reutens et al, 1991 **Level II**). IN lignocaine may be effective (Maizels et al, 1996 **Level II**).

IV magnesium may be useful in the treatment of migraine, however the studies are contradictory. Magnesium sulphate was effective in a small placebo-controlled trial (Demirkaya et al, 2001 **Level II**), with another trial demonstrating a reduction in all of the symptoms of migraine with aura (including headache), but only in photo/phonophobia in migraine without aura (Bigal, Bordini, Tepper et al, 2002 **Level II**). However, other studies showed that a combination of magnesium and metoclopramide was less effective than metoclopramide plus placebo (Corbo et al, 2001 **Level II**) and there was no significant difference between magnesium, metoclopramide or placebo (Cete et al, 2005 **Level II**).

IV sodium valproate was ineffective in treating a migraine attack (Tanen et al, 2003 **Level II**).

### **Placebo**

A significant placebo effect was observed in migraine trials, particularly if the treatment was administered by injection (Macedo et al, 2006 **Level I**) and it may be more common in children and adolescents (Evers et al, 2009 **Level I**).

### **Hyperbaric oxygen therapy**

Limited evidence demonstrated that hyperbaric oxygen therapy was effective in terminating migraine attacks within 40 minutes in at least 70% of patients, compared with sham therapy (NNT 2; 95% CI 1 to 2), but there was no effect on nausea and vomiting, rescue analgesic requirements or migraine prevention; further research was recommended (Bennett et al, 2008 **Level I**).

### **Status migrainosis**

Status migrainosis is described as a severe, unremitting, debilitating, migraine, lasting more than 72 hours, which is not attributable to another disorder and is otherwise typical in quality to the patient's usual migraine; it is considered a neurological emergency and usually requires hospital admission (Headache Classification Subcommittee of the IHS, 2004). 'Status' is often associated with a super-imposed TTH and multiple unsuccessful trials of migraine treatments, usually triptans, therefore medication overuse headache must also be considered.

Treatment of status migrainosus with parenteral nsNSAIDs or steroids (usually dexamethasone) is recommended (Evers et al, 2006; Steiner et al, 2007; Colman et al, 2008 **Level I**; Singh et al, 2008 **Level I**). IV droperidol was effective within 2 hours in 88% to 100% of patients with refractory migraine or 'status' respectively; the recurrence rate within 24 hours was 10% to 23%. Sedation or extrapyramidal symptoms (usually restlessness) developed in two-thirds of patients (Wang et al, 1997 **Level IV**).

### **Paediatric migraine**

Migraine headaches are common in children and increase in frequency through to adolescence from 3% (ages 3 to 6) to 8% to 23% (ages 11 to 16). General principles of treatment are in accordance with adult migraine management but require due consideration of paediatric pharmacological issues. Not all children require pharmacological intervention. Medications shown to be effective in adults may not be appropriate for children, where paediatric safety and efficacy studies have not been conducted.

Guidelines and evidence-based reviews for the treatment of migraine in children and adolescents have been promulgated (Lewis et al, 2004; Bailey & McManus, 2008 **Level I**; Silver et al, 2008 **Level I**).

In children, ibuprofen or paracetamol are recommended as first-line treatments for acute migraine. For adolescents (over 12 years of age), sumatriptan nasal spray is effective and should be considered (Lewis et al 2004). Ibuprofen or sumatriptan were effective for relief of headache (NNT 2.4 and 7.4 respectively) and complete pain relief (NNT 4.9 and 6.9 respectively) at 2 hours. Paracetamol, zolmitriptan, rizatriptan or dihydroergotamine were not significantly better than placebo, but the number of RCTs in children is small (Silver et al, 2008 **Level I**). For adolescents (over 12 years of age), IN sumatriptan was effective, however the data are limited and further studies are required (Damen et al, 2005 **Level I**).

A systematic review of migraine treatments for children in the emergency department found only one RCT performed in this setting after other treatments had failed. This showed that prochlorperazine was more effective than ketorolac; other RCTs reported that ibuprofen or paracetamol were more effective than placebo; the data for triptans were unclear, with oral sumatriptan or ergotamine being ineffective (Bailey & McManus, 2008 **Level I**).

Psychological interventions, such as relaxation training, biofeedback and cognitive-behavioural therapy, reduced the intensity of headache in children and treatment success could be maintained for at least 1 year, although comparative efficacy with pharmacological treatments has not been investigated (Trautmann et al, 2006 **Level I**).

### **Menstruation-related migraine**

Management of acute migraine during menstruation does not differ from treatment at other times of the menstrual cycle, but prophylaxis is based on significant oestrogen and progesterone fluctuations with appropriate hormone replacement, usually oestradiol (Evers et al, 2006). nsNSAIDs and triptans were effective in the treatment and prophylaxis of menstruation-related headaches (Evers et al, 2006). Menstruation-related migraine was effectively treated with an OTC combination of paracetamol, aspirin, and caffeine (Silberstein et al, 1999 **Level II**).

### **Migraine in pregnancy and breastfeeding**

Migraine can occur for the first time during pregnancy, and pre-existing migraine may worsen, particularly during the first trimester or the patient may become headache-free later in pregnancy. Approximately 60% to 70% of migraineurs improve during pregnancy. The true incidence of migraine in pregnancy is uncertain and most cases are of migraine with aura (Silberstein, 2001).

The major concerns in the management of migraine in pregnancy are the effects of medication and the disease itself on the fetus. Medication use should ideally be limited.

Paracetamol, metoclopramide, caffeine, codeine (or perhaps other opioids) can be used during pregnancy, although aspirin, nsNSAIDs or coxibs may be of concern, especially during the third trimester (Evers et al, 2006) (see Section 11.1 and Tables 11.1 and 11.2).

Ergot alkaloids and triptans are contraindicated in pregnancy (Steiner et al, 2007; Evers et al, 2006). In one study, the use of sumatriptan in early pregnancy did not result in a large increase in teratogenic risk, but the possibility of a moderate increase in risk for a specific birth defect was not excluded. Among sixteen infants who had major malformations, nine had been exposed to sumatriptan; 1.3% of infants exposed to sumatriptan alone and 2.8% of infants exposed to other drugs for migraine had such malformations (Kallen & Lygner, 2001). Ergot alkaloids during pregnancy may disrupt feto-placental blood supply and cause uterine contraction, which can result in fetal injury or loss. Birth defects and stillbirths due to vascular spasm have been reported. On the basis of current data, all ergotamines are contraindicated in pregnancy and are category X (see Table 11.1).

Ibuprofen, diclofenac, metoclopramide or paracetamol are considered safe for the treatment of migraine in mothers who are breastfeeding. There is no clear consensus on the safety of triptans. Although the transfer of eletriptan or sumatriptan to breast milk is considered 'negligible', the manufacturers of most triptans recommend avoiding breastfeeding for at least 24 hours postadministration (Steiner et al, 2007) (see Table 11.3).

### **Cluster headache and other trigeminal autonomic cephalalgias**

Cluster headache is a rare primary headache disorder, presenting almost exclusively in males with recurrent, acute episodes of brief, severe, unilateral, periorbital pain associated with autonomic phenomena such as conjunctival injection and tearing.

Consensus guidelines for the treatment of cluster headache attacks recommended high-flow oxygen therapy or SC sumatriptan as therapies of first choice (May et al, 2006; Steiner et al, 2007). Acute steroid prophylaxis is recommended at the start of every cluster period (see below), either with prednisolone (Steiner et al, 2007) or methylprednisolone (orally or intravenously) (May et al, 2006), tapered over days to weeks.

#### **Oxygen**

Oxygen therapy may be useful in patients with cluster headache who have either a contraindication to sumatriptan or experience several cluster attacks per day (Dahlof, 2002). Although oxygen is recommended as a first-line treatment (May et al, 2006; Steiner et al, 2007), such recommendations are only supported by evidence from two small trials and clinical case reports (Bennett et al, 2008 **Level I**). High-flow oxygen provided symptomatic relief in approximately 50% of patients with acute cluster headache (Fogan, 1985 **Level II**) (NNT 2; CI 1 to 5); approximately 76% of patients responded to normobaric oxygen therapy (Bennett et al, 2008 **Level I**). The presence of nausea/vomiting and 'restlessness' was predictive of a poor response to oxygen (Schurks et al, 2007 **Level IV**).

Hyperbaric oxygen was no more effective than sham hyperbaric treatment in reducing the frequency or duration of cluster headaches (Bennett et al, 2008 **Level I**); however, 83% of patients with episodic cluster headache improved significantly with either treatment, suggesting either a placebo effect or therapeutic benefit from the hyperbaric process itself (Nilsson Remahl et al, 2002 **Level II**).

### ***Triptans***

SC sumatriptan injection (Ekblom, 1995 **Level II**) or IN sumatriptan spray (van Vliet et al, 2003 **Level II**) were effective first-line treatments for cluster headache attacks, with SC administration providing faster onset and greater reliability of analgesia (Hardebo & Dahlof, 1998 **Level II**). IN zolmitriptan was rapidly effective (Cittadini et al, 2006 **Level II**; Rapoport et al, 2007 **Level II**) and oral zolmitriptan was effective in treating 'episodic' but not chronic cluster headache (Bahra et al, 2000 **Level II**). Increased age was associated with a reduced response to triptans (Schurks et al, 2007 **Level IV**).

### ***Other treatments***

There have been no RCTs of ergotamines in the treatment of cluster headache, although injectable or IN dihydroergotamine may be of benefit (its use has been superseded by sumatriptan) (Dodick et al, 2000). IN (Dahlof, 2002) or IV (May et al, 2006) lignocaine may be effective. A single suboccipital steroid injection with betamethasone completely suppressed cluster headache attacks in 80% of patients for weeks, compared with a placebo control injection (Ambrosini et al, 2005 **Level II**).

Bilateral occipital nerve stimulation has been used successfully to treat otherwise intractable cluster headaches (Burns et al, 2009 **Level IV**).

### ***Paroxysmal hemicrania and SUNCT***

Paroxysmal hemicrania and SUNCT are rarer forms of trigeminal autonomic cephalgia. Paroxysmal hemicrania is similar to cluster headache except that it is more common in females, episodes are shorter but more frequent, and diagnosis requires the complete abolition of symptoms with indomethacin (Headache Classification Subcommittee of the IHS, 2004), which is the suggested treatment of choice (May et al, 2006). There is no high-level evidence to guide the treatment of SUNCT, however consensus guidelines based on case-series data suggest that lamotrigine or possibly topiramate or gabapentin may be useful prophylactics (May et al, 2006).

### ***Postdural puncture headache***

PDPH usually following spinal anaesthesia, inadvertent dural puncture with an epidural needle, diagnostic or therapeutic lumbar puncture or neurosurgery, occurs with an incidence of approximately 0.7% to 50%, (Halpern & Preston, 1994 **Level I**; Gaiser, 2006); up to 90% of cases improve spontaneously within 10 days (Candido & Stevens, 2003).

PDPH is more common in patients under 50 years of age and parturients (Candido & Stevens, 2003), and following inadvertent dural puncture with an epidural needle. The odds of developing PDPH are significantly lower in males compared with (non-pregnant) females (Wu et al, 2006 **Level I**). A history of previous PDPH significantly increases the risk of developing a headache with subsequent spinal anaesthesia (Amorim & Valenca, 2008 **Level IV**). Children who undergo lumbar puncture may present a special group (Janssens et al, 2003).

### ***Spinal needle size, type and lumbar puncture technique***

Data from the anaesthesiology and neurology literature indicate that needle calibre, bevel type and lumbar puncture technique affects the incidence of PDPH. The incidence of PDPH following spinal anaesthesia was reduced significantly by using a smaller gauge needle (26 gauge or less [NNT: 3]) or a needle with a 'non-cutting' bevel (eg 'pencil point') (NNT: 27) (Halpern & Preston, 1994 **Level I**). The incidence of PDPH was also reduced by orientating the cutting bevel parallel to the spinal saggital plane (dural fibres) (Richman et al, 2006 **Level I**) or by replacing the stylette prior to withdrawing a non-cutting needle (Strupp et al, 1998 **Level II**); both of these techniques (presumably) reduced cerebrospinal fluid (CSF) loss.

Although the American Academy of Neurology determined that non-cutting needles (eg pencil point) clearly reduced PDPH following spinal anaesthesia, data for their effectiveness in diagnostic lumbar puncture were conflicting and inconclusive (Evans et al, 2000). Subsequent trials have demonstrated that, for diagnostic lumbar punctures, non-cutting (pencil point) needles significantly reduce the incidence of PDPH compared with cutting needles (eg Quincke) (Lavi et al, 2006 **Level II**; Strupp et al, 2001 **Level II**), leading to a recommendation to now use non-cutting needles routinely in neurology practice (Arendt et al, 2009).

The incidence of accidental dural puncture was not reduced by using an 18-gauge epidural Sprotte (pencil point) needle, compared with a 17-gauge epidural Tuohy needle, however the incidence of PDPH was significantly lower with the Sprotte needle (Morley-Forster et al, 2006 **Level II**).

### ***Epidural blood patch***

The use of an epidural blood patch (EBP) for the treatment of PDPH has been recommended as first-line therapy, especially in obstetric patients (Thew & Paech, 2008) and following inadvertent dural puncture with an epidural needle (Gaiser, 2006). However, further high quality trials are required to clearly determine the efficacy of EBP administration for the treatment of PDPH (Sudlow & Warlow, 2002a **Level I**). The potential risks, adverse effects, optimal timing and blood volume and other technical issues associated with EBP therapy remain unclear.

Compared with 'conventional treatment' (fluids, analgesia and caffeine), an EBP significantly reduced the intensity of PDPH (following spinal anaesthesia or diagnostic lumbar puncture) at 24 hours (Sandesc et al, 2005 **Level II**) and also reduced the incidence and severity of PDPH at 1 week, following lumbar puncture (van Kooten et al, 2008 **Level II**).

The most effective blood volume for EBP administration is not known. Significant relief of PDPH was obtained in 93% of patients who received a mean EBP volume of 23 (+/-5) mL, with 20 mL recommended as the 'optimal' target volume, beyond which there was a higher incidence of lumbar discomfort on injection (Safa-Tisseront et al, 2001 **Level IV**). EBP volumes in the range of 10 to 20 mL were effective in relieving PDPH in 98% of patients, following spinal or epidural anaesthesia (Wu et al, 1994 **Level IV**). There was no difference in the frequency of PDPH resolution (approximately 91%) with either 10 or 15 mL blood volumes randomised according to patient height (Taivainen et al, 1993 **Level III-1**). In parturients, there was no difference in the severity of PDPH to 3 days in patients who received either a 7.5 or 15 mL EBP, except for a lower incidence of nerve root irritation during injection with the lower volume (Chen et al, 2007 **Level II**).

EBP is sometimes performed prophylactically to prevent PDPH after an inadvertent dural puncture (by an epidural needle). However, there is conflicting evidence of benefit with prophylactic EBP administration. One study demonstrated a reduced incidence of PDPH (Colonna-Romano & Shapiro, 1989 **Level II**); another reported no reduction in the incidence of PDPH or subsequent blood patch requirements in parturients, but headache duration was shorter (Scavone et al, 2004 **Level II**).

The use of autologous blood patch may be contraindicated in patients with leukaemia, coagulopathy or infection including HIV.

### ***Bed rest and hydration***

There was no evidence of benefit with bed rest in the treatment or prevention of PDPH (Sudlow & Warlow, 2002b **Level I**). However, patients with PDPH may have difficulty in mobilising and the headache subsides with bed rest. The role of fluid therapy (hydration) in the prevention of PDPH remains unclear (Sudlow & Warlow, 2002b **Level I**).

### **Other treatments**

Although caffeine is often prescribed to prevent or treat PDPH, evidence for its efficacy is limited and conflicting (Halker et al, 2007). Administration of caffeine combined with paracetamol for 3 days following spinal anaesthesia did not reduce the incidence of PDPH (or associated symptoms such as nausea and photophobia) compared with placebo (Esmoğlu et al, 2005 **Level II**). IV caffeine administered during spinal anaesthesia reduced pain scores, analgesia requirements and the incidence of moderate-to-severe PDPH for up to 5 days (Yucel et al, 1999 **Level II**). IV theophylline also reduced the severity of PDPH (Ergun et al, 2008 **Level II**). Oral caffeine reduced the severity PDPH at 4 hours (Camann et al, 1990 **Level II**) but did not reduce the rate of EBP administration (Candido & Stevens, 2003; Halker et al, 2007).

The addition of IV hydrocortisone to conventional therapy (bed rest and analgesia) for 48 hours decreased the intensity of PDPH following spinal anaesthesia for Caesarean section (Rucklidge et al, 2004 **Level II**). There was no evidence to support the efficacy of adrenocorticotrophic hormone in PDPH (Candido & Stevens, 2003).

There was no evidence to support the efficacy of sumatriptan (Connelly et al, 2000 **Level II**) in PDPH, although in open-label studies other triptans have been reported to have sufficient benefit to warrant further evaluation (Bussone et al, 2007).

There was no evidence to support the use of epidurally administered saline, dextran or fibrin glue or neuraxial opioids in the treatment of PDPH (Turnbull & Shepherd, 2003), however prophylactic epidural morphine in saline significantly reduced the incidence of PDPH and EBP compared with epidural saline alone following inadvertent dural puncture in parturients (Al-metwalli, 2008 **Level II**).

### **Other headaches**

There is little evidence to guide the treatment of acute cervicogenic headache, post-traumatic headache or acute headache attributed to substance use or its withdrawal, although general principles of evaluation of headache and management of acute pain must apply (Silberstein, 2000). The treatment of giant cell arteritis is with high-dose steroids, but there are no evidence-based guidelines.

#### ***Headache attributed to substance withdrawal (severe analgesic ‘rebound’ headache)***

Patients may present with severe acute-on-chronic headache due to the overuse and/or withdrawal of antimigrainal (triptans or ergot alkaloids) or analgesics. Inpatient treatment is often required and may include cessation of analgesics, IV hydration, steroids, nsNSAIDs, antiemetics and benzodiazepines (Trucco et al, 2005). Evidence for the benefit of steroids is mixed. One study showed that administration of prednisone led to a significant reduction in the duration of severe headache compared with placebo (Pageler et al, 2008 **Level II**). However, another found that prednisolone did not have a significant effect on ‘rebound headache’ outcomes during the withdrawal phase (Boe et al, 2007 **Level II**).

A 12-week open-label study of a single daily dose of tizanidine in combination with a single morning dose of NSAID, resolved chronic daily headache in 62% of patients (Smith, 2002 **Level III-3**).

### **Complementary and alternative medicines and therapies**

There is no high-level evidence of efficacy for acupuncture, hypnotherapy, chiropractic, spinal manipulation or homeopathy in the treatment of migraine (Vernon et al, 1999 **Level I**; Astin & Ernst, 2002 **Level I**; Melchart et al, 2001 **Level I**). However, acupuncture is an effective non-pharmacological intervention in TTH (Linde et al, 2009 **Level I**).



## Opioids and acute headache

Although opioids are commonly used for the emergency treatment of headache (Vinson, 2002), they cannot be recommended for use on a regular basis because of the risk of dependency and other opioid-related adverse effects. The Australian Association of Neurologists recommended that opioids should not be used for migraine unless the patient is unresponsive to all other measures or where the use of ergot agents and triptans is contraindicated (Lance et al, 1997). Pethidine in particular should be avoided in the treatment of headache, due to evidence of poor efficacy compared with other migraine treatments (Friedman et al, 2008 **Level I**) and a higher risk of opioid dependency.

### Key messages

#### *Tension-type headache*

1. Acupuncture is effective in the treatment of tension-type headache (**N**) (**Level I** [Cochrane Review]).
2. The addition of caffeine to aspirin or paracetamol improves analgesia in the treatment of episodic tension-type headache (**U**) (**Level I**).
3. Simple analgesics such as aspirin, paracetamol or NSAIDs, either alone or in combination, are effective in the treatment of episodic tension-type headache (**U**) (**Level II**).

#### *Migraine*

4. Triptans are effective in the treatment of severe migraine (**U**) (**Level I**).
5. Aspirin-metoclopramide is effective in the treatment of mild-to-moderate migraine (**U**) (**Level I**).
6. Parenteral metoclopramide is effective in the treatment of migraine (**U**) (**Level I**).
7. Over-the-counter medications, including combined paracetamol-aspirin-caffeine preparations, are effective in the treatment of migraine with mild-to-moderate symptoms and disability (**N**) (**Level I**).
8. Effervescent aspirin, ibuprofen or dipyron are effective in the treatment of migraine (**N**) (**Level I**).
9. In children or adolescents with migraine, ibuprofen or intranasal sumatriptan (over 12 years of age) are effective treatments (**N**) (**Level I**).
10. Pethidine is less effective than most other migraine treatments and should not be used (**N**) (**Level I**).
11. Parenteral prochlorperazine, chlorpromazine or droperidol are effective in the treatment of migraine, especially in the emergency department (**N**) (**Level II**).
12. Paracetamol is effective in the treatment of mild-to-moderate migraine (**U**) (**Level II**).
13. A 'stratified care strategy' is effective in treating migraine (**U**) (**Level II**).

#### *Cluster headache*

14. Parenteral triptans (sumatriptan or zolmitriptan) (**S**) or oxygen therapy (**U**), are effective treatments for cluster headache attacks (**Level II**).

### *Postdural puncture headache*

15. There is no evidence that bed rest is beneficial in the treatment and prevention of postdural puncture headache (**U**) (**Level I** [Cochrane Review]).
16. The incidence of postdural puncture headache is reduced by using small-gauge spinal needles and/or a non-cutting bevel (**U**) (**Level I**).
17. Further high quality trials are required to determine the efficacy of epidural blood patch administration in the treatment of postdural puncture headache (**U**) (**Level I**), however benefit is likely (**N**) (**Level II**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Opioids should be used with extreme caution in the treatment of headache (**U**).
- Frequent use of analgesics, triptans and ergot derivatives in the treatment of recurrent acute headache may lead to medication overuse headache (**U**).

### **9.6.6 Acute pain associated with neurological disorders**

Pain associated with neurological disorders is usually neuropathic in nature, although nociceptive pain due to problems such as muscle spasms may also occur. Neuropathic pain may be acute or chronic and may be due to a lesion or dysfunction of the peripheral nervous system (PNS) (eg painful peripheral neuropathy) or the CNS (central pain, eg poststroke pain) (Loeser & Treede, 2008).

Treatment of acute neuropathic pain is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain disorders. Effective treatments for neuropathic pain include TCAs, anticonvulsants, membrane stabilisers, NMDA-receptor antagonists, opioids or tramadol (see Sections 4.1 and 4.3.2 to 4.3.6).

Associated psychosocial problems and physical disabilities must also be managed within a multidisciplinary framework.

#### **Multiple sclerosis**

Chronic pain is experienced by 49% to 73.5% of patients with multiple sclerosis (Osterberg et al, 2005; Hadjimichael et al, 2007; Khan & Pallant, 2007; Brochet et al, 2009) and the type of pain may vary. In one survey, central pain was reported in 27.5% of patients (17.3% of these had trigeminal neuralgia); another 20.9% had nociceptive pain and 2.2% described peripheral neuropathic pain (Osterberg et al, 2005). In another survey, of those patients with chronic pain, 60.7% had dysaesthetic pain and just 6.6% reported nociceptive pain (Khan & Pallant, 2007).

Pain related to trigeminal neuralgia responds to carbamazepine (Wiffen et al, 2005 **Level I**). Cannabinoids reduced the intensity of neuropathic pain associated with multiple sclerosis by approximately 1.5/10 (VAS or verbal numerical rating scale [VNRS]), compared with placebo; there were significant side effects, particularly dizziness (Iskedjian et al, 2007 **Level I**). Safety concerns regarding cannabinoid use need to be considered. There was no evidence to guide the use of antispasticity agents such as baclofen in the treatment of multiple sclerosis-related acute pain (Shakespeare et al, 2003 **Level I**). Nortriptyline was as effective as transcutaneous nerve stimulation in reducing pain intensity and/or sensory complaints in patients with multiple sclerosis (Chitsaz et al, 2009 **Level II**). Levetiracetam was effective in reducing pain in multiple sclerosis (Rossi et al, 2009 **Level II**).

### **Central poststroke pain**

Central pain develops in 8% to 35% of stroke patients; its pathophysiology and treatment options have been reviewed by Kumar et al (Kumar et al, 2009). Intravenous lignocaine (Attal et al, 2000 **Level II**) and IV propofol in subhypnotic doses (Canavero & Bonicalzi, 2004 **Level II**) may provide short-term relief in central poststroke pain, and amitriptyline was more effective than placebo and carbamazepine (which was not different from placebo) (Leijon & Boivie, 1989 **Level II**). Lamotrigine was moderately effective and well-tolerated in central poststroke pain (Vestergaard et al, 2001 **Level II**).

### **Trigeminal neuralgia**

Exacerbations of trigeminal neuralgia can present as acute neuropathic pain. Published guidelines identified insufficient evidence for the effectiveness of any IV medication in this setting (Crucchi et al, 2008 **Level I**). The same guidelines rate carbamazepine as effective and oxcarbazepine as probably effective in this condition and suggest that baclofen, lamotrigine, and pimozone may be considered if the first line medications are ineffective. Topical ophthalmic anaesthesia is described as probably ineffective.

### **Guillain-Barre syndrome**

See Section 9.8.4.

#### **Key message**

The following tick box  represents conclusions based on clinical experience and expert opinion.

Treatment of acute pain associated with neurological disorders is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain states.

### **9.6.7 Orofacial pain**

Acute orofacial pain may be caused by infective, traumatic, neuropathic, vascular, neoplastic or other pathologies (Zakrzewska & Harrison, 2003; Keith, 2004; Ward & Levin, 2004). Most commonly acute orofacial pain is due to dental or sinus disease but it may also be associated with chronic facial pain syndromes (eg trigeminal neuralgia) or be referred from adjacent regions such as the cervical spine and the thorax. A thorough history (including dental) and examination (particularly of the oral cavity and cranial nerves) are essential components of the assessment of orofacial pain. Recurrent or persistent orofacial pain requires a biopsychosocial assessment and appropriate multidisciplinary management (Vickers et al, 2000). Neuropathic orofacial pain (atypical odontalgia, phantom pain) may be exacerbated by repeated dental procedures (eg extraction of teeth, root canal therapy, sectioning of nerves), incorrect drug therapy or psychological factors (Vickers et al, 1998).

#### **Acute postoperative dental pain**

Acute pain after third molar extraction is the most extensively studied model for testing postoperative analgesics. Ibuprofen, paracetamol, aspirin (Barden et al, 2004 **Level I**) and celecoxib (Derry et al, 2008 **Level I**; Cheung et al, 2007 **Level II**) were found to be effective in this setting. Interestingly, the placebo response for analgesia was significantly lower in postdental extraction pain than in other acute pain models (Barden et al, 2004 **Level I**).

NsNSAIDs or coxibs were recommended as 'first-line' analgesics following third molar extraction (Barden et al, 2004 **Level I**), however paracetamol was also safe and effective (Weil et al, 2007 **Level I**), with a dose of 1000 mg providing better pain relief than lower doses (NNT 3; NNH 33) (Dodson, 2007 **Level I**). NsNSAIDs were more effective than paracetamol or codeine

(either alone or in combination) (Ahmad et al, 1997 **Level I**) and ketorolac provided better analgesia with fewer adverse effects than pethidine (Fricke et al, 1992 **Level II**) or tramadol (Ong & Tan, 2004 **Level II**). The combination of paracetamol 1000 mg with ketoprofen 100 mg was more effective than either drug given alone (Akural et al, 2009 **Level II**).

Coxibs were of similar efficacy to nsNSAIDs in acute postoperative dental pain (Chen et al, 2004 **Level I**; Cicconetti et al, 2004 **Level I**). A single dose of celecoxib 400 mg provided similar analgesia to ibuprofen 400 mg, however with a longer duration of action and increased time to rescue analgesia following dental surgery (Cheung et al, 2007 **Level II**). A combination of oxycodone 5 mg /ibuprofen 400 mg was more effective than various other combinations of paracetamol, ibuprofen, oxycodone or hydrocodone or placebo for analgesia following dental surgery (Litkowski et al, 2005 **Level II**). Tramadol 100 mg had a similar efficacy to aspirin/opioid or paracetamol/opioid combinations in treating acute dental pain (Moore & McQuay, 1997 **Level I**). A tramadol/paracetamol combination was superior to tramadol alone with fewer adverse effects (Edwards, McQuay et al, 2002 **Level I**; Fricke et al, 2004 **Level II**).

Perioperative steroid administration reduced swelling and trismus but not pain, following third molar extraction (Markiewicz et al, 2008 **Level I**) and reduced postoperative nausea (Baxendale et al, 1993 **Level II**; Schmelzeisen & Frolich, 1993 **Level II**).

**Note: reversal of conclusion**

This reverses the Level 1 conclusion in the previous edition of this document; an earlier meta-analysis reported an improvement in analgesia.

A single postoperative IM injection of prednisolone combined with diclofenac reduced pain for the first 7 hours postextraction and reduced swelling and trismus at various times up to 7 days, compared with placebo; prednisolone alone reduced pain at 7 hours and swelling on day 2 (Buyukkurt et al, 2006 **Level II**). A submucosal injection of either 4 mg or 8 mg of dexamethasone at the time of third molar extraction reduced facial swelling but not pain or trismus compared with placebo for up to 48 hours (Grossi et al, 2007 **Level II**); injection of methylprednisolone into the masseter muscle following extraction reduced pain, swelling and trismus (Vegas-Bustamante et al, 2008 **Level II**).

Cryotherapy (ice packs) following third molar extraction did not reduce trismus but may have reduced facial swelling and pain, although the results were conflicting (Laureano Filho et al, 2005 **Level II**; van der Westhuijzen et al, 2005 **Level II**). Facial compression reduced pain for up to 3 days, with no additional benefit from co-application of ice packs (Forouzanfar et al, 2008 **Level II**).

Acupuncture may be of benefit in reducing postprocedural dental pain but better quality trials are required (Ernst & Pittler, 1998 **Level I**).

NSAIDs and emergency pulpectomy (Sutherland & Matthews, 2003 **Level I**) but not antibiotics (Keenan et al, 2005 **Level I**) reduced pain in patients with acute apical periodontitis.

### **Acute pain associated with pharyngitis**

Paracetamol, nsNSAIDs, coxibs and opioids, administered as monotherapy or in combination, were effective in the treatment of pain associated with acute pharyngitis (Thomas et al, 2000 **Level I**; Romsing et al, 2000 **Level II**). Aspirin (Thomas et al, 2000 **Level I**; Eccles et al, 2003 **Level II**) particularly when combined with caffeine (Schachtel et al, 1991 **Level II**) was also effective.

Topical analgesics such as benzydamine HCl 0.15% (as an anti-inflammatory spray) (Thomas et al, 2000 **Level I**) or flurbiprofen lozenges (Watson et al, 2000 **Level II**) provided effective analgesia in acute sore throat, with minimal side effects.

Steroids have been prescribed to reduce acute pain and swelling in severe pharyngitis. They provide symptomatic relief of pain, in particular in patients with severe or exudative sore throat (Hayward et al, 2009 **Level I**). In particular, steroids in combination with analgesics and antibiotics increased the likelihood of complete resolution of pain and the time to onset of pain relief. Oral dexamethasone (Olympia et al, 2005 **Level II**; Niland et al, 2006 **Level II**) or IM betamethasone (Marvez-Valls et al, 1998 **Level II**) significantly reduced dysphagia and the duration of symptoms in patients with severe streptococcal pharyngitis, although a study in children failed to find any benefit with oral dexamethasone (Bulloch et al, 2003 **Level II**). Following drainage and antibiotics for peritonsillar abscess, a single dose of IV steroid reduced pain, trismus and fever (Ozbek et al, 2004 **Level II**).

Antibiotics for sore throat reduced pain, headache and fever by 50% on day 3 and shortened the duration of symptoms by approximately one day. The NNT to prevent a sore throat at day 3 was approximately 6 (95% CI 4.9 to 7.0) and at day 7, 21 (95% CI 13.2 to 47.9) (Del Mar et al, 2006 **Level I**).

### **Acute pain associated with sinusitis and otitis media**

There is no evidence to guide the choice of analgesia for acute pain associated with sinusitis or otitis media. It may be appropriate to use nsNSAIDs, coxibs, paracetamol, weak opioids or tramadol, based on evidence for treatment of dental pain. Nasal irrigation with physiological saline may provide symptomatic relief (Clement et al, 1998; Low et al, 1997). Administration of penicillin V decreased pain scores over 3 days in patients with severe sinus pain (Hansen et al, 2000 **Level II**). Local anaesthetic eardrops reduced pain in otitis media (Bolt et al, 2008 **Level II**); however the overall effectiveness of eardrops in this condition was unclear (Foxlee et al, 2006 **Level I**).

### **Acute post-tonsillectomy pain**

(Also see Sections 10.5.1, 10.5.2 & 10.5.5)

Peritonsillar infiltration or topical application of local anaesthetics produced a modest reduction in post-tonsillectomy pain (7 to 19 mm on a 100 mm VAS) for up to 24 hours, with topical application and infiltration being equally effective (Grainger & Saravanappa, 2008 **Level I**).

#### **Note: reversal of conclusion**

This reverses the Level 1 conclusion in the previous edition of this document; an earlier meta-analysis had reported no improvement in analgesia.

Injection of local anaesthetics in the tonsillar fossa improved pain scores, and reduced time to first oral intake and the incidence of referred ear pain (Naja et al, 2005 **Level II**; Somdas et al, 2004 **Level II**). Ropivacaine 1.0% with adrenaline resulted in better pain relief for up to 3 days after tonsillectomy than bupivacaine 0.25% with adrenaline or placebo (Arikan et al, 2008 **Level II**). The addition of magnesium to levobupivacaine reduced analgesic requirements compared with levobupivacaine alone or saline control (Karaaslan et al, 2008 **Level II**) and bupivacaine 0.25% with pethidine reduced analgesic requirements at rest, but did not affect other pain outcomes compared with saline, following tonsillectomy in children (Nikandish et al, 2008 **Level II**).

Infiltration of the tonsillar bed with tramadol may reduce pain and analgesic requirements in the first few hours after tonsillectomy (Atef & Fawaz, 2008a **Level II**), although infiltration may be no more effective than an equivalent IM dose (Ugur et al, 2008 **Level II**). Peritonsillar infiltration of ketamine reduced pain and analgesic requirements for up to 24 hours post-tonsillectomy in

children (Honarmand et al, 2008 **Level II**; Erhan et al, 2007 **Level II**) although the effects of ketamine infiltration were not significantly different to an equivalent IV dose (Dal et al, 2007 **Level II**).

A systematic review of analgesia for tonsillectomy in children was unable to generate clear conclusions due to heterogeneity of the trials; however no single prophylactic dose of an analgesic provided adequate pain relief for the entire first postoperative day; orally administered paracetamol was more effective than rectal, and prophylactic NSAIDs were at least as effective as opioids in reducing post-tonsillectomy pain (Hamunen & Kontinen, 2005 **Level I**).

In meta-analyses of tonsillectomy in both adult and paediatric patients, nsNSAIDs were found to increase the risk of reoperation for bleeding (NNH 29 to 60) (Marret et al, 2003 **Level I**; Moiniche et al, 2003 **Level I**) but surgical blood loss was not significantly increased (Moiniche et al, 2003 **Level I**) (see also Section 4.2.2). Looking at studies in children only, there was no increase in the risk of reoperation for bleeding after tonsillectomy (Cardwell et al, 2005 **Level I**). Aspirin, which irreversibly inhibits platelet aggregation, increased the risk of post-tonsillectomy haemorrhage (Krishna et al, 2003 **Level I**).

Diclofenac (Romsing et al, 2000 **Level II**; Schmidt et al, 2001 **Level II**) or ketorolac (Rusy et al, 1995 **Level II**) were no more effective than paracetamol in providing analgesia in children post-tonsillectomy. Rofecoxib provided effective analgesia for up to 24 hours after surgery, and led to decreased nausea but no increased blood loss (Joshi et al, 2003 **Level II**). IV paracetamol administered 6-hourly for the first postoperative day reduced pain and rescue analgesia requirements in adults following tonsillectomy (Atef & Fawaz, 2008b **Level II**).

Gabapentin may reduce analgesia requirements for up to 48 hours and pain on swallowing for up to 4 hours, following tonsillectomy in adults (Jeon et al, 2008 **Level II**; Mikkelsen et al, 2006 **Level II**).

In children, dexamethasone produced a significant but clinically moderate reduction in post-tonsillectomy pain on the first postoperative day (Afman et al, 2006 **Level I**). There was a reduced risk of postoperative nausea and vomiting and reduced use of ibuprofen but also an increased risk of bleeding (Czarnetzki et al, 2008 **Level II**).

### **Acute pain associated with oral ulceration, including mucositis**

Acute oral ulceration due to trauma (physical, chemical, thermal), infection (eg herpes simplex), drugs, radiation or chemotherapy (mucositis) may be extremely painful and debilitating. Mucosal analgesia may be achieved by topical application of EMLA<sup>®</sup> cream (eutectic mixture of lignocaine and prilocaine) and 5% lignocaine (Vickers & Punnia-Moorthy, 1992 **Level II**).

Mucositis may also be due to side effects of chemoradiotherapy for solid and blood malignancies and may be complicated by opportunistic infections including HSV and candidiasis. Quality of life and nutrition can be greatly impaired.

In treating the pain of cancer-related acute mucositis, there was no significant difference in analgesia between PCA and continuous opioid infusion, except that PCA was associated with reduced opioid requirements and pain duration (Clarkson et al, 2007 **Level I**).

There was weak evidence that allopurinol mouthwash, granulocyte macrophage-colony stimulating factor (GM-CSF), immunoglobulin or human placental extract improved or eradicated mucositis; benzydamine HCl, sucralfate, tetrachlorodecaoxide, chlorhexidine, lignocaine solution, diphenhydramine hydrochloride and aluminum hydroxide suspensions were ineffective (Clarkson et al, 2007 **Level I**).

Polymyxin E, tobramycin and amphotericin B (PTA), GM-CSF, oral cooling and amifostine, significantly reduced the incidence and severity of oral mucositis (Stokman et al, 2006 **Level I**).

Povidone-iodine mouthwash also significantly reduced the severity of oral mucositis compared with sterile water, however chlorhexidine was ineffective (Potting et al, 2006 **Level I**). Preventive strategies for mucositis such as palifermin or oral cryotherapy, may be effective in specific circumstances (Bensinger et al, 2008).

Several topical measures have been postulated to treat the pain of oral mucositis. Two different formulation of 200 mcg dose transmucosal fentanyl citrate were equal in efficacy, tolerability and side-effects profile but no better than placebo for analgesia in radiation-induced mucositis (Shaiova et al, 2004 **Level II**). Topical morphine (Cerchiatti et al, 2003 **Level III-I**), doxepin (Epstein et al, 2006 **Level II**) and ketamine (Slatkin & Rhiner, 2003) may also provide analgesia, and IV ketamine 'burst therapy' may be effective in mucositis pain that is refractory to opioid analgesia (Jackson et al, 2005) (see Sections 9.7, 10.8).

Oral laser light therapy reduced mucositis pain and progression (Abramoff et al, 2008 **Level II**; Arora et al, 2008 **Level II**).

Clinical practice guidelines for the prevention and treatment of mucositis in cancer patients have been published by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (Keefe et al, 2007).

### Key messages

#### *Dental extraction*

1. Paracetamol 1000 mg provides safe and effective analgesia with minimal adverse effects, following dental extraction (**N**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs, coxibs, paracetamol, opioids or tramadol provide effective analgesia after dental extraction (**U**) (**Level I**).
3. Non-selective NSAIDs or coxibs provide better analgesia with fewer adverse effects, than paracetamol, paracetamol/opioid, paracetamol/tramadol, tramadol or weaker opioids, following dental extraction (**U**) (**Level I**).
4. Perioperative steroid administration reduces swelling (**S**) but not pain (**R**) (**Level I**) and reduces postoperative nausea (**U**) (**Level II**), following third molar extraction.
5. The combination of paracetamol with a non-selective NSAID provides analgesia that is superior to each drug given alone following third molar extraction (**N**) (**Level II**).

#### *Tonsillectomy*

6. Aspirin and some NSAIDs increase the risk of perioperative bleeding after tonsillectomy (**U**) except in children (**N**) (**Level I** [Cochrane Review]).
7. Peritonsillar infiltration or topical application of local anaesthetics produces a modest reduction in acute post-tonsillectomy pain (**R**) with topical application and infiltration being equally effective (**N**) (**Level I**).
8. Intraoperative dexamethasone administration reduces acute pain (**S**) (**Level I**), nausea and vomiting (**U**) (**Level I**) post-tonsillectomy, although there may be an increased bleeding risk (**N**) (**Level II**).
9. Peritonsillar infiltration with tramadol or ketamine may reduce post-tonsillectomy pain and analgesia requirements, but was no more effective than equivalent doses administered parenterally (**N**) (**Level II**).



### *Mucositis*

10. Opioids, via PCA or a continuous infusion, provide effective analgesia in mucositis, however PCA is associated with reduced opioid requirements and pain duration (**U**) (**Level I** [Cochrane Review]).
11. Topical treatments, including oral cooling or povidone-iodine solution, provide effective analgesia in mucositis (**N**) (**Level I**).
12. Oral laser light therapy reduces mucositis pain and progression (**N**) (**Level II**).

### *Pharyngitis*

13. Steroids improve analgesia in sore throat, in particular in severe and exudative conditions (**N**) (**Level I**).
14. Paracetamol, nsNSAIDs or coxibs and opioids, administered as monotherapy or in combination, are effective analgesics in acute pharyngitis (**N**) (**Level I**).
15. Steroids may reduce acute pain associated with severe pharyngitis or peritonsillar abscess (following drainage and antibiotics) (**N**) (**Level II**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Recurrent or persistent orofacial pain requires biopsychosocial assessment and appropriate multidisciplinary approaches. Neuropathic orofacial pain (atypical odontalgia, phantom pain) may be exacerbated by repeated dental procedures, incorrect drug therapy or psychological factors (**U**).

## 9.6.8 Acute pain in patients with HIV infection

Pain is a common problem in people infected with HIV, particularly when they develop the AIDS. Pain may be due to the effects of the virus, which is neurotropic, or an infective or neoplastic process associated with immunodeficiency. Pain may also be a side effect of treatment or related to debilitation (in patients with end-stage AIDS) or may be due to an unrelated comorbidity (O'Neill & Sherrard, 1993; Glare, 2001).

In patients with HIV/AIDS, pain is progressive, affecting approximately 25% with early stage disease, 50% to 75% with AIDS and almost all patients in the terminal phase (Singer et al, 1993 **Level IV**; Breitbart, McDonald et al, 1996; Kimball & McCormick, 1996). CD4+ T-cell count does not predict number of symptoms or severity of distress (Vogl et al, 1999 **Level IV**).

Pain occurs at multiple sites with the number of pains reported per patient increasing throughout the course of AIDS. The most frequent neurological diagnosis is a distal symmetrical polyneuropathy (DSP), found in 38% of patients. Common clinical features of DSP include non-painful paresthesias (71%), abnormalities of pain and temperature perception (71%), and reduced or absent ankle reflexes (66%). Increased age, immunosuppression, poor nutritional status and the presence of chronic disease all contribute to distal peripheral nerve dysfunction associated with HIV infection (Tagliati et al, 1999 **Level IV**).

Pain associated with HIV/AIDS is often undertreated due to patient and clinician-related barriers (Breitbart, Rosenfeld et al, 1996; **Level IV**; Larue et al, 1997; Breitbart et al, 1998; Breitbart et al, 1999; Frich & Borgbjerg, 2000). Therefore patients cite poorly treated pain as one of the most common reasons to use complementary or alternative medicines (Tsao et al, 2005 **Level IV**). Undertreatment is more common in certain patient groups — non-Caucasians, women, those with a substance abuse disorder, less educated individuals, and those with higher levels of psychosocial distress (Breitbart et al, 1998 **Level IV**). Physical and psychological symptoms

including pain had no impact on HIV-1 RNA levels in patients with stable suppression of viremia (Nettles et al, 2005 **Level IV**).

Disease-specific therapy, psychosocial interventions and physical modalities should accompany standard analgesic treatment (Jacox et al, 1994; Glare, 2001). Disease-specific therapy may need to be ceased prematurely if pain is a side effect (eg peripheral neuropathy caused by some antiretrovirals, in particular nucleoside reverse transcriptase inhibitors).

### **Treatment of HIV/AIDS-related pain**

A significant reduction in pain intensity was achievable with CR opioids in a variety of painful conditions with limited or manageable side effects, supporting the usefulness of opioid analgesia for HIV-related severe pain (Kaplan et al, 1996; Kaplan et al, 2000 **Level IV**).

Approximately 15% to 20% of patients need parenteral opioids in the terminal phase (Dixon & Higginson, 1991 **Level IV**; Kimball & McCormick, 1996 **Level IV**; Frich & Borgbjerg, 2000 **Level IV**).

Transdermal fentanyl provided better pain relief and improvement in daily functioning in patients with severe AIDS-related pain who were previously taking oral opioids (Newsham & Lefkowitz, 2001 **Level IV**).

Painful peripheral neuropathy associated with HIV infection has been the subject of a number of treatment trials. Lamotrigine (Simpson et al, 2000 **Level II**) and gabapentin (La Spina et al, 2001 **Level IV**) were better than placebo. A single application of a high-concentration capsaicin patch was safe and provided at least 12 weeks of pain reduction in patients with HIV-associated distal sensory polyneuropathy, suggesting that such patches could have a role in the analgesic regimens of people with painful HIV neuropathy (Simpson et al, 2008 **Level II**).

Smoking cannabis was significantly more effective in reducing HIV-related neuropathic pain than smoking placebo cigarettes (Abrams et al, 2007 **Level II**); the rate of responders (30% reduction in pain) in one trial was 46% with cannabis and 18% with placebo (Ellis et al, 2009 **Level II**).

The use of nucleoside reverse transcriptase inhibitors (NRTIs) can lead to a toxic neuropathy with neuropathic pain. Acetyl-L-carnitine (ALCAR) can provide neurotrophic support of sensory neurones and therefore its use in the setting of NRTI therapy may encourage nerve regeneration and analgesia. IM or oral ALCAR use was safe and well-tolerated and resulted in a reduction of pain intensity compared to placebo (Youle & Osio, 2007 **Level II**).

TCAs (Kiebertz et al, 1998 **Level II**; Shlay et al, 1998 **Level II**), antiarrhythmics (Kemper et al, 1998 **Level II**; Kiebertz et al, 1998 **Level II**), Peptide T (Simpson et al, 1996 **Level II**), vibratory counterstimulation (Paice et al, 2000 **Level III-1**) and acupuncture (Shlay et al, 1998 **Level II**) have not been shown to be effective.

Several complex drug interactions may occur between opioids and other medications taken by patients with HIV/AIDS; however the clinical relevance of most of these interactions is still unclear.

The HIV-1 protease inhibitor ritonavir inhibits the metabolism of methadone and buprenorphine (Iribarne et al, 1998) but this has no relevant clinical effect (McCance-Katz et al, 2003 **Level III-2**). However, ritonavir results in a clinically relevant inhibition of fentanyl metabolism (Oikkola et al, 1999 **Level II**) and leads to increased concentrations of the toxic metabolite norpethidine (normeperidine) if used in combination with pethidine (Piscitelli et al, 2000 **Level III-2**). Lopinavir induces metabolism of methadone leading to withdrawal symptoms in patients on maintenance doses (McCance-Katz et al, 2003 **Level III-2**). Rifampicin and rifabutin may increase opioid metabolism (particularly methadone) (Finch et al, 2002) and fluconazole may potentiate adverse effects of methadone (Tarumi et al, 2002). Zidovudine metabolism is

inhibited by methadone, thereby increasing its bioavailability and possibly toxicity (McCance-Katz et al, 1998 **Level III-3**).

### **Patients with a history of substance abuse**

HIV/AIDS patients with diagnosed mood/anxiety or substance-use disorders report much higher levels of pain than HIV/AIDS patients without these comorbidities or the general population (Tsao & Soto, 2009 **Level III-2**). Those with a history of substance abuse are also more likely to receive inadequate analgesia and suffer greater psychological distress (Breitbart et al, 1997 **Level III-2**). Two cohort studies showed that that even though HIV-positive patients with a history of problematic drug use report higher ongoing use of prescription analgesics specifically for pain, these patients continue to experience persistently higher levels of pain, relative to non-problematic users (Tsao et al, 2007 **Level III-2**; Passik et al, 2006 **Level III-2**).

Patients in a methadone maintenance program, who also suffered from HIV/AIDS related pain, gained improved analgesia without adverse effects by use of additional methadone (Blinderman et al, 2009 **Level IV**).

The principles of pain management in these patients are outlined in Section 11.8.

#### **Key messages**

1. High concentration capsaicin patches, smoking cannabis and lamotrigine are effective in treating neuropathic pain in patients with HIV/AIDS (**N**) (**Level II**).
2. Nucleoside reverse transcriptase inhibitor (NRTIs)-induced neuropathic pain in HIV/AIDS patients is treatable with acetyl-L-carnitine (ALCAR) (**N**) (**Level II**).
3. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use, but also more intense pain (**N**) (**Level III-2**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Neuropathic pain is common in patients with HIV/AIDS (**U**).
- In the absence of specific evidence, the treatment of pain in patients with HIV/AIDS should be based on similar principles to those for the management of cancer and chronic pain (**U**).
- Interaction between antiretroviral and antibiotic medications and opioids should be considered in this population (**U**).

## **9.7 ACUTE CANCER PAIN**

### **9.7.1 The scope of acute cancer pain**

Acute pain in the cancer patient may signify an acute oncological event including pathological fracture or microfracture, spinal cord or nerve compression, visceral obstruction or cutaneous ulceration due to tumour. Cancer pain may become acute in the presence of infection, and during diagnostic or therapeutic interventions. Anticancer therapies, including surgery, chemotherapy, hormonal therapy and radiotherapy, may be associated with both acute and chronic pain of a nociceptive or neuropathic nature.

Acute pain in the cancer patient requires urgent assessment and treatment. A thorough evaluation of the patient should include a full history and examination, and mechanism-based assessment of pain and, where indicated, appropriate investigations to determine the

presence of recurrent disease or serious complications of cancer that might require active intervention.

The European Association for Palliative Care recommends the use of standardised symptom assessment tools in the comprehensive assessment of cancer pain (Caraceni et al, 2002). Validated tools include the revised Edmonton Staging System (rESS) (Fainsinger et al, 2005; Nekolaichuk et al, 2005) and the McGill Pain Questionnaire and Brief Pain Inventory. All have been validated in different cultures (Uki et al, 1998; Aisyaturridha et al, 2006; Yesilbalkan et al, 2008). Pain assessment tools are available for non-verbal, cognitively impaired or dying patients.

Comprehensive consensus guidelines relating to cancer pain management have now been developed by several agencies worldwide (Hanks et al, 2001; Carr et al, 2002; Singapore Ministry of Health, 2003; NHS Quality Improvement Scotland, 2004; Broadfield et al, 2005; Miaskowski et al, 2005; SIGN, 2008; NCCN, 2009) all recommend best practice, but some sections are based on systematic reviews.

### 9.7.2 Principles of management of acute cancer pain

A pain crisis has been defined as ‘an event in which the patient reports pain that is severe, uncontrolled, and causing distress for the patient, family members, or both’ (Moryl et al, 2008). An acute pain crisis should be treated with a degree of urgency and a similar methodological approach as other medical crisis situations (Moryl et al, 2008).

In an acute pain crisis, rapid analgesic control may be achieved with a regular dose schedule of a parenteral opioid, with frequent reassessment and dose adjustment, or use of PCA technique. One clinical practical guideline for the administration of short-acting opioids, including IV morphine, in response to severe, moderate or increased pain has been published by the United States National Comprehensive Cancer Network (NCCN, 2009).

### 9.7.3 Breakthrough pain

The term breakthrough pain typically refers to a transitory flare of pain in the setting of chronic cancer pain managed with opioid drugs (Portenoy & Hagen, 1990). Despite stable therapy, exacerbations of pain are common, frequently severe or excruciating, often paroxysmal, occur a median 4 times daily and last from seconds to hours (Portenoy & Hagen, 1990 **Level IV**). Breakthrough pain may relate to waning opioid action prior to the next maintenance opioid dose (end-of-dose failure), be predictably precipitated by some movement or action (incident pain) or occur with some other random precipitant.

Consensus guidelines for management of breakthrough pain in adults have been based on limited evidence (Zeppetella & Ribeiro, 2006 **Level I**; Zeppetella, 2008 **Level IV**; Davies et al, 2009 **Level IV**). Medications used should ideally have a pharmacokinetic profile that mirrors the time-course of the breakthrough pain, with rapid onset, high potency and fast offset (SIGN, 2008). Dose requirements are subject to enormous interindividual variability and breakthrough medication doses should be titrated for each patient according to their response to these doses and separate from the background medication (Hagen et al, 2007 **Level II**). Conventional management guidelines dictate that the opioid breakthrough dose should be a proportion (one-sixth to one-tenth) of the daily dose; for example, an oral breakthrough dose of morphine would be equivalent to a 4-hourly dose, or one-sixth the oral morphine equivalent daily dose (MEDD) (Hanks et al, 2001).

Oral transmucosal fentanyl citrate (OTFC) was effective for the management of breakthrough pain (Zeppetella & Ribeiro, 2006 **Level I**). The effective dose was determined by upward titration and found to be independent of the daily opioid dose (Portenoy et al, 1999 **Level II**). Analysis of

three RCTs of OTFC confirmed that the optimal OTFC dose correlated poorly with scheduled or previous breakthrough opioid doses. The only clinical indicator of breakthrough dose was age; the average final OTFC dose significantly decreased with increasing age (Hagen et al, 2007 **Level II**). In one trial, where patients were titrated to a successful dose of OTFC (69% patients), OTFC was more successful than morphine in relieving breakthrough pain and patients preferred OTFC (Coluzzi et al, 2001 **Level II**). A comparative study of OTFC and IV morphine for breakthrough pain demonstrated analgesic superiority of IV morphine at 15 minutes but not 30 minutes and comparable adverse effects (Mercadante et al, 2007 **Level III-1**).

A buccal tablet formulation of fentanyl was superior to OTFC with respect to bioavailability and time to peak plasma concentration (Darwish et al, 2007 **Level II**), and provided relief from breakthrough pain within 10 minutes (Slatkin et al, 2007 **Level II**).

#### 9.7.4 Postoperative and procedural pain

Many of the issues relating to postoperative pain discussed in Sections 1.3 and 9.1 are particularly pertinent in the patient with cancer. Cancer patients represent a high proportion of patients undergoing thoracotomy, breast surgery, lymph node dissection from axillary, inguinal or cervical regions, and limb amputation, all associated with persistent pain syndromes that may respond to various interventions in the postoperative period. In addition, cancer patients often will undergo radio- or chemotherapy after surgery; both are risk factors for chronic postsurgical pain as outlined in Section 1.3. Chemotherapy has also been considered a risk factor for phantom limb pain, contributing to the higher incidence of phantom limb pain in children with cancer than with trauma (Smith & Thompson, 1995 **Level IV**), but no prospective trials have confirmed this association.

Identification of prior use and tolerance to opioids is essential to ensure adequate analgesia in the postoperative period, as discussed in Section 11.7.

The impact of analgesic techniques on immune response, and implications for cancer progression, are new areas of research. A review of patients undergoing radical prostatectomy, comparing outcomes after general anaesthesia plus epidural analgesia and regional anaesthesia plus opioid therapy, suggested a 57% (95% CI 17% to 78%) lower risk of cancer recurrence after the use of epidural analgesia (Biki et al, 2008 **Level IV**). Pre-emptive epidural analgesia with lignocaine and morphine, established prior to radical hysterectomy for cervical cancer, significantly reduced postoperative pain and modulated the immune response to surgery to a greater extent than epidural established after peritoneal closure; interleukin-6 rise was lowered and the duration of interleukin-2 suppression was shortened (Hong & Lim, 2008 **Level II**). Similarly, different analgesics may have different effects on postoperative immune suppression; in animals (Sacerdote et al, 1997) and in humans (Sacerdote et al, 2000 **Level II**) tramadol resulted in reduced immune suppression compared with morphine. The clinical implications of this effect have not yet been evaluated.

Patients with cancer may undergo multiple painful procedures and attention to adequate analgesia and anxiolysis is imperative, to reduce anticipatory stress prior to repeat interventions. Simple techniques include use of topical local anaesthetic, premedication or administration of breakthrough analgesia in advance, and administration of sedation by trained personnel. Few trials have evaluated procedural pain in adult patients with cancer. A review of interventions to decrease pain during mammography identified seven RCTs, but conclusions were few and based on single studies due to inability to combine data from different studies (Miller et al, 2008 **Level I**). The provision of prior information about the procedure, increasing self-control over the degree of breast compression, and the use of breast cushions all decreased pain, whereas paracetamol did not.

### 9.7.5 Acute cancer pain due to bone involvement

Primary cancers in bone and bone metastases are an important and common cause of acute and chronic cancer pain. Whereas some bone metastases are painless, others are associated with persistent pain with acute exacerbations precipitated by movement or mobilisation (incident pain), pathological fractures or compression of nerves or spinal cord. Hypercalcaemia may be a complication of bone malignancy that further heightens the pain experience.

In addition to pharmacological therapeutic options including opioids, NSAIDs, bisphosphonates and possibly calcitonin, patients require assessment to determine whether radiation therapy, tumour-targeting cytotoxic or hormonal therapy, or, in the case of imminent or actual pathological fracture or cord compression, surgical intervention may be of benefit.

#### **Radiotherapy**

Radiotherapy effectively reduces malignant bone pain and may reduce complications of bone cancer. At 1 month after radiation therapy around 25% patients experience complete pain relief, and 41% experience 50% pain relief (NNT for complete pain relief at one month 4.2; 95% CI 3.7 to 4.9) (McQuay et al, 2000 **Level I**).

One area of controversy has been the optimal fractionation schedule for radiotherapy. A systematic review and meta-analysis of single-fraction versus multi-fraction radiation therapy considered 11 trials (3435 patients) (Sze et al, 2004 **Level I**). Single-fraction treatment was as effective as multi-fraction radiation treatment in terms of overall pain response rates (60% vs 59%; OR 1.03; 95% CI 0.89 to 1.19), and complete pain relief (34% vs 32%; OR 1.11; 95% CI 0.94 to 0.13); however, the definition of a pain response (reduction by at least one category in a 4- or 5-point scale), and the time of pain assessment varied between studies. Despite equivalent pain relief outcomes, the incidence of retreatment and the pathological fracture rate were higher after single-dose therapy. The optimal treatment regimen must consider the clinical scenario and patient's life expectancy (Sze et al, 2004).

For patients with widespread bone metastases, radioisotopes had similar analgesic efficacy but were associated with increased risk of leukocytopenia and thrombocytopenia (McQuay et al, 2000 **Level I**).

#### **Bisphosphonates**

Evidence supports the use of bisphosphonates where analgesics and radiotherapy have provided inadequate pain relief (Wong & Wiffen, 2002 **Level I**). In multiple myeloma, bisphosphonates lowered the risk of vertebral pathological fracture (OR 0.59; 95% CI 0.45 to 0.78) and decreased pain (OR 0.59; 95% CI 0.46 to 0.76) (Djulgovic et al, 2002 **Level I**). Similarly, in breast cancer, bisphosphonates reduce skeletal events (median reduction 28%, range 14% to 48%); pain was significantly better after bisphosphonates in five of eleven studies (Pavlakis et al, 2005 **Level I**). Bisphosphonates for prostatic bone metastases improved pain, but not analgesic consumption (Yuen et al, 2006 **Level I**).

A prospective study indicated the incidence of osteonecrosis of the jaw after bisphosphonates to be 6.7% (17 of 252 patients); incidence may increase with time of exposure, a history of dental exposure and type of bisphosphonate (Bamias et al, 2005 **Level IV**).

Although calcitonin is used to reduce metastatic bone pain and skeletal events, there is limited evidence to support the practice. Of only two RCTS considered in a recent systematic review, calcitonin provided no analgesic benefit relative to placebo in one trial, a non-significant benefit in the other, and, overall, was associated with a higher rate of adverse events (Martinez-Zapata et al, 2006 **Level I**).

## **Percutaneous vertebroplasty**

Where other measures fail, percutaneous vertebroplasty is a minimally invasive procedure that aims to stabilise vertebral compression fractures by the injection of bone cement (polymethylmethacrylate) and achieve rapid pain relief. Two systematic reviews suggested that both vertebroplasty and kyphoplasty procedures for osteoporotic vertebral lesions were effective and safe (Hulme et al, 2006 **Level I**; McGirt et al, 2009 **Level I**). However results of more recent randomised-controlled trials found no benefit from these procedures compared with conservative management (Buchbinder et al, 2009 **Level II**; Kallmes et al, 2009 **Level II**).

Data to support these procedures for malignant bone lesions relies on low level evidence (Cheung et al, 2006 **Level IV**; Pflugmacher et al, 2006 **Level IV**; Ramos et al, 2006 **Level IV**; Anselmetti et al, 2007 **Level IV**; Brodano et al, 2007 **Level IV**; Calmels et al, 2007 **Level IV**; Chi & Gokaslan, 2008 **Level IV**; Masala et al, 2008 **Level IV**). All suggest a role for vertebroplasty for rapid relief of intractable pain and restoration of function in vertebral malignancy, and a low complication rate with experienced operators. An adverse event rate of 6.8% has been reported, including haematoma, radicular pain, and pulmonary embolism of cement (Barragan-Campos et al, 2006 **Level IV**).

Cementoplasty procedures for intractable pain also extend to percutaneous injection of bone cement under fluoroscopic guidance into pelvic bone malignancies, including metastases or sarcoma involving acetabulum, superior and inferior pubic rami, ischium and sacrum (Weill et al, 1998 **Level IV**; Marcy et al, 2000; Kelekis et al, 2005 **Level IV**; Harris et al, 2007 **Level IV**).

### **9.7.6 Other acute cancer pain syndromes**

Other acute pain syndromes in patients with cancer include malignant bowel obstruction and mucositis.

#### ***Malignant bowel obstruction***

Malignant bowel obstruction may present with generalised abdominal pain or visceral colicky pain. Very little trial data exists to guide choices between best medical care, surgery or endoscopic interventions.

Pharmacological management is based on analgesic, antiemetic and antisecretory agents. Acute pain in malignant bowel obstruction is best managed with parenteral opioids, which also reduce colicky pain by reducing bowel motility (Anthony et al, 2007). The parenteral route is utilised due to the unpredictability of absorption of oral medications. For exacerbations of colic, the antispasmodic hyoscine butylbromide is of benefit and less sedating than hyoscine hydrobromide (Anthony et al, 2007; Ripamonti et al, 2008 **Level IV**). Decompression and reduction in secretions may also assist with pain. In patients with inoperable malignant bowel obstruction and decompressive nasogastric tube, both hyoscine butylbromide and the somatostatin analog octreotide reduced both continuous and colicky pain intensity (Ripamonti et al, 2000 **Level III-1**). A Cochrane Database systematic review revealed a trend for improvement in bowel obstruction after dexamethasone (Feuer & Broadley, 2000 **Level I**). For malignant bowel obstruction with peritoneal carcinomatosis, treatment according to a staged protocol with analgesic, antiemetic, anticholinergic and corticosteroid as initial therapy (Stage 1), followed by a somatostatin analog for persistent vomiting (Stage 2) and then venting gastrostomy (Stage 3) was highly effective in relieving symptoms and avoiding permanent nasogastric tube, in one hospital centre (Laval et al, 2006 **Level IV**).

Whereas laparotomy may not always be an appropriate treatment option, endoscopic stenting may offer effective and safe palliation or act as a bridging step before surgery; analysis of many retrospective case series, single case reports and reviews indicated a wide variation in



symptom control from 42% to over 80% of patients (Khot et al, 2002 **Level IV**) and complications including perforation (3.76%), stent migration (11.81%) and reobstruction (7.34%) (Sebastian et al, 2004 **Level IV**).

### **Mucositis**

Mucositis may be due to side effects of chemoradiotherapy for solid and blood malignancies. For management see Section 9.6.7.

### **9.7.7 Interventional therapies for acute cancer pain**

Although pain is adequately controlled in the majority of patients with advanced cancer, those with an acute exacerbation of pain or prolonged intractable pain may benefit from an interventional procedure, including local anaesthetic nerve blocks, neuraxial infusions, neurolytic or neurosurgical procedures (Chambers, 2008).

A systematic review of the comparative efficacy of epidural, subarachnoid and intracerebroventricular (ICV) opioid infusions for cancer pain found no controlled trials, so conclusions were drawn from uncontrolled trials and case series of patients with ICV, epidural, or subarachnoid opioid infusions (Ballantyne & Carwood, 2005 **Level IV**). Excellent analgesia was reported in 73%, 72% and 62% of patients after ICV, epidural and subarachnoid opioids, respectively, and there were few treatment failures in all groups. Adverse effects more common with epidural and subarachnoid infusions were persistent nausea, urinary retention, pruritus and constipation, whereas respiratory depression, sedation and confusion were more common with ICV therapy.

Currently, intrathecal infusions of several classes of agents by a variety of drug delivery systems may provide effective analgesia to cancer patients with previously refractory pain, poor tolerance of oral or systemic analgesia and poor performance status. Consensus guidelines have been established for the use of intrathecal opioids, local anaesthetics, clonidine, baclofen and other medications in cancer patients (Stearns et al, 2005).

The issue of analgesia for breakthrough pain in patients with intrathecal analgesia was addressed in a small case series, where either an intrathecal local anaesthetic bolus or sublingual ketamine was used successfully (Mercadante et al, 2005 **Level IV**).

#### **Key messages**

1. Oral transmucosal fentanyl is effective in treating acute breakthrough pain in cancer patients (**S**) (**Level I** [Cochrane Review]).
2. Radiotherapy and bisphosphonates are effective treatments of acute cancer pain due to bone metastases (**N**) (**Level I** [Cochrane Review]).
3. Opioid doses for individual patients with cancer pain should be titrated to achieve maximum analgesic benefit with minimal adverse effects (**S**) (**Level II**).
4. Analgesic medications prescribed for cancer pain should be adjusted to alterations of pain intensity (**U**) (**Level III**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Acute pain in patients with cancer often signals disease progression; sudden severe pain in patients with cancer should be recognised as a medical emergency and immediately assessed and treated (**U**).
- Cancer patients receiving controlled-release opioids need access to immediate-release opioids for breakthrough pain; if the response is insufficient after 30 to 60 minutes, administration should be repeated (**U**).
- Breakthrough analgesia should be one-sixth of the total regular daily opioid dose in patients with cancer pain (except when methadone is used, because of its long and variable half life) (**U**).
- If nausea and vomiting accompany acute cancer pain, parenteral opioids are needed (**U**).

## 9.8 ACUTE PAIN MANAGEMENT IN INTENSIVE CARE

The management of pain in the intensive care unit (ICU) requires the application of many principles detailed elsewhere in these guidelines. Analgesia may be required for a range of painful conditions, for example after surgery and trauma, in association with invasive devices and procedures and acute neuropathic pain. There may also be a need for the intensivist to provide palliative care (Hawryluck et al, 2002).

Consensus guidelines have been published in the United States for the provision of analgesia and sedation in adult intensive care (Jacobi et al, 2002), but there remains a dearth of sufficient large-scale randomised ICU pain studies on which to base evidence-based guidelines. Some of the key consensus findings regarding IV analgesia and sedation in the ICU setting were (Jacobi et al, 2002):

- a therapeutic plan and goal of analgesia should be established and communicated to caregivers;
- assessment of pain and response to therapy should be performed regularly;
- the level of pain reported by the patient is the standard for assessment but subjective observation and physiological indicators may be used when the patient cannot communicate; and
- sedation of agitated critically ill patients should only be started after providing adequate analgesia and treating reversible physiological causes.

It is difficult to separate pain management from sedation in this context and intensive care sedation algorithms usually address both aspects. There has been a recent change in emphasis from sedative-based sedation (Soliman et al, 2001) to analgesia-based sedation (Park et al, 2007 **Level III-3**; Fraser & Riker, 2007). Although these measures have been widely recommended, they have not yet been universally incorporated into routine practice. This is despite the fact that the use of such protocols to preserve consciousness while treating pain appropriately has been demonstrated to produce a 57.3% decrease in the median duration of mechanical ventilation in one study (De Jonghe et al, 2005).

Probably the most useful intervention during sedation and analgesia in ICU is the provision of a daily drug 'holiday' (daily interruption of sedation [DIS]) to reassess the need for sedation and analgesia. This simple step is associated with significantly shorter periods of mechanical ventilation and shorter stays in the ICU (Kress et al, 2000 **Level II**), but does not cause adverse

psychological outcomes and reduces symptoms of post-traumatic stress disorder (Kress et al, 2003 **Level III-2**). Contrary to initial concerns, DIS is not associated with an increased risk of myocardial ischemia even in high-risk patients (Kress et al, 2007 **Level III-1**).

### **9.8.1 Pain assessment in the intensive care unit**

Assessment of pain in the ICU is difficult. The most important index of pain is the patient's own subjective experience, but it is frequently impossible to quantify this because of the presence of an endotracheal tube, or decreased conscious state due to illness or coadministered sedative agents. In 17 trauma patients admitted to an ICU, 95% of doctors and 81% of nurses felt that the patients had adequate analgesia whereas 74% of patients rated their pain as moderate or severe (Whipple et al, 1995 **Level IV**).

Traditional subjective scales including the VAS or numerical rating scale (NRS) are not applicable to the unresponsive patient. Instead, the observation of behavioural and physiological responses may be the only information available to modify pain management (Puntillo et al, 1997 **Level IV**; Puntillo et al, 2002 **Level IV**; Chong & Burchett, 2003).

A new behavioural pain scale has been described and validated for the evaluation of pain in sedated, mechanically ventilated, unresponsive patients (Aissaoui et al, 2005 **Level III-1**; Payen et al, 2001 **Level III-1**). A 'critical-care pain observation tool' that is based upon the response to noxious stimuli has undergone validation in diverse critically ill patient subgroups (Gelinas et al, 2009 **Level III-2**).

The available data support self-rating where possible, and where not, a nurse-administered NRS combined with the Behavioural Pain Scale (Ahlers et al, 2008 **Level III-3**).

The use of formal pain/ agitation assessment and subsequent treatment decreased the incidence overall of pain (63% vs 42%) and agitation (29% vs 12%). These findings were associated with a decrease in the duration of mechanical ventilation (Chanques et al, 2006 **Level III-1**). There were similar findings in critically ill trauma patients, where a formalised analgesia-delirium-sedation protocol shortened duration of ventilation, ICU and hospital stay while also decreasing total sedative doses (Robinson et al, 2008 **Level III-3**).

### **9.8.2 Non-pharmacological measures**

Much of the discomfort associated with a prolonged admission to intensive care can be alleviated by holistic nursing care. Attention to detail with positioning, pressure care, comfortable fixation of invasive devices, care in the management of secretions and excretions, minimisation of noise from spurious alarms and unnecessary equipment (such as the uncritical application of high-flow mask oxygen) can substantially lessen the burden of discomfort for the patient (Aaron et al, 1996; Chong & Burchett, 2003 **Level IV**; Puntillo et al, 2004 **Level III-3**). Maintenance of a day/night routine (lighting and activity) is thought to aid sleep quality (Horsburgh, 1995). A flexible and liberal visiting policy should decrease the pain of separation from family and friends. Physiotherapy maintains range of movement of joints and slows deconditioning while massage can trigger a relaxation response leading to improved sleep.

### **9.8.3 Pharmacological treatment**

The mainstay of treatment of acute pain in the ICU remains parenteral opioid analgesia (Shapiro et al, 1995; Hawryluck et al, 2002). Morphine is usually the first choice, but it is relatively contraindicated in the presence of renal impairment because of possible accumulation of its active metabolites. Pethidine is rarely used in the ICU because of concerns about accumulation of norpethidine, especially in the presence of renal dysfunction or prolonged exposure, and because of its potential interaction with several drugs (eg tramadol, monoamine oxidase

inhibitors [MAOIs] and SSRIs). Fentanyl is emerging as a useful alternative to morphine, with a lesser tendency to cause haemodynamic instability (Shapiro et al, 1995). It has a short duration of action after a single dose due to redistribution, but its long elimination half-life suggests that it may accumulate when given in high doses for long periods.

The newer opioids, alfentanil and remifentanil, have potentially favourable kinetics for use in patients with organ dysfunction. Alfentanil combined with propofol led to shorter time to extubation and ICU discharge compared with a morphine and midazolam combination (Manley et al, 1997 **Level II**). Remifentanil exhibits rapid clearance that is independent of renal function (Cohen & Royston, 2001; Breen et al, 2004) while remifentanil acid, a weak active metabolite, may accumulate in the presence of renal impairment (Pitsiu et al, 2004 **Level IV**). This has no clinical consequences (Breen et al, 2004 **Level IV**). When titrated carefully against a sedation scale, remifentanil did not reduce the need for supplementary sedation or the time to extubation after cessation compared with fentanyl (Muellejans et al, 2004 **Level II**). The use of remifentanil in postsurgical ICU patients provided superior analgesia and an accelerated extubation time compared with morphine (Dahaba et al, 2004 **Level II**). The combination of morphine and remifentanil provided better analgesia and sedation than morphine alone, with a lower incidence of side effects and a similar haemodynamic profile and patient satisfaction (Carrer et al, 2007 **Level II**). In a comparison between a remifentanil-based sedation regimen titrated to response before the addition of midazolam for further sedation, or a midazolam-based sedation regimen with fentanyl or morphine added for analgesia, remifentanil-based sedation reduced the duration of mechanical ventilation, improved the weaning process, and decreased overall sedative doses required in ICU patients requiring long-term ventilation (Breen et al, 2005 **Level II**).

Dexmedetomidine is a highly selective alpha-2 agonist sedative, with anxiolytic and analgesic properties. It has the advantage of providing titratable sedation with minimal respiratory depression (Martin et al, 2003 **Level II**). It can cause a temporary increase in blood pressure during administration, but the subsequent reductions in heart rate and blood pressure are more noticeable, especially in haemodynamically labile individuals. It has been introduced into intensive care practice as an aid to increase tolerance of intubation and mechanical ventilation and to smooth the transition to spontaneous respiration and extubation. After coronary artery surgery, dexmedetomidine was associated with similar ventilation times to propofol-based sedation but significantly lower morphine requirements and fewer ventricular arrhythmias (Herr et al, 2003 **Level II**). These findings were contradicted by a retrospective review in general ICU patients, where adjunctive dexmedetomidine reduced sedative requirements but did not alter analgesic requirements. (MacLaren et al, 2007 **Level III-2**).

In ventilated patients, the spread of thoracic epidural block increased with positive pressure ventilation (Visser et al, 2006 **Level II**).

#### **9.8.4 Guillain-Barre syndrome**

Patients with Guillain-Barre syndrome commonly need treatment in an ICU. They may report significant pain including painful paraesthesiae, backache, sciatica, meningism, muscle and joint pain. The distal to proximal distribution of pain that characterises peripheral neuropathies is not usually seen (Khatri & Pearlstein, 1997).

Early treatment of pain with carbamazepine improved analgesia and reduced requirements for pethidine and sedation in patients with Guillain-Barre syndrome (Tripathi & Kaushik, 2000 **Level II**). Gabapentin (Pandey et al, 2002 **Level II**) and ketamine infusions (Parisod, 2002) also improved pain relief. Gabapentin was more effective than carbamazepine for the treatment of pain in patients with Guillain-Barre syndrome admitted to ICU for mechanical ventilation

(Pandey et al, 2005 **Level II**). IV lignocaine may be useful in the treatment of acute neuropathic pain in Guillain-Barre syndrome based on evidence of benefit in other neuropathic pain disorders (Kalso et al, 1998 **Level I**).

Plasma exchange in acute Guillain-Barre syndrome was associated with a shortened duration of disease and improved outcomes, including pain (Guillain-Barre Syndrome Study Group, 1985 **Level II**).

While steroid therapy is not advocated as primary management in postinfectious polyneuropathy, it may provide rapid resolution of the severe backache associated with the acute phase of the neuropathy (Kabore et al, 2004 **Level IV**).

### 9.8.5 Procedure-related pain

There is often an assumption that patients who are intubated and sedated in intensive care will not recall or perceive pain during procedures. Lines and catheters are sometimes inserted without supplementary anaesthesia. A survey suggests that specific treatment of procedure-related pain occurs less than 25% of the time (Payen et al, 2007 **Level III-1**). Patients who have memories of ICU, recall discomfort in 54% and overt pain in 12% (Payen et al, 2007 **Level IV**). Endotracheal tube suctioning and other medical interventions are consistently reported as being uncomfortable or painful.

In conclusion, adequate local and/or parenteral anaesthesia should be provided during any noxious procedure (Puntillo et al, 2004).

#### Key messages

1. Daily interruptions of sedative infusions reduce duration of ventilation and ICU stay without causing adverse psychological outcomes (**U**) (**Level II**) or increasing the risk of myocardial ischaemia (**N**) (**Level III-1**).
2. Gabapentin is more effective than carbamazepine in reducing the pain associated with Guillain-Barre syndrome (**S**) (**Level II**).
3. Remifentanyl or remifentanyl with morphine provides better analgesia than morphine alone in ventilated intensive care unit patients (**N**) (**Level II**).
4. The use of formal pain and agitation assessment and subsequent treatment in ventilated intensive care unit patients decreases the incidence of pain and duration of ventilation (**N**) (**Level III-1**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Observation of behavioural and physiological responses permits assessment of pain in unconscious patients (**U**).
- Patients should be provided with appropriate sedation and analgesia during potentially painful procedures (**U**).

## 9.9 ACUTE PAIN MANAGEMENT IN EMERGENCY DEPARTMENTS

Pain is the most common reason for presentation to the emergency department and many patients will self-medicate for pain before attending (Kelly & Gunn, 2008). There is evidence that, as in many other areas of health care, patients in emergency departments around the world receive suboptimal pain management (Todd et al, 2007). Although 70% of patients presenting to an emergency department rated their analgesia as 'good' or 'very good', patient satisfaction with analgesia did not correlate with pain scores at presentation or discharge, or change in pain scores (Kelly, 2000 **Level IV**).

In the emergency department setting, analgesia should be simple to administer, condition-specific and where possible based on local-regional rather than systemic techniques. Systems should be adopted to ensure adequate pain assessment, timely and appropriate analgesia, frequent monitoring and reassessment of pain and additional analgesia as required. For example, the introduction of a protocol based fentanyl titration regimen improved timely and effective delivery of analgesia in the emergency department (Curtis et al, 2007 **Level II**).

### 9.9.1 Systemic analgesics

#### Opioids

In the emergency department, opioids are frequently prescribed for the treatment of severe pain and should preferably be administered via the IV route, given the wide interindividual variability in dose response and the delayed absorption via the IM or SC routes. However, IV and intraosseous morphine demonstrated similar pharmacokinetic profiles in adults (Von Hoff et al, 2008 **Level II**). Doses should be adjusted for age (see Section 4.1) and titrated to effect. Patients require close observation for sedation, respiratory depression and occasionally hypotension (Coman & Kelly, 1999 **Level IV**).

There is no clear consensus on what constitutes the most effective IV opioid or dosing regimen for analgesia in the emergency department. There was no difference between IV bolus dose fentanyl or morphine in providing effective analgesia for up to 30 minutes during prehospital care (Galinski et al, 2005 **Level II**). Similarly, in elderly patients attending an emergency department there were no differences in effects or adverse effects between IV bolus doses of morphine or hydromorphone (Chang, Bijur, Baccelieri et al, 2009 **Level II**). The addition of ultra-low-dose naloxone to bolus dose morphine failed to improve analgesia or reduce opioid adverse effects (Bijur et al, 2006 **Level II**).

Titrating (relatively) high doses of opioid frequently to clinical effect provides the best chance of delivering rapid and effective analgesia. Significantly more patients attained effective analgesia at 10 minutes with the administration of 0.1 mg/kg morphine, followed by 0.05 mg/kg, 5 minutely, compared with those who received half these doses; however there was no difference in analgesia outcomes at 30 minutes (Bounes et al, 2008 **Level II**). In non-elderly adults, a bolus dose of 2 mg hydromorphone IV provided good analgesia, but caused oxygen desaturation in one third of patients (Chang, Bijur, Napolitano et al, 2009 **Level III-3**); use of a 1 mg bolus dose was slightly less effective but caused oxygen desaturation in just 5% of patients (Chang, Bijur, Campbell et al, 2009 **Level III-3**). IV opioid PCA was as effective as nurse-administered IV bolus dosing in the emergency department (Evans et al, 2005 **Level II**).

In children requiring analgesia in the emergency department, IN (Borland et al, 2007 **Level II**), inhaled (nebulised) (Miner et al, 2007 **Level II**), or oral transmucosal (Mahar et al, 2007 **Level II**) fentanyl provided effective analgesia (see Sections 6.6.1 and 10.4.4 for details). IN fentanyl

and IV morphine were equally effective in reducing acute cardiac chest pain during prehospital transfer (Rickard et al, 2007 **Level II**). In a study of patients with post-traumatic thoracic pain, there was no difference in analgesia between nebulised morphine and morphine PCA (Fulda et al, 2005 **Level II**).

Opioid-tolerant patients pose a special challenge in the emergency department and their management is discussed in Section 11.7.

### **Tramadol**

In the management of severe trauma pain, IV tramadol had similar analgesic efficacy to morphine (Vergnion et al, 2001 **Level II**). In patients with right lower quadrant pain, presumably due to appendicitis, parenteral tramadol reduced the mean VAS by only 7.7/100 mm compared with placebo, and did not affect the clinical examination (Mahadevan & Graff, 2000 **Level II**). For renal colic, tramadol was as effective as parenteral ketorolac (Nicolas Torralba et al, 1999 **Level II**) but less effective than pethidine (Eray et al, 2002 **Level II**). For acute musculoskeletal pain, IM tramadol was similar to ketorolac in efficacy and side effects, when both were combined with oral paracetamol (Lee et al, 2008 **Level II**).

### **Non-steroidal anti-inflammatory drugs**

NSAIDs are useful for treating mild-to-moderate trauma pain, musculoskeletal pain, renal and biliary colic and some acute headaches, as discussed elsewhere in this document (see Section 4.2).

### **Inhalational analgesics**

N<sub>2</sub>O in oxygen (see Section 4.3.1) provided effective analgesia and anxiolysis for minor procedures in both adults and children (Gamis et al, 1989 **Level II**; Gregory & Sullivan, 1996 **Level II**; Burton et al, 1998 **Level II**; Gerhardt et al, 2001 **Level II**; Burnweit et al, 2004 **Level IV**) and may be useful as a temporising measure while definitive analgesia is instituted (eg insertion of a digital nerve block for finger injury).

Methoxyflurane (see Section 4.3) is used to provide analgesia, most commonly in prehospital emergency care (see Section 9.10.1).

### **Ketamine**

Ketamine-midazolam was more effective and had fewer adverse effects than fentanyl-midazolam or fentanyl-propofol, for paediatric fracture reduction in the emergency department (Migita et al, 2006 **Level I**) (for more information see Section 10.4.4).

IV ketamine boluses produced a significant morphine-sparing effect (without a change in pain scores) when used to treat severe trauma pain in the emergency department (Galinski et al, 2007 **Level II**). When treating acute musculoskeletal trauma pain, a low-dose, SC ketamine infusion provided better analgesia with less nausea, vomiting and sedation, and improved respiratory function, compared with intermittent SC morphine injections (Gurnani et al, 1996 **Level II**). IN ketamine provided effective pain relief (within 15 minutes); adverse effects were mild and transient (Christensen et al, 2007 **Level II**).

For further information on ketamine, see Section 4.3.2.

## **9.9.2 Analgesia in specific conditions**

### **Abdominal pain**

Patients and physicians differ in their assessment of the intensity of acute abdominal pain in the emergency department. Physician's VAS estimates of abdominal pain were significantly lower than the patient's reports. Administration of analgesia correlated with the physician's assessment of a pain score greater than 60/100 mm on VAS. A patient's satisfaction with



analgesia correlated with a reduction in pain of at least 20/100 mm on VAS and titration of analgesia to the patient's pain reports. Nevertheless, 60% of patients presenting to the emergency department with abdominal pain were satisfied with their analgesia on discharge (Marinsek et al, 2007 **Level IV**).

A common misconception is that analgesia masks the signs and symptoms of abdominal pathology and should be withheld until a diagnosis is established. Pain relief does not interfere with the diagnostic process in acute abdominal pain in adults (Ranji et al, 2006 **Level I**; Manterola et al, 2007 **Level I**) or in children (Kim et al, 2002 **Level II**; Green et al, 2005 **Level II**).

If pain is severe, opioids may be required. Although it has previously been recommended that pethidine be used in preference to morphine, particularly for renal and biliary colic due to the theoretical risk of smooth muscle spasm, there is no evidence to support this position (see Section 9.6.1).

### **Renal colic**

See Section 9.6.1.

### **Biliary colic and acute pancreatitis**

See Section 9.6.1.

### **Acute cardiac chest pain**

See Section 9.6.3.

### **Acute pain and sickle cell disease**

See Section 9.6.4.

### **Migraine**

Most migraine headaches are successfully managed by the patient and his or her family doctor. However a small number of patients fail to respond and present for treatment at the emergency department. Approximately 80% of patients have tried their usual medications (simple analgesics and triptans) before presentation (Larkin & Prescott, 1992; Shrestha et al, 1996).

Table 9.4 lists some of the drugs that have been shown to be effective agents for treating acute migraine in the emergency department. See Section 9.6.5 for a more detailed review of the treatment of migraine and other acute headache syndromes.

**Table 9.4 Pooled effectiveness data from emergency department studies of the treatment of migraine**

Agent	No. of studies	Total patients	Clinical success rate	NNT: Clinical success# (95% CI)	Level of evidence
Chlorpromazine	6	171	85%	1.7 (1.5, 2.0)	II
Droperidol IM	3	233	83%	1.7 (1.5, 2.0)	II
Prochlorperazine	4	113	79%	1.9 (1.5,2.3)	II
Sumatriptan	5	659	69%	2.3 (2.1,2.6)	II
Ketorolac IM	6	155	66%	2.5 (2.0, 3.3)	II
Tramadol [IM or IV]	3	191	60%	2.9 (2.3, 3.9)	II
Metoclopramide	6	374	57%	3.1 (2.6, 3.9)	I

Notes: Only agents used in an aggregate of 50 patients or more have been included.  
 # = assumes placebo success rate of 25% \* = As defined by study authors  
 Source: Adapted and updated from Kelly & Gunn (Kelly & Gunn, 2008).

### **Fractured neck of femur**

In patients with a fractured neck of femur in the emergency department, a '3 in 1' femoral nerve block with bupivacaine, combined with IV morphine was more effective than IV morphine alone, with a faster onset of analgesia (Fletcher et al, 2003 **Level II**). A fascia iliaca block with mepivacaine, significantly improved pain scores and reduced IV morphine requirements and sedation, compared with IM morphine (Foss et al, 2007 **Level II**). For safety reasons, ropivacaine or levobupivacaine may be the preferred local anaesthetics (see Section 5.1).

### **Wounds**

Local anaesthesia is frequently required for the treatment of wounds in the emergency department. Agents most commonly used for needle infiltration are lignocaine or longer acting agents such as ropivacaine or levobupivacaine, depending on the duration of anaesthesia required and whether analgesia following the procedure is desirable.

It is less painful to infiltrate local anaesthesia by injection through the wound rather than in the tissues surrounding it (Bartfield et al, 1998 **Level II**; Kelly et al, 1994 **Level III-1**). There are conflicting data on whether buffering of lignocaine reduces the pain of infiltration (Boyd, 2001 **Level II**).

Digital nerve block with 0.75 % ropivacaine, significantly prolonged analgesia and reduced rescue analgesia requirements to 24 hours, without a clinically significant increase in time to block onset, compared with 2% lignocaine (Keramidas & Rodopoulou, 2007 **Level II**).

Topical local anaesthetic preparations are also used, particularly for wound care in children. Topical tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lignocaine are as effective as EMLA cream for dermal instrumentation analgesia in the emergency department (Eidelman et al, 2005 **Level I**). Topical anaesthetic preparations such as mixtures of adrenaline, lignocaine and amethocaine are effective alternatives to infiltration with local anaesthesia for simple lacerations (Smith et al, 1997 **Level II**; Singer & Stark, 2000 **Level II**) and reduced the pain of infiltration when injecting local anaesthetics (Singer & Stark, 2000 **Level II**). Topical lignocaine and adrenaline applied to a wound in sequential layers, significantly reduced reports of pain during initial application, compared with a 2% lignocaine injection, but with no difference in pain scores during suturing (Gaufberg et al, 2007 **Level II**). A topical gel dressing containing morphine was no more effective than other gel dressings in reducing burns injury pain in the emergency department (Welling, 2007 **Level II**).

### **9.9.3 Non-pharmacological management of pain**

Although analgesic agents may be required to treat pain in the emergency department setting, the importance of non-pharmacological treatments should not be forgotten. These include ice, elevation and splinting for injuries and explanation of the cause of pain and its likely outcome to allay anxiety. Psychological techniques such as distraction, imagery or hypnosis may also be of value (see Sections 8.1 and 9.3.2).

Deep breathing exercises did not provide effective pain relief to patients in emergency departments (Downey & Zun, 2009 **Level II**).

### Key messages

*Abdominal pain (see Section 9.6.1)*

*Migraine (also see Section 9.6.5)*

1. Triptans or phenothiazines (prochlorperazine, chlorpromazine) are effective in at least 75% of patients presenting to the emergency department with migraine (**U**) (**Level II**).

*Local anaesthesia*

2. Topical local anaesthetic agents (including those in liposomal formulations) (**N**) (**Level I**) or topical local anaesthetic-adrenaline agents (**N**) (**Level II**) provide effective analgesia for wound care in the emergency department.
3. Femoral nerve blocks in combination with intravenous opioids are superior to intravenous opioids alone in the treatment of pain from a fractured neck of femur (**S**) (**Level II**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- To ensure optimal management of acute pain, emergency departments should adopt systems to ensure adequate assessment of pain, provision of timely and appropriate analgesia, frequent monitoring and reassessment of pain (**U**).

## 9.10 PREHOSPITAL ANALGESIA

The above section (9.9) considered management of acute pain in patients admitted to emergency departments. However, many of these patients will also have required prehospital pain relief when under the care of paramedic or medical retrieval teams. While the term 'prehospital' is also used to cover a greater variety of prehospital locations, it is beyond the scope of this document to look at pain relief administered in more complex situations such as war or disaster settings.

Many of the patients transported by ambulance services or retrieval teams will have pain that requires treatment prior to and during transport. However, there are some specific features of the prehospital environment that will impact on the way that the pain can and should be managed. The environment is often uncontrolled, there may well be a shortage of assistance, light, shelter and suitable equipment, and the patient is often in the acute or evolving stage of their condition, which may change rapidly.

Provision of prehospital analgesia is important, given that pain in the prehospital setting is common and that moderate or severe pain is present in at least 20% of patients (McLean et al, 2002), nearly one-third of all injured patients and over 80% of those with extremity fractures (Thomas & Shewakramani, 2008). Yet the proportion of patients given analgesics (opioid or inhalational) prior to transfer to an emergency department varies significantly. 'Unnecessary pain' was the second most common type of injury in 56 of 272 claims against ambulance trusts in the United Kingdom between 1995 and 2005 (Dobbie & Cooke, 2008).

One survey of 1073 adult patients with suspected extremity fractures showed that just 18 were given any analgesia and only 2 received morphine (White et al, 2000 **Level IV**). A later survey showed that only 12.5% of patients with isolated extremity injuries received any prehospital parenteral pain relief (Abbuhl & Reed, 2003 **Level IV**). Another study reported prehospital opioid administration in 18.3% of patients with lower extremity fractures; however older patients and those with a hip fractures were less likely to be given analgesia prior to arrival in the emergency department (McEachin et al, 2002 **Level IV**). In contrast, another group

reported that 51% of elderly patients with a fractured neck of femur were given prehospital analgesia — methoxyflurane in 47% of cases, N<sub>2</sub>O in 10%, and 6% received morphine (Vassiliadis et al, 2002 **Level IV**). Similarly, in a 2005 survey from Australia, 55% of patients in pain received analgesia by paramedics (Lord et al, 2009 **Level IV**).

Prehospital use of opioids may be increasing; in two surveys of 2005, 29% of patients with isolated extremity injuries (Michael et al, 2007 **Level IV**) and 13% of females and 17% of males in pain (Lord et al, 2009 **Level IV**) had been given morphine.

Paediatric patients may also not receive prehospital pain relief. One study of children with fractures or soft tissue injuries reported that 37% received prehospital analgesic drugs (Rogovik & Goldman, 2007 **Level IV**). Another, which included patients with a diagnosis of limb fracture or burns, reported that analgesia was given to 51% of children between the ages of 5 and 15 years, but not to any child aged less than 5 years; a greater proportion of this younger group (70% vs 54%) were given opioid analgesia once in the emergency department (Watkins, 2006 **Level IV**).

Despite such studies showing that pain relief prior to arrival in an emergency department needs to be improved, and although pain relief has been acknowledged as a key area for investigation, evidence regarding management of acute pain in patients in the prehospital setting remains limited with few randomised controlled studies available. Although many analgesic techniques that work in hospital environments have been transcribed to the prehospital environment, these do not always comply with the ideal of simplicity, safety and effectiveness when used in the field.

### 9.10.1 Assessment of pain in the prehospital environment

As in other settings, pain intensity is best assessed using patient self-report measures such as VASs (Galinski et al, 2005; Kober et al, 2002), VNRSs (McLean et al, 2004; Woollard et al, 2004; Rickard et al, 2007; Bounes et al, 2008), VDSs (McLean et al, 2004; Vergnion et al, 2001), faces pain scales (Rogovik & Goldman, 2007) (see Section 2). A ruler incorporating both visual analogue and faces pain scales (Lord & Parsell, 2003 **Level IV**) has also been used to measure pain in patients prior to arrival at hospital.

However, in some instances it may not be possible to obtain reliable self-reports of pain (eg patients with impaired consciousness or cognitive impairment, young children (see Section 10.3), elderly patients (see Section 11.2.3), or where there are failures of communication due to language difficulties, inability to understand the measures, unwillingness to cooperate or severe anxiety). In these circumstances other methods of pain assessment will be needed.

### 9.10.2 Systemic analgesics

The ideal prehospital analgesic agent should be simple to use, safe (both in terms of side effects and adverse effects on the patient's condition), effective, not lead to delays in transport and have a rapid onset and short duration of action (Alonso-Serra & Wesley, 2003) so that it can be repeated as often as necessary and titrated to effect for each patient. Consideration should be given to both choice of analgesic drug and route of administration.

#### ***Opioids and tramadol***

The administration of systemic opioids as an effective prehospital analgesic is widespread. Their application is influenced by not only the knowledge and judgment required to use them, but also by the different drugs of dependence legislation found in most countries. In this setting, use of IV or IN routes will enable a more rapid and predictable onset of action than other routes of administration. Occasionally morphine is given intramuscularly in the

prehospital environment, but this is not encouraged because of the unpredictable impact upon the pharmacokinetics in a poorly perfused patient.

Both morphine and fentanyl are commonly used for prehospital analgesia. Morphine (Bruns et al, 1992 **Level IV**; Fullerton-Gleason et al, 2002 **Level IV**) and fentanyl (Kanowitz et al, 2006 **Level IV**), as well as tramadol (Ward et al, 1997 **Level IV**) have been shown to provide effective and safe pain relief in patients being transported by road. Fentanyl was also safe and effective when given to patients during helicopter transfers (Thomas et al, 2005 **Level IV**; Krauss et al, 2009 **Level IV**).

Morphine doses of 0.1 mg/kg IV followed by 0.05 mg/kg every 5 mins as needed provided more rapid pain relief and patient satisfaction than doses that were 50% lower (Bounes et al, 2008 **Level II**).

In a comparison of IV fentanyl and morphine bolus doses given every 5 minutes as needed for prehospital analgesia, no difference was found in pain relief or incidence of side effects (Galinski et al, 2005 **Level II**). Similarly, there was no difference in pain relief or adverse effects reported in a comparison of IV tramadol and morphine (Vergnion et al, 2001 **Level II**).

When used to treat acute cardiac chest pain during prehospital transfer, IV alfentanil provided more rapid relief than IV morphine (Silfvast & Saarnivaara, 2001 **Level II**). IN fentanyl and IV morphine were equally effective for patients with cardiac and non-cardiac acute pain (Rickard et al, 2007 **Level II**).

A comparison of 5 mg and 10 mg nalbuphine doses given IV and repeated at 3-minute intervals to a total of 20 mg, showed that use of the larger dose led to better pain relief but higher patient-reported drowsiness; over half the patients in both groups still had significant pain on arrival at the hospital (Woollard et al, 2004 **Level II**).

### **Inhalational agents**

Inhalational analgesics can provide early pain relief in the prehospital environment and are used before opioids in many situations. However, variations in the availability of different agents have a marked impact on regional practices. In one series, patients with extremity fractures were more likely to receive N<sub>2</sub>O than morphine (White et al, 2000), whereas in another series N<sub>2</sub>O was not used (Rogovik & Goldman, 2007). Methoxyflurane is not available in many countries, but in Australia it has replaced N<sub>2</sub>O in most prehospital settings. Provision of N<sub>2</sub>O in ambulances is hampered by difficulties providing a scavenger system that minimises occupational exposure and the bulk/logistical issues associated with managing cylinders of oxygen and nitrous oxide (Entonox<sup>®</sup> cylinders are a mixture of 50% N<sub>2</sub>O and 50% oxygen) that separate at low temperatures. The demand valves are costly and require maintenance, and the inability to activate the valve and effectively use Entonox<sup>®</sup> equipment has been rated as a major factor limiting use in children under 5 year (Watkins, 2006). There have been no RCTs of methoxyflurane (Grindlay & Babl, 2009) or N<sub>2</sub>O (Faddy & Garlick, 2005), and no large case series comparing efficacy with other analgesic agents in the prehospital setting.

Methoxyflurane reduced pain scores (mean 2.47±0.24 on NRS 0 to 10) in adults, the majority of whom had musculoskeletal pain. The incidence of nausea was 8%, and 11% had increased drowsiness (Buntine et al, 2007 **Level IV**). When graded by the paramedic, methoxyflurane also reduced pain scores in children (Babl et al, 2006 **Level IV**). The overall incidence of drowsiness was 27%, but the risk of deep sedation was significantly higher in younger children. In both of these studies, methoxyflurane was delivered by a Pentrox<sup>®</sup> inhaler which contains 3 mL of methoxyflurane and lasts for 25 to 30 minutes (Medical Developments International, 2001). There have been no reports of toxicity with analgesic use if doses are limited to 3 mL repeated once with a maximum of 15 mL per week, or a maximum of 0.5% for one hour (Grindlay & Babl, 2009) (see also Section 4.3.1).

N<sub>2</sub>O is included in prehospital management protocols for manipulation, splinting and transfer of patients with lower limb fracture (Lee & Porter, 2005 **Level IV**) and as a second-line in burns patients if opioids are not available (Allison & Porter, 2004 **Level IV**). Although N<sub>2</sub>O has been reported to provide pain relief in over 80% of patients requiring prehospital analgesia (Thomas & Shewakramani, 2008 **Level IV**), this is not based on RCTs (Faddy & Garlick, 2005) and there are few studies comparing efficacy with other agents. In one paediatric series, a higher proportion of children receiving N<sub>2</sub>O rather than opioids had pain on arrival in the emergency department, but interruption of delivery during transfer from the ambulance may have contributed (Watkins, 2006 **Level IV**). Based on data from hospital studies, N<sub>2</sub>O has been suggested as a safe analgesic in prehospital settings, although specific contra-indications (such as pneumothorax and decreased consciousness) may be particularly relevant in this patient group (Faddy & Garlick, 2005) (see Section 4.3.1 for further details).

### **Ketamine**

Ketamine has been administered by physicians for prehospital procedural analgesia and sedation in both adults (Porter, 2004 **Level IV**; Svenson & Abernathy, 2007 **Level IV**; Bredmose, Lockey et al, 2009 **Level IV**) and children (Bredmose, Grier et al, 2009 **Level IV**) with good safety profile.

### **Non-steroidal anti-inflammatory drugs and paracetamol**

The use of parenterally administered NSAIDs has been suggested for prehospital analgesia (Alonso-Serra & Wesley, 2003; McManus & Sallee, 2005) but the slower onset of effect as well as the risk of adverse effects (eg bleeding, renal impairment [see Section 4.2]), especially in patients who have lost blood and may be hypovolaemic, means they are not commonly used. Similarly injectable paracetamol is not commonly used. Oral paracetamol or other analgesics have a limited role in the acute prehospital setting.

## **9.10.2 Anxiolytics**

Anxiolytics, for example low doses of midazolam, are sometimes used to alleviate some of the acute anxiety or agitation that may complicate effective control of pain in stressful prehospital conditions (McManus & Sallee, 2005). However, there are no studies looking at efficacy and safety. It should be remembered that their combination with opioids will increase the risk of respiratory depression and that anxiety and agitation may be indicators of other more serious underlying conditions such as a head injury or hypoxia (McManus & Sallee, 2005).

## **9.10.3 Regional analgesia**

Use of regional analgesia in the prehospital setting (excluding war or disaster situations) is uncommon. Initiation of a fascia iliaca block for analgesia in patients with isolated femoral shaft fractures provided effective pain relief prior to arrival at an emergency department (Lopez et al, 2003 **Level IV**).

## **9.10.4 Non-pharmacological management of pain**

Although analgesic agents are often used to treat pain in the prehospital setting, the importance of non-pharmacological treatments should not be forgotten. These include ice, elevation and splinting for injuries. The role of reassurance in the management of acute pain in an anxious patient is often undervalued.

TENS applied over the painful flank during prehospital transport reduced pain scores, anxiety and nausea in patients with renal colic (Mora et al, 2006 **Level II**).

Acupressure performed by during prehospital transport using ‘true points’ led to better pain relief and less anxiety than acupressure using ‘sham points’ (Kober et al, 2002 **Level II**; Barker et al, 2006 **Level II**; Lang et al, 2007 **Level II**) or no acupressure (Kober et al, 2002 **Level II**).

Local active warming resulted in significant analgesia for females in pelvic pain during prehospital transport (Bertalanffy et al, 2006 **Level II**).

## 9.10.5 Analgesia in specific conditions

### **Acute cardiac pain**

The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, including the use of supplemental oxygen (Pollack & Braunwald, 2008; Cannon, 2008) and nitroglycerine (Henrikson et al, 2003 **Level IV**). Opioid analgesia may also be required (see Section 9.6.3).

### **Abdominal pain**

As noted in Section 9.6, administration of opioid drugs does not interfere with the diagnostic process in acute abdominal pain.

### **Patients with a head injury**

Caution is often expressed about the use of opioids for pain relief in patients with a head injury (Thomas & Shewakramani, 2008). This is largely because of the potential adverse effects of opioids and their ability to interfere with recovery and neurological assessment, as well as the concern that opioid-induced respiratory depression will lead to hypercarbia and increased intracranial pressure (Nemergut et al, 2007). While there is little specific information regarding the use of opioids in patients with a head injury in the prehospital setting, they have been safely used in patients after craniotomy (see Section 9.1.5).

The use of opioids in patients with a head injury in the prehospital environment will need to be based on an individual risk-benefit assessment for each patient.

### **Key messages**

1. Intravenous morphine, fentanyl and tramadol are equally effective in the prehospital setting (**N**) (**Level II**).
2. Nitrous oxide is an effective analgesic agent in prehospital situations (**N**) (**Level IV**).
3. Methoxyflurane, in low concentrations, may be an effective analgesia in the hospital and prehospital setting (**N**) (**Level IV**).
4. Ketamine provides effective analgesia in the prehospital setting (**N**) (**Level IV**).
5. Moderate to severe pain is common in both adult and paediatric patients in the prehospital setting (**N**) (**Level IV**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- The ideal prehospital analgesic agent should be simple to use, safe, effective, not lead to delays in transport and have a rapid onset and short duration of action so that it can be repeated as often as necessary and titrated to effect for each patient. Consideration should be given to both choice of analgesic drug and route of administration (**N**).
- Non-pharmacological measures are effective in providing pain relief and should always be considered and used if practical (**N**).



## REFERENCES

- Aaron JN, Carlisle CC, Carskadon MA et al (1996) Environmental noise as a cause of sleep disruption in an intermediate respiratory care unit. *Sleep* **19**(9): 707–10.
- Aasvang EK & Kehlet H (2007) Chronic pain after childhood groin hernia repair. *J Pediatr Surg* **42**(8): 1403–8.
- Aasvang EK, Mohl B & Kehlet H (2007) Ejaculatory pain: a specific postherniotomy pain syndrome? *Anesthesiology* **107**(2): 298–304.
- Aasvang EK, Brandsborg B, Christensen B et al (2008) Neurophysiological characterization of postherniotomy pain. *Pain* **137**(1): 173–81.
- Aasvang EK & Kehlet H (2009) The effect of mesh removal and selective neurectomy on persistent postherniotomy pain. *Ann Surg* **249**(2): 327–34.
- Abbuhl FB & Reed DB (2003) Time to analgesia for patients with painful extremity injuries transported to the emergency department by ambulance. *Prehosp Emerg Care* **7**(4): 445–7.
- Abramoff MM, Lopes NN, Lopes LA et al (2008) Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients. *Photomed Laser Surg* **26**(4): 393–400.
- Abrams DI, Jay CA, Shade SB et al (2007) Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* **68**(7): 515–21.
- Afman CE, Welge JA & Steward DL (2006) Steroids for post-tonsillectomy pain reduction: meta-analysis of randomized controlled trials. *Otolaryngol Head Neck Surg* **134**(2): 181–6.
- Ahlers SJ, van Gulik L, van der Veen AM et al (2008) Comparison of different pain scoring systems in critically ill patients in a general ICU. *Crit Care* **12**(1): R15.
- Ahmad N, Grad HA, Haas DA et al (1997) The efficacy of nonopioid analgesics for postoperative dental pain: a meta-analysis. *Anesth Prog* **44**(4): 119–26.
- Aissaoui Y, Zeggwagh AA, Zekraoui A et al (2005) Validation of a behavioral pain scale in critically ill, sedated, and mechanically ventilated patients. *Anesth Analg* **101**(5): 1470–6.
- Aisyaturridha A, Naing L & Nizar AJ (2006) Validation of the Malay Brief Pain Inventory questionnaire to measure cancer pain. *J Pain Symptom Manage* **31**(1): 13–21.
- Akriviadis EA, Hatzigavriel M, Kapnias D et al (1997) Treatment of biliary colic with diclofenac: a randomized, double-blind, placebo-controlled study. *Gastroenterology* **113**(1): 225–31.
- Akural EI, Jarvimaki V, Lansineva A et al (2009) Effects of combination treatment with ketoprofen 100 mg + acetaminophen 1000 mg on postoperative dental pain: a single-dose, 10-hour, randomized, double-blind, active- and placebo-controlled clinical trial. *Clin Ther* **31**(3): 560–8.
- Al-metwalli RR (2008) Epidural morphine injections for prevention of post dural puncture headache. *Anaesthesia* **63**(8): 847–50.
- Al-Waili N & Saloom KY (1998) The analgesic effect of intravenous tenoxicam in symptomatic treatment of biliary colic: a comparison with hyoscine N-butylbromide. *Eur J Med Res* **3**(10): 475–9.
- Al Hajeri AA, Fedorowicz Z, Omran A et al (2007) Piracetam for reducing the incidence of painful sickle cell disease crises. *Cochrane Database Syst Rev*(2): CD006111.
- Allison K & Porter K (2004) Consensus on the prehospital approach to burns patient management. *Emerg Med J* **21**(1): 112–4.
- Alonso-Serra HM & Wesley K (2003) Prehospital pain management. *Prehosp Emerg Care* **7**(4): 482–8.
- Alston RP & Pechon P (2005) Dysaesthesia associated with sternotomy for heart surgery. *Br J Anaesth* **95**(2): 153–8.
- Ambrosini A, Vandenheede M, Rossi P et al (2005) Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. *Pain* **118**(1–2): 92–6.
- Amorim JA & Valenca MM (2008) Postdural puncture headache is a risk factor for new postdural puncture headache. *Cephalalgia* **28**(1): 5–8.
- Anderson KE, Bloomer JR, Bonkovsky HL et al (2005) Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* **142**(6): 439–50.

- Anselmetti GC, Corrao G, Monica PD et al (2007) Pain relief following percutaneous vertebroplasty: results of a series of 283 consecutive patients treated in a single institution. *Cardiovasc Intervent Radiol* **30**(3): 441–7.
- Anthony T, Baron T, Mercadante S et al (2007) Report of the clinical protocol committee: development of randomized trials for malignant bowel obstruction. *J Pain Symptom Manage* **34**(1 Suppl): S49–59.
- Arendt K, Demaerschalk BM, Wingerchuk DM et al (2009) Atraumatic lumbar puncture needles: after all these years, are we still missing the point? *Neurologist* **15**(1): 17–20.
- Arikan OK, Sahin S, Kazkayasi M et al (2008) High-dose ropivacaine versus bupivacaine for posttonsillectomy pain relief in adults. *J Otolaryngol Head Neck Surg* **37**(6): 836–43.
- Aronstam A, Wassef M, Hamad Z et al (1983) A double-blind controlled trial of two dose levels of factor VIII in the treatment of high risk haemarthroses in haemophilia A. *Clin Lab Haematol* **5**(2): 157–63.
- Arora H, Pai KM, Maiya A et al (2008) Efficacy of He-Ne Laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **105**(2): 180–6.
- Asao T, Kuwano H, Ide M et al (2003) Spasmolytic effect of peppermint oil in barium during double-contrast barium enema compared with Buscopan. *Clin Radiol* **58**(4): 301–5.
- Ashburn MA (1995) Burn pain: the management of procedure-related pain. *J Burn Care Rehabil* **16** (3 Pt 2): 365–71.
- Astin JA & Ernst E (2002) The effectiveness of spinal manipulation for the treatment of headache disorders: a systematic review of randomized clinical trials. *Cephalalgia* **22**(8): 617–23.
- Atef A & Fawaz AA (2008a) Peritonsillar infiltration with tramadol improves pediatric tonsillectomy pain. *Eur Arch Otorhinolaryngol* **265**(5): 571–4.
- Atef A & Fawaz AA (2008b) Intravenous paracetamol is highly effective in pain treatment after tonsillectomy in adults. *Eur Arch Otorhinolaryngol* **265**(3): 351–5.
- Attal N, Gaude V, Brasseur L et al (2000) Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology* **54**(3): 564–74.
- Attal N, Guirimand F, Brasseur L et al (2002) Effects of IV morphine in central pain: a randomized placebo-controlled study. *Neurology* **58**(4): 554–63.
- Ausems ME, Hulsewe KW, Hooymans PM et al (2007) Postoperative analgesia requirements at home after inguinal hernia repair: effects of wound infiltration on postoperative pain. *Anaesthesia* **62**(4): 325–31.
- Australian Acute Musculoskeletal Pain Guidelines Group (2003) *Evidence-based Management of Acute Musculoskeletal Pain*. <http://www.nhmrc.gov.au/publications/synopses/cp94syn.htm> Australian Academic Press. Accessed May 2009.
- Ayoub C, Girard F, Boudreault D et al (2006) A comparison between scalp nerve block and morphine for transitional analgesia after remifentanyl-based anesthesia in neurosurgery. *Anesth Analg* **103**(5): 1237–40.
- Babl FE, Jamison SR, Spicer M et al (2006) Inhaled methoxyflurane as a prehospital analgesic in children. *Emerg Med Australas* **18**(4): 404–10.
- Bahra A, Gawel MJ, Hardebo JE et al (2000) Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* **54**(9): 1832–9.
- Bailey B & McManus BC (2008) Treatment of children with migraine in the emergency department: a qualitative systematic review. *Pediatr Emerg Care* **24**(5): 321–30.
- Baker CL (1992) Acute hemarthrosis of the knee. *J Med Assoc Ga* **81**(6): 301–5.
- Bala I, Gupta B, Bhardwaj N et al (2006) Effect of scalp block on postoperative pain relief in craniotomy patients. *Anaesth Intensive Care* **34**(2): 224–7.
- Balakrishnan S, Bhushan K, Bhargava VK et al (2001) A randomized parallel trial of topical aspirin-moisturizer solution vs. oral aspirin for acute herpetic neuralgia. *Int J Dermatol* **40**(8): 535–8.
- Ballantyne JC & Carwood CM (2005) Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer. *Cochrane Database Syst Rev*(1): CD005178.

- Bamias A, Kastritis E, Bamia C et al (2005) Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol* **23**(34): 8580–7.
- Barber FA, McGuire DA & Click S (1998) Continuous-flow cold therapy for outpatient anterior cruciate ligament reconstruction. *Arthroscopy* **14**(2): 130–5.
- Barden J, Edwards JE, McQuay HJ et al (2004) Relative efficacy of oral analgesics after third molar extraction. *Br Dent J* **197**(7): 407–11.
- Barker R, Kober A, Hoerauf K et al (2006) Out-of-hospital auricular acupressure in elder patients with hip fracture: a randomized double-blinded trial. *Acad Emerg Med* **13**(1): 19–23.
- Barragan-Campos HM, Vallee JN, Lo D et al (2006) Percutaneous vertebroplasty for spinal metastases: complications. *Radiology* **238**(1): 354–62.
- Bartfield JM, Sokaris SJ & Raccio-Robak N (1998) Local anesthesia for lacerations: pain of infiltration inside vs outside the wound. *Acad Emerg Med* **5**(2): 100–4.
- Bates RE, Jr. & Stewart CM (1991) Atypical odontalgia: phantom tooth pain. *Oral Surg Oral Med Oral Pathol* **72**(4): 479–83.
- Batoz H, Verdonck O, Pellerin C et al (2009) The analgesic properties of scalp infiltrations with ropivacaine after intracranial tumoral resection. *Anesth Analg* **109**(1): 240–4.
- Baumann BM, Perrone J, Hornig SE et al (2000) Randomized, double-blind, placebo-controlled trial of diazepam, nitroglycerin, or both for treatment of patients with potential cocaine-associated acute coronary syndromes. *Acad Emerg Med* **7**(8): 878–85.
- Baxendale BR, Vater M & Lavery KM (1993) Dexamethasone reduces pain and swelling following extraction of third molar teeth. *Anaesthesia* **48**(11): 961–4.
- Bell R, Montoya D, Shuaib A et al (1990) A comparative trial of three agents in the treatment of acute migraine headache. *Ann Emerg Med* **19**(10): 1079–82.
- Bennett M, Jepson N & Lehm J (2005) Hyperbaric oxygen therapy for acute coronary syndrome. *Cochrane Database Syst Rev*(2): CD004818.
- Bennett MH, French C, Schnabel A et al (2008) Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. *Cochrane Database Syst Rev*(3): CD005219.
- Bensinger W, Schubert M, Ang KK et al (2008) NCCN Task Force Report. prevention and management of mucositis in cancer care. *J Natl Compr Canc Netw* **6 Suppl 1**: S1–21.
- Berry JD & Petersen KL (2005) A single dose of gabapentin reduces acute pain and allodynia in patients with herpes zoster. *Neurology* **65**(3): 444–7.
- Bertalanffy P, Kober A, Andel H et al (2006) Active warming as emergency interventional care for the treatment of pelvic pain. *BJOG* **113**(9): 1031–4.
- Beutner KR, Friedman DJ, Forszpaniak C et al (1995) Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother* **39**(7): 1546–53.
- Bigal ME, Bordini CA & Speciali JG (2002) Intravenous chlorpromazine in the emergency department treatment of migraines: a randomized controlled trial. *J Emerg Med* **23**(2): 141–8.
- Bigal ME, Bordini CA, Tepper SJ et al (2002) Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. A randomized, double-blind, placebo-controlled study. *Cephalalgia* **22**(5): 345–53.
- Bijur PE, Schechter C, Esses D et al (2006) Intravenous bolus of ultra-low-dose naloxone added to morphine does not enhance analgesia in emergency department patients. *J Pain* **7**(2): 75–81.
- Biki B, Mascha E, Moriarty DC et al (2008) Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology* **109**(2): 180–7.
- Bishop JY, Sprague M, Gelber J et al (2006) Interscalene regional anesthesia for arthroscopic shoulder surgery: a safe and effective technique. *J Shoulder Elbow Surg* **15**(5): 567–70.
- Biswas BK & Bithal PK (2003) Preincision 0.25% bupivacaine scalp infiltration and postcraniotomy pain: a randomized double-blind, placebo-controlled study. *J Neurosurg Anesthesiol* **15**(3): 234–9.
- Blinderman CD, Sekine R, Zhang B et al (2009) Methadone as an analgesic for patients with chronic pain in methadone maintenance treatment programs (MMTPs). *J Opioid Manag* **5**(2): 107–14.

- Bloomfield EL, Schubert A, Secic M et al (1998) The influence of scalp infiltration with bupivacaine on hemodynamics and postoperative pain in adult patients undergoing craniotomy. *Anesth Analg* **87**(3): 579–82.
- Boas RA, Schug SA & Acland RH (1993) Perineal pain after rectal amputation: a 5-year follow-up. *Pain* **52**(1): 67–70.
- Boe MG, Mygland A & Salvesen R (2007) Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. *Neurology* **69**(1): 26–31.
- Bolt P, Barnett P, Babl FE et al (2008) Topical lignocaine for pain relief in acute otitis media: results of a double-blind placebo-controlled randomised trial. *Arch Dis Child* **93**(1): 40–4.
- Bone M, Critchley P & Buggy DJ (2002) Gabapentin in postamputation phantom limb pain: A randomized, double-blind, placebo-controlled, cross-over study. *Reg Anesth Pain Med* **27**(5): 481–6.
- Bong CL, Samuel M, Ng JM et al (2005) Effects of preemptive epidural analgesia on post-thoracotomy pain. *J Cardiothorac Vasc Anesth* **19**(6): 786–93.
- Borjesson M, Eriksson P, Dellborg M et al (1997) Transcutaneous electrical nerve stimulation in unstable angina pectoris. *Coron Artery Dis* **8**(8-9): 543–50.
- Borland M, Jacobs I, King B et al (2007) A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* **49**(3): 335–40.
- Borland ML, Bergesio R, Pascoe EM et al (2005) Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns* **31**(7): 831–7.
- Bounes V, Charpentier S, Houze-Cerfon CH et al (2008) Is there an ideal morphine dose for prehospital treatment of severe acute pain? A randomized, double-blind comparison of 2 doses. *Am J Emerg Med* **26**(2): 148–54.
- Bowsher D (1997) The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage* **13**(6): 327–31.
- Boyd R (2001) *Plain or buffered lignocaine for local anaesthetic*. [www.bestbets.org/cgi-bin/bets.pl?record=00102](http://www.bestbets.org/cgi-bin/bets.pl?record=00102) [www.bestbets.org](http://www.bestbets.org). Accessed June 2009.
- Brandes JL, Kudrow D, Stark SR et al (2007) Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* **297**(13): 1443–54.
- Brandsborg B, Nikolajsen L, Hansen CT et al (2007) Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. *Anesthesiology* **106**(5): 1003–12.
- Brandsborg B, Nikolajsen L, Kehlet H et al (2008) Chronic pain after hysterectomy. *Acta Anaesthesiol Scand* **52**(3): 327–31.
- Brandsborg B, Dueholm M, Nikolajsen L et al (2009) A prospective study of risk factors for pain persisting 4 months after hysterectomy. *Clin J Pain* **25**(4): 263–8.
- Bredmose PP, Grier G, Davies GE et al (2009) Pre-hospital use of ketamine in paediatric trauma. *Acta Anaesthesiol Scand* **53**(4): 543–5.
- Bredmose PP, Lockey DJ, Grier G et al (2009) Pre-hospital use of ketamine for analgesia and procedural sedation. *Emerg Med J* **26**(1): 62–4.
- Breen D, Wilmer A, Bodenham A et al (2004) Offset of pharmacodynamic effects and safety of remifentanyl in intensive care unit patients with various degrees of renal impairment. *Crit Care* **8**(1): R21–30.
- Breen D, Karabinis A, Malbrain M et al (2005) Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanyl with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. *Crit Care* **9**(3): R200–10.
- Breitbart W, McDonald MV, Rosenfeld B et al (1996) Pain in ambulatory AIDS patients. I: Pain characteristics and medical correlates. *Pain* **68**(2-3): 315–21.
- Breitbart W, Rosenfeld BD, Passik SD et al (1996) The undertreatment of pain in ambulatory AIDS patients. *Pain* **65**(2-3): 243–9.

- Breitbart W, Rosenfeld B, Passik S et al (1997) A comparison of pain report and adequacy of analgesic therapy in ambulatory AIDS patients with and without a history of substance abuse. *Pain* **72**(1-2): 235-43.
- Breitbart W, Passik S, McDonald MV et al (1998) Patient-related barriers to pain management in ambulatory AIDS patients. *Pain* **76**(1-2): 9-16.
- Breitbart W, Kaim M & Rosenfeld B (1999) Clinicians' perceptions of barriers to pain management in AIDS. *J Pain Symptom Manage* **18**(3): 203-12.
- Brisson M (2008) Estimating the number needed to vaccinate to prevent herpes zoster-related disease, health care resource use and mortality. *Can J Public Health* **99**(5): 383-6.
- Broadfield L, Banerjee S, Jewers H et al (2005) *Cancer Care Nova Scotia: Guidelines for the Management of Cancer-Related Pain in Adults*. Cancer Care Nova Scotia  
<http://www.cancercare.ns.ca/en/home/healthprofessionals/resourcestools/cancermanagementguidelines/symptommanagement.aspx>. Accessed June 2009.
- Brochet B, Deloire MS, Ouallet JC et al (2009) Pain and quality of life in the early stages after multiple sclerosis diagnosis: a 2-year longitudinal study. *Clin J Pain* **25**(3): 211-7.
- Brodano GB, Cappuccio M, Gasbarrini A et al (2007) Vertebroplasty in the treatment of vertebral metastases: clinical cases and review of the literature. *Eur Rev Med Pharmacol Sci* **11**(2): 91-100.
- Brofeldt BT, Cornwell P, Doherty D et al (1989) Topical lidocaine in the treatment of partial-thickness burns. *J Burn Care Rehabil* **10**(1): 63-8.
- Brookoff D & Polomano R (1992) Treating sickle cell pain like cancer pain. *Ann Intern Med* **116**(5): 364-8.
- Bruns BM, Dieckmann R, Shagoury C et al (1992) Safety of pre-hospital therapy with morphine sulfate. *Am J Emerg Med* **10**(1): 53-7.
- Buchbinder R, Osborne RH, Ebeling PR et al (2009) A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* **361**(6): 557-68.
- Bulloch B, Kabani A & Tenenbein M (2003) Oral dexamethasone for the treatment of pain in children with acute pharyngitis: a randomized, double-blind, placebo-controlled trial. *Ann Emerg Med* **41**(5): 601-8.
- Buntine P, Thom O, Babl F et al (2007) Prehospital analgesia in adults using inhaled methoxyflurane. *Emerg Med Australas* **19**(6): 509-14.
- Burduk P, Guzik P, Piechocka M et al (2000) Comparison of fentanyl and droperidol mixture (neuroleptanalgesia II) with morphine on clinical outcomes in unstable angina patients. *Cardiovasc Drugs Ther* **14**(3): 259-69.
- Burns B, Watkins L & Goadsby PJ (2009) Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. *Neurology* **72**(4): 341-5.
- Burnweit C, Diana-Zerpa JA, Nahmad MH et al (2004) Nitrous oxide analgesia for minor pediatric surgical procedures: an effective alternative to conscious sedation? *J Pediatr Surg* **39**(3): 495-9.
- Burton JH, Auble TE & Fuchs SM (1998) Effectiveness of 50% nitrous oxide/50% oxygen during laceration repair in children. *Acad Emerg Med* **5**(2): 112-7.
- Bussone G, Tullo V, d'Onofrio F et al (2007) Frovatriptan for the prevention of postdural puncture headache. *Cephalalgia* **27**(7): 809-13.
- Buyukkurt MC, Gungormus M & Kaya O (2006) The effect of a single dose prednisolone with and without diclofenac on pain, trismus, and swelling after removal of mandibular third molars. *J Oral Maxillofac Surg* **64**(12): 1761-6.
- Calmels V, Vallee JN, Rose M et al (2007) Osteoblastic and mixed spinal metastases: evaluation of the analgesic efficacy of percutaneous vertebroplasty. *AJNR Am J Neuroradiol* **28**(3): 570-4.
- Camann WR, Murray RS, Mushlin PS et al (1990) Effects of oral caffeine on postdural puncture headache. A double-blind, placebo-controlled trial. *Anesth Analg* **70**(2): 181-4.
- Canavero S & Bonicalzi V (2004) Intravenous subhypnotic propofol in central pain: a double-blind, placebo-controlled, crossover study. *Clin Neuropharmacol* **27**(4): 182-6.
- Candido KD & Stevens RA (2003) Post-dural puncture headache: pathophysiology, prevention and treatment. *Best Pract Res Clin Anaesthesiol* **17**(3): 451-69.

- Cannon CP (2008) Updated Strategies and Therapies for Reducing Ischemic and Vascular Events (STRIVE) unstable angina/non-ST elevation myocardial infarction critical pathway toolkit. *Crit Pathw Cardiol* **7**(1): 43–81.
- Cantore F, Boni L, Di Giuseppe M et al (2008) Pre-incision local infiltration with levobupivacaine reduces pain and analgesic consumption after laparoscopic cholecystectomy: a new device for day-case procedure. *Int J Surg* **6 Suppl 1**: S89–92.
- Capdevila X, Barthelet Y, Biboulet P et al (1999) Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* **91**(1): 8–15.
- Capdevila X, Dadure C, Bringuier S et al (2006) Effect of patient-controlled perineural analgesia on rehabilitation and pain after ambulatory orthopedic surgery: a multicenter randomized trial. *Anesthesiology* **105**(3): 566–73.
- Capouet V, Dernovoi B & Azagra JS (1987) Induction of anaesthesia with ketamine during an acute crisis of hereditary coproporphyrria. *Can J Anaesth* **34**(4): 388–90.
- Caraceni A, Cherny N, Fainsinger R et al (2002) Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. *J Pain Symptom Manage* **23**(3): 239–55.
- Cardenas DD, Warms CA, Turner JA et al (2002) Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. *Pain* **96**(3): 365–73.
- Cardwell M, Siviter G & Smith A (2005) Non-steroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane Database Syst Rev*(2): CD003591.
- Carr D, Goudas L, Lawrence D et al (2002) *Management of Cancer Symptoms: Pain, Depression, and Fatigue. Evidence Report/Technology Assessment No. 61*  
<http://www.ahrq.gov/downloads/pub/evidence/pdf/cansymp/cansymp.pdf> Agency for Healthcare Research and Quality. Accessed July 2002.
- Carrer S, Bocchi A, Candini M et al (2007) Short term analgesia based sedation in the Intensive Care Unit: morphine vs remifentanyl + morphine. *Minerva Anestesiol* **73**(6): 327–32.
- Casale R, Ceccherelli F, Labeeb AA et al (2009) Phantom limb pain relief by contralateral myofascial injection with local anaesthetic in a placebo-controlled study: preliminary results. *J Rehabil Med* **41**(6): 418–22.
- Cerchiotti LC, Navigante AH, Korte MW et al (2003) Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study. *Pain* **105**(1-2): 265–73.
- Cete Y, Dora B, Ertan C et al (2005) A randomized prospective placebo-controlled study of intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the Emergency Department. *Cephalalgia* **25**(3): 199–204.
- Chambers WA (2008) Nerve blocks in palliative care. *Br J Anaesth* **101**(1): 95–100.
- Chang AK, Bijur PE, Baccellieri A et al (2009) Efficacy and safety profile of a single dose of hydromorphone compared with morphine in older adults with acute, severe pain: a prospective, randomized, double-blind clinical trial. *Am J Geriatr Pharmacother* **7**(1): 1–10.
- Chang AK, Bijur PE, Campbell CM et al (2009) Safety and efficacy of rapid titration using 1mg doses of intravenous hydromorphone in emergency department patients with acute severe pain: the "1+1" protocol. *Ann Emerg Med* **54**(2): 221–5.
- Chang AK, Bijur PE, Napolitano A et al (2009) Two milligrams i.v. hydromorphone is efficacious for treating pain but is associated with oxygen desaturation. *J Opioid Manag* **5**(2): 75–80.
- Chang SH, Mehta V & Langford RM (2009) Acute and chronic pain after breast surgery. *Acute Pain* **11**: 1–14.
- Chanques G, Jaber S, Barbotte E et al (2006) Impact of systematic evaluation of pain and agitation in an intensive care unit. *Crit Care Med* **34**(6): 1691–9.
- Chen LC, Elliott RA & Ashcroft DM (2004) Systematic review of the analgesic efficacy and tolerability of COX-2 inhibitors in post-operative pain control. *J Clin Pharm Ther* **29**(3): 215–29.
- Chen LK, Huang CH, Jean WH et al (2007) Effective epidural blood patch volumes for postdural puncture headache in Taiwanese women. *J Formos Med Assoc* **106**(2): 134–40.



- Cheng GS, Choy LP & Ilfeld BM (2008) Regional anesthesia at home. *Curr Opin Anaesthesiol* **21**(4): 488–93.
- Cheung G, Chow E, Holden L et al (2006) Percutaneous vertebroplasty in patients with intractable pain from osteoporotic or metastatic fractures: A prospective study using quality-of-life assessment. *Can Assoc Radiol J* **57**(1): 13–21.
- Cheung R, Krishnaswami S & Kowalski K (2007) Analgesic efficacy of celecoxib in postoperative oral surgery pain: a single-dose, two-center, randomized, double-blind, active- and placebo-controlled study. *Clin Ther* **29** Suppl: 2498–510.
- Chi JH & Gokaslan ZL (2008) Vertebroplasty and kyphoplasty for spinal metastases. *Curr Opin Support Palliat Care* **2**(1): 9–13.
- Chiodo A (2007) Neurologic injury associated with pelvic trauma: radiology and electrodiagnosis evaluation and their relationships to pain and gait outcome. *Arch Phys Med Rehabil* **88**(9): 1171–6.
- Chiou-Tan FY, Tuel SM, Johnson JC et al (1996) Effect of mexiletine on spinal cord injury dysesthetic pain. *Am J Phys Med Rehabil* **75**(2): 84–7.
- Chitsaz A, Janghorbani M, Shaygannejad V et al (2009) Sensory complaints of the upper extremities in multiple sclerosis: relative efficacy of nortriptyline and transcutaneous electrical nerve stimulation. *Clin J Pain* **25**(4): 281–5.
- Choiniere M, Melzack R, Rondeau J et al (1989) The pain of burns: characteristics and correlates. *J Trauma* **29**(11): 1531–9.
- Choiniere M, Grenier R & Paquette C (1992) Patient-controlled analgesia: a double-blind study in burn patients. *Anaesthesia* **47**(6): 467–72.
- Choiniere M (2001) Burn Pain: A unique challenge. *Pain: Clinical Updates* **IX**(1): 1–4.
- Chong C & Burchett K (2003) Pain management in critical care. *Br J Anaesth CEPD Reviews* **3**(6): 183–86.
- Chou R & Huffman LH (2007a) Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* **147**(7): 505–14.
- Chou R & Huffman LH (2007b) Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* **147**(7): 492–504.
- Chou R, Qaseem A, Snow V et al (2007) Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* **147**(7): 478–91.
- Christensen KS, Rogers E, Green GA et al (2007) Safety and efficacy of intranasal ketamine for acute postoperative pain. *Acute Pain* **9**: 183–92.
- Chung F, Ritchie E & Su J (1997) Postoperative pain in ambulatory surgery. *Anesth Analg* **85**(4): 808–16.
- Ciconetti A, Bartoli A, Ripari F et al (2004) COX-2 selective inhibitors: a literature review of analgesic efficacy and safety in oral-maxillofacial surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **97**(2): 139–46.
- Cittadini E, May A, Straube A et al (2006) Effectiveness of intranasal zolmitriptan in acute cluster headache: a randomized, placebo-controlled, double-blind crossover study. *Arch Neurol* **63**(11): 1537–42.
- Clarkson JE, Worthington HV & Eden OB (2007) Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev*(2): CD001973.
- Clement PA, Bluestone CD, Gordts F et al (1998) Management of rhinosinusitis in children: consensus meeting, Brussels, Belgium, September 13, 1996. *Arch Otolaryngol Head Neck Surg* **124**(1): 31–4.
- Cohen J & Royston D (2001) Remifentanyl. *Curr Opin Crit Care* **7**(4): 227–31.
- Coimbra C, Choiniere M & Hemmerling TM (2003) Patient-controlled sedation using propofol for dressing changes in burn patients: a dose-finding study. *Anesth Analg* **97**(3): 839–42.
- Colman I, Brown MD, Innes GD et al (2004) Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ* **329**(7479): 1369–73.
- Colman I, Brown MD, Innes GD et al (2005) Parenteral dihydroergotamine for acute migraine headache: a systematic review of the literature. *Ann Emerg Med* **45**(4): 393–401.



- Colman I, Friedman BW, Brown MD et al (2008) Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. *BMJ* **336**(7657): 1359–61.
- Colonna-Romano P & Shapiro BE (1989) Unintentional dural puncture and prophylactic epidural blood patch in obstetrics. *Anesth Analg* **69**(4): 522–3.
- Coluzzi PH, Schwartzberg L, Conroy JD et al (2001) Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain* **91**(1-2): 123–30.
- Coman M & Kelly A-M (1999) Safety of a nurse-managed, titrated analgesia protocol for the management of severe pain in the emergency department. *Emergency Medicine* **11**(3): 128–32.
- Connelly NR, Parker RK, Rahimi A et al (2000) Sumatriptan in patients with postdural puncture headache. *Headache* **40**(4): 316–9.
- Conti C, Tso E & Browne B (1996) Oral morphine protocol for sickle cell crisis pain. *Md Med J* **45**(1): 33–5.
- Coppola M, Yealy DM & Leibold RA (1995) Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* **26**(5): 541–6.
- Corbo J, Esses D, Bijur PE et al (2001) Randomized clinical trial of intravenous magnesium sulfate as an adjunctive medication for emergency department treatment of migraine headache. *Ann Emerg Med* **38**(6): 621–7.
- Cruccu G, Gronseth G, Alksne J et al (2008) AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol* **15**(10): 1013–28.
- Cuignet O, Pirson J, Soudon O et al (2007) Effects of gabapentin on morphine consumption and pain in severely burned patients. *Burns* **33**(1): 81–6.
- Cunningham AL, Breuer J, Dwyer DE et al (2008) The prevention and management of herpes zoster. *Med J Aust* **188**(3): 171–6.
- Curtis KM, Henriques HF, Fanciullo G et al (2007) A fentanyl-based pain management protocol provides early analgesia for adult trauma patients. *J Trauma* **63**(4): 819–26.
- Czarnetki C, Elia N, Lysakowski C et al (2008) Dexamethasone and risk of nausea and vomiting and postoperative bleeding after tonsillectomy in children: a randomized trial. *JAMA* **300**(22): 2621–30.
- Dahaba AA, Grabner T, Rehak PH et al (2004) Remifentanyl versus morphine analgesia and sedation for mechanically ventilated critically ill patients: a randomized double blind study. *Anesthesiology* **101**(3): 640–6.
- Dahlof CG & Jacobs LD (1996) Ketoprofen, paracetamol and placebo in the treatment of episodic tension-type headache. *Cephalalgia* **16**(2): 117–23.
- Dahlof CG (2002) Management of Primary Headaches: Current and Future Aspects. In: *Pain 2002 - An Updated Review: Refresher Course Syllabus* edn. Giamberardino MA (eds). Seattle, IASP Press.
- Dal D, Celebi N, Elvan EG et al (2007) The efficacy of intravenous or peritonsillar infiltration of ketamine for postoperative pain relief in children following adenotonsillectomy. *Paediatr Anaesth* **17**(3): 263–9.
- Damen L, Bruijn JK, Verhagen AP et al (2005) Symptomatic treatment of migraine in children: a systematic review of medication trials. *Pediatrics* **116**(2): e295–302.
- Darwish M, Kirby M, Robertson P, Jr. et al (2007) Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol* **47**(3): 343–50.
- Das DA, Grimmer KA, Sparnon AL et al (2005) The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: a randomized controlled trial [ISRCTN87413556]. *BMC Pediatr* **5**(1): 1.
- Dauber A, Osgood PF, Breslau AJ et al (2002) Chronic persistent pain after severe burns: a survey of 358 burn survivors. *Pain Med* **3**(1): 6–17.
- Davies AN, Dickman A, Reid C et al (2009) The management of cancer-related breakthrough pain: Recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain* **13**(4): 331–38.

- Davies JW (1982) Prompt cooling of burned areas: a review of benefits and the effector mechanisms. *Burns Incl Therm Inj* **9**(1): 1–6.
- Davies S & Olujohungbe A (2001) Hydroxyurea for sickle cell disease. *Cochrane Database Syst Rev*(2): CD002202.
- Davis CP, Torre PR, Williams C et al (1995) Ketorolac versus meperidine-plus-promethazine treatment of migraine headache: evaluations by patients. *Am J Emerg Med* **13**(2): 146–50.
- De Benedittis G, Besana F & Lorenzetti A (1992) A new topical treatment for acute herpetic neuralgia and post-herpetic neuralgia: the aspirin/diethyl ether mixture. An open-label study plus a double-blind controlled clinical trial. *Pain* **48**(3): 383–90.
- De Cosmo G, Aceto P, Gualtieri E et al (2008) Analgesia in thoracic surgery: review. *Minerva Anestesiol*.
- De Jonghe B, Bastuji-Garin S, Fangio P et al (2005) Sedation algorithm in critically ill patients without acute brain injury. *Crit Care Med* **33**(1): 120–7.
- Deeg MA & Rajamani K (1990) Normeperidine-induced seizures in hereditary coproporphyruria. *South Med J* **83**(11): 1307–8.
- Del Mar CB, Glasziou PP & Spinks AB (2006) Antibiotics for sore throat. *Cochrane Database Syst Rev*(4): CD000023.
- Dellabella M, Milanese G & Muzzonigro G (2005) Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol* **174**(1): 167–72.
- Demirkaya S, Vural O, Dora B et al (2001) Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. *Headache* **41**(2): 171–7.
- Derry S, Barden J, McQuay HJ et al (2008) Single dose oral celecoxib for acute postoperative pain in adults. *Cochrane Database Syst Rev*(4): CD004233.
- Dertwinkel R, Heinrichs C, Senne I et al (2002) Prevention of severe phantom limb pain by perioperative administration of ketamine - An observational study. *Acute Pain* **4**(1): 9–13.
- Di Monda V, Nicolodi M, Aloisio A et al (2003) Efficacy of a fixed combination of indomethacin, prochlorperazine, and caffeine versus sumatriptan in acute treatment of multiple migraine attacks: a multicenter, randomized, crossover trial. *Headache* **43**(8): 835–44.
- Diamond S, Freitag FG & Diamond ML (1992) Transnasal butorphanol in the treatment of migraine headache pain. *Headache Quarterly, Curr Treat Res* **3**(2): 164–70.
- Diamond S, Balm TK & Freitag FG (2000) Ibuprofen plus caffeine in the treatment of tension-type headache. *Clin Pharmacol Ther* **68**(3): 312–9.
- Diener HC, Pfaffenrath V, Pageler L et al (2005) The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* **25**(10): 776–87.
- Dijkers M, Bryce T & Zanca J (2009) Prevalence of chronic pain after traumatic spinal cord injury: a systematic review. *J Rehabil Res Dev* **46**(1): 13–29.
- Dijkstra PU, Rietman JS & Geertzen JH (2007) Phantom breast sensations and phantom breast pain: a 2-year prospective study and a methodological analysis of literature. *Eur J Pain* **11**(1): 99–108.
- Ding Y & White PF (1995) Post-herniorrhaphy pain in outpatients after pre-incision ilioinguinal-hypogastric nerve block during monitored anaesthesia care. *Can J Anaesth* **42**(1): 12–5.
- Dixon P & Higginson I (1991) AIDS and cancer pain treated with slow release morphine. *Postgrad Med J* **67 Suppl 2**: S92–4.
- Djulfbegovic B, Wheatley K, Ross J et al (2002) Bisphosphonates in multiple myeloma. *Cochrane Database Syst Rev*(3): CD003188.
- Dobbie AE & Cooke MW (2008) A descriptive review and discussion of litigation claims against ambulance services. *Emerg Med J* **25**(7): 455–8.
- Dodick DW, Rozen TD, Goadsby PJ et al (2000) Cluster headache. *Cephalalgia* **20**(9): 787–803.
- Dodson T (2007) Paracetamol is an effective drug to use for pain following oral surgery. *Evid Based Dent* **8**(3): 79–80.

- Doubova SV, Morales HR, Hernandez SF et al (2007) Effect of a *Psidium guajavae* folium extract in the treatment of primary dysmenorrhea: a randomized clinical trial. *J Ethnopharmacol* **110**(2): 305–10.
- Downey LV & Zun LS (2009) The effects of deep breathing training on pain management in the emergency department. *South Med J* **102**(7): 688–92.
- Drewes AM, Andreasen A & Poulsen LH (1994) Valproate for treatment of chronic central pain after spinal cord injury. A double-blind cross-over study. *Paraplegia* **32**(8): 565–9.
- Duale C, Sibaud F, Guastella V et al (2009) Perioperative ketamine does not prevent chronic pain after thoracotomy. *Eur J Pain* **13**(5): 497–505.
- Dula DJ, Anderson R & Wood GC (2001) A prospective study comparing i.m. ketorolac with i.m. meperidine in the treatment of acute biliary colic. *J Emerg Med* **20**(2): 121–4.
- Dunbar PJ, Visco E & Lam AM (1999) Craniotomy procedures are associated with less analgesic requirements than other surgical procedures. *Anesth Analg* **88**(2): 335–40.
- Dunlop RJ & Bennett KC (2006) Pain management for sickle cell disease. *Cochrane Database Syst Rev*(2): CD003350.
- Dworkin RH, Johnson RW, Breuer J et al (2007) Recommendations for the management of herpes zoster. *Clin Infect Dis* **44 Suppl 1**: S1–26.
- Dworkin RH, Gnann JW, Jr., Oaklander AL et al (2008) Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. *J Pain* **9**(1 Suppl 1): S37–44.
- Dworkin RH, Barbano RL, Tyring SK et al (2009) A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain* **142**(3): 209–17.
- Dwyer DE & Cunningham AL (2002) 10: Herpes simplex and varicella-zoster virus infections. *Med J Aust* **177**(5): 267–73.
- Eccles R, Loose I, Jawad M et al (2003) Effects of acetylsalicylic acid on sore throat pain and other pain symptoms associated with acute upper respiratory tract infection. *Pain Med* **4**(2): 118–24.
- Edlow JA, Panagos PD, Godwin SA et al (2008) Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. *Ann Emerg Med* **52**(4): 407–36.
- Edwards JE, McQuay HJ & Moore RA (2002) Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *J Pain Symptom Manage* **23**(2): 121–30.
- Edwards JE, Meseguer F, Faura C et al (2002) Single dose dipyrrone for acute renal colic pain. *Cochrane Database Syst Rev*(4): CD003867.
- Eichenberger U, Neff F, Svetlicic G et al (2008) Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg* **106**(4): 1265–73.
- Eide PK, Stubhaug A & Stenehjem AE (1995) Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. *Neurosurgery* **37**(6): 1080–7.
- Eidelman A, Weiss JM, Lau J et al (2005) Topical anesthetics for dermal instrumentation: a systematic review of randomized, controlled trials. *Ann Emerg Med* **46**(4): 343–51.
- Ekbom K (1995) Treatment of cluster headache: clinical trials, design and results. *Cephalalgia* **15 Suppl 15**: 33–6.
- Elenbaas RM, Iacono CU, Koellner KJ et al (1991) Dose effectiveness and safety of butorphanol in acute migraine headache. *Pharmacotherapy* **11**(1): 56–63.
- Ellis RJ, Toperoff W, Vaida F et al (2009) Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology* **34**(3): 672–80.
- Engindeniz Z, Demircan C, Karli N et al (2005) Intramuscular tramadol vs. diclofenac sodium for the treatment of acute migraine attacks in emergency department: a prospective, randomised, double-blind study. *J Headache Pain* **6**(3): 143–8.
- Epstein JB, Epstein JD, Epstein MS et al (2006) Oral doxepin rinse: the analgesic effect and duration of pain reduction in patients with oral mucositis due to cancer therapy. *Anesth Analg* **103**(2): 465–70.
- Eray O, Cete Y, Oktay C et al (2002) Intravenous single-dose tramadol versus meperidine for pain relief in renal colic. *Eur J Anaesthesiol* **19**(5): 368–70.

- Ergene U, Pekdemir M, Canda E et al (2001) Ondansetron versus diclofenac sodium in the treatment of acute ureteral colic: a double blind controlled trial. *Int Urol Nephrol* **33**(2): 315–9.
- Ergun U, Say B, Ozer G et al (2008) Intravenous theophylline decreases post-dural puncture headaches. *J Clin Neurosci* **15**(10): 1102–4.
- Erhan OL, Goksu H, Alpaz C et al (2007) Ketamine in post-tonsillectomy pain. *Int J Pediatr Otorhinolaryngol* **71**(5): 735–9.
- Eriksson H, Tenhunen A & Korttila K (1996) Balanced analgesia improves recovery and outcome after outpatient tubal ligation. *Acta Anaesthesiol Scand* **40**(2): 151–5.
- Ernst E & Pittler MH (1998) The effectiveness of acupuncture in treating acute dental pain: a systematic review. *Br Dent J* **184**(9): 443–7.
- Esmaoglu A, Akpınar H & Ugur F (2005) Oral multidose caffeine-paracetamol combination is not effective for the prophylaxis of postdural puncture headache. *J Clin Anesth* **17**(1): 58–61.
- Evans E, Turley N, Robinson N et al (2005) Randomised controlled trial of patient controlled analgesia compared with nurse delivered analgesia in an emergency department. *Emerg Med J* **22**(1): 25–9.
- Evans RW, Armon C, Frohman EM et al (2000) Assessment: prevention of post-lumbar puncture headaches: report of the therapeutics and technology assessment subcommittee of the american academy of neurology. *Neurology* **55**(7): 909–14.
- Evers S, Afra J, Frese A et al (2006) EFNS guideline on the drug treatment of migraine - report of an EFNS task force. *Eur J Neurol* **13**(6): 560–72.
- Evers S, Marziniak M, Frese A et al (2009) Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies. *Cephalalgia* **29**(4): 436–44.
- Everts B, Karlson BW, Herlitz J et al (1998) Morphine use and pharmacokinetics in patients with chest pain due to suspected or definite acute myocardial infarction. *Eur J Pain* **2**(2): 115–25.
- Everts B, Karlson B, Abdon NJ et al (1999) A comparison of metoprolol and morphine in the treatment of chest pain in patients with suspected acute myocardial infarction—the MEMO study. *J Intern Med* **245**(2): 133–41.
- Faddy SC & Garlick SR (2005) A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting? *Emerg Med J* **22**(12): 901–8.
- Fainsinger RL, Nikolaichuk CL, Lawlor PG et al (2005) A multicenter study of the revised Edmonton Staging System for classifying cancer pain in advanced cancer patients. *J Pain Symptom Manage* **29**(3): 224–37.
- Faryniarz D, Morelli C, Coleman S et al (2006) Interscalene block anesthesia at an ambulatory surgery center performing predominantly regional anesthesia: a prospective study of one hundred thirty-three patients undergoing shoulder surgery. *J Shoulder Elbow Surg* **15**(6): 686–90.
- Fassoulaki A, Sarantopoulos C, Melemini A et al (2000) EMLA reduces acute and chronic pain after breast surgery for cancer. *Reg Anesth Pain Med* **25**(4): 350–5.
- Fassoulaki A, Patris K, Sarantopoulos C et al (2002) The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* **95**(4): 985–91.
- Fassoulaki A, Triga A, Melemini A et al (2005) Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. *Anesth Analg* **101**(5): 1427–32.
- Fassoulaki A, Melemini A, Stamatakis E et al (2007) A combination of gabapentin and local anaesthetics attenuates acute and late pain after abdominal hysterectomy. *Eur J Anaesthesiol* **24**(6): 521–8.
- Felhendler D & Lisander B (1996) Pressure on acupoints decreases postoperative pain. *Clin J Pain* **12**(4): 326–9.
- Feuer DJ & Broadley KE (2000) Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev*(2): CD001219.
- Finch CK, Chrisman CR, Baciewicz AM et al (2002) Rifampin and rifabutin drug interactions: an update. *Arch Intern Med* **162**(9): 985–92.
- Finn J, Wright J, Fong J et al (2004) A randomised crossover trial of patient controlled intranasal fentanyl and oral morphine for procedural wound care in adult patients with burns. *Burns* **30**(3): 262–8.

- Finnerup NB, Sindrup SH, Bach FW et al (2002) Lamotrigine in spinal cord injury pain: a randomized controlled trial. *Pain* **96**(3): 375–83.
- Finnerup NB, Biering-Sorensen F, Johannesen IL et al (2005) Intravenous lidocaine relieves spinal cord injury pain: a randomized controlled trial. *Anesthesiology* **102**(5): 1023–30.
- Finnerup NB, Otto M, McQuay HJ et al (2005) Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* **118**(3): 289–305.
- Fletcher AK, Rigby AS & Heyes FL (2003) Three-in-one femoral nerve block as analgesia for fractured neck of femur in the emergency department: a randomized, controlled trial. *Ann Emerg Med* **41**(2): 227–33.
- Flor H, Denke C, Schaefer M et al (2001) Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. *Lancet* **357**(9270): 1763–4.
- Flynn BC & Nemergut EC (2006) Postoperative nausea and vomiting and pain after transsphenoidal surgery: a review of 877 patients. *Anesth Analg* **103**(1): 162–7.
- Fogan L (1985) Treatment of cluster headache. A double-blind comparison of oxygen v air inhalation. *Arch Neurol* **42**(4): 362–3.
- Fong SY, Pavy TJ, Yeo ST et al (2001) Assessment of wound infiltration with bupivacaine in women undergoing day-case gynecological laparoscopy. *Reg Anesth Pain Med* **26**(2): 131–6.
- Forouzanfar T, Sabelis A, Ausems S et al (2008) Effect of ice compression on pain after mandibular third molar surgery: a single-blind, randomized controlled trial. *Int J Oral Maxillofac Surg* **37**(9): 824–30.
- Foss NB, Kristensen BB, Bundgaard M et al (2007) Fascia iliaca compartment blockade for acute pain control in hip fracture patients: a randomized, placebo-controlled trial. *Anesthesiology* **106**(4): 773–8.
- Foxlee R, Johansson A, Wejfalk J et al (2006) Topical analgesia for acute otitis media. *Cochrane Database Syst Rev* **3**: CD005657.
- Frank LR, Olson CM, Shuler KB et al (2004) Intravenous magnesium for acute benign headache in the emergency department: a randomized double-blind placebo-controlled trial. *CJEM* **6**(5): 327–32.
- Fraser GL & Riker RR (2007) Comfort without coma: changing sedation practices. *Crit Care Med* **35**(2): 635–7.
- Fredrickson MJ, Ball CM & Dalglish AJ (2008) Successful continuous interscalene analgesia for ambulatory shoulder surgery in a private practice setting. *Reg Anesth Pain Med* **33**(2): 122–8.
- Frenay MC, Faymonville ME, Devlieger S et al (2001) Psychological approaches during dressing changes of burned patients: a prospective randomised study comparing hypnosis against stress reducing strategy. *Burns* **27**(8): 793–9.
- Frich LM & Borgbjerg FM (2000) Pain and pain treatment in AIDS patients: a longitudinal study. *J Pain Symptom Manage* **19**(5): 339–47.
- Fricke JR, Jr., Angelocci D, Fox K et al (1992) Comparison of the efficacy and safety of ketorolac and meperidine in the relief of dental pain. *J Clin Pharmacol* **32**(4): 376–84.
- Fricke JR, Jr., Hewitt DJ, Jordan DM et al (2004) A double-blind placebo-controlled comparison of tramadol/acetaminophen and tramadol in patients with postoperative dental pain. *Pain* **109**(3): 250–7.
- Friedman BW, Kapoor A, Friedman MS et al (2008) The relative efficacy of meperidine for the treatment of acute migraine: a meta-analysis of randomized controlled trials. *Ann Emerg Med* **52**(6): 705–13.
- Friedman EW, Webber AB, Osborn HH et al (1986) Oral analgesia for treatment of painful crisis in sickle cell anemia. *Ann Emerg Med* **15**(7): 787–91.
- Fulda GJ, Giberson F & Fagraeus L (2005) A prospective randomized trial of nebulized morphine compared with patient-controlled analgesia morphine in the management of acute thoracic pain. *J Trauma* **59**(2): 383–8.
- Fullerton-Gleason L, Crandall C & Sklar DP (2002) Prehospital administration of morphine for isolated extremity injuries: a change in protocol reduces time to medication. *Prehosp Emerg Care* **6**(4): 411–6.
- Gaiser R (2006) Postdural puncture headache. *Curr Opin Anaesthesiol* **19**(3): 249–53.
- Galinski M, Dolveck F, Borron SW et al (2005) A randomized, double-blind study comparing morphine with fentanyl in prehospital analgesia. *Am J Emerg Med* **23**(2): 114–9.
- Galinski M, Dolveck F, Combes X et al (2007) Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. *Am J Emerg Med* **25**(4): 385–90.

- Gallagher G, Rae CP, Kenny GN et al (2000) The use of a target-controlled infusion of alfentanil to provide analgesia for burn dressing changes: a dose finding study. *Anaesthesia* **55**(12): 1159–63.
- Gallagher G, Rae CP & Kinsella J (2000) Treatment of pain in severe burns. *Am J Clin Dermatol* **1**(6): 329–35.
- Gamis AS, Knapp JF & Glenski JA (1989) Nitrous oxide analgesia in a pediatric emergency department. *Ann Emerg Med* **18**(2): 177–81.
- Ganesh A, Rose JB, Wells L et al (2007) Continuous peripheral nerve blockade for inpatient and outpatient postoperative analgesia in children. *Anesth Analg* **105**(5): 1234–42.
- Gaufberg SV, Walta MJ & Workman TP (2007) Expanding the use of topical anesthesia in wound management: sequential layered application of topical lidocaine with epinephrine. *Am J Emerg Med* **25**(4): 379–84.
- Gaukroger PB, Chapman MJ & Davey RB (1991) Pain control in paediatric burns--the use of patient-controlled analgesia. *Burns* **17**(5): 396–9.
- Gazoni FM, Pouratian N & Nemergut EC (2008) Effect of ropivacaine skull block on perioperative outcomes in patients with supratentorial brain tumors and comparison with remifentanil: a pilot study. *J Neurosurg* **109**(1): 44–9.
- Gehling M & Tryba M (2003) [Prophylaxis of phantom pain: is regional analgesia ineffective?]. *Schmerz* **17**(1): 11–9.
- Gelb AW, Salevsky F, Chung F et al (2003) Remifentanil with morphine transitional analgesia shortens neurological recovery compared to fentanyl for supratentorial craniotomy. *Can J Anaesth* **50**(9): 946–52.
- Gelinas C, Harel F, Fillion L et al (2009) Sensitivity and specificity of the critical-care pain observation tool for the detection of pain in intubated adults after cardiac surgery. *J Pain Symptom Manage* **37**(1): 58–67.
- Gerhardt RT, King KM & Wiegert RS (2001) Inhaled nitrous oxide versus placebo as an analgesic and anxiolytic adjunct to peripheral intravenous cannulation. *Am J Emerg Med* **19**(6): 492–4.
- Gerlach K, Uhlig T, Huppe M et al (2003) Remifentanil-propofol versus sufentanil-propofol anaesthesia for supratentorial craniotomy: a randomized trial. *Eur J Anaesthesiol* **20**(10): 813–20.
- Glare PA (2001) Pain in patients with HIV infection: issues for the new millennium. *Eur J Pain* **5 Suppl A**: 43–8.
- Goadsby PJ (2003) Headache (chronic tension type). *Clin Evid*(9): 1432–40.
- Goldman G, Kahn PJ, Alon R et al (1989) Biliary colic treatment and acute cholecystitis prevention by prostaglandin inhibitor. *Dig Dis Sci* **34**(6): 809–11.
- Goldsack C, Scuplak SM & Smith M (1996) A double-blind comparison of codeine and morphine for postoperative analgesia following intracranial surgery. *Anaesthesia* **51**(11): 1029–32.
- Goldstein J, Silberstein SD, Saper JR et al (2005) Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the early treatment of migraine: results from the ASSET trial. *Headache* **45**(8): 973–82.
- Goldstein J, Silberstein SD, Saper JR et al (2006) Acetaminophen, aspirin, and caffeine in combination versus ibuprofen for acute migraine: results from a multicenter, double-blind, randomized, parallel-group, single-dose, placebo-controlled study. *Headache* **46**(3): 444–53.
- Gottschalk A, Berkow LC, Stevens RD et al (2007) Prospective evaluation of pain and analgesic use following major elective intracranial surgery. *J Neurosurg* **106**(2): 210–6.
- Grainger J & Saravanappa N (2008) Local anaesthetic for post-tonsillectomy pain: a systematic review and meta-analysis. *Clin Otolaryngol* **33**(5): 411–9.
- Gramke HF, de Rijke JM, van Kleef M et al (2009) Predictive factors of postoperative pain after day-case surgery. *Clin J Pain* **25**(6): 455–60.
- Gray P, Williams B & Cramond T (2008) Successful use of gabapentin in acute pain management following burn injury: a case series. *Pain Med* **9**(3): 371–6.
- Green R, Bulloch B, Kabani A et al (2005) Early analgesia for children with acute abdominal pain. *Pediatrics* **116**(4): 978–83.
- Greengrass RA & Nielsen KC (2005) Management of peripheral nerve block catheters at home. *Int Anesthesiol Clin* **43**(3): 79–87.



- Gregory PR & Sullivan JA (1996) Nitrous oxide compared with intravenous regional anesthesia in pediatric forearm fracture manipulation. *J Pediatr Orthop* **16**(2): 187–91.
- Griffin TC, McIntire D & Buchanan GR (1994) High-dose intravenous methylprednisolone therapy for pain in children and adolescents with sickle cell disease. *N Engl J Med* **330**(11): 733–7.
- Grimes DA, Hubacher D, Lopez LM et al (2006) Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use. *Cochrane Database Syst Rev*(4): CD006034.
- Grindlay J & Babl FE (2009) Review article: Efficacy and safety of methoxyflurane analgesia in the emergency department and prehospital setting. *Emerg Med Australas* **21**(1): 4–11.
- Grossi GB, Maiorana C, Garramone RA et al (2007) Effect of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective study. *J Oral Maxillofac Surg* **65**(11): 2218–26.
- Guillain-Barre Syndrome Study Group (1985) Plasmapheresis and acute Guillain-Barre syndrome. The Guillain-Barre Syndrome Study Group. *Neurology* **35**(8): 1096–104.
- Gurnani A, Sharma PK, Rautela RS et al (1996) Analgesia for acute musculoskeletal trauma: low-dose subcutaneous infusion of ketamine. *Anaesth Intensive Care* **24**(1): 32–6.
- Hadjimichael O, Kerns RD, Rizzo MA et al (2007) Persistent pain and uncomfortable sensations in persons with multiple sclerosis. *Pain* **127**(1-2): 35–41.
- Hadzic A, Arliss J, Kerimoglu B et al (2004) A comparison of infraclavicular nerve block versus general anesthesia for hand and wrist day-case surgeries. *Anesthesiology* **101**(1): 127–32.
- Hagen NA, Fisher K, Victorino C et al (2007) A titration strategy is needed to manage breakthrough cancer pain effectively: observations from data pooled from three clinical trials. *J Palliat Med* **10**(1): 47–55.
- Halbert J, Crotty M & Cameron ID (2002) Evidence for the optimal management of acute and chronic phantom pain: a systematic review. *Clin J Pain* **18**(2): 84–92.
- Halker RB, Demaerschalk BM, Wellik KE et al (2007) Caffeine for the prevention and treatment of postdural puncture headache: debunking the myth. *Neurologist* **13**(5): 323–7.
- Halpern S & Preston R (1994) Postdural puncture headache and spinal needle design. Metaanalyses. *Anesthesiology* **81**(6): 1376–83.
- Hamada H, Moriwaki K, Shiroyama K et al (2000) Myofascial pain in patients with postthoracotomy pain syndrome. *Reg Anesth Pain Med* **25**(3): 302–5.
- Hamunen K & Kontinen V (2005) Systematic review on analgesics given for pain following tonsillectomy in children. *Pain* **117**(1-2): 40–50.
- Han SH, Hur MH, Buckle J et al (2006) Effect of aromatherapy on symptoms of dysmenorrhea in college students: A randomized placebo-controlled clinical trial. *J Altern Complement Med* **12**(6): 535–41.
- Hanks GW, Conno F, Cherny N et al (2001) Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* **84**(5): 587–93.
- Hanley MA, Jensen MP, Smith DG et al (2007) Pre-amputation pain and acute pain predict chronic pain after lower extremity amputation. *J Pain* **8**(2): 102–9.
- Hansen JG, Schmidt H & Grinsted P (2000) Randomised, double blind, placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice. *Scand J Prim Health Care* **18**(1): 44–7.
- Hardebo JE & Dahlof C (1998) Sumatriptan nasal spray (20 mg/dose) in the acute treatment of cluster headache. *Cephalalgia* **18**(7): 487–9.
- Hardwick WE, Jr., Givens TG, Monroe KW et al (1999) Effect of ketorolac in pediatric sickle cell vaso-occlusive pain crisis. *Pediatr Emerg Care* **15**(3): 179–82.
- Hargrave DR, Wade A, Evans JP et al (2003) Nocturnal oxygen saturation and painful sickle cell crises in children. *Blood* **101**(3): 846–8.
- Harpaz R, Ortega-Sanchez IR & Seward JF (2008) Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **57**(RR-5): 1–30.
- Harris K, Pugash R, David E et al (2007) Percutaneous cementoplasty of lytic metastasis in left acetabulum. *Curr Oncol* **14**(1): 4–8.



- Harrison GG, Moore MR & Meissner PN (1985) Porphyrinogenicity of etomidate and ketamine as continuous infusions. Screening in the DDC-primed rat model. *Br J Anaesth* **57**(4): 420–3.
- Hawryluck LA, Harvey WR, Lemieux-Charles L et al (2002) Consensus guidelines on analgesia and sedation in dying intensive care unit patients. *BMC Med Ethics* **3**(1): E3.
- Hayes C, Browne S, Lantry G et al (2002) Neuropathic pain in the acute pain service: a prospective survey. *Acute Pain* **4**(2): 45–48.
- Hayes C, Armstrong-Brown A & Burstal R (2004) Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: a randomized, controlled trial. *Anaesth Intensive Care* **32**(3): 330–8.
- Hayward G, Thompson M, Heneghan C (2009) Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. *BMJ* **339**: b2976
- He L, Zhang D, Zhou M et al (2008) Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*(1): CD005582.
- Headache Classification Subcommittee of the IHS (2004) The international classification of headache disorders: 2nd edition. *Cephalalgia* **24**(Supp 1): 9–160.
- Henderson SO, Swadron S & Newton E (2002) Comparison of intravenous ketorolac and meperidine in the treatment of biliary colic. *J Emerg Med* **23**(3): 237–41.
- Henrikson CA, Howell EE, Bush DE et al (2003) Chest pain relief by nitroglycerin does not predict active coronary artery disease. *Ann Intern Med* **139**(12): 979–86.
- Herr DL, Sum-Ping ST & England M (2003) ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. *J Cardiothorac Vasc Anesth* **17**(5): 576–84.
- Herrick AL, McColl KE, Moore MR et al (1989) Controlled trial of haem arginate in acute hepatic porphyria. *Lancet* **1**(8650): 1295–7.
- Herrick AL & McColl KE (2005) Acute intermittent porphyria. *Best Pract Res Clin Gastroenterol* **19**(2): 235–49.
- Hiki N, Kurosaka H, Tatsutomi Y et al (2003) Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. *Gastrointest Endosc* **57**(4): 475–82.
- Hoffert MJ, Couch JR, Diamond S et al (1995) Transnasal butorphanol in the treatment of acute migraine. *Headache* **35**(2): 65–9.
- Hoffman HG, Patterson DR, Seibel E et al (2008) Virtual reality pain control during burn wound debridement in the hydrotank. *Clin J Pain* **24**(4): 299–304.
- Holdgate A & Oh CM (2005) Is there a role for antimuscarinics in renal colic? A randomized controlled trial. *J Urol* **174**(2): 572–5.
- Holdgate A & Pollock T (2005) Nonsteroidal anti-inflammatory drugs (NSAIDs) versus opioids for acute renal colic. *Cochrane Database Syst Rev*(2): CD004137.
- Holroyd KA (2002) Behavioral and psychologic aspects of the pathophysiology and management of tension-type headache. *Curr Pain Headache Rep* **6**(5): 401–7.
- Honarmand A, Safavi MR & Jamshidi M (2008) The preventative analgesic effect of preincisional peritonsillar infiltration of two low doses of ketamine for postoperative pain relief in children following adenotonsillectomy. A randomized, double-blind, placebo-controlled study. *Paediatr Anaesth* **18**(6): 508–14.
- Honderick T, Williams D, Seaberg D et al (2003) A prospective, randomized, controlled trial of benzodiazepines and nitroglycerine or nitroglycerine alone in the treatment of cocaine-associated acute coronary syndromes. *Am J Emerg Med* **21**(1): 39–42.
- Hong JY & Lim KT (2008) Effect of preemptive epidural analgesia on cytokine response and postoperative pain in laparoscopic radical hysterectomy for cervical cancer. *Reg Anesth Pain Med* **33**(1): 44–51.
- Horsburgh CR, Jr. (1995) Healing by design. *N Engl J Med* **333**(11): 735–40.
- Hu OY, Ho ST, Wang JJ et al (1993) Evaluation of gastric emptying in severe, burn-injured patients. *Crit Care Med* **21**(4): 527–31.

- Hulme PA, Krebs J, Ferguson SJ et al (2006) Vertebroplasty and kyphoplasty: a systematic review of 69 clinical studies. *Spine* **31**(17): 1983–2001.
- Huse E, Larbig W, Flor H et al (2001) The effect of opioids on phantom limb pain and cortical reorganization. *Pain* **90**(1-2): 47–55.
- ICSI (2008) *Health Care Guidelines: Low back pain, adult*. Institute for Clinical Systems Improvement. [www.icsi.org/guidelines\\_and\\_more/gl\\_os\\_prot/musculo-skeletal/low\\_back\\_pain/low\\_back\\_pain\\_\\_adult\\_5.html](http://www.icsi.org/guidelines_and_more/gl_os_prot/musculo-skeletal/low_back_pain/low_back_pain__adult_5.html). Accessed May 2009.
- Ilfeld BM, Morey TE & Enneking FK (2002) Continuous infraclavicular brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. *Anesthesiology* **96**(6): 1297–304.
- Ilfeld BM, Morey TE, Wang RD et al (2002) Continuous popliteal sciatic nerve block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. *Anesthesiology* **97**(4): 959–65.
- Ilfeld BM, Morey TE, Wright TW et al (2003) Continuous interscalene brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* **96**(4): 1089–95.
- Ilfeld BM, Morey TE, Wright TW et al (2004) Interscalene perineural ropivacaine infusion: a comparison of two dosing regimens for postoperative analgesia. *Reg Anesth Pain Med* **29**(1): 9–16.
- Ilfeld BM & Enneking FK (2005) Continuous peripheral nerve blocks at home: a review. *Anesth Analg* **100**(6): 1822–33.
- Ilfeld BM, Vandenborne K, Duncan PW et al (2006) Ambulatory continuous interscalene nerve blocks decrease the time to discharge readiness after total shoulder arthroplasty: a randomized, triple-masked, placebo-controlled study. *Anesthesiology* **105**(5): 999–1007.
- Ilfeld BM, Mariano ER, Williams BA et al (2007) Hospitalization costs of total knee arthroplasty with a continuous femoral nerve block provided only in the hospital versus on an ambulatory basis: a retrospective, case-control, cost-minimization analysis. *Reg Anesth Pain Med* **32**(1): 46–54.
- Ilfeld BM, Le LT, Meyer RS et al (2008) Ambulatory continuous femoral nerve blocks decrease time to discharge readiness after tricompartiment total knee arthroplasty: a randomized, triple-masked, placebo-controlled study. *Anesthesiology* **108**(4): 703–13.
- Ilfeld BM, Ball ST, Gearen PF et al (2008) Ambulatory continuous posterior lumbar plexus nerve blocks after hip arthroplasty: a dual-center, randomized, triple-masked, placebo-controlled trial. *Anesthesiology* **109**(3): 491–501.
- Ilkjaer S, Petersen KL, Brennum J et al (1996) Effect of systemic N-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans. *Br J Anaesth* **76**(6): 829–34.
- Ilkjaer S, Dirks J, Brennum J et al (1997) Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans. *Br J Anaesth* **79**(5): 600–5.
- Irefin SA, Schubert A, Bloomfield EL et al (2003) The effect of craniotomy location on postoperative pain and nausea. *J Anesth* **17**(4): 227–31.
- Iribarne C, Berthou F, Carlhant D et al (1998) Inhibition of methadone and buprenorphine N-dealkylations by three HIV-1 protease inhibitors. *Drug Metab Dispos* **26**(3): 257–60.
- Iskedjian M, Bereza B, Gordon A et al (2007) Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin* **23**(1): 17–24.
- Jackson JL, Gibbons R, Meyer G et al (1997) The effect of treating herpes zoster with oral acyclovir in preventing postherpetic neuralgia. A meta-analysis. *Arch Intern Med* **157**(8): 909–12.
- Jackson K, Ashby M & Goodchild C (2005) Subanesthetic ketamine for cancer pain: by insisting on level I/II evidence, do we risk throwing the baby out with the bath water? *J Pain Symptom Manage* **29**(4): 328–30.
- Jacobi J, Fraser GL, Coursin DB et al (2002) Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* **30**(1): 119–41.
- Jacobson SJ, Kopecky EA, Joshi P et al (1997) Randomised trial of oral morphine for painful episodes of sickle-cell disease in children. *Lancet* **350**(9088): 1358–61.

- Jacox A, Carr DB, Payne R et al (1994) *Management of Cancer Pain. Clinical Practice Guideline No. 9 AHCPR Publication No. 94-0592*. Rockville, MD, Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, Public Health Service.
- Jaeger H & Maier C (1992) Calcitonin in phantom limb pain: a double-blind study. *Pain* **48**(1): 21–7.
- Jamieson BD & Mariano ER (2007) Thoracic and lumbar paravertebral blocks for outpatient lithotripsy. *J Clin Anesth* **19**(2): 149–51.
- Janssens E, Aerssens P, Alliet P et al (2003) Post-dural puncture headaches in children. A literature review. *Eur J Pediatr* **162**(3): 117–21.
- Jeffrey HM, Charlton P, Mellor DJ et al (1999) Analgesia after intracranial surgery: a double-blind, prospective comparison of codeine and tramadol. *Br J Anaesth* **83**(2): 245–9.
- Jellish WS, Leonetti JP, Sawicki K et al (2006) Morphine/ondansetron PCA for postoperative pain, nausea, and vomiting after skull base surgery. *Otolaryngol Head Neck Surg* **135**(2): 175–81.
- Jensen MP, Barber J, Romano JM et al (2009) Effects of self-hypnosis training and EMG biofeedback relaxation training on chronic pain in persons with spinal-cord injury. *Int J Clin Exp Hypn* **57**(3): 239–68.
- Jensen TS, Krebs B, Nielsen J et al (1983) Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation. *Pain* **17**(3): 243–56.
- Jensen TS, Krebs B, Nielsen J et al (1985) Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation pain. *Pain* **21**(3): 267–78.
- Jeon EJ, Park YS, Park SS et al (2008) The effectiveness of gabapentin on post-tonsillectomy pain control. *Eur Arch Otorhinolaryngol*.
- Johnson RW & Whitton TL (2004) Management of herpes zoster (shingles) and postherpetic neuralgia. *Expert Opin Pharmacother* **5**(3): 551–9.
- Jones JB, Giles BK, Brizendine EJ et al (2001) Sublingual hyoscyamine sulfate in combination with ketorolac tromethamine for ureteral colic: a randomized, double-blind, controlled trial. *Ann Emerg Med* **37**(2): 141–6.
- Jones SJ, Cormack J, Murphy MA et al (2009) Parecoxib for analgesia after craniotomy. *Br J Anaesth* **102**(1): 76–9.
- Jonsson A, Cassuto J & Hanson B (1991) Inhibition of burn pain by intravenous lignocaine infusion. *Lancet* **338**(8760): 151–2.
- Joshi W, Connelly NR, Reuben SS et al (2003) An evaluation of the safety and efficacy of administering rofecoxib for postoperative pain management. *Anesth Analg* **97**(1): 35–8.
- Ju H, Feng Y, Yang BX et al (2008) Comparison of epidural analgesia and intercostal nerve cryoanalgesia for post-thoracotomy pain control. *Eur J Pain* **12**(3): 378–84.
- Kabore R, Magy L, Boukhris S et al (2004) [Contribution of corticosteroid to the treatment of pain in the acute phase of Guillain-Barre syndrome]. *Rev Neurol (Paris)* **160**(8-9): 821–3.
- Kairaluoma PM, Bachmann MS, Rosenberg PH et al (2006) Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery. *Anesth Analg* **103**(3): 703–8.
- Kallen B & Lygner PE (2001) Delivery outcome in women who used drugs for migraine during pregnancy with special reference to sumatriptan. *Headache* **41**(4): 351–6.
- Kallmes DF, Comstock BA, Heagerty PJ et al (2009) A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* **361**(6): 569–79.
- Kalso E, Tramer MR, McQuay HJ et al (1998) Systemic local-anaesthetic-type drugs in chronic pain: a systematic review. *Eur J Pain* **2**(1): 3–14.
- Kanbak M (1997) Ketamine in porphyria. *Anesth Analg* **84**(6): 1395.
- Kanowitz A, Dunn TM, Kanowitz EM et al (2006) Safety and effectiveness of fentanyl administration for prehospital pain management. *Prehosp Emerg Care* **10**(1): 1–7.
- Kaplan R, Conant M, Cundiff D et al (1996) Sustained-release morphine sulfate in the management of pain associated with acquired immune deficiency syndrome. *J Pain Symptom Manage* **12**(3): 150–60.
- Kaplan R, Slywka J, Slagle S et al (2000) A titrated morphine analgesic regimen comparing substance users and non-users with AIDS-related pain. *J Pain Symptom Manage* **19**(4): 265–73.

- Kapoor DA, Weitzel S, Mowad JJ et al (1989) Use of indomethacin suppositories in the prophylaxis of recurrent ureteral colic. *J Urol* **142**(6): 1428–30.
- Karaaslan K, Yilmaz F, Gulcu N et al (2008) The effects of levobupivacaine versus levobupivacaine plus magnesium infiltration on postoperative analgesia and laryngospasm in pediatric tonsillectomy patients. *Int J Pediatr Otorhinolaryngol* **72**(5): 675–81.
- Karmakar MK & Ho AM (2004) Postthoracotomy pain syndrome. *Thorac Surg Clin* **14**(3): 345–52.
- Katz J & Melzack R (1990) Pain 'memories' in phantom limbs: review and clinical observations. *Pain* **43**(3): 319–36.
- Keefe DM, Schubert MM, Elting LS et al (2007) Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* **109**(5): 820–31.
- Keenan JV, Farman AG, Fedorowicz Z et al (2005) Antibiotic use for irreversible pulpitis. *Cochrane Database Syst Rev*(2): CD004969.
- Kehlet H, Wilkinson RC, Fischer HB et al (2007) PROSPECT: evidence-based, procedure-specific postoperative pain management. *Best Pract Res Clin Anaesthesiol* **21**(1): 149–59.
- Keith DA (2004) Orofacial pain. In: *Principles and Practice of Pain Medicine* 2nd edn. Warfield CA and Bajwa ZH (eds). New York, McGraw-Hill. 252–59.
- Kelekis A, Lovblad KO, Mehdizade A et al (2005) Pelvic osteoplasty in osteolytic metastases: technical approach under fluoroscopic guidance and early clinical results. *J Vasc Interv Radiol* **16**(1): 81–8.
- Kelly A & Gunn B (2008) Acute pain management in the emergency department. In: *Clinical Pain Management: Acute Pain* 2nd edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold. 360–73.
- Kelly AM, Cohen M & Richards D (1994) Minimizing the pain of local infiltration anesthesia for wounds by injection into the wound edges. *J Emerg Med* **12**(5): 593–5.
- Kelly AM (2000) Patient satisfaction with pain management does not correlate with initial or discharge VAS pain score, verbal pain rating at discharge, or change in VAS score in the Emergency Department. *J Emerg Med* **19**(2): 113–6.
- Kemper CA, Kent G, Burton S et al (1998) Mexiletine for HIV-infected patients with painful peripheral neuropathy: a double-blind, placebo-controlled, crossover treatment trial. *J Acquir Immune Defic Syndr Hum Retrovirol* **19**(4): 367–72.
- Keramidas EG & Rodopoulou SG (2007) Ropivacaine versus lidocaine in digital nerve blocks: a prospective study. *Plast Reconstr Surg* **119**(7): 2148–52.
- Kern U, Busch V, Rockland M et al (2009) [Prevalence and risk factors of phantom limb pain and phantom limb sensations in Germany: A nationwide field survey.]. *Schmerz*. (Epub ahead of print).
- Khan F & Pallant J (2007) Chronic pain in multiple sclerosis: prevalence, characteristics, and impact on quality of life in an Australian community cohort. *J Pain* **8**(8): 614–23.
- Khatri A & Pearlstein L (1997) Pain in Guillain-Barre syndrome. *Neurology* **49**(5): 1474.
- Khot UP, Lang AW, Murali K et al (2002) Systematic review of the efficacy and safety of colorectal stents. *Br J Surg* **89**(9): 1096–102.
- Kiebertz K, Simpson D, Yiannoutsos C et al (1998) A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. AIDS Clinical Trial Group 242 Protocol Team. *Neurology* **51**(6): 1682–8.
- Kim MK, Strait RT, Sato TT et al (2002) A randomized clinical trial of analgesia in children with acute abdominal pain. *Acad Emerg Med* **9**(4): 281–7.
- Kimball LR & McCormick WC (1996) The pharmacologic management of pain and discomfort in persons with AIDS near the end of life: use of opioid analgesia in the hospice setting. *J Pain Symptom Manage* **11**(2): 88–94.
- Kinsella J & Booth MG (1991) Pain relief in burns: James Laing memorial essay 1990. *Burns* **17**(5): 391–5.
- Kinsella J & Rae CP (2008) Acute pain management in burns injury. In: *Clinical Pain Management: Acute Pain* 2nd edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
- Klein SM, Nielsen KC, Greengrass RA et al (2002) Ambulatory discharge after long-acting peripheral nerve blockade: 2382 blocks with ropivacaine. *Anesth Analg* **94**(1): 65–70.

- Klimek M, Ubben JF, Ammann J et al (2006) Pain in neurosurgically treated patients: a prospective observational study. *J Neurosurg* **104**(3): 350–9.
- Kober A, Scheck T, Greher M et al (2002) Prehospital analgesia with acupressure in victims of minor trauma: a prospective, randomized, double-blinded trial. *Anesth Analg* **95**(3): 723–7.
- Kooijman CM, Dijkstra PU, Geertzen JH et al (2000) Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. *Pain* **87**(1): 33–41.
- Kopecky EA, Jacobson S, Joshi P et al (2004) Systemic exposure to morphine and the risk of acute chest syndrome in sickle cell disease. *Clin Pharmacol Ther* **75**(3): 140–6.
- Krauss WC, Shah S & Thomas SH (2009) Fentanyl in the Out-of-Hospital Setting: Variables Associated with Hypotension and Hypoxemia. *J Emerg Med*. (Epub ahead of print).
- Kress JP, Pohlman AS, O'Connor MF et al (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* **342**(20): 1471–7.
- Kress JP, Gehlbach B, Lacy M et al (2003) The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med* **168**(12): 1457–61.
- Kress JP, Vinayak AG, Levitt J et al (2007) Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Crit Care Med* **35**(2): 365–71.
- Krishna S, Hughes LF & Lin SY (2003) Postoperative hemorrhage with nonsteroidal anti-inflammatory drug use after tonsillectomy: a meta-analysis. *Arch Otolaryngol Head Neck Surg* **129**(10): 1086–9.
- Kumar A, Deed JS, Bhasin B et al (2004) Comparison of the effect of diclofenac with hyoscine-N-butylbromide in the symptomatic treatment of acute biliary colic. *ANZ J Surg* **74**(7): 573–6.
- Kumar B, Kalita J, Kumar G et al (2009) Central poststroke pain: a review of pathophysiology and treatment. *Anesth Analg* **108**(5): 1645–57.
- Kumar V, Krone K & Mathieu A (2004) Neuraxial and sympathetic blocks in herpes zoster and postherpetic neuralgia: an appraisal of current evidence. *Reg Anesth Pain Med* **29**(5): 454–61.
- Kvarnstrom A, Karlsten R, Quiding H et al (2004) The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. *Acta Anaesthesiol Scand* **48**(4): 498–506.
- La Spina I, Porazzi D, Maggiolo F et al (2001) Gabapentin in painful HIV-related neuropathy: a report of 19 patients, preliminary observations. *Eur J Neurol* **8**(1): 71–5.
- Laerum E, Ommundsen OE, Gronseth JE et al (1995) Oral diclofenac in the prophylactic treatment of recurrent renal colic. A double-blind comparison with placebo. *Eur Urol* **28**(2): 108–11.
- Lambert AW, Dashfield AK, Cosgrove C et al (2001) Randomized prospective study comparing preoperative epidural and intraoperative perineural analgesia for the prevention of postoperative stump and phantom limb pain following major amputation. *Reg Anesth Pain Med* **26**(4): 316–21.
- Lampl C, Voelker M & Diener HC (2007) Efficacy and safety of 1,000mg effervescent aspirin: individual patient data meta-analysis of three trials in migraine headache and migraine accompanying symptoms. *J Neurol* **254**(6): 705–12.
- Lance JW, Anthony M, Spira PJ et al (1997) *Report of the Australian Association of Neurologists Ad Hoc Committee on the use of Opioids in the Management of Migraine*. Sydney, AAN.
- Lane PL, McLellan BA & Baggoley CJ (1989) Comparative efficacy of chlorpromazine and meperidine with dimenhydrinate in migraine headache. *Ann Emerg Med* **18**(4): 360–5.
- Lang T, Hager H, Funovits V et al (2007) Prehospital analgesia with acupressure at the Baihui and Hegu points in patients with radial fractures: a prospective, randomized, double-blind trial. *Am J Emerg Med* **25**(8): 887–93.
- Lange R & Lentz R (1995) Comparison ketoprofen, ibuprofen and naproxen sodium in the treatment of tension-type headache. *Drugs Exp Clin Res* **21**(3): 89–96.
- Larkin GL & Prescott JE (1992) A randomized, double-blind, comparative study of the efficacy of ketorolac tromethamine versus meperidine in the treatment of severe migraine. *Ann Emerg Med* **21**(8): 919–24.
- Larue F, Fontaine A & Colleau SM (1997) Underestimation and undertreatment of pain in HIV disease: multicentre study. *Bmj* **314**(7073): 23–8.
- Lau H, Patil NG & Lee F (2003) Randomized clinical trial of postoperative subfascial infusion with bupivacaine following ambulatory open mesh repair of inguinal hernia. *Dig Surg* **20**(4): 285–9.

- Laureano Filho JR, de Oliveira e Silva ED, Batista CI et al (2005) The influence of cryotherapy on reduction of swelling, pain and trismus after third-molar extraction: a preliminary study. *J Am Dent Assoc* **136**(6): 774–8.
- Laval G, Arvieux C, Stefani L et al (2006) Protocol for the treatment of malignant inoperable bowel obstruction: a prospective study of 80 cases at Grenoble University Hospital Center. *J Pain Symptom Manage* **31**(6): 502–12.
- Lavi R, Yarnitsky D, Rowe JM et al (2006) Standard vs atraumatic Whitacre needle for diagnostic lumbar puncture: a randomized trial. *Neurology* **67**(8): 1492–4.
- Law-Koune JD, Szekely B, Fermanian C et al (2005) Scalp infiltration with bupivacaine plus epinephrine or plain ropivacaine reduces postoperative pain after supratentorial craniotomy. *J Neurosurg Anesthesiol* **17**(3): 139–43.
- Lee C & Porter KM (2005) Prehospital management of lower limb fractures. *Emerg Med J* **22**(9): 660–3.
- Lee C, Gnanasegaram D & Maloba M (2005) Best evidence topic report. Rectal or intravenous non-steroidal anti-inflammatory drugs in acute renal colic. *Emerg Med J* **22**(9): 653–4.
- Lee HKH, Ting SM & Lau FL (2008) A randomised control trial comparing the efficacy of tramadol and paracetamol against ketorolac and paracetamol in the management of musculoskeletal pain in the emergency department. *Hong Kong J Emerg Med* **15**: 5–11.
- Leijon G & Boivie J (1989) Central post-stroke pain—a controlled trial of amitriptyline and carbamazepine. *Pain* **36**(1): 27–36.
- Levendoglu F, Ogun CO, Ozerbil O et al (2004) Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine* **29**(7): 743–51.
- Lewis D, Ashwal S, Hershey A et al (2004) Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology* **63**(12): 2215–24.
- Lewis PJ, Barrington SF, Marsden PK et al (1997) A study of the effects of sumatriptan on myocardial perfusion in healthy female migraineurs using <sup>13</sup>NH<sub>3</sub> positron emission tomography. *Neurology* **48**(6): 1542–50.
- Li Q, Chen N, Yang J et al (2009) Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*(2): CD006866.
- Limmroth V, Katsarava Z, Fritsche G et al (2002) Features of medication overuse headache following overuse of different acute headache drugs. *Neurology* **59**(7): 1011–4.
- Lin PL, Fan SZ, Huang CH et al (2008) Analgesic effect of lidocaine patch 5% in the treatment of acute herpes zoster: a double-blind and vehicle-controlled study. *Reg Anesth Pain Med* **33**(4): 320–5.
- Linde M, Elam M, Lundblad L et al (2004) Sumatriptan (5-HT<sub>1B/1D</sub>-agonist) causes a transient allodynia. *Cephalalgia* **24**(12): 1057–66.
- Linde K, Allais G, Brinkhaus B et al (2009) Acupuncture for tension-type headache. *Cochrane Database Syst Rev*(1): CD007587.
- Linneman PK, Terry BE & Burd RS (2000) The efficacy and safety of fentanyl for the management of severe procedural pain in patients with burn injuries. *J Burn Care Rehabil* **21**(6): 519–22.
- Lipton RB, Baggish JS, Stewart WF et al (2000) Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med* **160**(22): 3486–92.
- Lipton RB, Stewart WF, Stone AM et al (2000) Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial. *JAMA* **284**(20): 2599–605.
- Lipton RB, Bigal ME & Goadsby PJ (2004) Double-blind clinical trials of oral triptans vs other classes of acute migraine medication - a review. *Cephalalgia* **24**(5): 321–32.
- Litkowski LJ, Christensen SE, Adamson DN et al (2005) Analgesic efficacy and tolerability of oxycodone 5 mg/ibuprofen 400 mg compared with those of oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 7.5 mg/acetaminophen 500 mg in patients with moderate to severe postoperative pain: a randomized, double-blind, placebo-controlled, single-dose, parallel-group study in a dental pain model. *Clin Ther* **27**(4): 418–29.



- Loeser JD & Treede RD (2008) The Kyoto protocol of IASP Basic Pain Terminology. *Pain* **137**(3): 473–7.
- Long TD, Cathers TA, Twillman R et al (2001) Morphine-Infused silver sulfadiazine (MISS) cream for burn analgesia: a pilot study. *J Burn Care Rehabil* **22**(2): 118–23.
- Lopes T, Dias JS, Marcelino J et al (2001) An assessment of the clinical efficacy of intranasal desmopressin spray in the treatment of renal colic. *BJU Int* **87**(4): 322–5.
- Lopez S, Gros T, Bernard N et al (2003) Fascia iliaca compartment block for femoral bone fractures in prehospital care. *Reg Anesth Pain Med* **28**(3): 203–7.
- Lord B, Cui J & Kelly AM (2009) The impact of patient sex on paramedic pain management in the prehospital setting. *Am J Emerg Med* **27**(5): 525–9.
- Lord BA & Parsell B (2003) Measurement of pain in the prehospital setting using a visual analogue scale. *Prehosp Disaster Med* **18**(4): 353–8.
- Low DE, Desrosiers M, McSherry J et al (1997) A practical guide for the diagnosis and treatment of acute sinusitis. *Cmaj* **156** Suppl 6: S1–14.
- Ludot H, Berger J, Pichenot V et al (2008) Continuous peripheral nerve block for postoperative pain control at home: a prospective feasibility study in children. *Reg Anesth Pain Med* **33**(1): 52–6.
- Macedo A, Farre M & Banos JE (2006) A meta-analysis of the placebo response in acute migraine and how this response may be influenced by some of the characteristics of clinical trials. *Eur J Clin Pharmacol* **62**(3): 161–72.
- MacIver K, Lloyd DM, Kelly S et al (2008) Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. *Brain* **131**(Pt 8): 2181–91.
- MacLaren R, Forrest LK & Kiser TH (2007) Adjunctive dexmedetomidine therapy in the intensive care unit: a retrospective assessment of impact on sedative and analgesic requirements, levels of sedation and analgesia, and ventilatory and hemodynamic parameters. *Pharmacotherapy* **27**(3): 351–9.
- MacPherson RD, Woods D & Penfold J (2008) Ketamine and midazolam delivered by patient-controlled analgesia in relieving pain associated with burns dressings. *Clin J Pain* **24**(7): 568–71.
- Mahadevan M & Graff L (2000) Prospective randomized study of analgesic use for ED patients with right lower quadrant abdominal pain. *Am J Emerg Med* **18**(7): 753–6.
- Mahar PJ, Rana JA, Kennedy CS et al (2007) A randomized clinical trial of oral transmucosal fentanyl citrate versus intravenous morphine sulfate for initial control of pain in children with extremity injuries. *Pediatr Emerg Care* **23**(8): 544–8.
- Maizels M, Scott B, Cohen W et al (1996) Intranasal lidocaine for treatment of migraine: a randomized, double-blind, controlled trial. *JAMA* **276**(4): 319–21.
- Manley NM, Fitzpatrick RW, Long T et al (1997) A cost analysis of alfentanil+propofol vs morphine+midazolam for the sedation of critically ill patients. *Pharmacoeconomics* **12**(2 Pt 2): 247–55.
- Manterola C, Astudillo P, Losada H et al (2007) Analgesia in patients with acute abdominal pain. *Cochrane Database Syst Rev*(3): CD005660.
- Marcy PY, Palussiere J, Descamps B et al (2000) Percutaneous cementoplasty for pelvic bone metastasis. *Support Care Cancer* **8**(6): 500–3.
- Mariano ER, Afra R, Loland VJ et al (2009) Continuous interscalene brachial plexus block via an ultrasound-guided posterior approach: a randomized, triple-masked, placebo-controlled study. *Anesth Analg* **108**(5): 1688–94.
- Marinsek M, Kovacic D, Versnik D et al (2007) Analgesic treatment and predictors of satisfaction with analgesia in patients with acute undifferentiated abdominal pain. *Eur J Pain* **11**(7): 773–8.
- Marjoribanks J, Proctor ML & Farquhar C (2003) Nonsteroidal anti-inflammatory drugs for primary dysmenorrhoea. *Cochrane Database Syst Rev*(4): CD001751.
- Markiewicz MR, Brady MF, Ding EL et al (2008) Corticosteroids reduce postoperative morbidity after third molar surgery: a systematic review and meta-analysis. *J Oral Maxillofac Surg* **66**(9): 1881–94.
- Marret E, Flahault A, Samama CM et al (2003) Effects of postoperative, nonsteroidal, antiinflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized, controlled trials. *Anesthesiology* **98**(6): 1497–502.



- Martin E, Ramsay G, Mantz J et al (2003) The role of the alpha2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. *J Intensive Care Med* **18**(1): 29–41.
- Martinez-Zapata MJ, Roque M, Alonso-Coello P et al (2006) Calcitonin for metastatic bone pain. *Cochrane Database Syst Rev* **3**: CD003223.
- Marvez-Valls EG, Ernst AA, Gray J et al (1998) The role of betamethasone in the treatment of acute exudative pharyngitis. *Acad Emerg Med* **5**(6): 567–72.
- Masala S, Anselmetti GC, Marcia S et al (2008) Percutaneous vertebroplasty in multiple myeloma vertebral involvement. *J Spinal Disord Tech* **21**(5): 344–8.
- Mattila K & Hynynen M (2009) Day surgery in Finland: a prospective cohort study of 14 day-surgery units. *Acta Anaesthesiol Scand* **53**(4): 455–63.
- May A, Leone M, Afra J et al (2006) EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol* **13**(10): 1066–77.
- McCance-Katz EF, Rainey PM, Jatlow P et al (1998) Methadone effects on zidovudine disposition (AIDS Clinical Trials Group 262). *J Acquir Immune Defic Syndr Hum Retrovirol* **18**(5): 435–43.
- McCance-Katz EF, Rainey PM, Friedland G et al (2003) The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. *Clin Infect Dis* **37**(4): 476–82.
- McEachin CC, McDermott JT & Swor R (2002) Few emergency medical services patients with lower-extremity fractures receive prehospital analgesia. *Prehosp Emerg Care* **6**(4): 406–10.
- McGirt MJ, Parker SL, Wolinsky JP et al (2009) Vertebroplasty and kyphoplasty for the treatment of vertebral compression fractures: an evidenced-based review of the literature. *Spine J* **9**(6): 501–8.
- McLean SA, Maio RF & Domeier RM (2002) The epidemiology of pain in the prehospital setting. *Prehosp Emerg Care* **6**(4): 402–5.
- McLean SA, Domeier RM, DeVore HK et al (2004) The feasibility of pain assessment in the prehospital setting. *Prehosp Emerg Care* **8**(2): 155–61.
- McManus JG, Jr. & Sallee DR, Jr. (2005) Pain management in the prehospital environment. *Emerg Med Clin North Am* **23**(2): 415–31.
- McQuay HJ, Collins SL, Carroll D et al (2000) Radiotherapy for the palliation of painful bone metastases. *Cochrane Database Syst Rev*(2): CD001793.
- Medical Developments International (2001) *Methoxyflurane inhalation analgesic*. [http://www.medicaldev.com/pdf\\_files/Products\\_Pain\\_Relief\\_Healthcare\\_Professionals\\_Medical/Penthr ox\\_MSDS.pdf](http://www.medicaldev.com/pdf_files/Products_Pain_Relief_Healthcare_Professionals_Medical/Penthr ox_MSDS.pdf). Accessed March 2009.
- Meine TJ, Roe MT, Chen AY et al (2005) Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J* **149**(6): 1043–9.
- Melchart D, Linde K, Fischer P et al (2001) Acupuncture for idiopathic headache. *Cochrane Database Syst Rev*(1): CD001218.
- Mercadante S, Arcuri E, Ferrera P et al (2005) Alternative treatments of breakthrough pain in patients receiving spinal analgesics for cancer pain. *J Pain Symptom Manage* **30**(5): 485–91.
- Mercadante S, Villari P, Ferrera P et al (2007) Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. *Br J Cancer* **96**(12): 1828–33.
- Merskey H & Bogduk N, Eds (1994) *Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle, IASP Press.
- Miaskowski C, Cleary J, Burney R et al (2005) *Guideline for the management of cancer pain in adults and children*. Glenview (IL), American Pain Society (APS).
- Michael GE, Sporer KA & Youngblood GM (2007) Women are less likely than men to receive prehospital analgesia for isolated extremity injuries. *Am J Emerg Med* **25**(8): 901–6.
- Michaloliakou C, Chung F & Sharma S (1996) Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. *Anesth Analg* **82**(1): 44–51.
- Michigan Quality Improvement Consortium (2008) *Management of acute low back pain*. [http://www.guideline.gov/summary/summary.aspx?doc\\_id=12491&nbr=6422&ss=6&xl=999](http://www.guideline.gov/summary/summary.aspx?doc_id=12491&nbr=6422&ss=6&xl=999) Michigan Quality Improvement Consortium. Accessed May 2009.

- Migita RT, Klein EJ & Garrison MM (2006) Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. *Arch Pediatr Adolesc Med* **160**(1): 46–51.
- Migliardi JR, Armellino JJ, Friedman M et al (1994) Caffeine as an analgesic adjuvant in tension headache. *Clin Pharmacol Ther* **56**(5): 576–86.
- Mikkelsen S, Hilsted KL, Andersen PJ et al (2006) The effect of gabapentin on post-operative pain following tonsillectomy in adults. *Acta Anaesthesiol Scand* **50**(7): 809–15.
- Miller D, Livingstone V & Herbison P (2008) Interventions for relieving the pain and discomfort of screening mammography. *Cochrane Database Syst Rev*(1): CD002942.
- Miner JR, Kletti C, Herold M et al (2007) Randomized clinical trial of nebulized fentanyl citrate versus i.v. fentanyl citrate in children presenting to the emergency department with acute pain. *Acad Emerg Med* **14**(10): 895–8.
- Mitchell P, Wang JJ, Currie J et al (1998) Prevalence and vascular associations with migraine in older Australians. *Aust N Z J Med* **28**(5): 627–32.
- Moiniche S, Romsing J, Dahl JB et al (2003) Nonsteroidal antiinflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. *Anesth Analg* **96**(1): 68–77.
- Moore A, Edwards J, Barden J et al (2003) Bandolier's Little Book of Pain. In: edn. (eds). Oxford, Oxford University Press.
- Moore RA & McQuay HJ (1997) Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain* **69**(3): 287–94.
- Mora B, Giorni E, Dobrovits M et al (2006) Transcutaneous electrical nerve stimulation: an effective treatment for pain caused by renal colic in emergency care. *J Urol* **175**(5): 1737–41.
- Morad AH, Winters BD, Yaster M et al (2009) Efficacy of intravenous patient-controlled analgesia after supratentorial intracranial surgery: a prospective randomized controlled trial. *J Neurosurg* (E-pub ahead of print).
- Morley-Forster PK, Singh S, Angle P et al (2006) The effect of epidural needle type on postdural puncture headache: a randomized trial. *Can J Anaesth* **53**(6): 572–8.
- Morrissey LK, Shea JO, Kalish LA et al (2009) Clinical practice guideline improves the treatment of sickle cell disease vasoocclusive pain. *Pediatr Blood Cancer* **52**(3): 369–72.
- Moryl N, Coyle N & Foley KM (2008) Managing an acute pain crisis in a patient with advanced cancer: "this is as much of a crisis as a code". *JAMA* **299**(12): 1457–67.
- Moseley GL (2006) Graded motor imagery for pathologic pain: a randomized controlled trial. *Neurology* **67**(12): 2129–34.
- Mott J, Bucolo S, Cuttle L et al (2008) The efficacy of an augmented virtual reality system to alleviate pain in children undergoing burns dressing changes: a randomised controlled trial. *Burns* **34**(6): 803–8.
- Muellejans B, Lopez A, Cross MH et al (2004) Remifentanyl versus fentanyl for analgesia based sedation to provide patient comfort in the intensive care unit: a randomized, double-blind controlled trial [ISRCTN43755713]. *Crit Care* **8**(1): R1–R11.
- Mulroy MF, Larkin KL, Batra MS et al (2001) Femoral nerve block with 0.25% or 0.5% bupivacaine improves postoperative analgesia following outpatient arthroscopic anterior cruciate ligament repair. *Reg Anesth Pain Med* **26**(1): 24–9.
- Naja MZ, El-Rajab M, Kabalan W et al (2005) Pre-incisional infiltration for pediatric tonsillectomy: a randomized double-blind clinical trial. *Int J Pediatr Otorhinolaryngol* **69**(10): 1333–41.
- Namavar Jahromi B, Tartifzadeh A & Khabnadideh S (2003) Comparison of fennel and mefenamic acid for the treatment of primary dysmenorrhea. *Int J Gynaecol Obstet* **80**(2): 153–7.
- NCCN (2009) *NCCN Clinical Practice Guidelines in Oncology - V.1.2009: Adult Cancer Pain*. www.nccn.org National Comprehensive Cancer Network, Inc. Accessed January 2009.
- NCEPOD (2008) *Sickle Crisis? A report of the National Confidential Enquiry into Patient Outcome and Death (2008)*. www.ncepod.org.uk/2008report1/Downloads/Sickle\_summary.pdf NCEPOD. Accessed May 2009.

- Nekolaichuk CL, Fainsinger RL & Lawlor PG (2005) A validation study of a pain classification system for advanced cancer patients using content experts: the Edmonton Classification System for Cancer Pain. *Palliat Med* **19**(6): 466–76.
- Nemergut EC, Durieux ME, Missaghi NB et al (2007) Pain management after craniotomy. *Best Pract Res Clin Anaesthesiol* **21**(4): 557–73.
- Nettles RE, Keiffer TL, Cofrancesco J, Jr. et al (2005) Psychological distress and physical pain appear to have no short-term adverse impact on plasma HIV-1 RNA levels in patients on successful HAART. *HIV Clin Trials* **6**(5): 262–71.
- Neugebauer EA, Wilkinson RC, Kehlet H et al (2007) PROSPECT: a practical method for formulating evidence-based expert recommendations for the management of postoperative pain. *Surg Endosc* **21**(7): 1047–53.
- Newshan G & Lefkowitz M (2001) Transdermal fentanyl for chronic pain in AIDS: a pilot study. *J Pain Symptom Manage* **21**(1): 69–77.
- Nguyen A, Girard F, Boudreault D et al (2001) Scalp nerve blocks decrease the severity of pain after craniotomy. *Anesth Analg* **93**(5): 1272–6.
- NHS Quality Improvement Scotland (2004) *Best Practice Statement: The management of pain in patients with cancer*. <http://www.nhshealthquality.org/nhsqis/1368.html>. Accessed Jan 2009.
- Nicolas Torralba JA, Rigabert Montiel M, Banon Perez V et al (1999) [Intramuscular ketorolac compared to subcutaneous tramadol in the initial emergency treatment of renal colic]. *Arch Esp Urol* **52**(5): 435–8.
- Nicolodi M (1996) Differential sensitivity to morphine challenge in migraine sufferers and headache-exempt subjects. *Cephalalgia* **16**(5): 297–304.
- Nielsen JR, Pedersen KE, Dahlstrom CG et al (1984) Analgetic treatment in acute myocardial infarction. A controlled clinical comparison of morphine, nicomorphine and pethidine. *Acta Med Scand* **215**(4): 349–54.
- Nikandish R, Maghsoodi B, Khademi S et al (2008) Peritonsillar infiltration with bupivacaine and pethidine for relief of post-tonsillectomy pain: a randomised double-blind study. *Anaesthesia* **63**(1): 20–5.
- Nikolajsen L, Hansen CL, Nielsen J et al (1996) The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain* **67**(1): 69–77.
- Nikolajsen L, Ilkjaer S, Kroner K et al (1997) The influence of preamputation pain on postamputation stump and phantom pain. *Pain* **72**(3): 393–405.
- Nikolajsen L & Jensen TS (2001) Phantom limb pain. *Br J Anaesth* **87**(1): 107–16.
- Nikolajsen L, Finnerup NB, Kramp S et al (2006) A randomized study of the effects of gabapentin on postamputation pain. *Anesthesiology* **105**(5): 1008–15.
- Niland ML, Bonsu BK, Nuss KE et al (2006) A pilot study of 1 versus 3 days of dexamethasone as add-on therapy in children with streptococcal pharyngitis. *Pediatr Infect Dis J* **25**(6): 477–81.
- Nilsson Remahl AI, Ansjon R, Lind F et al (2002) Hyperbaric oxygen treatment of active cluster headache: a double-blind placebo-controlled cross-over study. *Cephalalgia* **22**(9): 730–9.
- Nicola P, Sorrentino F, Scaramucci L et al (2009) Pain syndromes in sickle cell disease: an update. *Pain Med* **10**(3): 470–80.
- Norrbrink C & Lundeberg T (2009) Tramadol in neuropathic pain after spinal cord injury: a randomized, double-blind, placebo-controlled trial. *Clin J Pain* **25**(3): 177–84.
- O'Connor A, Schug SA & Cardwell H (2000) A comparison of the efficacy and safety of morphine and pethidine as analgesia for suspected renal colic in the emergency setting. *J Accid Emerg Med* **17**(4): 261–4.
- O'Leary U, Puglia C, Friehling TD et al (1987) Nitrous oxide anesthesia in patients with ischemic chest discomfort: effect on beta-endorphins. *J Clin Pharmacol* **27**(12): 957–61.
- O'Neill WM & Sherrard JS (1993) Pain in human immunodeficiency virus disease: a review. *Pain* **54**(1): 3–14.
- Okomo U & Meremikwu MM (2007) Fluid replacement therapy for acute episodes of pain in people with sickle cell disease. *Cochrane Database Syst Rev*(2): CD005406.

- Oldman AD, Smith LA, McQuay HJ et al (2002) Pharmacological treatments for acute migraine: quantitative systematic review. *Pain* **97**(3): 247–57.
- Olkkola KT, Palkama VJ & Neuvonen PJ (1999) Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. *Anesthesiology* **91**(3): 681–5.
- Olsen JC, McGrath NA, Schwarz DG et al (2008) A double-blind randomized clinical trial evaluating the analgesic efficacy of ketorolac versus butorphanol for patients with suspected biliary colic in the emergency department. *Acad Emerg Med* **15**(8): 718–22.
- Olympia RP, Khine H & Avner JR (2005) Effectiveness of oral dexamethasone in the treatment of moderate to severe pharyngitis in children. *Arch Pediatr Adolesc Med* **159**(3): 278–82.
- Ong KS & Tan JM (2004) Preoperative intravenous tramadol versus ketorolac for preventing postoperative pain after third molar surgery. *Int J Oral Maxillofac Surg* **33**(3): 274–8.
- Osterberg A, Boivie J & Thuomas KA (2005) Central pain in multiple sclerosis—prevalence and clinical characteristics. *Eur J Pain* **9**(5): 531–42.
- Oxman MN, Levin MJ, Johnson GR et al (2005) A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* **352**(22): 2271–84.
- Ozbek C, Aygenc E, Tuna EU et al (2004) Use of steroids in the treatment of peritonsillar abscess. *J Laryngol Otol* **118**(6): 439–42.
- Pageler L, Katsarava Z, Diener HC et al (2008) Prednisone vs. placebo in withdrawal therapy following medication overuse headache. *Cephalalgia* **28**(2): 152–6.
- Paice JA, Shott S, Oldenburg FP et al (2000) Efficacy of a vibratory stimulus for the relief of HIV-associated neuropathic pain. *Pain* **84**(2-3): 291–6.
- Palmer JD, Sparrow OC & Iannotti F (1994) Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. *Neurosurgery* **35**(6): 1061–4.
- Pandey CK, Bose N, Garg G et al (2002) Gabapentin for the treatment of pain in guillain-barre syndrome: a double-blinded, placebo-controlled, crossover study. *Anesth Analg* **95**(6): 1719–23.
- Pandey CK, Raza M, Tripathi M et al (2005) The comparative evaluation of gabapentin and carbamazepine for pain management in Guillain-Barre syndrome patients in the intensive care unit. *Anesth Analg* **101**(1): 220–5.
- Parisod E (2002) Management of pain in a patient with Guillain-Barre syndrome. *ANZCA Bulletin* **11**: 53–61.
- Park G, Lane M, Rogers S et al (2007) A comparison of hypnotic and analgesic based sedation in a general intensive care unit. *Br J Anaesth* **98**(1): 76–82.
- Pasqualucci A, Pasqualucci V, Galla F et al (2000) Prevention of post-herpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone. *Acta Anaesthesiol Scand* **44**(8): 910–8.
- Passik SD, Kirsh KL, Donaghy KB et al (2006) Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clin J Pain* **22**(2): 173–81.
- Patterson DR, Ptacek JT, Carrougher GJ et al (1997) Lorazepam as an adjunct to opioid analgesics in the treatment of burn pain. *Pain* **72**(3): 367–74.
- Pavlakis N, Schmidt R & Stockler M (2005) Bisphosphonates for breast cancer. *Cochrane Database Syst Rev*(3): CD003474.
- Pavlin DJ, Chen C, Penalosa DA et al (2002) Pain as a factor complicating recovery and discharge after ambulatory surgery. *Anesth Analg* **95**(3): 627–34.
- Payen JF, Bru O, Bosson JL et al (2001) Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med* **29**(12): 2258–63.
- Payen JF, Chanques G, Mantz J et al (2007) Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology* **106**(4): 687–95.
- PBAC (2008) *Public summary document for Zoster Virus Vaccine Live Injection*. <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-zoster-mar08>. Accessed July 2009.

- Perkins FM & Kehlet H (2000) Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology* **93**(4): 1123–33.
- Perreault S, Choiniere M, du Souich PB et al (2001) Pharmacokinetics of morphine and its glucuronidated metabolites in burn injuries. *Ann Pharmacother* **35**(12): 1588–92.
- Peuckmann V, Ekholm O, Rasmussen NK et al (2009) Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. *Eur J Pain* **13**(5): 478–85.
- Pflugmacher R, Schleicher P, Schroder RJ et al (2006) Maintained pain reduction in five patients with multiple myeloma 12 months after treatment of the involved cervical vertebrae with vertebroplasty. *Acta Radiol* **47**(8): 823–9.
- Pinzur MS, Garla PG, Pluth T et al (1996) Continuous postoperative infusion of a regional anesthetic after an amputation of the lower extremity. A randomized clinical trial. *J Bone Joint Surg Am* **78**(10): 1501–5.
- Piscitelli SC, Kress DR, Bertz RJ et al (2000) The effect of ritonavir on the pharmacokinetics of meperidine and normeperidine. *Pharmacotherapy* **20**(5): 549–53.
- Pitsiu M, Wilmer A, Bodenham A et al (2004) Pharmacokinetics of remifentanyl and its major metabolite, remifentanyl acid, in ICU patients with renal impairment. *Br J Anaesth* **92**(4): 493–503.
- Pittler MH & Ernst E (1998) Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. *Am J Gastroenterol* **93**(7): 1131–5.
- Pollack CV, Jr. & Braunwald E (2008) 2007 update to the ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: implications for emergency department practice. *Ann Emerg Med* **51**(5): 591–606.
- Portenoy RK & Hagen NA (1990) Breakthrough pain: definition, prevalence and characteristics. *Pain* **41**(3): 273–81.
- Portenoy RK, Payne R, Coluzzi P et al (1999) Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain* **79**(2-3): 303–12.
- Porter K (2004) Ketamine in prehospital care. *Emerg Med J* **21**(3): 351–4.
- Potting CM, Uitterhoeve R, Op Reimer WS et al (2006) The effectiveness of commonly used mouthwashes for the prevention of chemotherapy-induced oral mucositis: a systematic review. *Eur J Cancer Care (Engl)* **15**(5): 431–9.
- Prakash S, Fatima T & Pawar M (2004) Patient-controlled analgesia with fentanyl for burn dressing changes. *Anesth Analg* **99**(2): 552–5.
- Prior MJ, Cooper KM, May LG et al (2002) Efficacy and safety of acetaminophen and naproxen in the treatment of tension-type headache. A randomized, double-blind, placebo-controlled trial. *Cephalalgia* **22**(9): 740–8.
- Proctor ML & Murphy PA (2001) Herbal and dietary therapies for primary and secondary dysmenorrhoea. *Cochrane Database Syst Rev*(3): CD002124.
- Proctor ML, Smith CA, Farquhar CM et al (2002) Transcutaneous electrical nerve stimulation and acupuncture for primary dysmenorrhoea. *Cochrane Database Syst Rev*(1): CD002123.
- PROSPECT (2009) *Procedure specific postoperative pain management*. <http://www.postoppain.org/frameset.htm>. Accessed May 2009.
- Puntillo KA, Miaskowski C, Kehrl K et al (1997) Relationship between behavioral and physiological indicators of pain, critical care patients' self-reports of pain, and opioid administration. *Crit Care Med* **25**(7): 1159–66.
- Puntillo KA, Stannard D, Miaskowski C et al (2002) Use of a pain assessment and intervention notation (P.A.I.N.) tool in critical care nursing practice: nurses' evaluations. *Heart Lung* **31**(4): 303–14.
- Puntillo KA, Morris AB, Thompson CL et al (2004) Pain behaviors observed during six common procedures: results from Thunder Project II. *Crit Care Med* **32**(2): 421–7.
- Quartero AO, Meineche-Schmidt V, Muris J et al (2005) Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*(2): CD003460.
- Rahimi SY, Vender JR, Macomson SD et al (2006) Postoperative pain management after craniotomy: evaluation and cost analysis. *Neurosurgery* **59**(4): 852–7.

- Ramacciotti AS, Soares BG & Atallah AN (2007) Dipyron for acute primary headaches. *Cochrane Database Syst Rev*(2): CD004842.
- Ramos L, de Las Heras JA, Sanchez S et al (2006) Medium-term results of percutaneous vertebroplasty in multiple myeloma. *Eur J Haematol* **77**(1): 7–13.
- Ranji SR, Goldman LE, Simel DL et al (2006) Do opiates affect the clinical evaluation of patients with acute abdominal pain? *JAMA* **296**(14): 1764–74.
- Rapoport AM, Mathew NT, Silberstein SD et al (2007) Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology* **69**(9): 821–6.
- Rasmussen PV, Sindrup SH, Jensen TS et al (2004) Symptoms and signs in patients with suspected neuropathic pain. *Pain* **110**(1-2): 461–9.
- Rawal N, Allvin R, Axelsson K et al (2002) Patient-controlled regional analgesia (PCRA) at home: controlled comparison between bupivacaine and ropivacaine brachial plexus analgesia. *Anesthesiology* **96**(6): 1290–6.
- Rees DC, Olujohungbe AD, Parker NE et al (2003) Guidelines for the management of the acute painful crisis in sickle cell disease. *Br J Haematol* **120**(5): 744–52.
- Reutens DC, Fatovich DM, Stewart-Wynne EG et al (1991) Is intravenous lidocaine clinically effective in acute migraine? *Cephalalgia* **11**(6): 245–7.
- Richardson C, Glenn S, Horgan M et al (2007) A prospective study of factors associated with the presence of phantom limb pain six months after major lower limb amputation in patients with peripheral vascular disease. *J Pain* **8**(10): 793–801.
- Richman JM, Joe EM, Cohen SR et al (2006) Bevel direction and postdural puncture headache: a meta-analysis. *Neurologist* **12**(4): 224–8.
- Richman PB, Allegra J, Eskin B et al (2002) A randomized clinical trial to assess the efficacy of intramuscular droperidol for the treatment of acute migraine headache. *Am J Emerg Med* **20**(1): 39–42.
- Rickard C, O'Meara P, McGrail M et al (2007) A randomized controlled trial of intranasal fentanyl vs intravenous morphine for analgesia in the prehospital setting. *Am J Emerg Med* **25**(8): 911–7.
- Riddington C & De Franceschi L (2002) Drugs for preventing red blood cell dehydration in people with sickle cell disease. *Cochrane Database Syst Rev*(4): CD003426.
- Rintala DH, Holmes SA, Courtade D et al (2007) Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Arch Phys Med Rehabil* **88**(12): 1547–60.
- Ripamonti C, Mercadante S, Groff L et al (2000) Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective randomized trial. *J Pain Symptom Manage* **19**(1): 23–34.
- Ripamonti CI, Easson AM & Gerdes H (2008) Management of malignant bowel obstruction. *Eur J Cancer* **44**(8): 1105–15.
- Roberts GC (2005) Post-craniotomy analgesia: current practices in British neurosurgical centres--a survey of post-craniotomy analgesic practices. *Eur J Anaesthesiol* **22**(5): 328–32.
- Roberts DM & Meyer-Witting M (2005) High-dose buprenorphine: perioperative precautions and management strategies. *Anaesth Intensive Care* **33**(1): 17–25.
- Robieux IC, Kellner JD, Coppes MJ et al (1992) Analgesia in children with sickle cell crisis: comparison of intermittent opioids vs. continuous intravenous infusion of morphine and placebo-controlled study of oxygen inhalation. *Pediatr Hematol Oncol* **9**(4): 317–26.
- Robinson BR, Mueller EW, Henson K et al (2008) An analgesia-delirium-sedation protocol for critically ill trauma patients reduces ventilator days and hospital length of stay. *J Trauma* **65**(3): 517–26.
- Rocha-Filho PA, Gherpelli JL, de Siqueira JT et al (2008) Post-craniotomy headache: characteristics, behaviour and effect on quality of life in patients operated for treatment of supratentorial intracranial aneurysms. *Cephalalgia* **28**(1): 41–8.
- Rogers PD (1997) Cimetidine in the treatment of acute intermittent porphyria. *Ann Pharmacother* **31**(3): 365–7.



- Rogovik AL & Goldman RD (2007) Prehospital use of analgesics at home or en route to the hospital in children with extremity injuries. *Am J Emerg Med* **25**(4): 400–5.
- Romsing J, Ostergaard D, Drozdiewicz D et al (2000) Diclofenac or acetaminophen for analgesia in paediatric tonsillectomy outpatients. *Acta Anaesthesiol Scand* **44**(3): 291–5.
- Rose KM, Carson AP, Sanford CP et al (2004) Migraine and other headaches: associations with Rose angina and coronary heart disease. *Neurology* **63**(12): 2233–9.
- Rossi S, Mataluni G, Codeca C et al (2009) Effects of levetiracetam on chronic pain in multiple sclerosis: results of a pilot, randomized, placebo-controlled study. *Eur J Neurol* **16**(3): 360–6.
- Rothrock SG, Green SM & Gorton E (1993) Atropine for the treatment of biliary tract pain: a double-blind, placebo-controlled trial. *Ann Emerg Med* **22**(8): 1324–7.
- Rowlison JC & Rawal N (2003) Postoperative pain guidelines—targeted to the site of surgery. *Reg Anesth Pain Med* **28**(4): 265–7.
- Rucklidge MW, Yentis SM & Paech MJ (2004) Synacthen Depot for the treatment of postdural puncture headache. *Anaesthesia* **59**(2): 138–41.
- Rusy LM, Houck CS, Sullivan LJ et al (1995) A double-blind evaluation of ketorolac tromethamine versus acetaminophen in pediatric tonsillectomy: analgesia and bleeding. *Anesth Analg* **80**(2): 226–9.
- Sacerdote P, Bianchi M, Manfredi B et al (1997) Effects of tramadol on immune responses and nociceptive thresholds in mice. *Pain* **72**(3): 325–30.
- Sacerdote P, Bianchi M, Gaspani L et al (2000) The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesth Analg* **90**(6): 1411–4.
- Safa-Tisseront V, Thormann F, Malassine P et al (2001) Effectiveness of epidural blood patch in the management of post-dural puncture headache. *Anesthesiology* **95**(2): 334–9.
- Safdar B, Degutis LC, Landry K et al (2006) Intravenous morphine plus ketorolac is superior to either drug alone for treatment of acute renal colic. *Ann Emerg Med* **48**(2): 173–81.
- Salman MA, Yucebas ME, Coskun F et al (2000) Day-case laparoscopy: a comparison of prophylactic opioid, NSAID or local anesthesia for postoperative analgesia. *Acta Anaesthesiol Scand* **44**(5): 536–42.
- Sandesc D, Lupei MI, Sirbu C et al (2005) Conventional treatment or epidural blood patch for the treatment of different etiologies of post dural puncture headache. *Acta Anaesthesiol Belg* **56**(3): 265–9.
- Scavone BM, Wong CA, Sullivan JT et al (2004) Efficacy of a prophylactic epidural blood patch in preventing post dural puncture headache in parturients after inadvertent dural puncture. *Anesthesiology* **101**(6): 1422–7.
- Schachtel BP, Fillingim JM, Lane AC et al (1991) Caffeine as an analgesic adjuvant. A double-blind study comparing aspirin with caffeine to aspirin and placebo in patients with sore throat. *Arch Intern Med* **151**(4): 733–7.
- Scherl ER & Wilson JF (1995) Comparison of dihydroergotamine with metoclopramide versus meperidine with promethazine in the treatment of acute migraine. *Headache* **35**(5): 256–9.
- Schifferdecker B & Spodick DH (2003) Nonsteroidal anti-inflammatory drugs in the treatment of pericarditis. *Cardiol Rev* **11**(4): 211–7.
- Schmader KE & Dworkin RH (2008) Natural history and treatment of herpes zoster. *J Pain* **9**(1 Suppl 1): S3–9.
- Schmelzeisen R & Frolich JC (1993) Prevention of postoperative swelling and pain by dexamethasone after operative removal of impacted third molar teeth. *Eur J Clin Pharmacol* **44**(3): 275–7.
- Schmidt A, Bjorkman S & Akeson J (2001) Preoperative rectal diclofenac versus paracetamol for tonsillectomy: effects on pain and blood loss. *Acta Anaesthesiol Scand* **45**(1): 48–52.
- Schurks M, Roskopf D, de Jesus J et al (2007) Predictors of acute treatment response among patients with cluster headache. *Headache* **47**(7): 1079–84.
- Schurr MJ, Gordon DB, Pellino TA et al (2004) Continuous local anesthetic infusion for pain management after outpatient inguinal herniorrhaphy. *Surgery* **136**(4): 761–9.
- Sebastian S, Johnston S, Geoghegan T et al (2004) Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction. *Am J Gastroenterol* **99**(10): 2051–7.



- Segerdahl M, Warren–Stomberg M, Rawal N et al (2008a) Clinical practice and routines for day surgery in Sweden: results from a nation-wide survey. *Acta Anaesthesiol Scand* **52**(1): 117–24.
- Segerdahl M, Warren–Stomberg M, Rawal N et al (2008b) Children in day surgery: clinical practice and routines. The results from a nation-wide survey. *Acta Anaesthesiol Scand* **52**(6): 821–8.
- Senturk M, Ozcan PE, Talu GK et al (2002) The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* **94**(1): 11–5.
- Shafraan SD, Tyring SK, Ashton R et al (2004) Once, twice, or three times daily famciclovir compared with aciclovir for the oral treatment of herpes zoster in immunocompetent adults: a randomized, multicenter, double-blind clinical trial. *J Clin Virol* **29**(4): 248–53.
- Shaiova L, Lapin J, Manco LS et al (2004) Tolerability and effects of two formulations of oral transmucosal fentanyl citrate (OTFC; ACTIQ) in patients with radiation-induced oral mucositis. *Support Care Cancer* **12**(4): 268–73.
- Shakespeare DT, Boggild M & Young C (2003) Anti-spasticity agents for multiple sclerosis. *Cochrane Database Syst Rev*(4): CD001332.
- Shapiro BA, Warren J, Ego AB et al (1995) Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. *Crit Care Med* **23**(9): 1596–600.
- Sharar SR, Bratton SL, Carrougher GJ et al (1998) A comparison of oral transmucosal fentanyl citrate and oral hydromorphone for inpatient pediatric burn wound care analgesia. *J Burn Care Rehabil* **19**(6): 516–21.
- Sharar SR, Carrougher GJ, Selzer K et al (2002) A comparison of oral transmucosal fentanyl citrate and oral oxycodone for pediatric outpatient wound care. *J Burn Care Rehabil* **23**(1): 27–31.
- Sharar SR, Carrougher GJ, Nakamura D et al (2007) Factors influencing the efficacy of virtual reality distraction analgesia during postburn physical therapy: preliminary results from 3 ongoing studies. *Arch Phys Med Rehabil* **88**(12 Suppl 2): S43–9.
- Sharma S, Prasad A, Nehru R et al (2002) Efficacy and tolerability of prochlorperazine buccal tablets in treatment of acute migraine. *Headache* **42**(9): 896–902.
- Shen MC, Lin HH, Lee SS et al (2004) Double-blind, randomized, acyclovir-controlled, parallel-group trial comparing the safety and efficacy of famciclovir and acyclovir in patients with uncomplicated herpes zoster. *J Microbiol Immunol Infect* **37**(2): 75–81.
- Sherman RA, Sherman CJ & Gall NG (1980) A survey of current phantom limb pain treatment in the United States. *Pain* **8**(1): 85–99.
- Shlay JC, Chaloner K, Max MB et al (1998) Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beinr Community Programs for Clinical Research on AIDS. *JAMA* **280**(18): 1590–5.
- Shrestha M, Singh R, Moreden J et al (1996) Ketorolac vs chlorpromazine in the treatment of acute migraine without aura. A prospective, randomized, double-blind trial. *Arch Intern Med* **156**(15): 1725–8.
- Siddall PJ, Taylor DA, McClelland JM et al (1999) Pain report and the relationship of pain to physical factors in the first 6 months following spinal cord injury. *Pain* **81**(1–2): 187–97.
- Siddall PJ, Yezierski RP & Loeser JD (2002) Taxonomy and epidemiology of spinal cord injury pain. In: *Spinal Cord Injury Pain: Assessment, Mechanisms, Management*. edn. Burchiel KJ and Yezierski RP (eds). Seattle, IASP Press. 23: 9–23.
- Siddall PJ & Middleton JW (2006) A proposed algorithm for the management of pain following spinal cord injury. *Spinal Cord* **44**(2): 67–77.
- Siddall PJ, Cousins MJ, Otte A et al (2006) Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* **67**(10): 1792–800.
- SIGN (2008) *SIGN 106: Control of pain in adults with cancer* www.sign.ac.uk Scottish Intercollegiate Guidelines Network (SIGN). Accessed March 2009.
- Silberstein SD (2000) Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* **55**(6): 754–62.

- Silberstein SD, Armellino JJ, Hoffman HD et al (1999) Treatment of menstruation-associated migraine with the nonprescription combination of acetaminophen, aspirin, and caffeine: results from three randomized, placebo-controlled studies. *Clin Ther* **21**(3): 475–91.
- Silberstein SD (2001) Headaches, pregnancy and lactation. In: *Drug therapy in pregnancy* 3rd edn. Yankowitz J and Niebyl JR (eds). Philadelphia, Lippincott, Williams and Wilkins. 231–46.
- Silberstein SD & Welch KM (2002) Painkiller headache. *Neurology* **59**(7): 972–4.
- Silberstein SD, Freitag FG, Rozen TD et al (2005) Tramadol/acetaminophen for the treatment of acute migraine pain: findings of a randomized, placebo-controlled trial. *Headache* **45**(10): 1317–27.
- Silfvast T & Saarnivaara L (2001) Comparison of alfentanil and morphine in the prehospital treatment of patients with acute ischaemic-type chest pain. *Eur J Emerg Med* **8**(4): 275–8.
- Silver S, Gano D & Gerretsen P (2008) Acute treatment of paediatric migraine: a meta-analysis of efficacy. *J Paediatr Child Health* **44**(1-2): 3–9.
- Sim KM, Hwang NC, Chan YW et al (1996) Use of patient-controlled analgesia with alfentanil for burns dressing procedures: a preliminary report of five patients. *Burns* **22**(3): 238–41.
- Simpson DM, Dorfman D, Olney RK et al (1996) Peptide T in the treatment of painful distal neuropathy associated with AIDS: results of a placebo-controlled trial. The Peptide T Neuropathy Study Group. *Neurology* **47**(5): 1254–9.
- Simpson DM, Olney R, McArthur JC et al (2000) A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. *Neurology* **54**(11): 2115–9.
- Simpson DM, Brown S & Tobias J (2008) Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology* **70**(24): 2305–13.
- Singapore Ministry of Health (2003) *Cancer pain*. [http://www.moh.gov.sg/mohcorp/uploadedFiles/Publications/Guidelines/Clinical\\_Practice\\_Guidelines/Cancer%20Pain.pdf](http://www.moh.gov.sg/mohcorp/uploadedFiles/Publications/Guidelines/Clinical_Practice_Guidelines/Cancer%20Pain.pdf) Singapore Ministry of Health. Accessed March 2009.
- Singer AJ & Stark MJ (2000) Pretreatment of lacerations with lidocaine, epinephrine, and tetracaine at triage: a randomized double-blind trial. *Acad Emerg Med* **7**(7): 751–6.
- Singer EJ, Zorilla C, Fahy-Chandon B et al (1993) Painful symptoms reported by ambulatory HIV-infected men in a longitudinal study. *Pain* **54**(1): 15–9.
- Singh A, Alter HJ & Zaia B (2008) Does the Addition of Dexamethasone to Standard Therapy for Acute Migraine Headache Decrease the Incidence of Recurrent Headache for Patients Treated in the Emergency Department? A Meta-analysis and Systematic Review of the Literature. *Acad Emerg Med*. **15**(12): 1223–1233.
- Slatkin NE & Rhiner M (2003) Topical ketamine in the treatment of mucositis pain. *Pain Med* **4**(3): 298–303.
- Slatkin NE, Xie F, Messina J et al (2007) Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol* **5**(7): 327–34.
- Smith GA, Strausbaugh SD, Harbeck-Weber C et al (1997) Comparison of topical anesthetics with lidocaine infiltration during laceration repair in children. *Clin Pediatr (Phila)* **36**(1): 17–23.
- Smith J & Thompson JM (1995) Phantom limb pain and chemotherapy in pediatric amputees. *Mayo Clin Proc* **70**(4): 357–64.
- Smith TR (2002) Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. *Headache* **42**(3): 175–7.
- Snir N, Moskovitz B, Nativ O et al (2008) Papaverine hydrochloride for the treatment of renal colic: an old drug revisited. A prospective, randomized study. *J Urol* **179**(4): 1411–4.
- Soliman HM, Melot C & Vincent JL (2001) Sedative and analgesic practice in the intensive care unit: the results of a European survey. *Br J Anaesth* **87**(2): 186–92.
- Somdas MA, Senturk M, Ketenci I et al (2004) Efficacy of bupivacaine for post-tonsillectomy pain: a study with the intra-individual design. *Int J Pediatr Otorhinolaryngol* **68**(11): 1391–5.
- Stapelfeldt C, Lobo EP, Brown R et al (2005) Intraoperative clonidine administration to neurosurgical patients. *Anesth Analg* **100**(1): 226–32.

- Stearns L, Boortz-Marx R, Du Pen S et al (2005) Intrathecal drug delivery for the management of cancer pain: a multidisciplinary consensus of best clinical practices. *J Support Oncol* **3**(6): 399–408.
- Steiner TJ & Fontebasso M (2002) Headache. *BMJ* **325**(7369): 881–6.
- Steiner TJ, Lange R & Voelker M (2003) Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. *Cephalalgia* **23**(1): 59–66.
- Steiner TJ, MacGregor EA & Davies PTG (2007) British Association for the Study of Headache: Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache: Writing Committee. [http://216.25.100.131/upload/NS\\_BASH/BASH\\_guidelines\\_2007.pdf](http://216.25.100.131/upload/NS_BASH/BASH_guidelines_2007.pdf). Accessed July 2009.
- Stiell IG, Dufour DG, Moher D et al (1991) Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. *Ann Emerg Med* **20**(11): 1201–5.
- Stoelting RK & Dierdorf SF, Eds (1993) *Anaesthesia and co-existing disease*. New York, Churchill Livingstone.
- Stokman MA, Spijkervet FK, Boezen HM et al (2006) Preventive intervention possibilities in radiotherapy- and chemotherapy-induced oral mucositis: results of meta-analyses. *J Dent Res* **85**(8): 690–700.
- Stoneham MD & Walters FJ (1995) Post-operative analgesia for craniotomy patients: current attitudes among neuroanaesthetists. *Eur J Anaesthesiol* **12**(6): 571–5.
- Strassels SA, Chen C & Carr DB (2002) Postoperative analgesia: economics, resource use, and patient satisfaction in an urban teaching hospital. *Anesth Analg* **94**(1): 130–7.
- Strupp M, Brandt T & Muller A (1998) Incidence of post-lumbar puncture syndrome reduced by reinserting the stylet: a randomized prospective study of 600 patients. *J Neurol* **245**(9): 589–92.
- Strupp M, Schueler O, Straube A et al (2001) "Atraumatic" Sprotte needle reduces the incidence of post-lumbar puncture headaches. *Neurology* **57**(12): 2310–2.
- Stubhaug A, Romundstad L, Kaasa T et al (2007) Methylprednisolone and ketorolac rapidly reduce hyperalgesia around a skin burn injury and increase pressure pain thresholds. *Acta Anaesthesiol Scand* **51**(9): 1138–46.
- Sudheer PS, Logan SW, Terblanche C et al (2007) Comparison of the analgesic efficacy and respiratory effects of morphine, tramadol and codeine after craniotomy. *Anaesthesia* **62**(6): 555–60.
- Sudlow C & Warlow C (2002a) Epidural blood patching for preventing and treating post-dural puncture headache. *Cochrane Database Syst Rev*(2): CD001791.
- Sudlow C & Warlow C (2002b) Posture and fluids for preventing post-dural puncture headache. *Cochrane Database Syst Rev*(2): CD001790.
- Sutherland S & Matthews DC (2003) Emergency management of acute apical periodontitis in the permanent dentition: a systematic review of the literature. *J Can Dent Assoc* **69**(3): 160.
- Suthisang C, Poolsup N, Kittikulsuth W et al (2007) Efficacy of low-dose ibuprofen in acute migraine treatment: systematic review and meta-analysis. *Ann Pharmacother* **41**(11): 1782–91.
- Suzuki M, Haraguti S, Sugimoto K et al (2006) Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* **105**(1): 111–9.
- Svenson JE & Abernathy MK (2007) Ketamine for prehospital use: new look at an old drug. *Am J Emerg Med* **25**(8): 977–80.
- Swenson JD, Bay N, Loose E et al (2006) Outpatient management of continuous peripheral nerve catheters placed using ultrasound guidance: an experience in 620 patients. *Anesth Analg* **103**(6): 1436–43.
- Symon DN & Russell G (1995) Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. *Arch Dis Child* **72**(1): 48–50.
- Sze WM, Shelley M, Held I et al (2004) Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. *Cochrane Database Syst Rev*(2): CD004721.
- Tagliati M, Grinnell J, Godbold J et al (1999) Peripheral nerve function in HIV infection: clinical, electrophysiologic, and laboratory findings. *Arch Neurol* **56**(1): 84–9.

- Tai Q, Kirshblum S, Chen B et al (2002) Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial. *J Spinal Cord Med* **25**(2): 100–5.
- Taivainen T, Pitkanen M, Tuominen M et al (1993) Efficacy of epidural blood patch for postdural puncture headache. *Acta Anaesthesiol Scand* **37**(7): 702–5.
- Tanen DA, Miller S, French T et al (2003) Intravenous sodium valproate versus prochlorperazine for the emergency department treatment of acute migraine headaches: a prospective, randomized, double-blind trial. *Annals of Emergency Medicine* **41**(6): 847–53.
- Tanskanen P, Kytta J & Randell T (1999) Patient-controlled analgesia with oxycodone in the treatment of postcraniotomy pain. *Acta Anaesthesiol Scand* **43**(1): 42–5.
- Tarumi Y, Pereira J & Watanabe S (2002) Methadone and fluconazole: respiratory depression by drug interaction. *J Pain Symptom Manage* **23**(2): 148–53.
- Terheggen MA, Wille F, Borel Rinkes IH et al (2002) Paravertebral blockade for minor breast surgery. *Anesth Analg* **94**(2): 355–9.
- Tfelt-Hansen P (2008) Triptans vs other drugs for acute migraine. Are there differences in efficacy? A comment. *Headache* **48**(4): 601–5.
- Thew M & Paech MJ (2008) Management of postdural puncture headache in the obstetric patient. *Curr Opin Anaesthesiol* **21**(3): 288–92.
- Thibault M, Girard F, Moumdjian R et al (2007) Craniotomy site influences postoperative pain following neurosurgical procedures: a retrospective study. *Can J Anaesth* **54**(7): 544–8.
- Thomas M, Del Mar C & Glasziou P (2000) How effective are treatments other than antibiotics for acute sore throat? *Br J Gen Pract* **50**(459): 817–20.
- Thomas SH, Rago O, Harrison T et al (2005) Fentanyl trauma analgesia use in air medical scene transports. *J Emerg Med* **29**(2): 179–87.
- Thomas SH & Shewakramani S (2008) Prehospital trauma analgesia. *J Emerg Med* **35**(1): 47–57.
- Thompson DR (2001) Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol* **96**(4): 1266–72.
- Thune A, Baker RA, Saccone GT et al (1990) Differing effects of pethidine and morphine on human sphincter of Oddi motility. *Br J Surg* **77**(9): 992–5.
- Todd KH, Ducharme J, Choiniere M et al (2007) Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. *J Pain* **8**(6): 460–6.
- Toivonen J, Permi J & Rosenberg PH (2001) Effect of preincisional ilioinguinal and iliohypogastric nerve block on postoperative analgesic requirement in day-surgery patients undergoing herniorrhaphy under spinal anaesthesia. *Acta Anaesthesiol Scand* **45**(5): 603–7.
- Tosun Z, Esmoğlu A & Coruh A (2008) Propofol-ketamine vs propofol-fentanyl combinations for deep sedation and analgesia in pediatric patients undergoing burn dressing changes. *Paediatr Anaesth* **18**(1): 43–7.
- TRACsa (2008) *Whiplash-associated disorders information for health practitioners*. [www.tracsa.org.au/resources-whiplashassociated\\_disorders\\_information\\_for\\_health\\_practitioners](http://www.tracsa.org.au/resources-whiplashassociated_disorders_information_for_health_practitioners). Accessed July 2009.
- Tramèr MR, Williams JE, Carroll D et al (1998) Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiol Scand* **42**(1): 71–9.
- Trautmann E, Lackschewitz H & Kroner-Herwig B (2006) Psychological treatment of recurrent headache in children and adolescents—a meta-analysis. *Cephalalgia* **26**(12): 1411–26.
- Tripathi M & Kaushik S (2000) Carbamezapine for pain management in Guillain-Barre syndrome patients in the intensive care unit. *Crit Care Med* **28**(3): 655–8.
- Trucco M, Meineri P & Ruiz L (2005) Preliminary results of a withdrawal and detoxification therapeutic regimen in patients with probable chronic migraine and probable medication overuse headache. *J Headache Pain* **6**(4): 334–7.
- Tsao JC, Dobalian A, Myers CD et al (2005) Pain and use of complementary and alternative medicine in a national sample of persons living with HIV. *J Pain Symptom Manage* **30**(5): 418–32.

- Tsao JC, Stein JA & Dobalian A (2007) Pain, problem drug use history, and aberrant analgesic use behaviors in persons living with HIV. *Pain* **133**(1-3): 128–37.
- Tsao JC & Soto T (2009) Pain in persons living with HIV and comorbid psychological and substance use disorders. *Clin J Pain* **25**(4): 307–12.
- Tseng YF, Chen CH & Yang YH (2005) Rose tea for relief of primary dysmenorrhea in adolescents: a randomized controlled trial in Taiwan. *J Midwifery Womens Health* **50**(5): e51–7.
- Turnbull DK & Shepherd DB (2003) Post-dural puncture headache: pathogenesis, prevention and treatment. *Br J Anaesth* **91**(5): 718–29.
- Tyring SK, Beutner KR, Tucker BA et al (2000) Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. *Arch Fam Med* **9**(9): 863–9.
- Ugur MB, Yilmaz M, Altunkaya H et al (2008) Effects of intramuscular and peritonsillar injection of tramadol before tonsillectomy: a double blind, randomized, placebo-controlled clinical trial. *Int J Pediatr Otorhinolaryngol* **72**(2): 241–8.
- Uki J, Mendoza T, Cleeland CS et al (1998) A brief cancer pain assessment tool in Japanese: the utility of the Japanese Brief Pain Inventory–BPI-J. *J Pain Symptom Manage* **16**(6): 364–73.
- Ulger O, Topuz S, Bayramlar K et al (2009) Effectiveness of phantom exercises for phantom limb pain: a pilot study. *J Rehabil Med* **41**(7): 582–4.
- van Beers EJ, van Tuijn CF, Nieuwkerk PT et al (2007) Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. *Am J Hematol* **82**(11): 955–60.
- van der Westhuijzen AJ, Becker PJ, Morkel J et al (2005) A randomized observer blind comparison of bilateral facial ice pack therapy with no ice therapy following third molar surgery. *Int J Oral Maxillofac Surg* **34**(3): 281–6.
- van Kooten F, Oedit R, Bakker SL et al (2008) Epidural blood patch in post dural puncture headache: a randomised, observer-blind, controlled clinical trial. *J Neurol Neurosurg Psychiatry* **79**(5): 553–8.
- van Twillert B, Bremer M & Faber AW (2007) Computer-generated virtual reality to control pain and anxiety in pediatric and adult burn patients during wound dressing changes. *J Burn Care Res* **28**(5): 694–702.
- van Vliet JA, Bahra A, Martin V et al (2003) Intranasal sumatriptan in cluster headache: randomized placebo-controlled double-blind study. *Neurology* **60**(4): 630–3.
- van Wijck AJ, Opstelten W, Moons KG et al (2006) The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. *Lancet* **367**(9506): 219–24.
- Vassiliadis J, Hitos K & Hill CT (2002) Factors influencing prehospital and emergency department analgesia administration to patients with femoral neck fractures. *Emerg Med (Fremantle)* **14**(3): 261–6.
- Vegas-Bustamante E, Mico-Llorens J, Gargallo-Albiol J et al (2008) Efficacy of methylprednisolone injected into the masseter muscle following the surgical extraction of impacted lower third molars. *Int J Oral Maxillofac Surg* **37**(3): 260–3.
- Verchere E, Grenier B, Mesli A et al (2002) Postoperative pain management after supratentorial craniotomy. *J Neurosurg Anesthesiol* **14**(2): 96–101.
- Vergnion M, Degesves S, Garcet L et al (2001) Tramadol, an alternative to morphine for treating posttraumatic pain in the prehospital situation. *Anesth Analg* **92**(6): 1543–6.
- Vernon H, McDermaid CS & Hagino C (1999) Systematic review of randomized clinical trials of complementary/alternative therapies in the treatment of tension-type and cervicogenic headache. *Complement Ther Med* **7**(3): 142–55.
- Vestergaard K, Andersen G, Gottrup H et al (2001) Lamotrigine for central poststroke pain: a randomized controlled trial. *Neurology* **56**(2): 184–90.
- Vickers ER & Punnia-Moorthy A (1992) A clinical evaluation of three topical anaesthetic agents. *Aust Dent J* **37**(4): 267–70.

- Vickers ER, Cousins MJ, Walker S et al (1998) Analysis of 50 patients with atypical odontalgia. A preliminary report on pharmacological procedures for diagnosis and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **85**(1): 24–32.
- Vickers ER, Cousins M & Nicholas M (2000) Facial pain: a biopsychosocial problem. *Medicine Today*: 42–48.
- Viggiano M, Badetti C, Roux F et al (1998) [Controlled analgesia in a burn patient: fentanyl sparing effect of clonidine]. *Ann Fr Anesth Reanim* **17**(1): 19–26.
- Vilholm OJ, Cold S, Rasmussen L et al (2008a) The postmastectomy pain syndrome: an epidemiological study on the prevalence of chronic pain after surgery for breast cancer. *Br J Cancer* **99**(4): 604–10.
- Vilholm OJ, Cold S, Rasmussen L et al (2008b) Effect of levetiracetam on the postmastectomy pain syndrome. *Eur J Neurol* **15**(8): 851–7.
- Vilholm OJ, Cold S, Rasmussen L et al (2009) Sensory function and pain in a population of patients treated for breast cancer. *Acta Anaesthesiol Scand* **53**(6): 800–6.
- Vinson DR (2002) Treatment patterns of isolated benign headache in US emergency departments. *Ann Emerg Med* **39**(3): 215–22.
- Visser WA, Gielen MJ & Giele JL (2006) Continuous positive airway pressure breathing increases the spread of sensory blockade after low-thoracic epidural injection of lidocaine. *Anesth Analg* **102**(1): 268–71.
- Visser EJ & Goucke CR (2008) Acute Pain and Medical Disorders. In: *Clinical Pain Management: Acute Pain* 2nd edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
- Vogl D, Rosenfeld B, Breitbart W et al (1999) Symptom prevalence, characteristics, and distress in AIDS outpatients. *J Pain Symptom Manage* **18**(4): 253–62.
- Von Hoff DD, Kuhn JG, Burris HA, 3rd et al (2008) Does intraosseous equal intravenous? A pharmacokinetic study. *Am J Emerg Med* **26**(1): 31–8.
- Walker J, MacCallum M, Fischer C et al (2006) Sedation using dexmedetomidine in pediatric burn patients. *J Burn Care Res* **27**(2): 206–10.
- Wall GC & Heyneman CA (1999) Calcitonin in phantom limb pain. *Ann Pharmacother* **33**(4): 499–501.
- Wallny T, Hess L, Seuser A et al (2001) Pain status of patients with severe haemophilic arthropathy. *Haemophilia* **7**(5): 453–8.
- Wambebe C, Khamofu H, Momoh JA et al (2001) Double-blind, placebo-controlled, randomised cross-over clinical trial of NIPRISAN in patients with Sickle Cell Disorder. *Phytomedicine* **8**(4): 252–61.
- Wang SJ, Silberstein SD & Young WB (1997) Droperidol treatment of status migrainosus and refractory migraine. *Headache* **37**(6): 377–82.
- Ward ME, Radburn J & Morant S (1997) Evaluation of intravenous tramadol for use in the prehospital situation by ambulance paramedics. *Prehosp Disaster Med* **12**(2): 158–62.
- Ward TN & Levin M (2004) Facial pain. In: *Principles and Practice of Pain Medicine* 2nd edn. Warfield CA and Bajwa ZH (eds). New York, McGraw-Hill.
- Wasiak J & Cleland H (2007) Lidocaine for pain relief in burn injured patients. *Cochrane Database Syst Rev*(3): CD005622.
- Wasiak J, Cleland H & Campbell F (2008) Dressings for superficial and partial thickness burns. *Cochrane Database Syst Rev*(4): CD002106.
- Watkins N (2006) Paediatric prehospital analgesia in Auckland. *Emerg Med Australas* **18**(1): 51–6.
- Watson N, Nimmo WS, Christian J et al (2000) Relief of sore throat with the anti-inflammatory throat lozenge flurbiprofen 8.75 mg: a randomised, double-blind, placebo-controlled study of efficacy and safety. *Int J Clin Pract* **54**(8): 490–6.
- Watson R & Leslie K (2001) Nerve blocks versus subcutaneous infiltration for stereotactic frame placement. *Anesth Analg* **92**(2): 424–7.
- Weil K, Hooper L, Afzal Z et al (2007) Paracetamol for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database Syst Rev*(3): CD004487.
- Weill A, Kobaiter H & Chiras J (1998) Acetabulum malignancies: technique and impact on pain of percutaneous injection of acrylic surgical cement. *Eur Radiol* **8**(1): 123–9.



- Weiner DL, Hibberd PL, Betit P et al (2003) Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease. *JAMA* **289**(9): 1136–42.
- Weiss P & Ritz R (1988) [Analgesic effect and side-effects of buprenorphine in acute coronary heart disease. A randomized double-blind comparison with morphine]. *Anasth Intensivther Notfallmed* **23**(6): 309–12.
- Welling A (2007) A randomised controlled trial to test the analgesic efficacy of topical morphine on minor superficial and partial thickness burns in accident and emergency departments. *Emerg Med J* **24**(6): 408–12.
- Weltz CR, Greengrass RA & Lyerly HK (1995) Ambulatory surgical management of breast carcinoma using paravertebral block. *Ann Surg* **222**(1): 19–26.
- Wenzel RG, Sarvis CA & Krause ML (2003) Over-the-counter drugs for acute migraine attacks: literature review and recommendations. *Pharmacotherapy* **23**(4): 494–505.
- Whipple JK, Lewis KS, Quebbeman EJ et al (1995) Analysis of pain management in critically ill patients. *Pharmacotherapy* **15**(5): 592–9.
- White LJ, Cooper JD, Chambers RM et al (2000) Prehospital use of analgesia for suspected extremity fractures. *Prehosp Emerg Care* **4**(3): 205–8.
- Whitley RJ, Weiss H, Gnann JW, Jr. et al (1996) Acyclovir with and without prednisone for the treatment of herpes zoster. A randomized, placebo-controlled trial. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *Ann Intern Med* **125**(5): 376–83.
- Wiffen P, Collins S, McQuay H et al (2005) Anticonvulsant drugs for acute and chronic pain. *Cochrane Database Syst Rev*(3): CD001133.
- Wilder-Smith CH, Hill LT & Laurent S (2005) Postamputation pain and sensory changes in treatment-naïve patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo. *Anesthesiology* **103**(3): 619–28.
- Wildgaard K, Ravn J & Kehlet H (2009) Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. *Eur J Cardiothorac Surg* **36**(1): 170–80.
- Williams BA, Kentor ML, Vogt MT et al (2003) Femoral-sciatic nerve blocks for complex outpatient knee surgery are associated with less postoperative pain before same-day discharge: a review of 1,200 consecutive cases from the period 1996–1999. *Anesthesiology* **98**(5): 1206–13.
- Williams BA, Kentor ML, Vogt MT et al (2004) Economics of nerve block pain management after anterior cruciate ligament reconstruction: potential hospital cost savings via associated postanesthesia care unit bypass and same-day discharge. *Anesthesiology* **100**(3): 697–706.
- Wilson JA, Nimmo AF, Fleetwood-Walker SM et al (2008) A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. *Pain* **135**(1-2): 108–18.
- Winner P, Ricalde O, Le Force B et al (1996) A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol* **53**(2): 180–4.
- Wong R & Wiffen PJ (2002) Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database Syst Rev*(2): CD002068.
- Wood MJ, Johnson RW, McKendrick MW et al (1994) A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *N Engl J Med* **330**(13): 896–900.
- Wood MJ, Kay R, Dworkin RH et al (1996) Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. *Clin Infect Dis* **22**(2): 341–7.
- Woollard M, Whitfield R, Smith K et al (2004) Less is less: a randomised controlled trial comparing cautious and rapid nalbuphine dosing regimens. *Emerg Med J* **21**(3): 362–4.
- Worster A & Richards C (2005) Fluids and diuretics for acute ureteric colic. *Cochrane Database Syst Rev*(3): CD004926.
- Wright SW, Norris RL & Mitchell TR (1992) Ketorolac for sickle cell vaso-occlusive crisis pain in the emergency department: lack of a narcotic-sparing effect. *Ann Emerg Med* **21**(8): 925–8.
- Wu CL, Tella P, Staats PS et al (2002) Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial. *Anesthesiology* **96**(4): 841–8.



- Wu CL, Rowlingson AJ, Cohen SR et al (2006) Gender and post-dural puncture headache. *Anesthesiology* **105**(3): 613–8.
- Wu CL, Agarwal S, Tella PK et al (2008) Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. *Anesthesiology* **109**(2): 289–96.
- Wu YW, Hui YL & Tan PP (1994) Experience of epidural blood patch for post-dural puncture headache. *Acta Anaesthesiol Sin* **32**(2): 137–40.
- Yang H, Liu CZ, Chen X et al (2008) Systematic review of clinical trials of acupuncture-related therapies for primary dysmenorrhea. *Acta Obstet Gynecol Scand* **87**(11): 1114–22.
- Yaster M, Tobin JR, Billett C et al (1994) Epidural analgesia in the management of severe vaso-occlusive sickle cell crisis. *Pediatrics* **93**(2): 310–5.
- Yencilek F, Aktas C, Goktas C et al (2008) Role of papaverine hydrochloride administration in patients with intractable renal colic: randomized prospective trial. *Urology* **72**(5): 987–90.
- Yesilbalkan OU, Ozkutuk N, Karadakovan A et al (2008) Validity and reliability of the Edmonton Symptom Assessment Scale in Turkish cancer patients. *Turkish Journal of Cancer*. **38**(2): 62–67.
- Youle M & Osio M (2007) A double-blind, parallel-group, placebo-controlled, multicentre study of acetyl L-carnitine in the symptomatic treatment of antiretroviral toxic neuropathy in patients with HIV-1 infection. *HIV Med* **8**(4): 241–50.
- Yucel A, Ozyalcin S, Talu GK et al (1999) Intravenous administration of caffeine sodium benzoate for postdural puncture headache. *Reg Anesth Pain Med* **24**(1): 51–4.
- Yuen KK, Shelley M, Sze WM et al (2006) Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev*(4): CD006250.
- Zakrzewska JM & Harrison SH (2003) Facial pain. In: *Clinical Pain Management, Chronic Pain* edn. Jensen TS, Wilson PR and Rice ASC (eds). London, Arnold. 481–504.
- Zaric D, Boysen K, Christiansen J et al (2004) Continuous popliteal sciatic nerve block for outpatient foot surgery—a randomized, controlled trial. *Acta Anaesthesiol Scand* **48**(3): 337–41.
- Zeppetella G & Ribeiro MD (2006) Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database Syst Rev*(1): CD004311.
- Zeppetella G (2008) Opioids for cancer breakthrough pain: a pilot study reporting patient assessment of time to meaningful pain relief. *J Pain Symptom Manage* **35**(5): 563–7.
- Zhang WY & Li Wan Po A (1998) Efficacy of minor analgesics in primary dysmenorrhoea: a systematic review. *Br J Obstet Gynaecol* **105**(7): 780–9.
- Zhu X, Proctor M, Bensoussan A et al (2007) Chinese herbal medicine for primary dysmenorrhoea. *Cochrane Database Syst Rev*(4): CD005288.
- Ziaei S, Zakeri M & Kazemnejad A (2005) A randomised controlled trial of vitamin E in the treatment of primary dysmenorrhoea. *BJOG* **112**(4): 466–9.
- Zipursky A, Robieux IC, Brown EJ et al (1992) Oxygen therapy in sickle cell disease. *Am J Pediatr Hematol Oncol* **14**(3): 222–8.

# 10. THE PAEDIATRIC PATIENT

## 10.1 DEVELOPMENTAL NEUROBIOLOGY OF PAIN

Following birth, the neural pathways required for nociception are functional and cortical responses to noxious stimuli such as blood tests can be demonstrated in even the most premature neonate (Slater et al, 2006). However, as significant functional and structural changes occur in nociceptive pathways during the postnatal period, pain does not evoke the same pattern of activity in the infant and adult central nervous system (Fitzgerald & Walker, 2009). The expression of a number of molecules and channels involved in nociception are developmentally regulated, there are changes in the distribution and density of many important receptors, and the levels and effects of several neurotransmitters alter significantly during early life (Fitzgerald, 2005).

Although C-fibre polymodal nociceptors are mature in their pattern of firing at birth and are capable of being activated in the periphery by exogenous stimuli, their central synaptic connections in the dorsal horn are initially immature. However, 'wind up' can be produced by relatively low intensity A-fibre (rather than C-fibre) stimulation, as A-beta fibres initially extend up into laminae I and II and only withdraw once C fibres have matured. This overlap means there is less discrimination between noxious and non-noxious stimuli, and as the receptive fields of dorsal horn neurones are large, peripheral stimuli can excite a greater number of central neurones. In addition, descending inhibitory pathways and inhibitory networks in the dorsal horn are not fully mature in early development. Therefore, rather than neonates being less sensitive to painful stimuli as was once thought, the relative excess of excitatory mechanisms and delayed maturation of inhibitory mechanisms produce more generalised and exaggerated reflex responses to lower intensity stimuli during early development (Fitzgerald, 2005). Although the underlying mechanisms may differ, nociceptive pathways can be sensitised by painful stimuli in early life, as demonstrated by a reduction in reflex thresholds in neonates following repeated heel lance (Fitzgerald et al, 1988 **Level IV**) and infants following abdominal surgery (Andrews & Fitzgerald, 2002 **Level IV**).

Factors affecting the pharmacokinetic profile of analgesic drugs (body water and fat composition, plasma protein binding, hepatic metabolism and renal function) change rapidly during the first weeks of life. Postnatal changes in the pharmacokinetic profile of a number of analgesic drugs (eg morphine and paracetamol [acetaminophen]) resulted in significant age-related changes in dose requirements during infancy and childhood (Bouwmeester et al, 2004; Palmer et al, 2008; Prins et al, 2008). In addition, changes in nociceptive processing may have significant effects on the pharmacodynamic response to analgesics in early life (Walker, 2008). Therefore, developmental age and not just weight should be considered when calculating analgesic dosing. Laboratory studies have demonstrated postnatal changes in the mechanism of action, analgesic efficacy, and side-effect profile of analgesics that can inform subsequent clinical trials (Nandi & Fitzgerald, 2005; Walker, 2008; Fitzgerald & Walker, 2009). In addition, prolonged reductions in synaptic activity by general anaesthetics and analgesics can produce unexpected neurotoxic effects, such as apoptosis, in the developing nervous system (Mellon et al, 2007), although the clinical significance of these findings requires further research.

## 10.2 LONG-TERM CONSEQUENCES OF EARLY PAIN AND INJURY

Significant reorganisation of synaptic connections occurs in the postnatal period. Activity within sensory pathways is required for normal development, but abnormal or excessive activity related to pain and injury during the neonatal period may alter normal development and produce persistent changes in sensitivity that outlast the injury (Fitzgerald & Walker, 2009).

In clinical studies, neonatal intensive care and surgery have been associated with: alterations in pain-related behaviour (Grunau et al, 2006 **Level IV**); enhanced response to future noxious stimuli (Taddio & Katz, 2005 **Level III-2**); increased perioperative analgesic requirements when subsequent surgery is performed (Peters, Koot, de Boer et al, 2003 **Level III-2**); and long-term changes in sensory processing (Hermann et al, 2006; Walker et al, 2009 **Level III-2**). In laboratory studies, the degree of long-term change varies with the type and severity of injury (Fitzgerald & Walker, 2009). Inflammation, full thickness skin wounds, and skin incision produce prolonged alterations in sensitivity and in the response to future injury in the absence of any visible persistent peripheral injury. By contrast, allodynia following nerve injury is less apparent in early life (Howard et al, 2005; Moss et al, 2007). These findings are of considerable importance as pain and injury in neonates may have effects on nociceptive processing that differ in mechanism and duration from that experienced by older children and adults.

Importantly, analgesia at the time of the initial painful stimulus may modulate long-term effects. Male neonates circumcised without analgesia showed an increased behavioural pain response to immunisation several months later, but this was reduced if local anaesthetic was used prior to the procedure (Taddio et al, 1995 **Level III-2**). Infants who had undergone surgery in the neonatal period with perioperative morphine did not show any increase in later response to immunisation when compared with infants without significant previous pain experience (Peters, Koot, de Boer et al, 2003 **Level III-2**). Further research is required to determine the most developmentally appropriate and effective analgesic regimen for modulating the effects of early pain and injury.

### Key messages

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Following birth, even the most premature neonate responds to nociceptive stimuli (**U**).
- In early development more generalised reflex nociceptive responses occur in response to lower intensity stimuli (**U**).
- Due to the increased plasticity of the developing nervous system, pain and injury in early life may have adverse long-term consequences (**U**).

## 10.3 PAEDIATRIC PAIN ASSESSMENT

Pain assessment is a prerequisite to optimal pain management in children and should involve a clinical interview with the child and/or their parent/carer, physical assessment and use of an age- and context-appropriate pain intensity measurement tool (Howard et al, 2008). However, pain in hospitalised children is often assessed infrequently (Johnston et al, 2007; Twycross, 2007; Taylor et al, 2008). Improvements in pain management and in patient, parent and staff satisfaction have been associated with regular assessment and measurement of pain (Treadwell

et al, 2002). Adoption of written guidelines or algorithms for pain management improved both assessment and management of pain in neonates and children (Falanga et al, 2006 **Level IV**; Gharavi et al, 2007). As in adults, other domains of pain (eg location, quality) and the multidimensional nature of the pain experience (eg concomitant emotional distress, coping style of the child, previous pain experience) and parental expectations (Lioffi et al, 2007) should be incorporated into overall assessment. Clinical trials have focussed on assessment of pain intensity and further evaluation and validation of tools for measuring global satisfaction, adverse effects and physical recovery following paediatric acute pain are required (McGrath et al, 2008).

Verbal self-report is considered to be the best measure of pain in adults. Although self-report should be used in children whenever possible, it is not always possible as a child's understanding of pain and their ability to describe it changes with age. Therefore measurement tools must be appropriate to the different stages of their development. Examples of acute pain measurement tools are listed in Tables 10.1, 10.2 and 10.3.

### 10.3.1 Pain assessment in neonates

A large number of scales have been developed for neonates and infants, encompassing a number of surrogate measures (eg physical signs such as increased heart rate) or behavioural responses (eg facial characteristics and cry). Choice of the most appropriate tool depends on the age of the infant, the stimulus (eg procedural or postoperative pain) and the purpose of the measurement (eg clinical care or research).

#### **Physiological measures**

Changes in physiological parameters associated with procedural interventions are assumed to indicate the presence of pain, including: increases in heart rate, respiratory rate, blood pressure, intracranial pressure, cerebral blood flow and palmar sweating; and decreases in oxygen saturation, transcutaneous carbon dioxide tension and vagal tone (Sweet & McGrath 1998). As these changes are reduced by analgesia, they are useful surrogate outcome measures of pain, but as their sensitivity and specificity will also be influenced by concurrent clinical conditions (eg increased heart rate due to sepsis) and other factors (eg distress, environment, movement), they should be used in conjunction with other behavioural measures (Howard et al, 2008 **Level IV**). Cortical pain responses to noxious stimuli can be demonstrated in premature neonates (Bartocci et al, 2006 **Level III-3**; Slater et al, 2006 **Level III-3**). This technique is currently utilised solely as a research tool, but the level of cortical activity has been shown to correlate with the premature infant pain profile (PIPP) score (Slater et al, 2008 **Level IV**).

#### **Behavioural measures**

Noxious stimuli produce a series of behavioural responses in neonates and infants that can be used as surrogate measures of pain (McGrath, 1998; Gaffney et al, 2003) including crying, changes in facial activity, movement of torso and limbs, consolability and sleep state. Crying can be described in terms of its presence or absence, duration and amplitude or pitch.

The reliability and validity of behavioural measures is best established for short sharp pain associated with procedural interventions such as heel stick. The specificity and sensitivity of the response can be influenced by previous interventions and handling (Holsti et al, 2006), motor development, and manifestations of other states of distress (eg hunger and fatigue), particularly in neonates requiring intensive care (Ranger et al, 2007).

Ten facial actions are included in the Neonatal Facial Coding Scale (NFCS), which was originally validated for procedural pain in neonates and infants (see Table 10.1) (Grunau & Craig, 1987).

A reduced scale with five items (brow bulge, eye squeeze, nasolabial furrow, horizontal mouth stretch and taut tongue) has been found to be a sensitive and valid measure of postoperative pain in infants ages 0 to 18 months (Peters, Koot, Grunau et al, 2003). In neonatal intensive care, facial actions were found to be more reliable than physiological measures for evaluating pain responses (Stevens, Franck et al, 2007), but may be dampened in preterm neonates (Holsti & Grunau, 2007) in whom cortical responses to pain have been demonstrated in the absence of a change in facial expression (Slater et al, 2008).

Many neonatal pain assessment tools have not been rigorously evaluated, but the following are widely used (McNair et al, 2004; Howard et al, 2008) (see Table 10.1 and 10.2):

- acute procedural pain — PIPP, Cries, Requires oxygen, Increased vital signs, Expression, Sleeplessness (CRIES), NFCS;
- postoperative pain — PIPP, CRIES; and
- intensive care — COMFORT.

### 10.3.2 Observational and behavioural measures in infants and children

Many scales incorporate both physiological and behavioural parameters to determine an overall pain score and may result in more comprehensive measurement (Franck et al, 2000). Some examples are included in Table 10.2 but a wider range of measures, their strengths and limitations, and issues of testing reliability and validity have been reviewed (Johnston et al, 2002; von Baeyer & Spagrud, 2007; McGrath et al, 2008). In infants and young children, behavioural items that predicted analgesic demand in the postoperative period were crying, facial expression, posture of the trunk, posture of the legs and motor restlessness (Buttner & Finke, 2000).

There is still no single gold standard for pain assessment as requirements vary with the age and developmental stage of the child, the type of pain (eg procedural vs postoperative), and the context (eg clinical utility versus research reliability). Based on current data the following observational / behavioural measurement tools were recommended for pain measurement in infants 1 year and above (McGrath et al, 2008 **Level I**), children and adolescents (von Baeyer & Spagrud, 2007 **Level I**) (see Table 10.2).

- acute procedural pain — Face Legs Activity Cry and Consolability (FLACC) and Children's Hospital of Eastern Ontario Pain Scale (CHEOPS);
- postoperative pain — FLACC;
- postoperative pain managed by parents at home — Parents Postoperative Pain Measure (PPPM); and
- intensive care — COMFORT.

### 10.3.3 Self-report in children and adolescents

Self-report of pain is preferred when feasible, and is usually possible by 4 years of age, but this will depend on the cognitive and emotional maturity of the child. Scales for self-report need to consider the child's age, ability to differentiate levels of intensity, and to separate the emotional from the physical components of pain. It is important that a measurement tool be used regularly and uniformly within each centre as staff familiarity and ease of use are major factors in the successful implementation of a pain management strategy. At 4 to 5 years of age, children can differentiate 'more', 'less' or 'the same', and can use a Faces Pain Scale (Figure 10.1) if it is explained appropriately and is a relatively simple scale with a limited number of options. At this age, children have some capacity to appraise current pain and match it to previous experience but they are more likely to choose the extremes of the scale

(Hicks et al, 2001). In scales anchored with smiling or tearful faces, pain may be confused with other emotional states such as happiness, sadness or anxiety (Champion et al, 1998).

Between 7 and 10 years of age children develop skills with measurement, classification and seriation (ie putting things in ascending or descending order). The upper end of the scale is less static than in adults as it will change with the individual child's ability to objectify, label and remember previous pain experiences (Gaffney et al, 2003). It is not until 10 to 12 years of age that children can clearly discriminate the sensory intensity and the affective emotional components of pain and report them independently (McGrath et al, 1996). Verbally competent children aged 12 years and above can understand and use the McGill Pain Questionnaire (Gaffney et al, 2003).

Six self-report tools have well-established evidence of reliability and validity (Pieces of Hurt tool; Faces Pain Scale and Faces Pain Scale-Revised; Oucher; Wong-Baker Faces; visual analogue scale [VAS]) for acute pain assessment in children (over 3 years) and adolescents (Stinson et al, 2006 **Level I**; McGrath et al, 2008 **Level I**). Although chronological age may not always be an accurate indicator of developmental stage, the following general age ranges are suggested (see also Howard et al, 2008):

- 3 to 4 years — Pieces of Hurt (Poker Chip) tool;
- 4 to 12 years — Faces Pain Scale-Revised; and
- over 8 years — 0 to 100 VAS.

### 10.3.4 Children with cognitive impairment

In children with cognitive impairment and/or communication problems, assessment of pain is difficult and can contribute to inadequate analgesia. Neonates at risk for neurological impairment required more procedural interventions in intensive care, but received less analgesia (Stevens et al, 2003) and may be perceived as being less responsive to painful stimuli (Breau et al, 2006; Stevens, McGrath et al, 2007). A retrospective chart review of children who had undergone spine fusion surgery, found that pain was assessed less frequently in cognitively impaired children and that they received less analgesia (Malviya et al, 2001 **Level IV**). Another group found that while cognitively impaired children received less analgesia during surgery, they received comparable amounts and types of analgesics as cognitively intact children in the postoperative period (Koh et al, 2004 **Level III-2**).

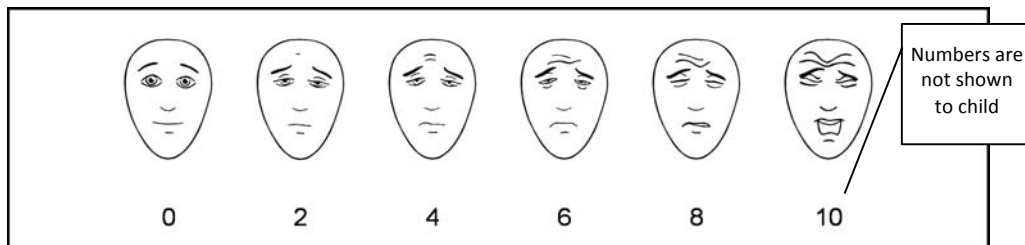
Specific tools have been developed for cognitively impaired children (Howard et al, 2008). Behaviours reported by caregivers to be associated with potentially painful stimuli and that discriminate these from distressful or calm events, have been compiled in the revised Non-Communicating Children's Pain Checklist (NCCPC-R) (Breau, McGrath et al, 2002), which also has a postoperative version (NCCPC-PV) (Breau, Finley et al, 2002). The Paediatric Pain Profile (PPP) also rates 20 behaviours to assess pain in children with severe neurological disability (Hunt et al, 2004). A revised FLACC scale, which incorporates specific descriptors and parent-identified behaviours for individual children, has also been developed for cognitively impaired children (Malviya et al, 2006).

## Key messages

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Pain assessment and measurement are important components of paediatric pain management (U).
- Pain measurement tools are available for children of all ages (U).
- Pain measurement tools must be matched to the age and development of the child, be appropriate for the clinical context and be explained and used consistently (U).

**Figure 10.1** Faces Pain Scale — Revised



Note: The full-size version of the Faces Pain Scale (FPS-R), together with instructions for administration (available in many languages), are freely available for non-commercial clinical and research use from [www.painsourcebook.ca](http://www.painsourcebook.ca).

Source: FPS-R; Hicks et al 2001; adapted from Bieri et al (1990).

Copyright ©2001 International Association for the Study of Pain (IASP). Used with permission from IASP.

**Table 10.1** Acute pain intensity measurement tools — neonates

Scale	Indicators	Score	Utility
Premature Infant Pain Profile (PIPP) (Stevens et al 1996)	gestational age behavioural state heart rate oxygen saturation brow bulge eye squeeze nasolabial furrow	each scored on 4-point scale (0,1,2,3); total score 0–21; 6 or less = minimal pain; >12 = moderate to severe pain	preterm and term neonates; procedural pain; postoperative pain in term neonates
Neonatal Infant Pain Scale (NIPS) (Lawrence et al 1993)	facial expression cry breathing patterns arms legs state of arousal	each scored on 2 (0,1) or 3-point (0,1,2) scale; total score 0–7	preterm and term neonates; procedural pain



Scale	Indicators	Score	Utility
Neonatal Facial Coding Scale (NFCS) (Grunau & Craig 1987; Johnston et al 1993)	brow bulge deep nasolabial fold eyes squeezed shut open mouth taut tongue horizontal mouth stretch vertical mouth stretch pursing of lips chin quiver tongue protrusion	presence or absence of action during discrete time intervals scored; total score 0–10	preterm to 4 months; procedural pain
Children's Revised Impact of Event Scale (CRIES) (Krechel & Bildner 1995)	cries requires oxygen increased vital signs (heart rate/blood pressure) expression sleeplessness	each scored 3-point scale (0,1,2); total score 0–10	preterm and term neonates; postoperative pain

Further details available in Howard et al, 2008 and Bandstra & Chambers, 2008

**Table 10.2 Composite scales for infants and children**

Scale	Indicators	Score	Utility
Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (McGrath et al 1985)	cry facial expression verbal expression torso position touch leg position	each scored as 0, 1, 2 or 3; total score 4–18	1–7 years; postoperative pain procedural pain
Face Legs Activity Cry and Consolability (FLACC) (Merkel et al 1997)	face legs activity cry consolability	each scored on 3-point scale (0,1,2); total score 0–10	young children; postoperative pain
COMFORT scale (Ambuel et al 1992)	alertness calmness/agitation respiratory response physical movement muscle tone facial expression mean arterial pressure heart rate	total score 8–40	newborn to adolescent; distress in paediatric intensive care unit; postoperative pain 0–3 year olds (Van Dijk et al 2000)

Further details available in Howard et al, 2008 and Bandstra & Chambers, 2008.

**Table 10.3 Self-report tools for children**

Scale	Components	Anchors	Utility
Poker Chip Tool (Hester 1979)	4 chips = pieces of 'hurt'	± white 'no pain' chip; 1 chip = 'a little hurt'; 4 chips = 'most hurt you could ever have'	4–8 years
Faces Pain Scale - Revised (Hicks et al 2001)	6 line drawn faces	graded faces with neutral anchors (ie no smiling or tears)	> 4 years
Wong-Baker Faces Pain Rating Scale (Wong & Baker 1988)	6 cartoon faces	faces graded from smiling to tears	3–8 years; postoperative and procedural pain
Coloured Analogue Scale (McGrath et al, 1996)	modification of 10 cm horizontal VAS; scored 0–10 in 0.25 increments	gradations in colour (white to dark red) and area (progressively wider tetragon); labels 'no pain' to 'most pain'	5 years and above

Further details available in Howard et al, 2008 and Bandstra & Chambers, 2008.

## 10.4 MANAGEMENT OF PROCEDURAL PAIN

Procedure-related pain is a frequent and distressing component of medical care for children, their families and hospital staff (Cummings et al, 1996 **Level IV**; Ljungman et al, 1996 **Level IV**; Gale et al, 2004 **Level III-2**). Repeated interventions are often required and the level of pain and memory of the first procedure affect the pain (Weisman et al, 1998) and distress (Chen et al, 2000) associated with subsequent procedures.

The aim of procedural pain management is to minimise physical discomfort, pain, movement and psychological disturbance without compromising patient safety. Management may include analgesic agents via different routes of administration, concurrent sedation or general anaesthesia, and non-pharmacological methods. The choice of technique will depend on the age and previous experience of the child, the type of procedure, the expected intensity and duration of pain, the treatment environment and available resources (Murat et al, 2003). Sedation alone must not be seen as an alternative to appropriate analgesia, particularly when pain is expected after completion of the procedure. Further information is available from the Association of Paediatric Anaesthetists (Howard et al, 2008), Royal Australasian College of Physicians (Royal Australasian College of Physicians, 2005) and the Italian Society of Neonatology (Lago et al, 2009).

## 10.4.1 Procedural pain in the neonate

### ***Blood sampling and intravenous cannulation***

Neonates in intensive care often require frequent blood sampling. Heel lance produced more pain than venipuncture (Shah & Ohlsson, 2007 **Level I**), but fewer attempts were required and less pain behaviour was exhibited with spring loaded automated devices for heel lance (Shah et al, 2003 **Level II**). Topical local anaesthesia reduced the physiological and behavioural response to venipuncture (Taddio et al, 1998 **Level I**). Sucrose (Stevens et al, 2004 **Level I**) and breastfeeding (Shah et al, 2006 **Level I**) reduced pain responses to venipuncture. The optimal dose of sucrose, its efficacy and the safety of repeated doses have not been determined. Background morphine infusions in ventilated neonates had limited efficacy for acute procedural interventions in intensive care (Bellu et al, 2008 **Level I**). IV morphine bolus with topical amethocaine provided more effective analgesia than morphine or amethocaine alone for peripheral central venous line placement in preterm neonates (Taddio et al, 2006 **Level II**).

### ***Lumbar puncture***

EMLA® (eutectic mixture of lignocaine and prilocaine) reduced the physiological and behavioural response with needle insertion for lumbar puncture in preterm and term neonates (Kaur et al, 2003 **Level II**).

### ***Urine sampling***

EMLA® reduced pain scores in neonates and young infants undergoing suprapubic aspiration (Nahum et al, 2007 **Level II**). Transurethral catheterisation after the urethral application of 2% lignocaine (lidocaine) was less painful than suprapubic aspiration after the topical application of EMLA® (Kozar et al, 2006 **Level II**). Sucrose reduced pain scores during transurethral catheterisation in neonates (Rogers et al, 2006 **Level III-2**).

### ***Ocular examination for retinopathy of prematurity***

Screening for retinopathy of prematurity in neonates is painful (Belda et al, 2004 **Level IV**). Topical local anaesthesia reduced pain scores (Marsh et al, 2005 **Level II**), and sucrose in addition to topical local anaesthetic had a greater effect (Gal et al, 2005 **Level II**, Mitchell et al, 2004 **Level II**).

## 10.4.2 Procedural pain in infants and older children

### ***Venipuncture and intravenous cannulation***

Venipuncture causes pain and significant distress in many children (Humphrey et al, 1992 **Level IV**). Topical local anaesthesia reduced pain associated with IV cannulation, but amethocaine was more effective than EMLA® and had more rapid onset (Lander et al, 2006 **Level I**). Lignocaine administered by iontophoresis (Zempsky et al, 2004 **Level II**) or liposomal lignocaine 4% cream (Eidelman, Weiss, Lau et al, 2005 **Level I**) had a more rapid onset and was as effective as EMLA® for venipuncture and IV cannulation. A needleless device that delivers 1% buffered lignocaine under high pressure from a compressed carbon dioxide gas cartridge was effective within 3 minutes, and produced more effective skin anaesthesia than EMLA® (Jimenez et al, 2006 **Level II**).

Vapocoolant sprays have variably been reported to be ineffective (Costello et al, 2006 **Level II**) or reduce pain (Farion et al, 2008 **Level II**) associated with IV cannulation, and to be as effective as topical amethocaine in children undergoing venipuncture (Davies & Molloy, 2006 **Level III-1**).

Nitrous oxide (N<sub>2</sub>O) reduced pain and anxiety associated with IV cannulation (Henderson et al, 1990 **Level II**). Use of 70% N<sub>2</sub>O in oxygen was more effective than 50% (Furuya et al, 2009 **Level II**). The combination of N<sub>2</sub>O and topical EMLA® for IV cannulation was more effective in reducing

pain scores and increased satisfaction when compared with either method alone (Hee et al, 2003 **Level III-2**; Ekblom et al, 2005 **Level III-2**).

Non-pharmacological strategies such as distraction, hypnosis and combined cognitive-behavioural interventions reduced needle-related pain and distress in children and adolescents (Uman et al, 2006 **Level 1**). Positioning the child vertically and being held by a parent reduced distress in children during IV cannulation (Sparks et al, 2007 **Level II**). Combination of hypnosis with EMLA<sup>®</sup> reduced pain, anxiety and distress associated with venipuncture, and was more effective than either intervention alone (Liossi et al, 2009 **Level II**).

### **Lumbar puncture and bone marrow aspiration**

Addition of fentanyl to propofol sedation improved analgesia (Nagel et al, 2008 **Level II**) and satisfaction (Cechvala et al, 2008 **Level II**) in children with leukaemia undergoing bone marrow aspirations and lumbar punctures. Oral transmucosal fentanyl reduced pain scores (Schechter et al, 1995 **Level IV**). Oral or IV ketamine was associated with less distress during lumbar puncture and /or bone marrow aspiration in children with cancer (Tobias et al, 1992 **Level III-3**; Evans et al, 2005 **Level IV**). For some patients, general anaesthesia is preferred to sedation, and has been associated with less distress and pain for children requiring multiple procedures (Crock et al, 2003 **Level III-3**) (see also 10.1.8). Topical anaesthesia with EMLA<sup>®</sup> was effective for lumbar puncture (Juarez Gimenez et al, 1996 **Level II**). Anticipatory and procedure-related anxiety and pain was reduced when hypnosis was combined with EMLA<sup>®</sup> (Liossi et al, 2006 **Level II**).

### **Urethral catheterisation and micturating cystourethrogram**

Local anaesthetic lubricant reduced pain when administered 10 minutes (Gerard et al, 2003 **Level II**) but not 2 to 3 minutes (Vaughan et al, 2005 **Level II**) prior to urethral catheterisation.

N<sub>2</sub>O reduced pain and distress in children undergoing urethral catheterisation for micturating cystourethrogram investigation (Zier et al, 2007 **Level III-2**). Preparing the child for the procedure using a story booklet or play preparation reduced distress (Phillips et al, 1998 **Level III-2**; Butler et al, 2005 **Level II**), as did hypnosis (Butler et al, 2005 **Level II**).

### **Chest drain removal**

IV morphine, topical anaesthesia with EMLA<sup>®</sup>, and N<sub>2</sub>O reduced pain but did not provide adequate analgesia for chest drain removal in children (Rosen et al, 2000 **Level III-2**; Bruce et al, 2006 **Level III-2**).

### **Nasogastric tube insertion**

Nasogastric tube insertion causes pain and distress in children (Juhl & Connors, 2005 **Level IV**). In adults, topical anaesthesia of the nose and pharynx reduced pain associated with nasogastric tube insertion (Singer & Konia, 1999 **Level II**; Wolfe et al, 2000 **Level II**) and nebulised lignocaine after intranasal (IN) lignocaine gel was more effective than sprayed lignocaine (Spektor et al, 2000 **Level II**). In children aged 1 to 5 years a benefit of nebulised lignocaine could not be confirmed, but the study was terminated early due to the distress associated with nebulisation (Babl et al, 2009 **Level II**).

### **Burns dressings**

Children who have sustained burn injuries often require repeated, painful and distressing dressing changes. Considerable interindividual variation occurs and analgesia needs to be titrated to effect as requirements differ according to the surface area involved, the location, and the child's previous experiences. It is important to consider that one-third will have post-traumatic stress disorder (Stoddard et al, 2006 **Level IV**).

Opioids are frequently required, and in the early phases general anaesthesia may be preferred. Oral transmucosal (Robert et al, 2003 **Level II**) or IN fentanyl (Borland et al, 2005

**Level II**), oral hydromorphone, morphine and oxycodone reduced pain associated with dressing changes (Sharar et al, 1998 **Level II**; Sharar et al, 2002 **Level II**).

Non-pharmacological strategies such as distraction, preparation, parental presence and hypnosis may be effective. Music (Frattianne et al, 2001 **Level II**), virtual reality games (Das et al, 2005 **Level II**) and massage therapy (Hernandez-Reif et al, 2001 **Level IV**) reduced self-reported pain scores associated with burn dressing changes.

### 10.4.3 Immunisation pain in infants and children

Procedure modifications, such as rapid injection and needle withdrawal (Ipp et al, 2007 **Level II**) and using a longer needle (Schechter et al, 2007 **Level I**) reduced pain associated with immunisations. Parental responses during injection such as excessive reassurance, criticism or apology increase distress, whereas humour and distraction tend to decrease distress (Schechter et al, 2007 **Level I**).

Oral sucrose in infants aged 2 to 4 months or breastfeeding in neonates reduced the duration of pain behaviour after but not during immunisation (Efe & Ozer, 2007 **Level II**; Hatfield, 2008 **Level II**). Combining sucrose, oral tactile stimulation and parental holding reduced the duration of crying in infants receiving multiple vaccinations (Reis et al, 2003 **Level II**). Combination of EMLA<sup>®</sup> and oral glucose reduced the behavioural and physiologic response to immunisation (Lindh et al, 2003 **Level II**).

Selective use of topical local anaesthetic has been recommended in older children (Schechter et al, 2007 **Level I**) and the combination of topical EMLA<sup>®</sup>, preparation, parental presence and distraction reduced pain scores during immunisation in 4 to 12 year old children (Boivin et al, 2008 **Level III-1**).

### 10.4.4 Procedural pain management in the emergency department

#### ***Laceration repair***

Topical anaesthesia for wound closure can avoid the distress caused by intradermal injection of local anaesthetic, but cocaine-containing preparations are no longer recommended (Eidelman, Weiss, Enu et al, 2005). Topical anaesthetics, such as lignocaine-adrenaline-amethocaine solutions were safe and effective in children (Schilling et al, 1995 **Level II**; Smith et al, 1997 **Level II**; White et al, 2004 **Level III-1**), and had equivalent or superior efficacy when compared with intradermal administration (Eidelman, Weiss, Enu et al, 2005 **Level I**). Application of topical anaesthetic solution to wounds at triage reduced treatment time (31 minutes less than controls) (Priestley et al, 2003 **Level II**) and reduced pain associated with subsequent intradermal injection of lignocaine (Singer & Stark, 2000 **Level II**). Topical anaesthesia reduced the requirement for procedural sedation for wound management (Pierluisi & Terndrup, 1989 **Level III-3**).

Tissue adhesives (Farion et al, 2003 **Level I**) and hair apposition for scalp lacerations (Hock et al, 2002 **Level III-1**) were as effective as suturing for simple lacerations but produced less pain and may be more acceptable to children.

Inhaled 50% N<sub>2</sub>O / 50% oxygen reduced pain and anxiety during laceration repair (Burton et al, 1998 **Level II**; Luhmann et al, 2001 **Level II**) in children.

#### ***Fracture pain and reduction***

In order to provide analgesia rapidly, opioids are increasingly being administered at triage in children with suspected fractures. To avoid the distress associated with IV access or IM injections, alternative routes of opioid delivery have been investigated in the emergency department. IN diamorphine (Kendall et al, 2001 **Level III-1**) and fentanyl via IN (Borland et al,

2007 **Level II**), transmucosal (Mahar et al, 2007 **Level III-1**), and inhaled routes (Miner et al, 2007 **Level III-2**; Furyk et al, 2009 **Level III-2**) provided comparable analgesia to IM or IV morphine, with a similar side-effect profile. Oral oxycodone was more effective and produced less itching than codeine, but early administration at triage was required as having Xrays, rather than examination or casting, was identified as the most painful period (Charney et al, 2008 **Level II**).

Although no longer used as an anaesthetic, methoxyflurane is available as a self-administered 'Penthrox<sup>®</sup>' inhaler that dispenses 0.2 to 0.7% methoxyflurane (Medical Developments International, 2001). Use of the Penthrox<sup>®</sup> inhaler in children reduced pain associated with extremity injuries (Babl et al, 2006 **Level IV**) but did not provide adequate analgesia for subsequent fracture manipulation (Babl et al, 2007 **Level IV**). Side effects included hallucinations, vomiting, confusion and dizziness, and sedation/drowsiness was common (26%) in children (Babl et al, 2006 **Level IV**; Buntine et al, 2007).

Closed fracture reduction is a major procedure, which may be performed in emergency departments with a variety of analgesic techniques (Kennedy et al, 2004). IV regional block with local anaesthetic was safe and effective in 90% to 98% of cases (Murat et al, 2003 **Level I**), but complications may arise with faulty equipment, inappropriate use of local anaesthetic, or inadequate monitoring and training of staff. Inhalation of N<sub>2</sub>O was as effective as IV regional anaesthesia using lignocaine (Gregory & Sullivan, 1996 **Level III-1**) and better than IM analgesia and sedation with pethidine (meperidine) and promethazine (Evans et al, 1995 **Level III-1**), although N<sub>2</sub>O has recently been reported to have limited efficacy as a sole agent for fracture manipulation (Babl et al, 2008 **Level IV**). N<sub>2</sub>O and a haematoma block with lignocaine produced similar analgesia but fewer side-effects and more rapid recovery than IV ketamine and midazolam (Luhmann et al, 2006 **Level III-1**). Ketamine-midazolam reduced distress during fracture manipulation and fewer paediatric patients required airway interventions than those receiving fentanyl-midazolam and propofol-fentanyl (Migita et al, 2006 **Level I**). As there is the potential for complications and a high incidence of side effects with sedative agents, particularly when given in combination (Cote et al, 2000; Cote, 2008) or in children with comorbidities (Morton, 2008), fully monitored general anaesthesia may be more appropriate than sedation or local anaesthesia in some clinical settings (Murat et al, 2003).

Additional paediatric guidelines for procedural sedation, as opposed to analgesia, have been produced by the American Academy of Pediatrics (Cote & Wilson, 2006) and the Scottish Intercollegiate Guidelines Network (Scottish Intercollegiate Guidelines Network, 2004).

### ***Psychological interventions***

In addition to pharmacological interventions, the planning of procedures for children in the emergency department should include age-appropriate psychological interventions, such as distraction techniques. Distraction reduced self-reported pain following needle-related procedural pain (Uman et al, 2006 **Level I**). Age-appropriate distraction techniques reduced situational anxiety in older children and lowered parental perception of distress in younger children undergoing laceration repair (Sinha et al, 2006 **Level II**).

**Key messages**

1. Sucrose reduces the behavioural response to heel-stick blood sampling in neonates (**U**) (**Level I** [Cochrane Review]).
2. Breastfeeding or breast milk reduces measures of distress in neonates undergoing a single painful procedure compared to positioning or no intervention (**U**) (**Level I** [Cochrane Review]).
3. Distraction, hypnosis, and combined cognitive-behavioural interventions reduce pain and distress associated with needle-related procedures in children and adolescents (**S**) (**Level I** [Cochrane Review]).
4. EMLA® is an effective topical anaesthetic for children, but amethocaine is superior for reducing needle insertion pain (**N**) (**Level I** [Cochrane Review]).
5. Topical local anaesthetic application, inhalation of nitrous oxide (50%) or the combination of both provides effective and safe analgesia for minor procedures (**U**) (**Level I**).
6. Combinations of hypnotic and analgesic agents are effective for procedures of moderate severity (**U**) (**Level II**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Inadequate monitoring of the child, lack of adequate resuscitation skills and equipment, and the use of multiple drug combinations has been associated with major adverse outcomes during procedural analgesia and sedation (**U**).

## 10.5 ANALGESIC AGENTS

### 10.5.1 Paracetamol

Paracetamol (acetaminophen) is effective for mild pain in children (Anderson, 2008), but the dose required for analgesia is greater than for an antipyretic effect (Anderson, 2004). It has similar efficacy to non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs), and may be a useful adjunct to other treatments for more severe pain. Supplemental opioid requirements were reduced after day case surgery by 40 mg/kg but not 20 mg/kg rectal paracetamol (Korpela et al, 1999 **Level II**) and after tonsillectomy by 40 mg/kg oral paracetamol (Anderson et al, 1996 **Level II**). Rectal paracetamol did not reduce morphine requirements in infants following major surgery (van der Marel et al, 2007 **Level II**).

#### **Pharmacokinetics and pharmacodynamics**

Paracetamol's bioavailability is dependent on the route of administration. Oral doses are subject to first pass hepatic metabolism of 10% to 40% and peak plasma concentrations are reached in 30 minutes (Arana et al, 2001). Rectal administration is associated with slower and more erratic absorption and loading doses of 30 to 40 mg/kg paracetamol may be required to achieve therapeutic plasma concentrations (Anderson et al, 1996 **Level II**; Howell & Patel, 2003 **Level II**). An IV formulation of paracetamol increased dosing accuracy with less pharmacokinetic variability attributable to absorption, but also had more rapid offset than a rectal preparation (Capici et al, 2008 **Level II**).

Dose regimens that target a steady state plasma concentration of 10 to 20 mg/L have been determined. There is some evidence for analgesic efficacy at this concentration in children (Anderson et al, 2001 **Level III-3**) but a relationship between plasma concentration and analgesia



has not been confirmed (Palmer et al, 2008 **Level III-3**). The volume of distribution of paracetamol decreases and clearance increases from 28 weeks postconceptional age resulting in a gradual fall in elimination half-life. Suggested maximum oral or rectal doses are: 25 mg/kg/day at 30 weeks postconceptional age; 45 mg/kg/day at 34 weeks postconceptional age; 60 mg/kg/day in term neonates and infants; and 90 mg/kg/day in children aged between 6 months and 12 years. These doses are suitable for acute administration for 2 to 3 days (Anderson et al, 2002 **Level III-3**). Following IV dosing in neonates aged 28 to 45 weeks postmenstrual age, volume of distribution was similar to the adult value, suggesting higher IV doses may be tolerated in neonates (Palmer et al, 2008 **Level III-3**), but current recommended maximum doses of IV paracetamol are 30 mg/kg/day in neonates and infants, and 40 to 60 mg/kg/day in infants and children (Palmer et al, 2007; Howard et al, 2008).

### **Adverse effects**

Paracetamol is metabolised in the liver, predominantly via glucuronidation and sulphation. Increased production of a reactive oxidative product N-acetyl-p-benzoquinoneimine occurs if the usual metabolic enzyme systems become saturated (eg acute overdose) or if glutathione is depleted (eg with prolonged fasting). An increased contribution of sulphation to metabolism and reduced production of oxidative metabolites may reduce the risk of toxicity in neonates, particularly in the presence of unconjugated hyperbilirubinaemia (Palmer et al, 2008), but as overall clearance is reduced a lower dose is appropriate. Risk factors for paracetamol hepatotoxicity may include fasting, vomiting, dehydration, systemic sepsis, pre-existing liver disease and prior paracetamol intake, however the situation remains unclear (Kaplowitz, 2004).

## **10.5.2 Non-selective non-steroidal anti-inflammatory drugs**

nsNSAIDs are effective analgesic agents for mild to moderate pain. Although the product information states that safety in children less than 2 years is not established, nsNSAIDs have been studied and used in all age groups including infants (Eustace & O'Hare, 2007 **Level IV**). The choice between ibuprofen, diclofenac and ketorolac mainly depends on the available formulation and convenience of administration.

Clinical studies suggest similar efficacy of nsNSAIDs and paracetamol (Tay & Tan, 2002 **Level II**; Hiller et al, 2006 **Level II**; Riad & Moussa, 2007 **Level II**), as long as equieffective doses are being given. Combining nsNSAIDs and paracetamol has been shown to improve analgesia and/or decrease the need for additional analgesia after adenoidectomy (Viitanen et al, 2003 **Level II**), tonsillectomy (Pickering et al, 2002 **Level II**), inguinal surgery (Riad & Moussa, 2007 **Level II**), multiple dental extractions (Gazal & Mackie, 2007 **Level II**), and orthopaedic surgery (Hiller et al, 2006 **Level II**). As a component of multimodal analgesia, nsNSAIDs decrease opioid consumption (Antila et al, 2006 **Level II**; Ruyte & Kokki, 2007 **Level II**). A combination of individually titrated intraoperative opioids and regularly administered perioperative mild analgesics (NSAID and/or paracetamol) is recommended for management of pain following tonsillectomy (Hamunen & Kontinen, 2005 **Level I**).

### **Pharmacokinetics and pharmacodynamics**

The elimination half-life of ketorolac (Lynn et al, 2007), ibuprofen (Kyllonen et al, 2005) and diclofenac (Litalien & Jacqz-Aigrain, 2001) is longest in neonates, with the value in toddlers approaching that of adults. Rectal bioavailability of diclofenac is high in children (van der Marel et al, 2004). Ibuprofen plasma concentrations of 10 to 25 mg/L have been suggested post paediatric inguinal hernia repair (Kokki et al, 2007). Target analgesic concentrations for other NSAIDs, developmental changes in pharmacodynamics, and the impact of different stereoisomer forms on the differential pharmacokinetics, efficacy and side-effect profile of NSAIDs (Kyllonen et al, 2005) require further evaluation (Anderson & Palmer, 2006).

## Adverse effects

In large series of children with febrile illnesses, the risk of serious adverse events following short-term use of ibuprofen was low, and similar to that following the use of paracetamol (Lesko & Mitchell, 1995 **Level II**; Lesko & Mitchell, 1999 **Level II**). Aspirin should be avoided in children with a febrile illness, as it has been associated with Reye's syndrome (encephalopathy and liver dysfunction) (Schrör, 2007).

nsNSAIDs should be avoided in children with a sensitivity reaction to aspirin or other nsNSAIDs. A subset of children with moderate to severe asthma and nasal disease/polyps are susceptible to NSAID-exacerbated respiratory disease (Palmer, 2005). nsNSAIDs may be safe in children with mild asthma as single dose diclofenac had no significant effect on respiratory function tests (spirometry) in children with asthma (Short et al, 2000 **Level III-3**) and short-term use of ibuprofen did not increase outpatient visits for asthma (Lesko et al, 2002 **Level II**). The use of nsNSAIDs in children undergoing tonsillectomy remains controversial (see Section 4.2.2). In a meta-analysis that included only paediatric trials, an increased risk of bleeding requiring either non-surgical (OR 1.23; 95% CI 0.44 to 3.43) or surgical intervention (OR 1.46; 95% CI 0.49 to 4.0) after tonsillectomy could not be confirmed (Cardwell et al, 2005 **Level I**). Although neither represented a statistically significant increase, risk of bleeding requiring surgical intervention tended to be higher following high dose ketorolac 1mg/kg (OR 3.1; 95%CI 0.53 to 18.4) than other nsNSAIDs (OR 0.91; 95% CI 0.22 to 3.71) (Cardwell et al, 2005 **Level I**).

### Note: reversal of conclusions

This partially reverses the Level 1 conclusion in the previous edition of this document; earlier meta-analyses had reported an increased risk of reoperation for post-tonsillectomy bleeding in studies that included adults and children.

In a small trial, ketorolac did not increase the risk of bleeding complications after congenital cardiac surgery (Gupta et al, 2004 **Level II**).

nsNSAIDs affect renal blood flow, glomerular filtration and renal drug clearance (Allegaert, Vanhole et al, 2005). Renal failure in association with nsNSAID use has occurred in neonates (Andreoli, 2004) and older children (Taber & Mueller, 2006), usually in the setting of other haemodynamic compromise.

nsNSAID use for analgesia has been restricted in infants less than 3 months of age. Neonatal bolus and short-term use for patent ductus arteriosus closure can produce pulmonary hypertension and alterations in cerebral (Naulaers et al, 2005), gastrointestinal and renal blood flow (Allegaert, Vanhole et al, 2005; Aranda & Thomas, 2006). Relative effects of indomethacin (indometacin) and ibuprofen on the risk of intraventricular haemorrhage continue to be debated (Aranda et al, 1997; Ment et al, 2004).

### 10.5.3 Coxibs

Coxibs (COX-2 specific inhibitors) have been used off-license in children. Celecoxib was as effective as naproxen in children with juvenile rheumatoid arthritis (Foeldvari et al, 2008 **Level II**). Small-scale efficacy studies evaluated different perioperative doses of rofecoxib (prior to its withdrawal from the market): low dose (0.625 mg/kg) was inferior to ibuprofen (in combination with paracetamol) (Pickering et al, 2002 **Level II**); 1 mg/kg was superior to placebo (Joshi et al, 2003 **Level II**; Sheeran et al, 2004 **Level II**), and multi-day postoperative dosing provided superior analgesia to paracetamol (Vallee et al, 2007 **Level III-3**) or hydrocodone combined with paracetamol (Bean-Lijewski et al, 2007 **Level II**). The degree of COX-2 selectivity, pharmacokinetic

profile, adverse effects and use of parenteral forms (eg parecoxib) of coxibs have not been adequately studied in children.

### 10.5.4 Opioids and tramadol

As there are significant developmental changes in the pharmacokinetic handling (Bouwmeester et al, 2004) and pharmacodynamic response to opioids (Nandi & Fitzgerald, 2005), doses must be adjusted according to age and individual response. Routine and regular assessment of pain severity, the analgesic response, and the incidence of side effects (particularly nausea and vomiting and sedation) is essential, with titration of opioid treatment according to individual needs. As with adult patients, appropriate dose regimens, guidelines for monitoring, documentation, management of side effects, and education of staff and carers are required (Wrona et al, 2007 **Level IV**) (see Section 4).

#### **Morphine**

The clearance of morphine is reduced and half-life prolonged in neonates and infants (Bouwmeester et al, 2004; Anand et al, 2008). Within age groups, individual variability in kinetics results in 2 to 3-fold differences in plasma concentration with the same rate of infusion (Lynn et al, 1998). In neonates, infants and children to 3 years, age was the most important factor affecting morphine requirements and plasma morphine concentrations (Bouwmeester, van den Anker et al, 2003 **Level II**), and in older children average patient-controlled morphine requirements also change with age (Hansen et al, 1996 **Level IV**).

The risk of respiratory depression is reduced when infusions are targeted to plasma morphine concentrations less than 20 ng/mL. However, no minimum effective concentration for analgesia has been determined (Kart, Christrup et al, 1997). No clear relationship between plasma concentration and analgesia has been identified due to variability in individual requirements, the clinical state of the child, the type of surgery, the assessment measure used and the small sample size in many studies (Bouwmeester, Hop et al, 2003 **Level II**; Anand et al, 2008 **Level II**). Analysis of 35 paediatric RCTs of morphine, administered via IV, epidural, IM and intrathecal routes, reported analgesic efficacy in comparison with inactive controls, but with significantly increased vomiting and sedation. The majority of studies analysed compared single perioperative doses and only one study evaluated a postoperative infusion of morphine (Duedahl & Hansen, 2007 **Level II**).

#### **Fentanyl**

Fentanyl is a potent mu-opioid agonist and highly lipophilic. Rapid redistribution contributes to offset of action, fentanyl is metabolised by CYP3A4 to inactive metabolites, and clearance is only 70-80% of adult levels in neonates but rapidly matures (Tibboel et al, 2005). Fentanyl has been administered by multiple routes for perioperative pain management in neonates (Simons & Anand, 2006) and children (Howard et al, 2008), including: IV infusion or PCA (Antila et al, 2006 **Level II**; Butkovic et al, 2007 **Level III-1**); intrathecal (Batra et al, 2008 **Level II**) injection; epidural infusion (Lerman et al, 2003 **Level II**) and patient-controlled epidural analgesia (PCEA) (Saudan et al, 2008 **Level III-3**). Prolonged IV infusion of fentanyl during neonatal intensive care has been associated with more rapid dose escalation than morphine, but both can produce opioid withdrawal symptoms following rapid cessation (Simons & Anand, 2006).

Due to its rapid onset and short duration of action, fentanyl can be used alone or in combination with sedatives, to control procedural pain (Tibboel et al, 2005), but opioid-related side effects, such as nausea and vomiting and respiratory complications may also be increased (Migita et al, 2006 **Level I**). Due to its high lipophilicity, fentanyl can also be administered via transmucosal, IN, and inhaled routes (Robert et al, 2003 **Level II**) (Borland et al, 2005 **Level II**). Transdermal fentanyl has approximately 30% of the IV bioavailability (Tibboel et al, 2005).

In children, the time to reach steady-state serum drug concentrations following transdermal application is longer, and the elimination half-life is shorter as clearance is enhanced, but there have been no randomised trials of efficacy (Zernikow et al, 2007).

### **Codeine**

Codeine is a weak opioid and conversion to morphine (by CYP2D6) is required for analgesia. Intermediate or poor metabolisers — 46% of children undergoing tonsillectomy in a United Kingdom population (Williams et al, 2002) — may have reduced or minimal effect from codeine; while ultra metabolisers may attain high peak morphine levels and are at risk of sedation and respiratory depression (Kirchheiner et al, 2007 **Level III-3**; Voronov et al, 2007). Perceived advantages of codeine include less respiratory depression in neonates and reduced nausea and vomiting compared with morphine (Williams et al, 2002 **Level II**) but may relate to low levels of active metabolites and be associated with reduced efficacy (Williams et al, 2001).

Oral codeine has a similar time to peak effect but decreased total absorption compared with rectal and IM delivery (McEwan et al, 2000 **Level II**). IV administration should be avoided as severe hypotension may result (Shanahan et al, 1983 **Level IV**).

There are conflicting reports of efficacy for postoperative pain. Addition of codeine to paracetamol has been reported to improve analgesia (Pappas et al, 2003 **Level II**) or have no effect (Moir et al, 2000 **Level II**). Comparison of codeine and morphine for tonsillectomy has shown either no difference (Semple et al, 1999 **Level II**) or an increased requirement for rescue analgesia following codeine (Williams et al, 2002 **Level II**). Codeine was less effective than ibuprofen for acute musculoskeletal pain in children (Clark et al, 2007 **Level II**).

### **Oxycodone**

Oxycodone is increasingly used in children, with efficacy shown in multiple settings: oral use in the emergency department for children with orthopaedic injuries (Charney et al, 2008 **Level II**; Koller et al, 2007 **Level II**); use of an oral controlled-release (CR) preparation as a step-down following PCA in adolescents after spinal fusion (Czarnecki et al, 2004 **Level IV**); IV bolus dose administration for postoperative rescue analgesia (Kokki, Laisalmi et al, 2006 **Level IV**); and IV PCA (in adolescents and adults) (Silvasti et al, 1999 **Level II**).

In infants over 6 months of age, the pharmacokinetic profile of oxycodone is similar to adults and dosing can be based on the weight of the child (El-Tahtawy et al, 2006). Similar absorption is seen following buccal and sublingual absorption (Kokki, Rasanen et al, 2006), but there is less interindividual variability following IV administration (Kokki et al, 2004). In neonates and infants, the half-life is prolonged and interindividual variability in kinetics is increased even following IV administration (Pokela et al, 2005).

### **Other opioids**

A large number of opioid preparations have been utilised in children, but availability varies in different countries, and many have not been investigated in controlled trials. See Howard et al (Howard et al, 2008) for additional details. A review of paediatric and adult studies using hydromorphone found no clear advantage over other opioids in terms of analgesic efficacy or side-effect profile (Quigley, 2002 **Level I**). Several opioids are used as spinal analgesics in children, but the lack of comparative studies provide limited evidence for superiority of one agent (Williams & Howard, 2003 **Level IV**).

### **Tramadol**

Evidence for the use of tramadol in paediatric acute pain is currently limited by studies of small sample size, difficulty determining comparative analgesic doses, and licensing only for 16 years and over. Dosing is the same in children as in adults (1 to 2 mg/kg 6 hourly), with some reporting use of a 2 to 3 mg/kg IV loading dose then infusion of 5 to 8 mg/kg/24hours

(Allegaert et al, 2008). A review of 20 studies (**Level II** to **Level III-3**) indicated efficacy following oral, rectal, and IV administration, but dose sparing and safety have not been demonstrated with spinal administration (Bozkurt, 2005). Many studies for post-tonsillectomy pain have low sensitivity (Hamunen & Kontinen, 2005) and tramadol has been variably reported to be more effective than low-dose paracetamol (Pendeville et al, 2000 **Level II**), have similar efficacy to morphine (Engelhardt et al, 2003 **Level II**), and be less effective than pure agonist opioids (Ozer et al, 2003 **Level II**; Ozalevli et al, 2005 **Level III-1**) or ketoprofen (Antila et al, 2006 **Level II**). Further controlled trials are required to determine the role and optimum dose of tramadol in children. The side effects of tramadol are similar to opioids, with similar or reduced rates of nausea and vomiting (10% to 40%), sedation and fatigue, but less constipation and pruritus and no reports of respiratory depression in children (Bozkurt, 2005).

### **Pharmacokinetics**

Oral administration is subject to extensive first-pass hepatic metabolism. Rectal bioavailability is good with low interindividual variability (Zwaveling et al, 2004). Maximum plasma concentrations post IV, oral and rectal dosing are achieved between 0.3 and 2.4 hours postadministration (Bozkurt, 2005). Analgesic efficacy is associated with a plasma concentration of tramadol of 100 ng/mL in adults and children and O-desmethyl tramadol (M1) of 15 ng/mL (Garrido et al, 2006).

The primary metabolite is O-desmethyl tramadol (M1), formed by the enzyme CYP2D6. In addition to inter-individual variability in functional allele expression (resulting in poor, normal, extensive or ultra metabolisers), there are age-related changes in maturation of CYP2D6 (Allegaert, Van den Anker et al, 2005; Allegaert et al, 2008). Tramadol clearance is linked to weight and postmenstrual age (PMA): increasing rapidly from 25 weeks PMA to 80% of the adult value by 45 weeks PMA (Garrido et al, 2006; Allegaert et al, 2008).

## **10.5.5 Corticosteroids**

Dexamethasone reduced vomiting and resulted in an earlier return to soft diet following tonsillectomy (Steward et al, 2003 **Level I**). A single dose of intraoperative dexamethasone (0.4 to 1 mg/kg; maximum 8 to 50 mg) reduced pain (by 1 on VAS scale 0 to 10 cm) on the first postoperative day (Afman et al, 2006 **Level I**). A reduction in postoperative analgesic requirements following tonsillectomy, and a dose-dependent reduction in postoperative nausea and vomiting following dexamethasone 0.05 mg/kg, 0.15 mg/kg or 0.5 mg/kg (maximum 20 mg) has recently been confirmed. However, the study was terminated after randomisation of 215 children as dexamethasone, but not postoperative use of ibuprofen, was associated with an increased risk of bleeding, which was highest after the largest dose (RR 6.8; 95% CI 1.8 to 16.5) (Czarnetzki et al, 2008 **Level II**).

## **10.5.6 Other pharmacological therapies**

Acute otitis media is common in children. Analysis of four RCTs investigating topical local anaesthetic drops for pain associated with acute otitis media, found insufficient evidence to evaluate efficacy or adverse effects (Foxlee et al, 2006 **Level I**). Administration of lignocaine 2% as ear drops reduced pain at 10, but not 20 or 30 minutes (Bolt et al, 2008 **Level II**).

In children with acute migraine, ibuprofen and sumatriptan reduced headache (NNT 2.4 and 7.4 respectively) or completely relieved pain (NNT 4.9 and 6.9 respectively) (Silver et al, 2008 **Level I**). Paracetamol, zolmitriptan, rizatriptan and dihydroergotamine were not significantly better than placebo, but the number of RCTs in children was small.

**Key messages**

1. Non-selective NSAIDs do not increase the risk of reoperation for bleeding after tonsillectomy in paediatric patients (**R**) (**Level I** [Cochrane Review]).
2. Dexamethasone reduces post-tonsillectomy pain and postoperative nausea and vomiting (**N**) (**Level I**) but high doses may increase the risk of bleeding (**N**) (**Level II**).
3. Paracetamol and non-selective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major surgery (**U**) (**Level II**).
4. The efficacy of oral codeine in children is variable, individual differences in the ability to generate active metabolites may reduce efficacy (**U**) (**Level II**) or increase side effects (**N**) (**Level IV**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Safe dosing of paracetamol requires consideration of the age and body weight of the child, and the duration of therapy (**U**).
- Aspirin should be avoided in children, but serious adverse events after non-selective NSAIDs are rare in children over 6 months of age (**U**).

## 10.6 OPIOID INFUSIONS AND PCA

### 10.6.1 Opioid infusions

The safety and efficacy of IV opioid infusion for the management of acute postoperative pain are well established for children of all ages (van Dijk et al, 2002 **Level II**). Further procedure-specific evidence and dose recommendations are available (Howard et al, 2008). As intermittent IM injections are distressing for children, the IV route is preferred, but if peripheral perfusion is normal, the SC route can be used for continuous infusion (McNicol, 1993 **Level IV**) or for PCA, with similar safety and efficacy to the IV route (Doyle, Morton et al, 1994 **Level II**).

Differences between intermittent bolus doses and continuous infusions of opioid relate more to the total dose given than to the method of administration (Lynn et al, 2000 **Level III-2**). Comparison of the same total dose of morphine given via infusion (10 mcg/kg/hr) or bolus (30 mcg/kg every 3 hours) found no difference in pain scores (COMFORT scale and observer VAS) (van Dijk et al, 2002 **Level II**) or stress response to surgery (Bouwmeester et al, 2001 **Level II**) in neonates and young infants. However, these doses were inadequate in older children (1 to 3 years of age) who required additional bolus doses and the 3-hourly interval was less effective (possibly due to more rapid clearance) (van Dijk et al, 2002 **Level II**).

In ventilated preterm neonates, opioid infusions have limited efficacy for control of acute procedural pain (Bellu et al, 2008 **Level I**). Initial associations between routine morphine infusion and improved neurological outcome were not confirmed in a subsequent large multicentre study (Anand et al, 2004 **Level II**). A subsequent meta-analysis found no statistically significant differences in mortality, duration of ventilation, or improvements in short or long-term neurological outcomes with routine use of opioid infusions in ventilated neonates (Bellu et al, 2008 **Level I**). Prolonged sedation may have detrimental effects in preterm neonates (Anand et al, 1999 **Level II**), but no association with poor 5-year neurological outcome has also been reported (Roze et al, 2008 **Level II**), as studies vary in the degree and manner of correction for confounding factors.



## 10.6.2 Patient-controlled analgesia

PCA can provide safe and effective analgesia for children as young as 5 years old. Patient selection depends on the ability of the child and carers to understand the concepts of PCA and the availability of suitable equipment and trained staff. Recognition of potential complications of PCA use was enhanced by providing set instructions for monitoring, and by acute pain service (APS) support (Wrona et al, 2007 **Level III-2**).

### **Efficacy**

Compared with continuous IV opioid infusions, PCA provided greater dosing flexibility, and similar analgesia. PCA has been associated with higher opioid consumption, but the incidence of side effects has varied, depending on the PCA dosing parameters (Bray et al, 1996 **Level III-2**; Peters et al, 1999 **Level II**).

PCA can be particularly useful in children with altered opioid requirements. Postoperative PCA morphine requirements in children with sickle-cell disease were almost double those of non-sickle children (Crawford, Galton et al, 2006 **Level III-3**). Intraoperative remifentanyl was associated with an increase in PCA morphine requirement in the 24 hours following scoliosis surgery (Crawford, Hickey et al, 2006 **Level II**), possibly due to acute opioid-induced hyperalgesia.

### **The PCA prescription**

Morphine is the drug used most frequently in PCA. A bolus dose of morphine 20 mcg/kg is a suitable starting dose and improved pain scores during movement when compared with 10 mcg/kg (Doyle, Mottart et al, 1994 **Level II**). The addition of a background infusion is more common in children than adults, and 4 mcg/kg/hour is often recommended as doses of 10 mcg/kg/hour and above increased side effects (Howard et al, 2008). Although use of a background infusion was associated with increased sleep disturbance in one audit (calculated from the number of hours PCA presses were required), numbers were too small to fully investigate the contribution of the degree of surgery (Kelly et al, 2006 **Level IV**).

Fentanyl is a useful alternative opioid, particularly for patients with renal impairment or those experiencing morphine-related side effects (Tobias & Baker, 1992 **Level IV**). Fentanyl PCA has been used safely and effectively following neurosurgery (Chiaretti et al, 2008 **Level IV**), thoracic surgery (Butkovic et al, 2007 **Level III-1**) and tonsillectomy (Antila et al, 2006 **Level II**), and for acute cancer-related pain (Ruggiero et al, 2007 **Level IV**). In comparison with morphine, tramadol PCA provided minor improvements in time to extubation post cardiac surgery (Chu et al, 2006 **Level II**) and reduced nausea post-tonsillectomy but at the cost of higher pain scores (Ozalevi et al, 2005 **Level II**). Pethidine does not have any advantage over other opioids and neurotoxicity from norpethidine (normeperidine) accumulation has been reported in a healthy adolescent (Kussman & Sethna, 1998).

Nausea and vomiting occurs in 30% to 45% of children using morphine PCA and can be reduced by prophylactic antiemetics (Carr et al, 2009 **Level I**). Adding antiemetics directly to PCA solutions for children was not effective (Munro et al, 2002 **Level II**). Addition of a low-dose naloxone infusion did not impair analgesia, but decreased pruritus and nausea in postoperative children treated with PCA (Maxwell et al, 2005 **Level II**) and also decreased pruritus in children requiring morphine infusions during a sickle cell crisis (Koch et al, 2008 **Level IV**).

## 10.6.3 Nurse-controlled analgesia

In younger children and infants, 'PCA' pumps have been used for nurses to administer intermittent bolus doses with or without a background infusion (ie nurse-controlled analgesia or NCA). This technique may increase ease of administration particularly prior to movement or



procedural interventions, increase dose flexibility, and improve parent and nurse satisfaction – see Howard et al (Howard et al, 2008) for dose recommendations. The incidence of adverse events was similar (24 or 22%) in children self-administering conventional PCA and those receiving NCA (administered by nurses or physicians). Rescue events (requiring naloxone, airway management or admission to high dependency unit or ICU) were more common in the NCA group, but this group was also younger and had a higher prevalence of comorbidities. Cognitive impairment and high opioid dose requirements on day 1 were associated with increased adverse events (Voepel-Lewis et al, 2008 **Level III-2**).

NCA has also been used in older children in intensive care who are unable to activate a conventional PCA device. Adequate analgesia comparable to PCA was reported, but efficacy was dependent on accurate nurse assessment of pain (Weldon et al, 1993 **Level III-2**).

Administration by a nurse trained in pain assessment, rather than parents, is recommended in most centres (Howard, 2003). ‘PCA by proxy’ has also been used to describe administration by nurses and/or parents. In a prospective series of PCA by proxy (parents or health care providers), effective analgesia was achieved in 81% to 95% of children under 6 years of age, 25% required supplemental oxygen, and 4% required naloxone for respiratory depression (Monitto et al, 2000 **Level IV**). In a retrospective series, PCA by proxy resulted in low pain scores in children with developmental delay, and somnolence or respiratory depression requiring naloxone occurred in 2.8% of patients (Czarnecki et al, 2008 **Level IV**). PCA by proxy in children with cancer pain was associated with comparable complication rates as conventional PCA in this specific patient group (Angheliescu et al, 2005 **Level III-3**).

### Key messages

1. Routine morphine infusion does not improve neurological outcome in ventilated preterm neonates (**N**) (**Level I** [Cochrane Review]).
2. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**N**) (**Level II**).
3. Effective PCA prescription in children incorporates a bolus that is adequate for control of movement-related pain, and may include a low dose background infusion (**U**) (**Level II**).
4. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Intravenous opioids can be used safely and effectively in children of all ages (**U**).
- Initial doses of opioid should be based on the age, weight and clinical status of the child and then titrated against the individual’s response (**U**).

## 10.7 REGIONAL ANALGESIA

### 10.7.1 Peripheral nerve blocks

Peripheral local anaesthetic techniques are an effective and safe adjunct for the management of procedural, perioperative, and injury-related acute pain (Giaufre et al, 1996 **Level IV**). As placebos are rarely used in children, many current studies compare two active treatments. Differences between groups can be difficult to detect if the sample size is small or the

outcome measure is relatively insensitive (eg supplemental analgesic requirements following procedures with low ongoing pain).

The use of ultrasound guidance has been shown to improve the accuracy, success rate and quality of blockade as well as reduce the volume of local anaesthetic required (Willschke et al, 2005 **Level IV**; Weintraud et al, 2008 **Level IV**). The efficacy of different local anaesthetic techniques has been compared for common paediatric surgical conditions. Additional procedure-specific data are available (Howard et al, 2008).

The use of peripheral nerve catheters and plexus techniques in children has increased (Ganesh et al, 2007; **Level IV** Rochette et al, 2007 **Level IV**). Descriptive studies of the efficacy and safety of continuous peripheral nerve block infusions in children are encouraging (Fisher et al, 2006 **Level IV**) but further controlled comparisons with other analgesic techniques are required.

Femoral nerve or fascia iliaca compartment blocks provided analgesia for surgery on the anterior aspect of the thigh and reduced pain associated with femoral fractures (Paut et al, 2001 **Level IV**), and psoas compartment block may be a useful alternative to neuraxial techniques for unilateral hip and lower limb surgery (Dadure et al, 2004 **Level IV**; Schuepfer & Jahr, 2005 **Level IV**). For children undergoing major foot and ankle surgery, continuous popliteal nerve block with 0.2% ropivacaine produced comparable analgesia but fewer adverse events (postoperative nausea and vomiting [PONV], early discontinuation) than continuous epidural infusion (Dadure et al, 2006 **Level II**).

Axillary brachial plexus blocks provided satisfactory analgesia for hand and forearm surgery in 75% to 94% of cases (Fisher et al, 1999 **Level IV**). The use of ultrasound guidance has led to new approaches to plexus anaesthesia in children (Fleischmann et al, 2003 **Level III-1**; Ponde, 2008 **Level IV**) with improved success rates (De Jose Maria et al, 2008 **Level III-1**).

Continuous paravertebral extrapleural infusions provided effective analgesia in infants following thoracotomy (Fisher et al, 1999 **Level IV**). Single-shot paravertebral injection provided effective analgesia after renal surgery (Berta et al, 2008 **Level IV**) and inguinal hernia repair (Naja et al, 2005 **Level IV**).

## **Specific procedures**

### ***Circumcision***

A dorsal penile nerve block provided similar analgesia to a caudal block (Cyna & Middleton, 2008 **Level I**) and a longer duration of effect than application of a topical local anaesthetic cream, EMLA® (Choi et al, 2003 **Level II**). Caudal analgesia reduced the need for early rescue analgesia when compared with parenteral analgesia (Allan et al, 2003 **Level I**).

Policy statements from the Royal Australasian College of Physicians (Royal Australasian College of Physicians, 2004) and British Association of Paediatric Urologists (BAPU, 2007) emphasise the need for adequate analgesia for neonatal circumcision. There are insufficient controlled trials to adequately rank the efficacy of all local anaesthetic techniques for circumcision in awake neonates, but as topical local anaesthetic cream only partially attenuates the pain response to circumcision, more effective analgesic techniques such as dorsal penile nerve block are recommended (Brady-Fryer et al, 2004 **Level I**).

### ***Inguinal surgery***

Similar analgesic efficacy following inguinal hernia repair has been found with wound infiltration, ilioinguinal / iliohypogastric nerve block or caudal analgesia (Splinter et al, 1995 **Level II**; Machotta et al, 2003 **Level II**). Ilioinguinal block is inherently safe, but ultrasound guidance may improve safety and efficacy (Willschke et al, 2005 **Level II**; Weintraud et al, 2008 **Level IV**). In a small study following umbilical surgery, rectus sheath block offered no benefits

compared with infiltration of local anaesthetic (Isaac et al, 2006 **Level II**). Addition of clonidine to bupivacaine for ilioinguinal block did not improve duration or quality of analgesia (Kaabachi et al, 2005 **Level II**).

### **Tonsillectomy**

Local anaesthetic by topical application or infiltration produced moderate reductions in pain (mean reduction 7 to 19 mm on 0 to 100 mm VAS) following tonsillectomy (Grainger & Saravanappa, 2008 **Level I**). Peritonsillar infiltration of ketamine 0.5 mg/kg reduced pain following tonsillectomy (Honarmand et al, 2008 **Level II**) but was no more effective than the same dose given systemically (Dal et al, 2007 **Level II**).

### **Head and neck surgery**

Blocks of scalp branches of the frontal (supraorbital, supratrochlear), maxillary (zygomaticotemporal), and auriculotemporal nerves as well as branches of the superficial cervical plexus (greater auricular and occipital nerves) reduced pain following neurosurgery (Pardey et al, 2008 **Level IV**).

Greater auricular nerve block provided similar analgesia with reduced PONV compared with morphine following mastoidectomy (Suresh et al, 2004 **Level II**). Combined with a lesser occipital nerve block, it was also effective following otoplasty (Pardey et al, 2008 **Level II**). Infraorbital nerve block was superior to IV fentanyl following cleft lip repair (Rajamani et al, 2007 **Level II**). Compared with intraoperative opioids, peribulbar and subtenon blocks reduced intraoperative oculocardiac reflexes and PONV following strabismus surgery, but effects on postoperative analgesic requirements were variable (Chhabra et al, 2005 **Level III-1**; Steib et al, 2005 **Level II**; Gupta et al, 2007 **Level II**); and relative risks of the procedures have not been fully evaluated. Following cataract surgery, fewer children required rescue analgesia when subtenon block was compared with intravenous fentanyl (Ghai et al, 2009 **Level II**).

Local anaesthetic infiltration reduced pain following dental extractions (Anand et al, 2005 **Level III-2**) but addition of a small dose of morphine (25 mcg/kg) to the local anaesthetic did not improve the quality or duration of analgesia (Bhananker et al, 2008 **Level II**).

## **10.7.2 Central neural blockade**

The use of regional analgesia in children is well established but patient selection, technique, choice of drugs, availability of experienced staff for performing blocks, APS resources and adequacy of follow-up vary in different centres (Williams & Howard, 2003).

### **Caudal analgesia**

Single-shot caudal analgesia is one of the most widely used regional techniques in children, and provides intra- and postoperative analgesia for surgery on the lower abdomen, perineum and lower limbs (Howard et al, 2008). Large series have reported a high success rate (particularly in children under 7 years of age), and a low incidence of serious complications (Giaufre et al, 1996 **Level IV**; Royal College of Anaesthetists, 2009 **Level IV**).

Caudal bupivacaine, levobupivacaine and ropivacaine, produced similar times to onset of block and quality of postoperative analgesia (Breschan et al, 2005 **Level II**; Ivani et al, 2005 **Level II**; Frawley et al, 2006 **Level II**; Ingelmo et al, 2006 **Level II**). Concentration-dependent differences have been noted; ropivacaine 0.175% was superior to lower concentrations, and was as effective as a 0.2% solution but produced less motor block (Khalil et al, 2006 **Level II**). Addition of adrenaline to bupivacaine has minimal effect on the duration of analgesia, particularly in older children (Ansermino et al, 2003 **Level I**).

Opioid and non-opioid adjuvants have been added to caudal local anaesthetic with the aim of improving the efficacy or duration of analgesia. Addition of morphine to caudal local anaesthetic prolonged analgesia, but dose-related side effects were relatively common (Bozkurt et al, 1997 **Level IV**; Cesur et al, 2007 **Level II**). Clinically significant respiratory depression has been reported, particularly with higher doses and in younger patients (de Beer & Thomas, 2003). Side effects are potentially less with lipid soluble opioids, but while fentanyl may prolong caudal analgesia slightly (Constant et al, 1998 **Level II**), others have shown no benefit (Kawaraguchi et al, 2006 **Level II**). Supplementing general anaesthesia with caudal blockade (bupivacaine with morphine) reduced time to extubation and the period of mechanical ventilation following cardiac surgery, but there was no difference in hospital stay or pain relief (Leyvi et al, 2005 **Level III-2**).

Addition of clonidine (1 to 2 mcg/kg) to caudal local anaesthetic prolonged analgesia (Ansermino et al, 2003 **Level I**). Effects on analgesic efficacy could not be assessed by meta-analysis due to variability in study design and outcome measures. Clinically important sedation occurred with higher doses (5 mcg/kg) (Ansermino et al, 2003 **Level I**). Clonidine 1 mcg/kg with ropivacaine 0.2% has been shown to have a longer duration than either ketamine 0.5% with ropivacaine or plain ropivacaine (Akbas et al, 2005 **Level II**).

Preservative-free ketamine 0.25 to 0.5 mg/kg prolonged analgesia without significant side effects, but higher doses (1 mg/kg) increased behavioural side effects (Ansermino et al, 2003 **Level I**). Levobupivacaine 0.175% with ketamine 0.5 mg/kg appears more effective than levobupivacaine 0.2% alone (Locatelli et al, 2008 **Level II**). Other adjuncts such as neostigmine and midazolam, while extending block duration offered little if any advantage over clonidine or preservative-free ketamine (Kumar et al, 2005 **Level II**). In addition, neostigmine was associated with a high incidence of dose-related vomiting when used as an adjunct (Batra et al, 2003 **Level II**).

The neurotoxicity of non-opioid spinal additives has not been systematically evaluated in neonates and children (Howard et al, 2008).

### **Epidural analgesia**

As the epidural space is relatively large with loosely packed fat in neonates, catheters can be threaded from the sacral hiatus to lumbar and thoracic levels (Tsui, 2004 **Level IV**). In older infants, various techniques have been suggested to improve correct placement including ultrasound, nerve stimulation and ECG guidance (Tsui & Finucane, 2002 **Level IV**; Tsui, 2004 **Level IV**; Willschke et al, 2006 **Level IV**). Insertion of epidural catheters at the segmental level required for surgery was more reliable in older children, and has been shown to be safe in experienced hands with appropriate size equipment (Giaufre et al, 1996 **Level IV**; Llewellyn & Moriarty, 2007 **Level IV**).

Continuous epidural infusions of bupivacaine are effective and safe in children (Llewellyn & Moriarty, 2007 **Level IV**) and can provide similar levels of analgesia to systemic opioids (Wolf & Hughes, 1993 **Level II**). In children 7 to 12 years of age, PCEA provided analgesia similar to a continuous infusion. Total local anaesthetic dose was reduced with PCEA but no differences in side effects were detected (Antok et al, 2003 **Level III-1**). Due to reduced clearance and the potential for accumulation of bupivacaine, the hourly dose should be reduced and the duration of therapy limited to 24 to 48 hours in neonates (Larsson et al, 1997 **Level IV**).

Postnatal age and weight influence the pharmacokinetic profile of levobupivacaine, with slower absorption and clearance in neonates and infants (Chalkiadis & Anderson, 2006 **Level IV**). Although plasma concentrations increased, they remained low after 24 hours of epidural levobupivacaine infusion in children aged over 6 months (Lerman et al, 2003 **Level II**). Epidural

infusions of ropivacaine were effective and safe in neonates (Bosenberg et al, 2005 **Level IV**) and children (Berde et al, 2008 **Level IV**) with minimal drug accumulation.

Epidural opioids alone have a limited role. Epidural morphine provided prolonged analgesia but no improvement in the quality of analgesia compared with systemic opioids (Bozkurt et al, 2004 **Level II**). Epidural fentanyl alone was less effective than both levobupivacaine alone and a combination of local anaesthetic and fentanyl (Lerman et al, 2003 **Level II**). Bolus doses of epidural morphine were less effective than epidural infusions of fentanyl and local anaesthetic (Kart, Walther-Larsen et al, 1997 **Level II**; Reinoso-Barbero et al, 2002 **Level II**). Ketoprofen improved analgesia when given in conjunction with epidural sufentanil (Kokki et al, 1999 **Level II**).

A combination of local anaesthetic and opioid is frequently used in epidural infusions, but there are limited data available to assess the relative merits of different regimens. Both improvements in analgesia (Lovstad & Stoen, 2001 **Level II**) and no change (Lerman et al, 2003 **Level II**) have been shown with addition of fentanyl to local anaesthetic infusions. Addition of fentanyl to bupivacaine or bupivacaine plus clonidine epidural infusions provided similar analgesia but increased side effects (Cucchiario et al, 2006 **Level II**). Addition of morphine to an epidural local anaesthetic infusion was more effective than clonidine (Cucchiario et al, 2003 **Level II**), but higher doses of clonidine improved analgesia when added to epidural ropivacaine infusions (De Negri et al, 2001 **Level II**).

### **Outcomes**

Perioperative regional analgesia modifies the stress response to surgery in children (Wolf et al, 1998 **Level II**; Humphreys et al, 2005 **Level II**). Suppression of the stress response may necessitate a local anaesthetic block that is more intense or extensive than required for analgesia, and therefore the risks of increased side effects or toxicity must be balanced against any potential benefit (Wolf et al, 1998 **Level II**). Use of caudal opioids alone (morphine 30 mcg/kg) was less effective than plain bupivacaine 0.25% in attenuating cortisol and glucose responses following hypospadias surgery (Teyin et al, 2006 **Level II**).

Improvements in respiratory outcome with regional analgesia have not been established in controlled comparative trials. Reductions in respiratory rate and oxygen saturation were less marked during epidural analgesia compared with systemic opioids, but the degree of difference was of limited clinical significance (Wolf & Hughes, 1993 **Level II**). Case series report improvements in respiratory function and/or a reduced need for mechanical ventilation with regional analgesia techniques (McNeely et al, 1997 **Level IV**; Hodgson et al, 2000 **Level IV**; Aspirot et al, 2008 **Level IV**; Raghavan & Montgomerie, 2008 **Level IV**). A meta-analysis of spinal versus general anaesthesia for inguinal herniorrhaphy in premature infants reported a reduction in postoperative apnoea in the spinal group (when infants having preoperative sedation were excluded) and a reduced need for postoperative ventilation (of borderline statistical significance) (Craven et al, 2003 **Level I**).

Epidural rather than systemic analgesia reduced hospital stay following fundoplication (McNeely et al, 1997 **Level IV**) and ligation of patent ductus arteriosus in infants (Lin et al, 1999 **Level IV**).

### **Complications**

Accidental intravascular injection remains the most life-threatening complication of caudal and epidural analgesia. As the sacrum is largely cartilaginous during infancy and early childhood, there is an increased risk of injecting local anaesthetic into the highly vascular medullary space of the sacrum (Veyckemans et al, 1992 **Level IV**). Sevoflurane attenuated cardiovascular (CV) responses to adrenaline 0.5 mcg/kg less than halothane, and may be a better agent to facilitate detection (Kozek-Langenecker et al, 2000 **Level III-2**). Almost all regional

blocks are performed under general anaesthesia in children, but there is no clear evidence that this obscures early signs of systemic local anaesthetic toxicity (Bernards et al, 2008).

Lipid emulsion infusion has been shown to be of value in managing acute CV toxicity due to accidental intravascular injection of local anaesthetics (Ludot et al, 2008) and is recommended as an early intervention. See Section 5.1.

Neurological damage attributable to paediatric regional analgesia is rare, and the benefit of ensuring a cooperative and immobile infant or child may outweigh the risk of performing regional anaesthesia under general anaesthesia in children (Bernards et al, 2008). Prolonged blockade and immobility may result in nerve compression accompanied by neurological deficit or neuropathic pain (Symons & Palmer, 2008). A retrospective review of 24 005 cases of regional block revealed five serious adverse outcomes, including three deaths, associated with difficult epidural insertions in young infants (Flandin-Blety & Barrier, 1995 **Level IV**). A prospective study including 15 013 central blocks (predominantly caudal blocks) reported 1.5 minor complications per 1000 (Giaufre et al, 1996 **Level IV**). An audit of 10 633 paediatric epidurals performed in the United Kingdom and Ireland reported five serious incidents: two epidural abscesses, and one each of meningism, severe postdural puncture headache requiring autologous blood patch, and a drug volume error resulting in cauda equina syndrome (which was the only case associated with residual symptoms at 12 months). Peripheral or nerve root damage was reported in six cases: three resolved spontaneously, two required chronic pain referral and gabapentin but resolved by 12 months, and one had residual symptoms at 1 year. Compartment syndrome was reported in four children, but symptoms were not masked by the epidural infusion (Llewellyn & Moriarty, 2007 **Level IV**).

Bacterial colonisation of catheters is more commonly associated with caudal than lumbar catheters (Kost-Byerly et al, 1998 **Level IV**), but epidural space infection is rare in the absence of prolonged or repeated insertion or immunodeficiency syndromes (Strafford et al, 1995 **Level IV**).

### ***Intrathecal opioids***

Following cardiac surgery, intrathecal morphine 20 mcg/kg prolonged time to first analgesia and decreased postoperative morphine requirements but did not alter time to discharge from intensive care (Suominen et al, 2004 **Level II**). Addition of intrathecal tetracaine and morphine to IV remifentanyl decreased pain scores and analgesic requirements after early extubation (Hammer et al, 2005 **Level II**).

In infants undergoing lower abdominal and urological surgery, addition of fentanyl 1 mcg/kg (but not lower doses) to intrathecal local anaesthetic prolonged the duration of analgesia and reduced supplemental analgesic requirements (Batra et al, 2008 **Level II**).

### ***Spinal fusion***

Low-dose intrathecal opioids given preoperatively, reduced blood loss and provided good analgesia in the immediate perioperative period (Eschertzhuber et al, 2008 **Level II**). Epidural infusion of local anaesthetic and opioid via a catheter placed prior to wound closure provided comparable (Cassady et al, 2000 **Level II**; O'Hara et al, 2004 **Level II**) or improved analgesia (Sucato et al, 2005 **Level IV**) compared with morphine PCA. Dual catheter techniques improved dermatomal spread and may be more effective (Ekatomdramis et al, 2002 **Level IV**), improving analgesia at rest and on movement (Blumenthal et al, 2005 **Level II**; Blumenthal et al, 2006 **Level II**). PCEA was effective with a high level of patient satisfaction in selected cases (Saudan et al, 2008 **Level IV**).

### Key messages

1. Topical local anaesthetic does not adequately control pain associated with circumcision in awake neonates (**U**) (**Level I** [Cochrane Review]).
2. Caudal local anaesthetic and dorsal penile nerve block provide perioperative analgesia for circumcision (**U**) (**Level I** [Cochrane Review]).
3. Clonidine prolongs analgesia when added to caudal local anaesthetic blocks (**U**) (**Level I**) and improves analgesia when added to epidural local anaesthetic infusions (**U**) (**Level II**).
4. Wound infiltration, peripheral nerve blocks, and caudal local anaesthetic provide effective analgesia after day-case inguinal surgery (**U**) (**Level II**).
5. Epidural infusions of local anaesthetic and systemic opioids provide similar levels of analgesia (**U**) (**Level II**).
6. Epidural opioids alone are less effective than local anaesthetic or combinations of local anaesthetic and opioid (**U**) (**Level II**).
7. Intrathecal opioids provide prolonged analgesia after surgery (**N**) (**Level II**) and reduce blood loss during spinal fusion (**N**) (**Level II**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Caudal local anaesthetic blocks provide effective analgesia for lower abdominal, perineal and lower limb surgery and have a low incidence of serious complications (**U**).
- Continuous epidural infusions provide effective postoperative analgesia in children of all ages and are safe if appropriate doses and equipment are used by experienced practitioners, with adequate monitoring and management of complications (**U**).

## 10.8 ACUTE PAIN IN CHILDREN WITH CANCER

Pain is a common symptom in children with cancer and is associated with significant fear and distress (Ljungman et al, 1999 **Level IV**). Compared with adults, the pattern and sources of acute pain differ significantly in children with cancer.

### 10.8.1 Cancer-related pain

Pain due to tumour is present at diagnosis in the majority of children (Miser et al, 1987 **Level IV**) and usually resolves with initial chemotherapy treatment. Breakthrough cancer pain in children is usually of sudden onset, severe, and of short duration (Friedrichsdorf et al, 2007 **Level IV**). Pain and opioid requirements may escalate in terminal stages of cancer, and benefit has been reported with use of PCA opioids to allow rapid dose titration (Schiessl et al, 2008 **Level IV**) and with addition of ketamine (Finkel et al, 2007 **Level IV**).

### 10.8.2 Procedure-related pain

Children, their parents, and physicians and nurses all rate pain due to procedural interventions and treatment as a significant source of pain (Ljungman et al, 1996; Ljungman et al, 1999). Multiple diagnostic and therapeutic interventions (eg lumbar punctures, bone marrow aspirations, blood samples) are required during the course of treatment and require analgesia matched to the type of procedure and needs of the child (see Section 10.4). EMLA® was evaluated as superior to placebo for pain relief during central venous port access in children



with cancer (Miser et al, 1994 **Level II**). Outcomes for second and subsequent procedures were improved if adequate analgesia was provided for the first procedure (Weisman et al, 1998 **Level III-2**).

### 10.8.3 Treatment-related pain

Pain related to side effects of chemotherapy and radiotherapy is a source of high distress to children with cancer (Collins et al, 2000 **Level IV**; Ljungman et al, 2000 **Level IV**). Mucositis is a common side effect of many chemotherapeutic regimens (Cella et al, 2003), can be difficult to assess (Tomlinson et al, 2008), and is a frequent indication for IV opioid therapy.

Opioid requirements are often high and escalate with the severity of mucositis (Dunbar et al, 1995 **Level IV**; Coda et al, 1997 **Level II**). In patients aged 12 to 18 years, morphine by PCA or continuous infusion provided similar analgesia, but morphine intake and opioid-related side effects were lower in the PCA group (Mackie et al, 1991 **Level II**). A systematic review (which included this study and additional adult studies) found no difference in pain control between PCA and continuous infusion, but reduced hourly opioid requirement and shorter duration of pain with PCA (Clarkson et al, 2007 **Level I**).

PCA morphine and hydromorphone had similar efficacy (Collins et al, 1996 **Level II**) but sufentanil was less effective (Coda et al, 1997 **Level II**). Prolonged administration is often required (6 to 74 days) (Dunbar et al, 1995 **Level IV**). If excessive or dose-limiting side effects occur, rotation to another opioid (morphine to fentanyl or fentanyl to hydromorphone) can produce improvement in the majority of patients, without loss of pain control (Drake et al, 2004 **Level IV**). Postoperative pain related to surgical procedures for diagnostic biopsies, insertion of long-term IV access devices and tumour resection is also a frequent source of treatment-related pain. In children with cancer requiring morphine infusions, the highest rate of breakthrough pain was found in postoperative cases, of which 92% had solid tumours (Flogegard & Ljungman, 2003 **Level IV**). In children with cancer, supplemental IV opioid boluses (either nurse-administered or via PCA) were safely combined with epidural bupivacaine and fentanyl infusion to control postoperative pain. One of 117 patients developed respiratory depression (due to a drug-dose error), but patients were closely monitored and had pre-existing tolerance to opioids (Angheliescu et al, 2008 **Level IV**).

For management of acute cancer pain in general see Section 9.7; for the management of acute mucositis pain see Section 9.6.7.

#### Key messages

1. PCA and continuous opioid infusions are equally effective in the treatment of pain in mucositis, but opioid consumption is less with PCA (**U**) (**Level I**).
2. PCA morphine and hydromorphone are equally effective for the control of pain associated with oral mucositis (**U**) (**Level II**).

## REFERENCES

- Afman CE, Welge JA & Steward DL (2006) Steroids for post-tonsillectomy pain reduction: meta-analysis of randomized controlled trials. *Otolaryngol Head Neck Surg* **134**(2): 181–6.
- Akbas M, Akbas H, Yegin A et al (2005) Comparison of the effects of clonidine and ketamine added to ropivacaine on stress hormone levels and the duration of caudal analgesia. *Paediatr Anaesth* **15**(7): 580–5.
- Allan CY, Jacqueline PA & Shubhda JH (2003) Caudal epidural block versus other methods of postoperative pain relief for circumcision in boys. *Cochrane Database Syst Rev*(2): CD003005.
- Allegaert K, Van den Anker JN, Verbesselt R et al (2005) O-demethylation of tramadol in the first months of life. *Eur J Clin Pharmacol* **61**(11): 837–42.
- Allegaert K, Vanhole C, de Hoon J et al (2005) Nonselective cyclo-oxygenase inhibitors and glomerular filtration rate in preterm neonates. *Pediatr Nephrol* **20**(11): 1557–61.
- Allegaert K, van den Anker JN, de Hoon JN et al (2008) Covariates of tramadol disposition in the first months of life. *Br J Anaesth* **100**(4): 525–32.
- Anand KJ, Barton BA, McIntosh N et al (1999) Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. *Arch Pediatr Adolesc Med* **153**(4): 331–8.
- Anand KJ, Hall RW, Desai N et al (2004) Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet* **363**(9422): 1673–82.
- Anand P, Wilson R & Sheehy EC (2005) Intraligamentary analgesia for post-operative pain control in children having dental extractions under general anaesthesia. *Eur J Paediatr Dent* **6**(1): 10–5.
- Anand KJ, Anderson BJ, Holford NH et al (2008) Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. *Br J Anaesth* **101**(5): 680–9.
- Anderson B, Kanagasundaram S & Woollard G (1996) Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. *Anaesth Intensive Care* **24**(6): 669–73.
- Anderson BJ, Woollard GA & Holford NH (2001) Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. *Eur J Clin Pharmacol* **57**(8): 559–69.
- Anderson BJ, van Lingen RA, Hansen TG et al (2002) Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. *Anesthesiology* **96**(6): 1336–45.
- Anderson BJ (2004) Comparing the efficacy of NSAIDs and paracetamol in children. *Paediatr Anaesth* **14**(3): 201–17.
- Anderson BJ & Palmer GM (2006) Recent pharmacological advances in paediatric analgesics. *Biomed Pharmacother* **60**(7): 303–9.
- Anderson BJ (2008) Paracetamol (Acetaminophen): mechanisms of action. *Paediatr Anaesth* **18**(10): 915–21.
- Andreoli SP (2004) Acute renal failure in the newborn. *Semin Perinatol* **28**(2): 112–23.
- Andrews K & Fitzgerald M (2002) Wound sensitivity as a measure of analgesic effects following surgery in human neonates and infants. *Pain* **99**(1-2): 185–95.
- Angelescu DL, Burgoyne LL, Oakes LL et al (2005) The safety of patient-controlled analgesia by proxy in pediatric oncology patients. *Anesth Analg* **101**(6): 1623–7.
- Angelescu DL, Ross CE, Oakes LL et al (2008) The safety of concurrent administration of opioids via epidural and intravenous routes for postoperative pain in pediatric oncology patients. *J Pain Symptom Manage* **35**(4): 412–9.
- Ansermino M, Basu R, Vandebek C et al (2003) Nonopioid additives to local anaesthetics for caudal blockade in children: a systematic review. *Paediatr Anaesth* **13**(7): 561–73.
- Antila H, Manner T, Kuurila K et al (2006) Ketoprofen and tramadol for analgesia during early recovery after tonsillectomy in children. *Paediatr Anaesth* **16**(5): 548–53.

- Antok E, Bordet F, Duflou F et al (2003) Patient-controlled epidural analgesia versus continuous epidural infusion with ropivacaine for postoperative analgesia in children. *Anesth Analg* **97**(6): 1608–11.
- Arana A, Morton NS & Hansen TG (2001) Treatment with paracetamol in infants. *Acta Anaesthesiol Scand* **45**(1): 20–9.
- Aranda JV, Varvarigou A, Beharry K et al (1997) Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. *Acta Paediatr* **86**(3): 289–93.
- Aranda JV & Thomas R (2006) Systematic review: intravenous ibuprofen in preterm newborns. *Semin Perinatol* **30**(3): 114–20.
- Aspirot A, Puligandla PS, Bouchard S et al (2008) A contemporary evaluation of surgical outcome in neonates and infants undergoing lung resection. *J Pediatr Surg* **43**(3): 508–12.
- Babl F, Barnett P, Palmer G et al (2007) A pilot study of inhaled methoxyflurane for procedural analgesia in children. *Paediatr Anaesth* **17**(2): 148–53.
- Babl FE, Jamison SR, Spicer M et al (2006) Inhaled methoxyflurane as a prehospital analgesic in children. *Emerg Med Australas* **18**(4): 404–10.
- Babl FE, Oakley E, Puspitadewi A et al (2008) Limited analgesic efficacy of nitrous oxide for painful procedures in children. *Emerg Med J* **25**(11): 717–21.
- Babl FE, Goldfinch C, Mandrawa C et al (2009) Does nebulized lidocaine reduce the pain and distress of nasogastric tube insertion in young children? A randomized, double-blind, placebo-controlled trial. *Pediatrics* **123**(6): 1548–55.
- Bandstra NF & Chambers CT (2008) Pain assessment in children. In: *Clinical Pain Management*. 2nd edn. Breivik H, Campbell WI and Nicholas MK (eds). London, Hodder Arnold. Practice and Procedures: 447–61.
- BAPU (2007) *British Association of Paediatric Urologists: Management of Foreskin Conditions*. [www.apagbi.org.uk/docs/circumcision2007.pdf](http://www.apagbi.org.uk/docs/circumcision2007.pdf). Accessed March 2009.
- Bartocci M, Bergqvist LL, Lagercrantz H et al (2006) Pain activates cortical areas in the preterm newborn brain. *Pain* **122**(1-2): 109–17.
- Batra YK, Arya VK, Mahajan R et al (2003) Dose response study of caudal neostigmine for postoperative analgesia in paediatric patients undergoing genitourinary surgery. *Paediatr Anaesth* **13**(6): 515–21.
- Batra YK, Lokesh VC, Panda NB et al (2008) Dose-response study of intrathecal fentanyl added to bupivacaine in infants undergoing lower abdominal and urologic surgery. *Paediatr Anaesth* **18**(7): 613–9.
- Bean-Lijewski JD, Kruitbosch SH, Hutchinson L et al (2007) Post-tonsillectomy pain management in children: can we do better? *Otolaryngol Head Neck Surg* **137**(4): 545–51.
- Belda S, Pallas CR, De la Cruz J et al (2004) Screening for retinopathy of prematurity: is it painful? *Biol Neonate* **86**(3): 195–200.
- Bellu R, de Waal KA & Zanini R (2008) Opioids for neonates receiving mechanical ventilation. *Cochrane Database Syst Rev*(1): CD004212.
- Berde CB, Yaster M, Meretoja O et al (2008) Stable plasma concentrations of unbound ropivacaine during postoperative epidural infusion for 24–72 hours in children. *Eur J Anaesthesiol* **25**(5): 410–7.
- Bernards CM, Hadzic A, Suresh S et al (2008) Regional anesthesia in anesthetized or heavily sedated patients. *Reg Anesth Pain Med* **33**(5): 449–60.
- Berta E, Spanhel J, Smakal O et al (2008) Single injection paravertebral block for renal surgery in children. *Paediatr Anaesth* **18**(7): 593–7.
- Bhananker SM, Azavedo LF & Splinter WM (2008) Addition of morphine to local anesthetic infiltration does not improve analgesia after pediatric dental extractions. *Paediatr Anaesth* **18**(2): 140–4.
- Blumenthal S, Min K, Nadig M et al (2005) Double epidural catheter with ropivacaine versus intravenous morphine: a comparison for postoperative analgesia after scoliosis correction surgery. *Anesthesiology* **102**(1): 175–80.
- Blumenthal S, Borgeat A, Nadig M et al (2006) Postoperative analgesia after anterior correction of thoracic scoliosis: a prospective randomized study comparing continuous double epidural catheter technique with intravenous morphine. *Spine* **31**(15): 1646–51.

- Boivin JM, Poupon-Lemarquis L, Iraqi W et al (2008) A multifactorial strategy of pain management is associated with less pain in scheduled vaccination of children. A study realized by family practitioners in 239 children aged 4-12 years old. *Fam Pract* **25**(6): 423–9.
- Bolt P, Barnett P, Babi FE et al (2008) Topical lignocaine for pain relief in acute otitis media: results of a double-blind placebo-controlled randomised trial. *Arch Dis Child* **93**(1): 40–4.
- Borland ML, Bergesio R, Pascoe EM et al (2005) Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns* **31**(7): 831–7.
- Borland M, Jacobs I, King B et al (2007) A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* **49**(3): 335–40.
- Bosenberg AT, Thomas J, Cronje L et al (2005) Pharmacokinetics and efficacy of ropivacaine for continuous epidural infusion in neonates and infants. *Paediatr Anaesth* **15**(9): 739–49.
- Bouwmeester NJ, Anand KJ, van Dijk M et al (2001) Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. *Br J Anaesth* **87**(3): 390–9.
- Bouwmeester NJ, Hop WC, van Dijk M et al (2003) Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Med* **29**(11): 2009–15.
- Bouwmeester NJ, van den Anker JN, Hop WC et al (2003) Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. *Br J Anaesth* **90**(5): 642–52.
- Bouwmeester NJ, Anderson BJ, Tibboel D et al (2004) Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. *Br J Anaesth* **92**(2): 208–17.
- Bozkurt P, Kaya G & Yeker Y (1997) Single-injection lumbar epidural morphine for postoperative analgesia in children: a report of 175 cases. *Reg Anesth* **22**(3): 212–7.
- Bozkurt P, Kaya G, Yeker Y et al (2004) Effectiveness of morphine via thoracic epidural vs intravenous infusion on postthoracotomy pain and stress response in children. *Paediatr Anaesth* **14**(9): 748–54.
- Bozkurt P (2005) Use of tramadol in children. *Paediatr Anaesth* **15**(12): 1041–7.
- Brady-Fryer B, Wiebe N & Lander JA (2004) Pain relief for neonatal circumcision. *Cochrane Database Syst Rev*(4): CD004217.
- Bray RJ, Woodhams AM, Vallis CJ et al (1996) Morphine consumption and respiratory depression in children receiving postoperative analgesia from continuous morphine infusion or patient controlled analgesia. *Paediatr Anaesth* **6**(2): 129–34.
- Breau LM, Finley GA, McGrath PJ et al (2002) Validation of the Non-communicating Children's Pain Checklist-Postoperative Version. *Anesthesiology* **96**(3): 528–35.
- Breau LM, McGrath PJ, Camfield CS et al (2002) Psychometric properties of the non-communicating children's pain checklist-revised. *Pain* **99**(1-2): 349–57.
- Breau LM, McGrath PJ, Stevens B et al (2006) Judgments of pain in the neonatal intensive care setting: a survey of direct care staffs' perceptions of pain in infants at risk for neurological impairment. *Clin J Pain* **22**(2): 122–9.
- Breschan C, Jost R, Krumholz R et al (2005) A prospective study comparing the analgesic efficacy of levobupivacaine, ropivacaine and bupivacaine in pediatric patients undergoing caudal blockade. *Paediatr Anaesth* **15**(4): 301–6.
- Bruce E, Franck L & Howard RF (2006) The efficacy of morphine and Entonox analgesia during chest drain removal in children. *Paediatr Anaesth* **16**(3): 302–8.
- Buntine P, Thom O, Babi F et al (2007) Prehospital analgesia in adults using inhaled methoxyflurane. *Emerg Med Australas* **19**(6): 509–14.
- Burton JH, Auble TE & Fuchs SM (1998) Effectiveness of 50% nitrous oxide/50% oxygen during laceration repair in children. *Acad Emerg Med* **5**(2): 112–7.
- Butkovic D, Kralik S, Matolic M et al (2007) Postoperative analgesia with intravenous fentanyl PCA vs epidural block after thoracoscopic pectus excavatum repair in children. *Br J Anaesth* **98**(5): 677–81.

- Butler L, Symons B, Henderson S et al (2005) Hypnosis reduces distress and duration of an invasive medical procedure for children. *Pediatrics* **115**(1): e77–85.
- Buttner W & Finke W (2000) Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: a comprehensive report on seven consecutive studies. *Paediatr Anaesth* **10**(3): 303–18.
- Capici F, Ingelmo PM, Davidson A et al (2008) Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children. *Br J Anaesth* **100**(2): 251–5.
- Cardwell M, Siviter G & Smith A (2005) Non-steroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane Database of Systematic Reviews*(2): CD003591.
- Carr AS, Brennan L, Courtman S et al (2009) *Association of Paediatric Anaesthetists of Great Britain and Ireland. Guidelines on the Prevention of Post-operative Vomiting in Children.* <http://www.apagbi.org.uk/docs/Final%20APA%20POV%20Guidelines%20ASC%2002%2009%20compress.pdf>. Accessed April 2009.
- Cassady JF, Jr., Lederhaas G, Cancel DD et al (2000) A randomized comparison of the effects of continuous thoracic epidural analgesia and intravenous patient-controlled analgesia after posterior spinal fusion in adolescents. *Reg Anesth Pain Med* **25**(3): 246–53.
- Cechvala MM, Christenson D, Eickhoff JC et al (2008) Sedative preference of families for lumbar punctures in children with acute leukemia: propofol alone or propofol and fentanyl. *J Pediatr Hematol Oncol* **30**(2): 142–7.
- Cella D, Pulliam J, Fuchs H et al (2003) Evaluation of pain associated with oral mucositis during the acute period after administration of high-dose chemotherapy. *Cancer* **98**(2): 406–12.
- Cesur M, Alici HA, Erdem AF et al (2007) Effects of reduction of the caudal morphine dose in paediatric circumcision on quality of postoperative analgesia and morphine-related side-effects. *Anaesth Intensive Care* **35**(5): 743–7.
- Chalkiadis GA & Anderson BJ (2006) Age and size are the major covariates for prediction of levobupivacaine clearance in children. *Paediatr Anaesth* **16**(3): 275–82.
- Champion GD, Goodenough B, von Baeyer CL et al (1998) Measurement of pain by self-report. In: *Measurement of Pain in Infants and Children. Progress in Pain Research and Management* edn. Finley GA and McGrath PJ (eds). Seattle, IASP Press. 10: 123–60.
- Charney RL, Yan Y, Schootman M et al (2008) Oxycodone versus codeine for triage pain in children with suspected forearm fracture: a randomized controlled trial. *Pediatr Emerg Care* **24**(9): 595–600.
- Chen E, Joseph M & Zeltzer L (2000) Behavioral and cognitive interventions in the treatment of acute pain in children. *Pediatr Clin North Am* **47**(3): 513–25.
- Chhabra A, Pandey R, Khandelwal M et al (2005) Anesthetic techniques and postoperative emesis in pediatric strabismus surgery. *Reg Anesth Pain Med* **30**(1): 43–7.
- Chiaretti A, Genovese O, Antonelli A et al (2008) Patient-controlled analgesia with fentanyl and midazolam in children with postoperative neurosurgical pain. *Childs Nerv Syst* **24**(1): 119–24.
- Choi WY, Irwin MG, Hui TW et al (2003) EMLA cream versus dorsal penile nerve block for postcircumcision analgesia in children. *Anesth Analg* **96**(2): 396–9.
- Chu YC, Lin SM, Hsieh YC et al (2006) Intraoperative administration of tramadol for postoperative nurse-controlled analgesia resulted in earlier awakening and less sedation than morphine in children after cardiac surgery. *Anesth Analg* **102**(6): 1668–73.
- Clark E, Plint AC, Correll R et al (2007) A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics* **119**(3): 460–7.
- Clarkson JE, Worthington HV & Eden OB (2007) Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev*(2): CD001973.
- Coda BA, O'Sullivan B, Donaldson G et al (1997) Comparative efficacy of patient-controlled administration of morphine, hydromorphone, or sufentanil for the treatment of oral mucositis pain following bone marrow transplantation. *Pain* **72**(3): 333–46.

- Collins JJ, Geake J, Grier HE et al (1996) Patient-controlled analgesia for mucositis pain in children: a three-period crossover study comparing morphine and hydromorphone. *J Pediatr* **129**(5): 722–8.
- Collins JJ, Byrnes ME, Dunkel IJ et al (2000) The measurement of symptoms in children with cancer. *J Pain Symptom Manage* **19**(5): 363–77.
- Constant I, Gall O, Gouyet L et al (1998) Addition of clonidine or fentanyl to local anaesthetics prolongs the duration of surgical analgesia after single shot caudal block in children. *Br J Anaesth* **80**(3): 294–8.
- Costello M, Ramundo M, Christopher NC et al (2006) Ethyl vinyl chloride vapocoolant spray fails to decrease pain associated with intravenous cannulation in children. *Clin Pediatr (Phila)* **45**(7): 628–32.
- Cote CJ, Notterman DA, Karl HW et al (2000) Adverse sedation events in pediatrics: a critical incident analysis of contributing factors. *Pediatrics* **105**(4 Pt 1): 805–14.
- Cote CJ & Wilson S (2006) Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. *Pediatrics* **118**(6): 2587–602.
- Cote CJ (2008) Round and round we go: sedation - what is it, who does it, and have we made things safer for children? *Paediatr Anaesth* **18**(1): 3–8.
- Craven PD, Badawi N, Henderson-Smart DJ et al (2003) Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy. *Cochrane Database Syst Rev*(3): CD003669.
- Crawford MW, Galton S & Naser B (2006) Postoperative morphine consumption in children with sickle-cell disease. *Paediatr Anaesth* **16**(2): 152–7.
- Crawford MW, Hickey C, Zaarour C et al (2006) Development of acute opioid tolerance during infusion of remifentanyl for pediatric scoliosis surgery. *Anesth Analg* **102**(6): 1662–7.
- Crock C, Olsson C, Phillips R et al (2003) General anaesthesia or conscious sedation for painful procedures in childhood cancer: the family's perspective. *Arch Dis Child* **88**(3): 253–7.
- Cucchiario G, Dagher C, Baujard C et al (2003) Side-effects of postoperative epidural analgesia in children: a randomized study comparing morphine and clonidine. *Paediatr Anaesth* **13**(4): 318–23.
- Cucchiario G, Adzick SN, Rose JB et al (2006) A comparison of epidural bupivacaine-fentanyl and bupivacaine-clonidine in children undergoing the Nuss procedure. *Anesth Analg* **103**(2): 322–7.
- Cummings E, Reid G, Finley G et al (1996) Prevalence and source of pain in pediatric inpatients. *Pain* **68**: 25–31.
- Cyna AM & Middleton P (2008) Caudal epidural block versus other methods of postoperative pain relief for circumcision in boys. *Cochrane Database Syst Rev*(4): CD003005.
- Czarnecki ML, Jandrisevits MD, Theiler SC et al (2004) Controlled-release oxycodone for the management of pediatric postoperative pain. *J Pain Symptom Manage* **27**(4): 379–86.
- Czarnecki ML, Ferrise AS, Jastrowski Mano KE et al (2008) Parent/nurse-controlled analgesia for children with developmental delay. *Clin J Pain* **24**(9): 817–24.
- Czarnetzki C, Elia N, Lysakowski C et al (2008) Dexamethasone and risk of nausea and vomiting and postoperative bleeding after tonsillectomy in children: a randomized trial. *JAMA* **300**(22): 2621–30.
- Dadure C, Acosta C & Capdevila X (2004) Perioperative pain management of a complex orthopedic surgical procedure with double continuous nerve blocks in a burned child. *Anesth Analg* **98**(6): 1653–5.
- Dadure C, Bringuier S, Nicolas F et al (2006) Continuous epidural block versus continuous popliteal nerve block for postoperative pain relief after major podiatric surgery in children: a prospective, comparative randomized study. *Anesth Analg* **102**(3): 744–9.
- Dal D, Celebi N, Elvan EG et al (2007) The efficacy of intravenous or peritonsillar infiltration of ketamine for postoperative pain relief in children following adenotonsillectomy. *Paediatr Anaesth* **17**(3): 263–9.
- Das DA, Grimmer KA, Sparnon AL et al (2005) The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: a randomized controlled trial [ISRCTN87413556]. *BMC Pediatr* **5**(1): 1.
- Davies EH & Molloy A (2006) Comparison of ethyl chloride spray with topical anaesthetic in children experiencing venepuncture. *Paediatr Nurs* **18**(3): 39–43.
- de Beer DA & Thomas ML (2003) Caudal additives in children—solutions or problems? *Br J Anaesth* **90**(4): 487–98.



- De Jose Maria B, Banus E, Navarro Egea M et al (2008) Ultrasound-guided supraclavicular vs infraclavicular brachial plexus blocks in children. *Paediatr Anaesth* **18**(9): 838–44.
- De Negri P, Ivani G, Visconti C et al (2001) The dose-response relationship for clonidine added to a postoperative continuous epidural infusion of ropivacaine in children. *Anesth Analg* **93**(1): 71–6.
- Doyle E, Morton NS & McNicol LR (1994) Comparison of patient-controlled analgesia in children by i.v. and s.c. routes of administration. *Br J Anaesth* **72**(5): 533–6.
- Doyle E, Mottart KJ, Marshall C et al (1994) Comparison of different bolus doses of morphine for patient-controlled analgesia in children. *Br J Anaesth* **72**(2): 160–3.
- Drake R, Longworth J & Collins JJ (2004) Opioid rotation in children with cancer. *J Palliat Med* **7**(3): 419–22.
- Duedahl TH & Hansen EH (2007) A qualitative systematic review of morphine treatment in children with postoperative pain. *Paediatr Anaesth* **17**(8): 756–74.
- Dunbar PJ, Buckley P, Gavrin JR et al (1995) Use of patient-controlled analgesia for pain control for children receiving bone marrow transplant. *J Pain Symptom Manage* **10**(8): 604–11.
- Efe E & Ozer ZC (2007) The use of breast-feeding for pain relief during neonatal immunization injections. *Appl Nurs Res* **20**(1): 10–6.
- Eidelman A, Weiss JM, Enu IK et al (2005) Comparative efficacy and costs of various topical anesthetics for repair of dermal lacerations: a systematic review of randomized, controlled trials. *J Clin Anesth* **17**(2): 106–16.
- Eidelman A, Weiss JM, Lau J et al (2005) Topical anesthetics for dermal instrumentation: a systematic review of randomized, controlled trials. *Ann Emerg Med* **46**(4): 343–51.
- Ekatodramis G, Min K, Cathrein P et al (2002) Use of a double epidural catheter provides effective postoperative analgesia after spine deformity surgery. *Can J Anaesth* **49**(2): 173–7.
- Ekbom K, Jakobsson J & Marcus C (2005) Nitrous oxide inhalation is a safe and effective way to facilitate procedures in paediatric outpatient departments. *Arch Dis Child* **90**(10): 1073–6.
- El-Tahtawy A, Kokki H & Reidenberg BE (2006) Population pharmacokinetics of oxycodone in children 6 months to 7 years old. *J Clin Pharmacol* **46**(4): 433–42.
- Engelhardt T, Steel E, Johnston G et al (2003) Tramadol for pain relief in children undergoing tonsillectomy: a comparison with morphine. *Paediatr Anaesth* **13**(3): 249–52.
- Eschertzhuber S, Hohlieder M, Keller C et al (2008) Comparison of high- and low-dose intrathecal morphine for spinal fusion in children. *Br J Anaesth* **100**(4): 538–43.
- Eustace N & O'Hare B (2007) Use of nonsteroidal anti-inflammatory drugs in infants. A survey of members of the Association of Paediatric Anaesthetists of Great Britain and Ireland. *Paediatr Anaesth* **17**(5): 464–9.
- Evans D, Turnham L, Barbour K et al (2005) Intravenous ketamine sedation for painful oncology procedures. *Paediatr Anaesth* **15**(2): 131–8.
- Evans JK, Buckley SL, Alexander AH et al (1995) Analgesia for the reduction of fractures in children: a comparison of nitrous oxide with intramuscular sedation. *J Pediatr Orthop* **15**(1): 73–7.
- Falanga IJ, Lafrenaye S, Mayer SK et al (2006) Management of acute pain in children: safety and efficacy of a nurse-controlled algorithm for pain relief. *Acute Pain* **8**(2): 45–54.
- Farion KJ, Osmond MH, Hartling L et al (2003) Tissue adhesives for traumatic lacerations: a systematic review of randomized controlled trials. *Acad Emerg Med* **10**(2): 110–8.
- Farion KJ, Splinter KL, Newhook K et al (2008) The effect of vapocoolant spray on pain due to intravenous cannulation in children: a randomized controlled trial. *CMAJ* **179**(1): 31–6.
- Finkel JC, Pestieau SR & Quezado ZM (2007) Ketamine as an adjuvant for treatment of cancer pain in children and adolescents. *J Pain* **8**(6): 515–21.
- Fisher P, Wilson SE, Brown M et al (2006) Continuous infraclavicular brachial plexus block in a child. *Paediatr Anaesth* **16**(8): 884–6.
- Fisher WJ, Bingham RM & Hall R (1999) Axillary brachial plexus block for perioperative analgesia in 250 children. *Paediatr Anaesth* **9**(5): 435–8.
- Fitzgerald M, Millard C & MacIntosh N (1988) Hyperalgesia in premature infants. *Lancet* **1**(8580): 292.



- Fitzgerald M (2005) The development of nociceptive circuits. *Nat Rev Neurosci* **6**(7): 507–20.
- Fitzgerald M & Walker SM (2009) Infant pain management: a developmental neurobiological approach. *Nat Clin Pract Neurol* **5**(1): 35–50.
- Flandin-Blety C & Barrier G (1995) Accidents following extradural analgesia in children. The results of a retrospective study. *Paediatr Anaesth* **5**(1): 41–6.
- Fleischmann E, Marhofer P, Greher M et al (2003) Brachial plexus anaesthesia in children: lateral infraclavicular vs axillary approach. *Paediatr Anaesth* **13**(2): 103–8.
- Flogegard H & Ljungman G (2003) Characteristics and adequacy of intravenous morphine infusions in children in a paediatric oncology setting. *Med Pediatr Oncol* **40**(4): 233–8.
- Foeldvari I, Szer IS, Zemel LS et al (2008) A Prospective Study Comparing Celecoxib with Naproxen in Children with Juvenile Rheumatoid Arthritis. *J Rheumatol*.
- Foxlee R, Johansson A, Wejfalk J et al (2006) Topical analgesia for acute otitis media. *Cochrane Database Syst Rev* **3**: CD005657.
- Franck LS, Greenberg CS & Stevens B (2000) Pain assessment in infants and children. *Pediatr Clin North Am* **47**(3): 487–512.
- Fratianne RB, Prensner JD, Huston MJ et al (2001) The effect of music-based imagery and musical alternate engagement on the burn debridement process. *J Burn Care Rehabil* **22**(1): 47–53.
- Frawley GP, Downie S & Huang GH (2006) Levobupivacaine caudal anesthesia in children: a randomized double-blind comparison with bupivacaine. *Paediatr Anaesth* **16**(7): 754–60.
- Friedrichsdorf SJ, Finney D, Bergin M et al (2007) Breakthrough pain in children with cancer. *J Pain Symptom Manage* **34**(2): 209–16.
- Furuya A, Ito M, Fukao T et al (2009) The effective time and concentration of nitrous oxide to reduce venipuncture pain in children. *J Clin Anesth* **21**(3): 190–3.
- Furyk JS, Grabowski WJ, Black LH (2009) Nebulized fentanyl versus intravenous morphine in children with suspected limb fractures in the emergency department: a randomized controlled trial. *Emerg Med Australas* **21**: 203–9.
- Gaffney A, McGrath PJ & Dick B (2003) Measuring pain in children: developmental and instrument issues. In: *Pain in Infants, Children and Adolescents* edn. Schecter NL, Berde CB and Yaster M (eds). Baltimore, Lippincott Williams and Wilkins. 128–41.
- Gal P, Kissling GE, Young WO et al (2005) Efficacy of sucrose to reduce pain in premature infants during eye examinations for retinopathy of prematurity. *Ann Pharmacother* **39**(6): 1029–33.
- Gale G, Franck LS, Kools S et al (2004) Parents' perceptions of their infant's pain experience in the NICU. *Int J Nurs Stud* **41**(1): 51–8.
- Ganesh A, Rose JB, Wells L et al (2007) Continuous peripheral nerve blockade for inpatient and outpatient postoperative analgesia in children. *Anesth Analg* **105**(5): 1234–42.
- Garrido MJ, Habre W, Rombout F et al (2006) Population pharmacokinetic/pharmacodynamic modelling of the analgesic effects of tramadol in pediatrics. *Pharm Res* **23**(9): 2014–23.
- Gazal G & Mackie IC (2007) A comparison of paracetamol, ibuprofen or their combination for pain relief following extractions in children under general anaesthesia: a randomized controlled trial. *Int J Paediatr Dent* **17**(3): 169–77.
- Gerard LL, Cooper CS, Duethman KS et al (2003) Effectiveness of lidocaine lubricant for discomfort during pediatric urethral catheterization. *J Urol* **170**(2 Pt 1): 564–7.
- Ghai B, Ram J, Makkar JK et al (2009) Subtenon block compared to intravenous fentanyl for perioperative analgesia in pediatric cataract surgery. *Anesth Analg* **108**(4): 1132–8.
- Gharavi B, Schott C, Nelle M et al (2007) Pain management and the effect of guidelines in neonatal units in Austria, Germany and Switzerland. *Pediatr Int* **49**(5): 652–8.
- Giafre E, Dalens B & Gombert A (1996) Epidemiology and morbidity of regional anesthesia in children: a one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists. *Anesth Analg* **83**(5): 904–12.
- Grainger J & Saravanappa N (2008) Local anaesthetic for post-tonsillectomy pain: a systematic review and meta-analysis. *Clin Otolaryngol* **33**(5): 411–9.

- Gregory PR & Sullivan JA (1996) Nitrous oxide compared with intravenous regional anesthesia in pediatric forearm fracture manipulation. *J Pediatr Orthop* **16**(2): 187–91.
- Grunau RE, Holsti L & Peters JW (2006) Long-term consequences of pain in human neonates. *Semin Fetal Neonatal Med* **11**(4): 268–75.
- Grunau RV & Craig KD (1987) Pain expression in neonates: facial action and cry. *Pain* **28**(3): 395–410.
- Gupta A, Daggett C, Drant S et al (2004) Prospective randomized trial of ketorolac after congenital heart surgery. *J Cardiothorac Vasc Anesth* **18**(4): 454–7.
- Gupta N, Kumar R, Kumar S et al (2007) A prospective randomised double blind study to evaluate the effect of peribulbar block or topical application of local anaesthesia combined with general anaesthesia on intra-operative and postoperative complications during paediatric strabismus surgery. *Anaesthesia* **62**(11): 1110–3.
- Hammer GB, Ramamoorthy C, Cao H et al (2005) Postoperative analgesia after spinal blockade in infants and children undergoing cardiac surgery. *Anesth Analg* **100**(5): 1283–8.
- Hamunen K & Kontinen V (2005) Systematic review on analgesics given for pain following tonsillectomy in children. *Pain* **117**(1-2): 40–50.
- Hansen TG, Henneberg SW & Hole P (1996) Age-related postoperative morphine requirements in children following major surgery—an assessment using patient-controlled analgesia (PCA). *Eur J Pediatr Surg* **6**(1): 29–31.
- Hatfield LA (2008) Sucrose decreases infant biobehavioral pain response to immunizations: a randomized controlled trial. *J Nurs Scholarsh* **40**(3): 219–25.
- Hee HI, Goy RW & Ng AS (2003) Effective reduction of anxiety and pain during venous cannulation in children: a comparison of analgesic efficacy conferred by nitrous oxide, EMLA and combination. *Paediatr Anaesth* **13**(3): 210–6.
- Henderson JM, Spence DG, Komocar LM et al (1990) Administration of nitrous oxide to pediatric patients provides analgesia for venous cannulation. *Anesthesiology* **72**(2): 269–71.
- Hermann C, Hohmeister J, Demirakca S et al (2006) Long-term alteration of pain sensitivity in school-aged children with early pain experiences. *Pain* **125**(3): 278–85.
- Hernandez-Reif M, Field T, Largie S et al (2001) Childrens' distress during burn treatment is reduced by massage therapy. *J Burn Care Rehabil* **22**(2): 191–5.
- Hicks CL, von Baeyer CL, Spafford PA et al (2001) The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain* **93**(2): 173–83.
- Hiller A, Meretoja OA, Korpela R et al (2006) The analgesic efficacy of acetaminophen, ketoprofen, or their combination for pediatric surgical patients having soft tissue or orthopedic procedures. *Anesth Analg* **102**(5): 1365–71.
- Hock MO, Ooi SB, Saw SM et al (2002) A randomized controlled trial comparing the hair apposition technique with tissue glue to standard suturing in scalp lacerations (HAT study). *Ann Emerg Med* **40**(1): 19–26.
- Hodgson R, Bosenberg A & Hadley L (2000) Congenital diaphragmatic hernia repair—impact of delayed surgery and epidural analgesia. *S Afr J Surg* **38**(2): 31–4.
- Holsti L, Grunau RE, Whifield MF et al (2006) Behavioral responses to pain are heightened after clustered care in preterm infants born between 30 and 32 weeks gestational age. *Clin J Pain* **22**(9): 757–64.
- Holsti L & Grunau RE (2007) Initial validation of the Behavioral Indicators of Infant Pain (BIIP). *Pain* **132**(3): 264–72.
- Honarmand A, Safavi MR & Jamshidi M (2008) The preventative analgesic effect of preincisional peritonsillar infiltration of two low doses of ketamine for postoperative pain relief in children following adenotonsillectomy. A randomized, double-blind, placebo-controlled study. *Paediatr Anaesth* **18**(6): 508–14.
- Howard R, Carter B, Curry J et al (2008) Pain assessment. *Paediatr Anaesth* **18** Suppl 1: 14–8.
- Howard RF (2003) Current status of pain management in children. *JAMA* **290**(18): 2464–9.

- Howard RF, Walker SM, Mota PM et al (2005) The ontogeny of neuropathic pain: postnatal onset of mechanical allodynia in rat spared nerve injury (SNI) and chronic constriction injury (CCI) models. *Pain* **115**(3): 382–9.
- Howard RF, Carter B, Curry J et al (2008) Association of Paediatric Anaesthetists: Good Practice in Postoperative and Procedural Pain. *Pediatric Anesthesia* **18** (Suppl. 1): 1–81.
- Howell TK & Patel D (2003) Plasma paracetamol concentrations after different doses of rectal paracetamol in older children A comparison of 1 g vs. 40 mg x kg(-1). *Anaesthesia* **58**(1): 69–73.
- Humphrey GB, Boon CM, van Linden van den Heuvell GF et al (1992) The occurrence of high levels of acute behavioral distress in children and adolescents undergoing routine venipunctures. *Pediatrics* **90**(1 Pt 1): 87–91.
- Humphreys N, Bays SM, Parry AJ et al (2005) Spinal anesthesia with an indwelling catheter reduces the stress response in pediatric open heart surgery. *Anesthesiology* **103**(6): 1113–20.
- Hunt A, Goldman A, Seers K et al (2004) Clinical validation of the paediatric pain profile. *Dev Med Child Neurol* **46**(1): 9–18.
- Ingelmo PM, Locatelli BG, Sonzogni V et al (2006) Caudal 0.2% ropivacaine is less effective during surgery than 0.2% levobupivacaine and 0.2% bupivacaine: a double-blind, randomized, controlled trial. *Paediatr Anaesth* **16**(9): 955–61.
- Ipp M, Taddio A, Sam J et al (2007) Vaccine-related pain: randomised controlled trial of two injection techniques. *Arch Dis Child* **92**(12): 1105–8.
- Isaac LA, McEwen J, Hayes JA et al (2006) A pilot study of the rectus sheath block for pain control after umbilical hernia repair. *Paediatr Anaesth* **16**(4): 406–9.
- Ivani G, De Negri P, Lonnqvist PA et al (2005) Caudal anesthesia for minor pediatric surgery: a prospective randomized comparison of ropivacaine 0.2% vs levobupivacaine 0.2%. *Paediatr Anaesth* **15**(6): 491–4.
- Jimenez N, Bradford H, Seidel KD et al (2006) A comparison of a needle-free injection system for local anesthesia versus EMLA for intravenous catheter insertion in the pediatric patient. *Anesth Analg* **102**(2): 411–4.
- Johnston CC, Stevens BJ, Boyer K et al (2002) Development of psychologic responses to pain and assessment of pain in infants and toddlers. In: *Pain in Infants, Children and Adolescents* edn. Schecter NL, Berde CB and Yaster M (eds). Baltimore, Lippincott Williams and Wilkins. 105–27.
- Johnston CC, Gagnon A, Rennick J et al (2007) One-on-one coaching to improve pain assessment and management practices of pediatric nurses. *J Pediatr Nurs* **22**(6): 467–78.
- Joshi W, Connelly NR, Reuben SS et al (2003) An evaluation of the safety and efficacy of administering rofecoxib for postoperative pain management. *Anesth Analg* **97**(1): 35–8.
- Juarez Gimenez J, Oliveras M, Hidalgo E et al (1996) Anesthetic efficacy of eutectic prilocaine-lidocaine cream in pediatric oncology patients undergoing lumbar puncture. *Ann Pharmacother* **30**(11): 1235–7.
- Juhl GA & Connors GP (2005) Emergency physicians' practices and attitudes regarding procedural anaesthesia for nasogastric tube insertion. *Emerg Med J* **22**(4): 243–5.
- Kaabachi O, Zerelli Z, Methamem M et al (2005) Clonidine administered as adjuvant for bupivacaine in ilioinguinal-iliohypogastric nerve block does not prolong postoperative analgesia. *Paediatr Anaesth* **15**(7): 586–90.
- Kaplowitz N (2004) Acetaminophen hepatotoxicity: what do we know, what don't we know, and what do we do next? *Hepatology* **40**(1): 23–6.
- Kart T, Christrup LL & Rasmussen M (1997) Recommended use of morphine in neonates, infants and children based on a literature review: Part 2--Clinical use. *Paediatr Anaesth* **7**(2): 93–101.
- Kart T, Walther-Larsen S, Svejborg TF et al (1997) Comparison of continuous epidural infusion of fentanyl and bupivacaine with intermittent epidural administration of morphine for postoperative pain management in children. *Acta Anaesthesiol Scand* **41**(4): 461–5.
- Kaur G, Gupta P & Kumar A (2003) A randomized trial of eutectic mixture of local anesthetics during lumbar puncture in newborns. *Arch Pediatr Adolesc Med* **157**(11): 1065–70.
- Kawaraguchi Y, Otomo T, Ota C et al (2006) A prospective, double-blind, randomized trial of caudal block using ropivacaine 0.2% with or without fentanyl 1 microg kg-1 in children. *Br J Anaesth* **97**(6): 858–61.

- Kelly JJ, Donath S, Jansen K et al (2006) Postoperative sleep disturbance in pediatric patients using patient-controlled devices (PCA). *Paediatr Anaesth* **16**(10): 1051–6.
- Kendall JM, Reeves BC & Latter VS (2001) Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical fractures. *BMJ* **322**(7281): 261–5.
- Kennedy RM, Luhmann JD & Luhmann SJ (2004) Emergency department management of pain and anxiety related to orthopedic fracture care: a guide to analgesic techniques and procedural sedation in children. *Paediatr Drugs* **6**(1): 11–31.
- Khalil S, Lingadevaru H, Bolos M et al (2006) Caudal regional anesthesia, ropivacaine concentration, postoperative analgesia, and infants. *Anesth Analg* **102**(2): 395–9.
- Kirchheiner J, Schmidt H, Tzvetkov M et al (2007) Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics Journal* **7**(4): 257–65.
- Koch J, Manworren R, Clark L et al (2008) Pilot study of continuous co-infusion of morphine and naloxone in children with sickle cell pain crisis. *Am J Hematol* **83**(9): 728–31.
- Koh JL, Fanurik D, Harrison RD et al (2004) Analgesia following surgery in children with and without cognitive impairment. *Pain* **111**(3): 239–44.
- Kokki H, Tuovinen K & Hendolin H (1999) The effect of intravenous ketoprofen on postoperative epidural sufentanil analgesia in children. *Anesth Analg* **88**(5): 1036–41.
- Kokki H, Rasanen I, Reinikainen M et al (2004) Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children. *Clin Pharmacokinet* **43**(9): 613–22.
- Kokki H, Laisalmi M & Vanamo K (2006) Interpleural bupivacaine and intravenous oxycodone for pain treatment after thoracotomy in children. *J Opioid Manag* **2**(5): 290–4.
- Kokki H, Rasanen I, Lasalmi M et al (2006) Comparison of oxycodone pharmacokinetics after buccal and sublingual administration in children. *Clin Pharmacokinet* **45**(7): 745–54.
- Kokki H, Kumpulainen E, Lehtonen M et al (2007) Cerebrospinal fluid distribution of ibuprofen after intravenous administration in children. *Pediatrics* **120**(4): e1002–8.
- Koller DM, Myers AB, Lorenz D et al (2007) Effectiveness of oxycodone, ibuprofen, or the combination in the initial management of orthopedic injury-related pain in children. *Pediatr Emerg Care* **23**(9): 627–33.
- Korpela R, Korvenoja P & Meretoja OA (1999) Morphine-sparing effect of acetaminophen in pediatric day-case surgery. *Anesthesiology* **91**(2): 442–7.
- Kost-Byerly S, Tobin JR, Greenberg RS et al (1998) Bacterial colonization and infection rate of continuous epidural catheters in children. *Anesth Analg* **86**(4): 712–6.
- Kozek-Langenecker SA, Marhofer P, Jonas K et al (2000) Cardiovascular criteria for epidural test dosing in sevoflurane- and halothane-anesthetized children. *Anesth Analg* **90**(3): 579–83.
- Kozer E, Rosenbloom E, Goldman D et al (2006) Pain in infants who are younger than 2 months during suprapubic aspiration and transurethral bladder catheterization: a randomized, controlled study. *Pediatrics* **118**(1): e51–6.
- Kumar P, Rudra A, Pan AK et al (2005) Caudal additives in pediatrics: a comparison among midazolam, ketamine, and neostigmine coadministered with bupivacaine. *Anesth Analg* **101**(1): 69–73.
- Kussman BD & Sethna NF (1998) Pethidine-associated seizure in a healthy adolescent receiving pethidine for postoperative pain control. *Paediatr Anaesth* **8**(4): 349–52.
- Kyllonen M, Olkkola KT, Seppala T et al (2005) Perioperative pharmacokinetics of ibuprofen enantiomers after rectal administration. *Paediatr Anaesth* **15**(7): 566–73.
- Lago P, Garetti E, Merazzi D, Pieragostini L, Ancora G, Pirelli A, Bellieni CV; Pain Study Group of the Italian Society of Neonatology (2009). Guidelines for procedural pain in the newborn. *Acta Paediatr* **98**: 932–9.
- Lander JA, Weltman BJ & So SS (2006) EMLA and amethocaine for reduction of children's pain associated with needle insertion. *Cochrane Database Syst Rev* **3**: CD004236.
- Larsson BA, Lonnqvist PA & Olsson GL (1997) Plasma concentrations of bupivacaine in neonates after continuous epidural infusion. *Anesth Analg* **84**(3): 501–5.

- Lerman J, Nolan J, Eyres R et al (2003) Efficacy, safety, and pharmacokinetics of levobupivacaine with and without fentanyl after continuous epidural infusion in children: a multicenter trial. *Anesthesiology* **99**(5): 1166–74.
- Lesko SM & Mitchell AA (1995) An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA* **273**(12): 929–33.
- Lesko SM & Mitchell AA (1999) The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics* **104**(4): e39.
- Lesko SM, Louik C, Vezina RM et al (2002) Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* **109**(2): E20.
- Leyvi G, Taylor DG, Reith E et al (2005) Caudal anesthesia in pediatric cardiac surgery: does it affect outcome? *J Cardiothorac Vasc Anesth* **19**(6): 734–8.
- Lin YC, Sentivany-Collins SK, Peterson KL et al (1999) Outcomes after single injection caudal epidural versus continuous infusion epidural via caudal approach for postoperative analgesia in infants and children undergoing patent ductus arteriosus ligation. *Paediatr Anaesth* **9**(2): 139–43.
- Lindh V, Wiklund U, Blomquist HK et al (2003) EMLA cream and oral glucose for immunization pain in 3-month-old infants. *Pain* **104**(1-2): 381–8.
- Liossi C, White P & Hatira P (2006) Randomized clinical trial of local anesthetic versus a combination of local anesthetic with self-hypnosis in the management of pediatric procedure-related pain. *Health Psychol* **25**(3): 307–15.
- Liossi C, White P, Franck L et al (2007) Parental pain expectancy as a mediator between child expected and experienced procedure-related pain intensity during painful medical procedures. *Clin J Pain* **23**(5): 392–9.
- Liossi C, White P & Hatira P (2009) A randomized clinical trial of a brief hypnosis intervention to control venepuncture-related pain of paediatric cancer patients. *Pain* **142**(3): 255–63.
- Litalien C & Jacqz-Aigrain E (2001) Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. *Paediatr Drugs* **3**(11): 817–58.
- Ljungman G, Kreuger A, Gordh T et al (1996) Treatment of pain in pediatric oncology: a Swedish nationwide survey. *Pain* **68**(2-3): 385–94.
- Ljungman G, Gordh T, Sorensen S et al (1999) Pain in paediatric oncology: interviews with children, adolescents and their parents. *Acta Paediatr* **88**(6): 623–30.
- Ljungman G, Gordh T, Sorensen S et al (2000) Pain variations during cancer treatment in children: a descriptive survey. *Pediatr Hematol Oncol* **17**(3): 211–21.
- Llewellyn N & Moriarty A (2007) The national pediatric epidural audit. *Paediatr Anaesth* **17**(6): 520–33.
- Locatelli BG, Frawley G, Spotti A et al (2008) Analgesic effectiveness of caudal levobupivacaine and ketamine. *Br J Anaesth* **100**(5): 701–6.
- Lovstad RZ & Stoen R (2001) Postoperative epidural analgesia in children after major orthopaedic surgery. A randomised study of the effect on PONV of two anaesthetic techniques: low and high dose i.v. fentanyl and epidural infusions with and without fentanyl. *Acta Anaesthesiol Scand* **45**(4): 482–8.
- Ludot H, Tharin JY, Belouadah M et al (2008) Successful resuscitation after ropivacaine and lidocaine-induced ventricular arrhythmia following posterior lumbar plexus block in a child. *Anesth Analg* **106**(5): 1572–4.
- Luhmann JD, Kennedy RM, Porter FL et al (2001) A randomized clinical trial of continuous-flow nitrous oxide and midazolam for sedation of young children during laceration repair. *Ann Emerg Med* **37**(1): 20–7.
- Luhmann JD, Schootman M, Luhmann SJ et al (2006) A randomized comparison of nitrous oxide plus hematoma block versus ketamine plus midazolam for emergency department forearm fracture reduction in children. *Pediatrics* **118**(4): e1078–86.
- Lynn A, Nespeca MK, Bratton SL et al (1998) Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. *Anesth Analg* **86**(5): 958–63.
- Lynn AM, Nespeca MK, Bratton SL et al (2000) Intravenous morphine in postoperative infants: intermittent bolus dosing versus targeted continuous infusions. *Pain* **88**(1): 89–95.

- Lynn AM, Bradford H, Kantor ED et al (2007) Postoperative ketorolac tromethamine use in infants aged 6-18 months: the effect on morphine usage, safety assessment, and stereo-specific pharmacokinetics. *Anesth Analg* **104**(5): 1040–51.
- Machotta A, Risse A, Bercker S et al (2003) Comparison between instillation of bupivacaine versus caudal analgesia for postoperative analgesia following inguinal herniotomy in children. *Paediatr Anaesth* **13**(5): 397–402.
- Mackie AM, Coda BC & Hill HF (1991) Adolescents use patient-controlled analgesia effectively for relief from prolonged oropharyngeal mucositis pain. *Pain* **46**(3): 265–9.
- Mahar PJ, Rana JA, Kennedy CS et al (2007) A randomized clinical trial of oral transmucosal fentanyl citrate versus intravenous morphine sulfate for initial control of pain in children with extremity injuries. *Pediatr Emerg Care* **23**(8): 544–8.
- Malviya S, Voepel-Lewis T, Tait AR et al (2001) Pain management in children with and without cognitive impairment following spine fusion surgery. *Paediatr Anaesth* **11**(4): 453–8.
- Malviya S, Voepel-Lewis T, Burke C et al (2006) The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. *Paediatr Anaesth* **16**(3): 258–65.
- Marsh VA, Young WO, Dunaway KK et al (2005) Efficacy of topical anesthetics to reduce pain in premature infants during eye examinations for retinopathy of prematurity. *Ann Pharmacother* **39**(5): 829–33.
- Maxwell LG, Kaufmann SC, Bitzer S et al (2005) The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: a double-blind, prospective, randomized, controlled study. *Anesth Analg* **100**(4): 953–8.
- McEwan A, Sigston PE, Andrews KA et al (2000) A comparison of rectal and intramuscular codeine phosphate in children following neurosurgery. *Paediatr Anaesth* **10**(2): 189–93.
- McGrath PA, Seifert CE, Speechley KN et al (1996) A new analogue scale for assessing children's pain: an initial validation study. *Pain* **64**(3): 435–43.
- McGrath PJ (1998) Behavioural measures of pain. In: *Measurement of Pain in Infants and Children. Progress in Pain Research and Management* edn. Finley GA and McGrath PJ (eds). Seattle, IASP Press. 10: 83–102.
- McGrath PJ, Walco GA, Turk DC et al (2008) Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *J Pain* **9**(9): 771–83.
- McNair C, Ballantyne M, Dionne K et al (2004) Postoperative pain assessment in the neonatal intensive care unit. *Arch Dis Child Fetal Neonatal Ed* **89**(6): F537–41.
- McNeely J, Farber N, Rusy L et al (1997) Epidural analgesia improves outcome following pediatric fundoplication. A retrospective analysis. *Reg Anesth* **22**(1): 16–23.
- McNicol R (1993) Postoperative analgesia in children using continuous s.c. morphine. *Br J Anaesth* **71**(5): 752–6.
- Medical Developments International (2001) *Methoxyflurane inhalation analgesic*. [http://www.medicaldev.com/pdf\\_files/Products\\_Pain\\_Relief\\_Healthcare\\_Professionals\\_Medical/Pentrox\\_MSDS.pdf](http://www.medicaldev.com/pdf_files/Products_Pain_Relief_Healthcare_Professionals_Medical/Pentrox_MSDS.pdf). Accessed April 2009.
- Mellon RD, Simone AF & Rappaport BA (2007) Use of anesthetic agents in neonates and young children. *Anesth Analg* **104**(3): 509–20.
- Ment LR, Vohr BR, Makuch RW et al (2004) Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr* **145**(6): 832–4.
- Migita RT, Klein EJ & Garrison MM (2006) Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. *Arch Pediatr Adolesc Med* **160**(1): 46–51.
- Miner JR, Kletti C, Herold M et al (2007) Randomized clinical trial of nebulized fentanyl citrate versus i.v. fentanyl citrate in children presenting to the emergency department with acute pain. *Acad Emerg Med* **14**(10): 895–8.



- Miser AW, McCalla J, Dothage JA et al (1987) Pain as a presenting symptom in children and young adults with newly diagnosed malignancy. *Pain* **29**(1): 85–90.
- Miser AW, Goh TS, Dose AM et al (1994) Trial of a topically administered local anesthetic (EMLA cream) for pain relief during central venous port accesses in children with cancer. *J Pain Symptom Manage* **9**(4): 259–64.
- Mitchell A, Stevens B, Mungan N et al (2004) Analgesic effects of oral sucrose and pacifier during eye examinations for retinopathy of prematurity. *Pain Manag Nurs* **5**(4): 160–8.
- Moir MS, Bair E, Shinnick P et al (2000) Acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy. *Laryngoscope* **110**(11): 1824–7.
- Monitto CL, Greenberg RS, Kost-Byerly S et al (2000) The safety and efficacy of parent-/nurse-controlled analgesia in patients less than six years of age. *Anesth Analg* **91**(3): 573–9.
- Morton NS (2008) Ketamine for procedural sedation and analgesia in pediatric emergency medicine: a UK perspective. *Paediatr Anaesth* **18**(1): 25–9.
- Moss A, Beggs S, Vega-Avelaira D et al (2007) Spinal microglia and neuropathic pain in young rats. *Pain* **128**(3): 215–24.
- Munro FJ, Fisher S, Dickson U et al (2002) The addition of antiemetics to the morphine solution in patient controlled analgesia syringes used by children after an appendicectomy does not reduce the incidence of postoperative nausea and vomiting. *Paediatr Anaesth* **12**(7): 600–3.
- Murat I, Gall O & Tourniaire B (2003) Procedural pain in children: evidence-based best practice and guidelines. *Reg Anesth Pain Med* **28**(6): 561–72.
- Nagel K, Willan AR, Lappan J et al (2008) Pediatric oncology sedation trial (POST): A double-blind randomized study. *Pediatr Blood Cancer* **51**(5): 634–8.
- Nahum Y, Tenenbaum A, Isaiah W et al (2007) Effect of eutectic mixture of local anesthetics (EMLA) for pain relief during suprapubic aspiration in young infants: a randomized, controlled trial. *Clin J Pain* **23**(9): 756–9.
- Naja ZM, Raf M, El Rajab M et al (2005) Nerve stimulator-guided paravertebral blockade combined with sevoflurane sedation versus general anesthesia with systemic analgesia for postherniorrhaphy pain relief in children: a prospective randomized trial. *Anesthesiology* **103**(3): 600–5.
- Nandi R & Fitzgerald M (2005) Opioid analgesia in the newborn. *Eur J Pain* **9**(2): 105–8.
- Naulaers G, Delanghe G, Allegaert K et al (2005) Ibuprofen and cerebral oxygenation and circulation. *Arch Dis Child Fetal Neonatal Ed* **90**(1): F75–6.
- O'Hara JF, Jr., Cywinski JB, Tetzlaff JE et al (2004) The effect of epidural vs intravenous analgesia for posterior spinal fusion surgery. *Paediatr Anaesth* **14**(12): 1009–15.
- Ozalevli M, Unlugenc H, Tuncer U et al (2005) Comparison of morphine and tramadol by patient-controlled analgesia for postoperative analgesia after tonsillectomy in children. *Paediatr Anaesth* **15**(11): 979–84.
- Ozer Z, Gorur K, Altuncan AA et al (2003) Efficacy of tramadol versus meperidine for pain relief and safe recovery after adenotonsillectomy. *Eur J Anaesthesiol* **20**(11): 920–4.
- Palmer GM (2005) A teenager with severe asthma exacerbation following ibuprofen. *Anaesth Intensive Care* **33**(2): 261–5.
- Palmer GM, Chen SP, Smith KR et al (2007) Introduction and audit of intravenous paracetamol at a tertiary paediatric teaching hospital. *Anaesth Intensive Care* **35**(5): 702–6.
- Palmer GM, Atkins M, Anderson BJ et al (2008) I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth* **101**(4): 523–30.
- Pappas AL, Fluder EM, Creech S et al (2003) Postoperative analgesia in children undergoing myringotomy and placement equalization tubes in ambulatory surgery. *Anesth Analg* **96**(6): 1621–4.
- Pardey G, Grousseau S, de Souza EP et al (2008) Levobupivacaine scalp nerve block in children. *Paediatr Anaesth* **18**(3): 271–2.
- Paut O, Sallabery M, Schreiber-Deturmeny E et al (2001) Continuous fascia iliaca compartment block in children: a prospective evaluation of plasma bupivacaine concentrations, pain scores, and side effects. *Anesth Analg* **92**(5): 1159–63.



- Pendeville PE, Von Montigny S, Dort JP et al (2000) Double-blind randomized study of tramadol vs. paracetamol in analgesia after day-case tonsillectomy in children. *Eur J Anaesthesiol* **17**(9): 576–82.
- Peters JW, Bandell Hoekstra IE, Huijter Abu-Saad H et al (1999) Patient controlled analgesia in children and adolescents: a randomized controlled trial. *Paediatr Anaesth* **9**(3): 235–41.
- Peters JW, Koot HM, de Boer JB et al (2003) Major surgery within the first 3 months of life and subsequent biobehavioral pain responses to immunization at later age: a case comparison study. *Pediatrics* **111**(1): 129–35.
- Peters JW, Koot HM, Grunau RE et al (2003) Neonatal Facial Coding System for assessing postoperative pain in infants: item reduction is valid and feasible. *Clin J Pain* **19**(6): 353–63.
- Phillips DA, Watson AR & MacKinlay D (1998) Distress and the micturating cystourethrogram: does preparation help? *Acta Paediatr* **87**(2): 175–9.
- Pickering AE, Bridge HS, Nolan J et al (2002) Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. *Br J Anaesth* **88**(1): 72–7.
- Pierluisi GJ & Terndrup TE (1989) Influence of topical anesthesia on the sedation of pediatric emergency department patients with lacerations. *Pediatr Emerg Care* **5**(4): 211–5.
- Pokela M-L, Anttila E, Seppala T et al (2005) Marked variation in oxycodone pharmacokinetics in infants. *Paediatr Anaesth* **15**(7): 560–5.
- Ponde VC (2008) Continuous infraclavicular brachial plexus block: a modified technique to better secure catheter position in infants and children. *Anesth Analg* **106**(1): 94–6.
- Priestley S, Kelly AM, Chow L et al (2003) Application of topical local anesthetic at triage reduces treatment time for children with lacerations: a randomized controlled trial. *Ann Emerg Med* **42**(1): 34–40.
- Prins SA, Van Dijk M, Van Leeuwen P et al (2008) Pharmacokinetics and analgesic effects of intravenous propacetamol vs rectal paracetamol in children after major craniofacial surgery. *Paediatr Anaesth* **18**(7): 582–92.
- Quigley C (2002) Hydromorphone for acute and chronic pain. *Cochrane Database Syst Rev*(1): CD003447.
- Raghavan M & Montgomerie J (2008) Anaesthetic management of gastroschisis - a review of our practice over the past 5 years. *Paediatr Anaesth* **18**(8): 731–5.
- Rajamani A, Kamat V, Rajavel VP et al (2007) A comparison of bilateral infraorbital nerve block with intravenous fentanyl for analgesia following cleft lip repair in children. *Paediatr Anaesth* **17**(2): 133–9.
- Ranger M, Johnston CC & Anand KJ (2007) Current controversies regarding pain assessment in neonates. *Semin Perinatol* **31**(5): 283–8.
- Reinoso-Barbero F, Saavedra B, Hervilla S et al (2002) Lidocaine with fentanyl, compared to morphine, marginally improves postoperative epidural analgesia in children. *Can J Anaesth* **49**(1): 67–71.
- Reis EC, Roth EK, Syphan JL et al (2003) Effective pain reduction for multiple immunization injections in young infants. *Arch Pediatr Adolesc Med* **157**(11): 1115–20.
- Riad W & Moussa A (2007) Pre-operative analgesia with rectal diclofenac and/or paracetamol in children undergoing inguinal hernia repair. *Anaesthesia* **62**(12): 1241–5.
- Robert R, Brack A, Blakeney P et al (2003) A double-blind study of the analgesic efficacy of oral transmucosal fentanyl citrate and oral morphine in pediatric patients undergoing burn dressing change and tubbing. *J Burn Care Rehabil* **24**(6): 351–5.
- Rochette A, Dadure C, Raux O et al (2007) A review of pediatric regional anesthesia practice during a 17-year period in a single institution. *Paediatr Anaesth* **17**(9): 874–80.
- Rogers A, Greenwald M, Deguzman M et al (2006) A randomized, controlled trial of sucrose analgesia in infants younger than 90 days of age who require bladder catheterization in the pediatric emergency department. *Acad Emerg Med* **13**(6): 617–22.
- Rosen DA, Morris JL, Rosen KR et al (2000) Analgesia for pediatric thoracostomy tube removal. *Anesth Analg* **90**(5): 1025–8.
- Royal Australasian College of Physicians PCHD (2004) *Policy Statement on Circumcision*. [www.racp.edu.au/page/health-policy-and-advocacy/paediatrics-and-child-health](http://www.racp.edu.au/page/health-policy-and-advocacy/paediatrics-and-child-health). Accessed March 2009.

- Royal Australasian College of Physicians PCHD (2005) *Guideline Statement: Management of Procedure-related Pain in Neonates*. <http://www.racp.edu.au/page/health-policy-and-advocacy/paediatrics-and-child-health>. Accessed April 2009.
- Royal College of Anaesthetists (2009) *Major Complications of Central Neural Blockade in the United Kingdom*. [www.rcoa.ac.uk/index.asp?PageID=717](http://www.rcoa.ac.uk/index.asp?PageID=717). Accessed April 2009.
- Roze JC, Denizot S, Carbajal R et al (2008) Prolonged sedation and/or analgesia and 5-year neurodevelopment outcome in very preterm infants: results from the EPIPAGE cohort. *Arch Pediatr Adolesc Med* **162**(8): 728–33.
- Ruggiero A, Barone G, Liotti L et al (2007) Safety and efficacy of fentanyl administered by patient controlled analgesia in children with cancer pain. *Support Care Cancer* **15**(5): 569–73.
- Rugyte D & Kokki H (2007) Intravenous ketoprofen as an adjunct to patient-controlled analgesia morphine in adolescents with thoracic surgery: a placebo controlled double-blinded study. *Eur J Pain* **11**(6): 694–9.
- Saudan S, Habre W, Ceroni D et al (2008) Safety and efficacy of patient controlled epidural analgesia following pediatric spinal surgery. *Paediatr Anaesth* **18**(2): 132–9.
- Schechter NL, Weisman SJ, Rosenblum M et al (1995) The use of oral transmucosal fentanyl citrate for painful procedures in children. *Pediatrics* **95**(3): 335–9.
- Schechter NL, Zempsky WT, Cohen LL et al (2007) Pain reduction during pediatric immunizations: evidence-based review and recommendations. *Pediatrics* **119**(5): e1184–98.
- Schiessl C, Gravou C, Zernikow B et al (2008) Use of patient-controlled analgesia for pain control in dying children. *Support Care Cancer* **16**(5): 531–6.
- Schilling CG, Bank DE, Borchert BA et al (1995) Tetracaine, epinephrine (adrenalin), and cocaine (TAC) versus lidocaine, epinephrine, and tetracaine (LET) for anesthesia of lacerations in children. *Ann Emerg Med* **25**(2): 203–8.
- Schrör K (2007) Aspirin and Reye syndrome: a review of the evidence. *Paediatr Drugs* **9**(3): 195–204.
- Schuepfer G & Johr M (2005) Psoas compartment block in children: Part I—description of the technique. *Paediatr Anaesth* **15**(6): 461–4.
- Scottish Intercollegiate Guidelines Network (2004) *Safe Sedation of Children Undergoing Diagnostic and Therapeutic Procedures*. <http://www.sign.ac.uk/pdf/sign58.pdf>. Accessed April 2009.
- Semple D, Russell S, Doyle E et al (1999) Comparison of morphine sulphate and codeine phosphate in children undergoing adenotonsillectomy. *Paediatr Anaesth* **9**(2): 135–8.
- Shah P, Aliwalas L & Shah V (2006) Breastfeeding or breast milk for procedural pain in neonates. *Cochrane Database Syst Rev* **3**: CD004950.
- Shah V & Ohlsson A (2007) Venepuncture versus heel lance for blood sampling in term neonates. *Cochrane Database Syst Rev*(4): CD001452.
- Shah V, Taddio A, Kulasekaran K et al (2003) Evaluation of a new lancet device (BD QuikHeel) on pain response and success of procedure in term neonates. *Arch Pediatr Adolesc Med* **157**(11): 1075–8.
- Shanahan EC, Marshall AG & Garrett CP (1983) Adverse reactions to intravenous codeine phosphate in children. A report of three cases. *Anaesthesia* **38**(1): 40–3.
- Sharar SR, Bratton SL, Carrougher GJ et al (1998) A comparison of oral transmucosal fentanyl citrate and oral hydromorphone for inpatient pediatric burn wound care analgesia. *J Burn Care Rehabil* **19**(6): 516–21.
- Sharar SR, Carrougher GJ, Selzer K et al (2002) A comparison of oral transmucosal fentanyl citrate and oral oxycodone for pediatric outpatient wound care. *J Burn Care Rehabil* **23**(1): 27–31.
- Sheeran PW, Rose JB, Fazi LM et al (2004) Rofecoxib administration to paediatric patients undergoing adenotonsillectomy. *Paediatr Anaesth* **14**(7): 579–83.
- Short JA, Barr CA, Palmer CD et al (2000) Use of diclofenac in children with asthma. *Anaesthesia* **55**(4): 334–7.
- Silvasti M, Tarkkila P, Tuominen M et al (1999) Efficacy and side effects of tramadol versus oxycodone for patient-controlled analgesia after maxillofacial surgery. *Eur J Anaesthesiol* **16**(12): 834–9.

- Silver S, Gano D & Gerretsen P (2008) Acute treatment of paediatric migraine: a meta-analysis of efficacy. *J Paediatr Child Health* **44**(1-2): 3–9.
- Simons SHP & Anand KJS (2006) Pain control: opioid dosing, population kinetics and side-effects. *Semin Fetal Neonatal Med* **11**(4): 260–7.
- Singer AJ & Konia N (1999) Comparison of topical anesthetics and vasoconstrictors vs lubricants prior to nasogastric intubation: a randomized, controlled trial. *Acad Emerg Med* **6**(3): 184–90.
- Singer AJ & Stark MJ (2000) Pretreatment of lacerations with lidocaine, epinephrine, and tetracaine at triage: a randomized double-blind trial. *Acad Emerg Med* **7**(7): 751–6.
- Sinha M, Christopher NC, Fenn R et al (2006) Evaluation of nonpharmacologic methods of pain and anxiety management for laceration repair in the pediatric emergency department. *Pediatrics* **117**(4): 1162–8.
- Slater R, Cantarella A, Gallella S et al (2006) Cortical pain responses in human infants. *J Neurosci* **26**(14): 3662–6.
- Slater R, Cantarella A, Franck L et al (2008) How well do clinical pain assessment tools reflect pain in infants? *PLoS Med* **5**(6): e129.
- Smith GA, Strausbaugh SD, Harbeck-Weber C et al (1997) New non-cocaine-containing topical anesthetics compared with tetracaine-adrenaline-cocaine during repair of lacerations. *Pediatrics* **100**(5): 825–30.
- Sparks LA, Setlik J & Luhman J (2007) Parental holding and positioning to decrease IV distress in young children: a randomized controlled trial. *J Pediatr Nurs* **22**(6): 440–7.
- Spektor M, Kaplan J, Kelley J et al (2000) Nebulized or sprayed lidocaine as anesthesia for nasogastric intubations. *Acad Emerg Med* **7**(4): 406–8.
- Splinter WM, Bass J & Komocar L (1995) Regional anaesthesia for hernia repair in children: local vs caudal anaesthesia. *Can J Anaesth* **42**(3): 197–200.
- Steib A, Karcenty A, Calache E et al (2005) Effects of subtenon anesthesia combined with general anesthesia on perioperative analgesic requirements in pediatric strabismus surgery. *Reg Anesth Pain Med* **30**(5): 478–83.
- Stevens B, McGrath P, Gibbins S et al (2003) Procedural pain in newborns at risk for neurologic impairment. *Pain* **105**(1-2): 27–35.
- Stevens B, Yamada J & Ohlsson A (2004) Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*(3): CD001069.
- Stevens B, Franck L, Gibbins S et al (2007) Determining the structure of acute pain responses in vulnerable neonates. *Can J Nurs Res* **39**(2): 32–47.
- Stevens B, McGrath P, Gibbins S et al (2007) Determining behavioural and physiological responses to pain in infants at risk for neurological impairment. *Pain* **127**(1-2): 94–102.
- Steward DL, Welge JA & Myer CM (2003) Steroids for improving recovery following tonsillectomy in children. *Cochrane Database Syst Rev*(1): CD003997.
- Stinson JN, Kavanagh T, Yamada J et al (2006) Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents. *Pain* **125**(1-2): 143–57.
- Stoddard FJ, Ronfeldt H, Kagan J et al (2006) Young burned children: the course of acute stress and physiological and behavioral responses. *Am J Psychiatry* **163**(6): 1084–90.
- Strafford MA, Wilder RT & Berde CB (1995) The risk of infection from epidural analgesia in children: a review of 1620 cases. *Anesth Analg* **80**(2): 234–8.
- Sucato DJ, Duey-Holtz A, Elerson E et al (2005) Postoperative analgesia following surgical correction for adolescent idiopathic scoliosis: a comparison of continuous epidural analgesia and patient-controlled analgesia. *Spine* **30**(2): 211–7.
- Suominen PK, Ragg PG, McKinley DF et al (2004) Intrathecal morphine provides effective and safe analgesia in children after cardiac surgery. *Acta Anaesthesiol Scand* **48**(7): 875–82.
- Suresh S, Barcelona SL, Young NM et al (2004) Does a preemptive block of the great auricular nerve improve postoperative analgesia in children undergoing tympanomastoid surgery? *Anesth Analg* **98**(2): 330–3.

- Symons JA & Palmer GM (2008) Neuropathic pain and foot drop related to nerve injury after short duration surgery and caudal analgesia. *Clin J Pain* **24**(7): 647–9.
- Taber SS & Mueller BA (2006) Drug-associated renal dysfunction. *Crit Care Clin* **22**(2): 357–74.
- Taddio A, Goldbach M, Ipp M et al (1995) Effect of neonatal circumcision on pain responses during vaccination in boys. *Lancet* **345**(8945): 291–2.
- Taddio A, Ohlsson A, Einarson TR et al (1998) A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates. *Pediatrics* **101**(2): E1.
- Taddio A & Katz J (2005) The effects of early pain experience in neonates on pain responses in infancy and childhood. *Paediatr Drugs* **7**(4): 245–57.
- Taddio A, Lee C, Yip A et al (2006) Intravenous morphine and topical tetracaine for treatment of pain in [corrected] neonates undergoing central line placement.[erratum appears in JAMA. 2006 Apr 5;295(13):1518]. *JAMA* **295**(7): 793–800.
- Tay CL & Tan S (2002) Diclofenac or paracetamol for analgesia in paediatric myringotomy outpatients. *Anaesth Intensive Care* **30**(1): 55–9.
- Taylor EM, Boyer K & Campbell FA (2008) Pain in hospitalized children: a prospective cross-sectional survey of pain prevalence, intensity, assessment and management in a Canadian pediatric teaching hospital. *Pain Res Manag* **13**(1): 25–32.
- Teyin E, Derbent A, Balcioglu T et al (2006) The efficacy of caudal morphine or bupivacaine combined with general anesthesia on postoperative pain and neuroendocrine stress response in children. *Paediatr Anaesth* **16**(3): 290–6.
- Tibboel D, Anand KJ & van den Anker JN (2005) The pharmacological treatment of neonatal pain. *Semin Fetal Neonatal Med* **10**(2): 195–205.
- Tobias JD & Baker DK (1992) Patient-controlled analgesia with fentanyl in children. *Clin Pediatr (Phila)* **31**(3): 177–9.
- Tobias JD, Phipps S, Smith B et al (1992) Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. *Pediatrics* **90**(4): 537–41.
- Tomlinson D, Judd P, Hendershot E et al (2008) Establishing literature-based items for an oral mucositis assessment tool in children. *J Pediatr Oncol Nurs* **25**(3): 139–47.
- Treadwell MJ, Franck LS & Vichinsky E (2002) Using quality improvement strategies to enhance pediatric pain assessment. *Int J Qual Health Care* **14**(1): 39–47.
- Tsui BC & Finucane B (2002) Verifying accurate placement of an epidural catheter tip using electrical stimulation. *Anesth Analg* **94**(6): 1670–1.
- Tsui BC (2004) Thoracic epidural catheter placement in infants via the caudal approach under electrocardiographic guidance: simplification of the original technique. *Anesth Analg* **98**(1): 273.
- Twycross A (2007) Children's nurses' post-operative pain management practices: an observational study. *Int J Nurs Stud* **44**(6): 869–81.
- Uman LS, Chambers CT, McGrath PJ et al (2006) Psychological interventions for needle-related procedural pain and distress in children and adolescents. *Cochrane Database Syst Rev*(4): CD005179.
- Vallee E, Carignan M, Lafrenaye S et al (2007) Comparative study of acetaminophen-morphine versus rofecoxib-morphine for post-tonsillectomy pain control. *J Otolaryngol* **36**(5): 264–9.
- van der Marel CD, Anderson BJ, Romsing J et al (2004) Diclofenac and metabolite pharmacokinetics in children. *Paediatr Anaesth* **14**(6): 443–51.
- van der Marel CD, Peters JW, Bouwmeester NJ et al (2007) Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. *Br J Anaesth* **98**(3): 372–9.
- van Dijk M, Bouwmeester NJ, Duivenvoorden HJ et al (2002) Efficacy of continuous versus intermittent morphine administration after major surgery in 0-3-year-old infants; a double-blind randomized controlled trial. *Pain* **98**(3): 305–13.
- Vaughan M, Paton EA, Bush A et al (2005) Does lidocaine gel alleviate the pain of bladder catheterization in young children? A randomized, controlled trial. *Pediatrics* **116**(4): 917–20.
- Veyckemans F, Van Obbergh LJ & Gouverneur JM (1992) Lessons from 1100 pediatric caudal blocks in a teaching hospital. *Reg Anesth* **17**(3): 119–25.

- Viitanen H, Tuominen N, Vaaraniemi H et al (2003) Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy. *Br J Anaesth* **91**(3): 363–7.
- Voepel-Lewis T, Marinkovic A, Kostrzewa A et al (2008) The prevalence of and risk factors for adverse events in children receiving patient-controlled analgesia by proxy or patient-controlled analgesia after surgery. *Anesth Analg* **107**(1): 70–5.
- von Baeyer CL & Spagrud LJ (2007) Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. *Pain* **127**(1-2): 140–50.
- Voronov P, Przybylo HJ & Jagannathan N (2007) Apnea in a child after oral codeine: a genetic variant – an ultra-rapid metabolizer. *Paediatr Anaesth* **17**(7): 684–7.
- Walker SM (2008) Pain in children: recent advances and ongoing challenges. *Br J Anaesth* **101**(1): 101–10.
- Walker SM, Franck LS, Fitzgerald M et al (2009) Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. *Pain* **141**(1-2): 79–87.
- Weintraud M, Marhofer P, Bosenberg A et al (2008) Ilioinguinal/iliohypogastric blocks in children: where do we administer the local anesthetic without direct visualization? *Anesth Analg* **106**(1): 89–93.
- Weisman S, Bernstein B & Schechter N (1998) Consequences of inadequate analgesia during painful procedures in children. *Arch Pediatr Adolesc Med* **152**(2): 147–9.
- Weldon BC, Connor M & White PF (1993) Pediatric PCA: the role of concurrent opioid infusions and nurse-controlled analgesia. *Clin J Pain* **9**(1): 26–33.
- White NJ, Kim MK, Brousseau DC et al (2004) The anesthetic effectiveness of lidocaine-adrenaline-tetracaine gel on finger lacerations. *Pediatr Emerg Care* **20**(12): 812–5.
- Williams DG, Hatch DJ & Howard RF (2001) Codeine phosphate in paediatric medicine. *Br J Anaesth* **86**(3): 413–21.
- Williams DG, Patel A & Howard RF (2002) Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* **89**(6): 839–45.
- Williams DG & Howard RF (2003) Epidural analgesia in children. A survey of current opinions and practices amongst UK paediatric anaesthetists. *Paediatr Anaesth* **13**(9): 769–76.
- Willschke H, Marhofer P, Bosenberg A et al (2005) Ultrasonography for ilioinguinal/iliohypogastric nerve blocks in children. *Br J Anaesth* **95**(2): 226–30.
- Willschke H, Marhofer P, Bosenberg A et al (2006) Epidural catheter placement in children: comparing a novel approach using ultrasound guidance and a standard loss-of-resistance technique. *Br J Anaesth* **97**(2): 200–7.
- Wolf AR & Hughes D (1993) Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine. *Br J Anaesth* **70**(1): 10–6.
- Wolf AR, Doyle E & Thomas E (1998) Modifying infant stress responses to major surgery: spinal vs extradural vs opioid analgesia. *Paediatr Anaesth* **8**(4): 305–11.
- Wolfe TR, Fosnocht DE & Linscott MS (2000) Atomized lidocaine as topical anesthesia for nasogastric tube placement: A randomized, double-blind, placebo-controlled trial. *Ann Emerg Med* **35**(5): 421–5.
- Wrona S, Chisolm DJ, Powers M et al (2007) Improving processes of care in patient-controlled analgesia: the impact of computerized order sets and acute pain service patient management. *Paediatr Anaesth* **17**(11): 1083–9.
- Zempsky WT, Sullivan J, Paulson DM et al (2004) Evaluation of a low-dose lidocaine iontophoresis system for topical anesthesia in adults and children: a randomized, controlled trial. *Clin Ther* **26**(7): 1110–9.
- Zernikow B, Michel E & Anderson B (2007) Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. *J Pain* **8**(3): 187–207.
- Zier JL, Kvam KA, Kurachek SC et al (2007) Sedation with nitrous oxide compared with no sedation during catheterization for urologic imaging in children. *Pediatr Radiol* **37**(7): 678–84.
- Zwaveling J, Bubbers S, van Meurs AH et al (2004) Pharmacokinetics of rectal tramadol in postoperative paediatric patients. *Br J Anaesth* **93**(2): 224–7.

# 11. OTHER SPECIFIC PATIENT GROUPS

## 11.1 THE PREGNANT PATIENT

### 11.1.1 Management of acute pain during pregnancy

Pregnant women with pain that is severe enough to warrant drug treatment (self-administered or prescribed by attendants) represent a problematic cohort in that drugs given to them almost always cross the placenta. While most drugs are safe there are particular times of concern, notably the period of organogenesis (weeks 4 to 10) and just before delivery. Where possible, non-pharmacological treatment options should be considered before analgesic medications are used and ongoing analgesic use requires close liaison between the obstetrician and the medical practitioner managing the pain.

#### **Drugs used in pregnancy**

Drugs that might be prescribed during pregnancy have been categorised according to foetal risk by the Australian Drug Evaluation Committee (ADEC). The categories used are listed in Table 11.1 and the classification of some of the drugs that might be used in pain management is summarised in Table 11.2. A list of these drugs, including regular updates is available from the Therapeutic Goods Administration (TGA, 1999).

#### **Paracetamol**

Paracetamol is regarded as the analgesic of choice during pregnancy (Niederhoff & Zahradnik, 1983), although it has been suggested that prostaglandin actions may have adverse effects in women at high risk of pre-eclampsia (Zelop, 2008 **Level IV**). A large Danish cohort study suggested an increase risk of preterm birth in mothers with pre-eclampsia (Rebordosa et al, 2009 **Level III-3**) following paracetamol exposure in early pregnancy; no increased prevalence of congenital anomalies (Rebordosa, Kogevinas, Horvath-Puho et al, 2008 **Level III-3**); but a slight increase in asthma in infants (Rebordosa, Kogevinas, Sorensen et al, 2008 **Level III-3**). A smaller study reported an increased risk of wheeze in offspring if exposure to paracetamol occurred in mid to late pregnancy (Persky et al, 2008 **Level IV**).

#### **Non-selective non-steroidal anti-inflammatory drugs**

Non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) are Category C drugs. Use of nsNSAIDs during pregnancy was associated with increased risk of miscarriage (Li et al, 2003 **Level III-2**; Nielsen et al, 2004 **Level III-2**). While relatively safe in early and mid pregnancy, they can precipitate fetal cardiac and renal complications in late pregnancy, as well as interfere with fetal brain development and the production of amniotic fluid; they should be discontinued in the 32<sup>nd</sup> gestational week (Ostensen & Skomsvoll, 2004). Fetal exposure to nsNSAIDs has been associated with persistent pulmonary hypertension in the neonate (Alano et al, 2001 **Level III-2**) and an increased risk of premature closure of the ductus arteriosus (Koren et al, 2006 **Level I**).

#### **Opioids**

Most opioids are Category C drugs. Much of the information about the effects of opioids on neonates comes from pregnant patients who abuse opioids or who are on maintenance programs for drug dependence. Maternal opioid use can have significant developmental effects in the fetus, although social and environmental factors (eg other drugs, smoking) may also have an impact (Farid et al, 2008; Winklbaur et al, 2008). Neonatal abstinence syndrome



(NAS) requiring treatment occurs in over 60% to 90% of infants exposed to opioids *in utero* (Farid et al, 2008) and there is no clear relationship between maternal dose and the likelihood or duration of NAS (Bakstad et al, 2009 **Level III-2**). Outcomes tend to be better in mothers on maintenance therapy rather than heroin (Farid et al, 2008 **Level IV**), and although initial studies suggested an advantage of buprenorphine over methadone (Farid et al, 2008 **Level IV**), a recent trial (Bakstad et al, 2009 **Level III-2**) and a meta-analysis (Minozzi et al, 2008 **Level I**) reported no difference in maternal or neonatal outcome with methadone, buprenorphine or oral morphine. A small study suggested that neonatal outcome was better in mothers receiving opioids for chronic pain rather than addiction, although differences in dose and other environmental factors may contribute (Sharpe & Kuschel, 2004 **Level III-2**). Overall, the short-term use of opioids to treat pain in pregnancy appears safe (Wunsch et al, 2003), but minimising use of opioid therapy for chronic pain during pregnancy has been recommended (Chou et al, 2009).

### **Musculoskeletal pain syndromes**

Low back pain and/or pelvic girdle pain are common during pregnancy (Gutke et al, 2008; Borg-Stein & Dugan, 2007) and although low back pain may persist, pelvic girdle pain tends to resolve following delivery (Elden et al, 2008; Vleeming et al, 2008). Epidural techniques in labour did not increase the risk of long-term backache (RR 1.0; 95%CI 0.89 to 1.12) (Anim-Somuah et al, 2005 **Level I**), headache or migraine (Orlikowski et al, 2006 **Level II**).

Pregnancy-specific back support garments reduced movement pain and analgesic use (Kalus et al, 2008 **Level III-2**) but strengthening exercises reduced back pain (Pennick & Young, 2007 **Level I**), and exercise rather than a pelvic belt was recommended for pelvic girdle pain during pregnancy (Vleeming et al, 2008 **Level I**). Weak evidence for improvements with acupuncture (Pennick & Young, 2007 **Level I**; Ee et al, 2008 **Level I**; Vleeming et al, 2008 **Level I**) and chiropractic care (Stuber & Smith, 2008 **Level I**) has been found in systematic reviews, but studies included were of low quality. Oral magnesium therapy did not reduce the frequency or severity of painful leg cramps during pregnancy (Nygaard et al, 2008 **Level II**).

### **Meralgia paresthetica**

This variable condition comprising some or all of the sensations of pain, tingling and numbness in the lateral thigh affects pregnant women in particular, with an increased odds ratio of 12 in comparison with a non-pregnant population (van Slobbe et al, 2004 **Level III-2**). Multiple therapies have been reported, but have not been fully evaluated or compared, including ice packs, local infiltration with steroid and local anaesthetic, topical lignocaine or capsaicin, transcutaneous electrical nerve stimulation (TENS), drug therapy (eg tricyclic antidepressants [TCAs], antiepileptics) and surgical intervention (Van Diver & Camann, 1995 **Level IV**; Harney & Patijn, 2007 **Level IV**). Other compressive neuropathies, such as carpal tunnel syndrome and Bell's palsy also occur more commonly during pregnancy (Sax & Rosenbaum, 2006 **Level IV**).

### **Symphysial diastasis**

This occasionally disabling disorder (sometimes called osteitis pubis) involving separation of the symphysis pubis during pregnancy or immediately after delivery, has a quoted incidence of 1:600 (Taylor & Sonson, 1986 **Level IV**) and can produce persistent pain, but there are limited data to inform management (Aslan & Fynes, 2007).



## Key messages

1. Exercises reduce back and pelvic pain during pregnancy. There is weak evidence for improvements with acupuncture and chiropractic care (**N**) (**Level I**).
2. Use of NSAIDs during pregnancy is associated with an increased risk of miscarriage (**U**) (**Level III-2**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- For pain management in pregnancy non-pharmacological treatment options should be considered where possible before analgesic medications are used (**U**).
- Use of medications for pain in pregnancy should be guided by published recommendations; ongoing analgesic use requires close liaison between the obstetrician and the medical practitioner managing the pain (**U**).
- NSAIDs should be used with caution in the last trimester of pregnancy and should be avoided after the 32<sup>nd</sup> week (**U**).

**Table 11.1 ADEC drug categorisation according to fetal risk**

A	Drugs that have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B1	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
B2	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
B3	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Drugs that, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Drugs that have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Notes: For drugs in the B1, B2 and B3 categories, human data are lacking or inadequate and subcategorisation is therefore based on available animal data. The allocation of a B category does NOT imply greater safety than the C category. Drugs in category D are not absolutely contraindicated in pregnancy (eg anticonvulsants). Moreover, in some cases the 'D' category has been assigned on the basis of 'suspicion'.

Due to legal considerations in Australia, sponsor companies have, in some cases, applied a more restrictive category than can be justified on the basis of the available data.

In some cases there may be discrepancies between the published product information and the information in this booklet due to the process of ongoing document revision.

Source: ADEC (1999). © Commonwealth of Australia. Reproduced with permission (see notes on verso page).

**Table 11.2** Categorisation of drugs used in pain management

Drug	Cat	Comments
<b>Opioids</b>		
alfentanil, buprenorphine, dextromoramide, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, remifentanil, tramadol	C	Opioid analgesics may cause respiratory depression in the newborn infant. Withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs.
codeine, dihydrocodeine	A	Prolonged high-dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate
<b>Paracetamol</b>		
	A	
<b>Aspirin</b>		
	C	Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause premature closure of the fetal ductus arteriosus, delay labour and birth. Aspirin increases the bleeding time both in the newborn infant and in the mother because of its antiplatelet effects. Products containing aspirin should be avoided in the last trimester. Low-dose aspirin (100 mg/day) does not affect bleeding time.
<b>Other nsNSAIDs</b>		
diclofenac, diflunisal, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, nabumetone, naproxen, phenylbutazone, piroxicam, sodium salicylate, sulindac, tenoxicam, tiaprofenic acid	C	These agents inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation and delayed labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.
<b>Coxibs</b>		
celecoxib	B3	
parecoxib	C	
<b>Local anaesthetics</b>		
bupivacaine, cinchocaine, lignocaine (lidocaine), mepivacaine, prilocaine	A	
etidocaine, ropivacaine	B1	
procaine hydrochloride	B2	
levobupivacaine	B3	
<b>Antidepressants</b>		
<b>SSRIs:</b>		
citalopram, fluoxetine, fluvoxamine, sertraline	C	SSRIs have had limited use in pregnancy without a reported increase in birth defects. The use of SSRIs in the third trimester may result in a withdrawal state in the newborn infant.
paroxetine	D	Category changed Sept 2005

Drug	Cat	Comments
<i>Tricyclic antidepressants:</i>		
amitriptyline, clomipramine, desipramine, dothiepin (dosulepin), doxepin, imipramine, nortriptyline, protriptyline, trimipramin	C	Withdrawal symptoms in newborn infants have been reported with prolonged maternal use of this class of drugs.
<i>Other antidepressants:</i>		
mirtazapine, moclobemide,	B3	
nefazodone	B2	
venlafaxine		
<b>Anticonvulsants</b>		
carbamazepine	D	Spina bifida occurs in about 1% of pregnancies in which carbamazepine is used as monotherapy. Carbamazepine taken during pregnancy also has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability. Carbamazepine also can cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn infant, which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.
phenytoin sodium	D	This drug taken during pregnancy has been associated with craniofacial defects, fingernail hypoplasia, developmental disability, growth retardation and less frequently, oral clefts and cardiac anomalies. This clinical pattern is sometimes called the 'fetal hydantoin syndrome'. Phenytoin can also cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn infant, which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.
sodium valproate	D	If taken in the first trimester of pregnancy, sodium valproate (valproic acid) is associated with a 1–2% risk of neural tube defects (especially spina bifida) in the exposed fetus. Women taking sodium valproate (valproic acid) who become pregnant should be encouraged to consider detailed mid-trimester morphology ultrasound for prenatal diagnosis of such abnormalities.
lamotrigine	D	Category changed June 2006
clonazepam	C	Clonazepam is a benzodiazepine. These drugs may cause hypotonia, respiratory depression and hypothermia in the newborn infant if used in high doses during labour. Withdrawal symptoms in newborn infants have been reported with this class of drugs.
gabapentin	B1	
tiagabine, topiramate, pregabalin	B3	
lamotrigine	D	

Drug	Cat	Comments
<b>Antiemetics, antinauseants</b>		
<i>Phenothiazines:</i>		
prochlorperazine, promethazine, thiethylperazine	C	When given in high doses during late pregnancy, phenothiazines have caused prolonged neurological disturbances in the infant.
<i>Others:</i>		
dimenhydrinate, diphenhydramine, metoclopramide	A	
dolasetron, granisetron, ondansetron	B1	
domperidone, hyoscine, hyoscine hydrobromide	B2	
tropisetron	B3	

Source: ADEC (1999). © Commonwealth of Australia. Reproduced with permission (see notes on verso page).

### 11.1.2 Management of pain during delivery

Pain during labour and delivery represents a complex interaction of multiple physiological and psychological factors involved in parturition. Women's desires for and expectations of pain relief during labour and delivery vary widely. High quality relief does not necessarily equate with a high level of satisfaction and no difference in satisfaction was reported following epidural or non-epidural analgesia (Anim-Somuah et al, 2005 **Level I**). Severe pain during labour is one of several factors associated with post-traumatic stress symptoms following childbirth (Slade, 2006 **Level IV**). Consistent with pain experience in other settings, high scores on a pain catastrophising scale have been associated with increased report of intense labour pain (Flink et al, 2009 **Level IV**).

Women should have access to safe and appropriate maternity services, including anaesthesia and analgesia (RANZCOG et al, March 2009). Guidelines from the American Society of Anesthesiologists (ASA) Taskforce on Obstetric Anesthesia include recommendations for analgesia during labour and delivery (ASA, 2007).

#### **Systemic analgesia in labour pain**

Systemic opioid analgesics continue to be used in labour although practice varies, as there are insufficient data to evaluate the comparative efficacy and safety of different opioids (Tuckey et al, 2008 **Level IV**). IM tramadol provided similar pain relief to pethidine in the first stage of labour, but pain scores remained high in both groups and side effects were more common following tramadol (Khooshideh & Shahriari, 2009 **Level II**). IV administration has greater efficacy than equivalent IM dosing (Isenor & Penny-MacGillivray, 1993 **Level II**).

In comparison with epidural analgesia, systemic opioids provided less analgesia and increased the need for additional pain relief methods, although with no measurable difference in maternal satisfaction (Anim-Somuah et al, 2005 **Level I**). Their use also worsened fetal acid-base balance (Reynolds et al, 2002 **Level I**).

A quantitative assessment of the efficacy of nitrous oxide (N<sub>2</sub>O) inhalational analgesia is currently not possible. However, although it is not a potent labour analgesic, it is safe (Rosen, 2002 **Level I**). In cross-over comparisons with N<sub>2</sub>O, self-administration of low-concentration sevoflurane (0.8%) (Yeo et al, 2007 **Level III-2**) and IV PCA remifentanil (Volmanen et al, 2005 **Level II**) reduced pain to a greater degree, but also increased sedation. Although, IV PCA remifentanil can reduce pain, particularly in early labour, it had less effect on pain scores and

produced greater maternal sedation when compared with epidural analgesia (Volmanen et al, 2008 **Level II**). In addition, PCA remifentanyl has been associated with maternal apnoea and there is currently no consensus on the optimal dosing regimen (Hill, 2008 **Level IV**).

### **Epidural and combined spinal-epidural analgesia for labour pain**

Epidural analgesia provided better pain relief than non-epidural analgesia (weighted mean difference [WMD] -2.6; CI -3.82 to -1.38; VAS 0 to 10). Although associated with an increased use of oxytocin (RR 1.18; CI 1.03 to 1.34) and longer second stage of labour (WMD 15.6 minutes; CI 7.5 to 23.6), there was no increase in the incidence of low neonatal 5-minute Apgar Scores (RR 1.18; CI 0.92 to 1.5) (Anim-Somuah et al, 2005 **Level I**). Epidural analgesia increased the risk of instrumental vaginal birth (RR 1.38; CI 1.24 to 1.53), but did not increase the rate of Caesarean section (RR 1.07; CI 0.93 to 1.23) (Anim-Somuah et al, 2005 **Level I**). Although almost 90% of women can achieve optimal analgesia with epidural techniques, suboptimal analgesia has been associated with an increased risk of second-stage outcomes (Caesarean section, mid-pelvic procedures and severe perineal tears) (Abenheim & Fraser, 2008 **Level III-2**).

The timing of neuraxial analgesia is based on the degree of cervical dilatation in some centres. In nulliparous women, on-demand administration of neuraxial analgesia from early labour (<4 cm cervical dilation) provided more effective pain relief and did not increase the rate of Caesarean section or instrumental vaginal delivery when compared with commencement of epidural analgesia later in labour (Marucci et al, 2007 **Level I**; Wong et al, 2009 **Level II**). By contrast, women receiving early systemic opioid analgesia before late epidural analgesia had a higher incidence of instrumental vaginal delivery. Infants of mothers receiving early neuraxial analgesia had improved neonatal acid-base status, a reduced requirement for naloxone, but no measurable difference in Apgar scores when compared with infants of mothers receiving parenteral opioid analgesia (Marucci et al, 2007 **Level I**). However, it was also noted that many of the included studies did not score highly for quality, and a lack of blinding may produce bias.

Combined spinal-epidural (CSE) analgesia in labour had a faster onset of analgesia than epidural analgesia (Goodman et al, 2009 **Level II**; Simmons et al, 2007 **Level I**). Foetal heart rate abnormalities have been reported following CSE: this has also been associated with increased uterine hypotonus (Abrao et al, 2009 **Level II**), high maternal pain scores and older maternal age (Nicolet et al, 2008 **Level IV**). As CSE does not improve satisfaction or mobilisation, and increases the risk of pruritus, clinical advantages over epidural analgesia (either traditional or low dose) are limited (Simmons et al, 2007 **Level I**).

#### **Note: reversal of conclusion**

This reverses the Level 1 conclusion in the previous edition of this document, which concluded that maternal satisfaction was increased.

Low dose (0.1%) bupivacaine/opioid infusions in comparison with 0.25% bupivacaine bolus dose injection reduced motor block and instrumental vaginal delivery rate (Comparative Obstetric Mobile Epidural Trial (COMET) Study Group, 2001 **Level II**). There was no significant difference in any outcome between the use of bupivacaine and ropivacaine (Halpern & Walsh, 2003 **Level I**).

Combination of epidural fentanyl with levobupivacaine 0.125%, bupivacaine 0.125% or ropivacaine 0.2% produced effective analgesia, although pain scores were higher in the levobupivacaine group and motor block was greater with bupivacaine (Atienzar et al, 2008

**Level II).** Respiratory depression related to epidural or intrathecal opioids during labour was rare (Carvalho, 2008 **Level IV**).

Patient-controlled epidural analgesia (PCEA) can provide effective analgesia but the optimal settings are not clear (Leo & Sia, 2008 **Level IV**; Halpern & Carvalho, 2009 **Level I**). A systematic review concluded that dilute concentrations of bupivacaine or ropivacaine provide acceptable analgesia, and that use of large bolus doses and background infusions with PCEA may improve analgesia (Halpern & Carvalho, 2009 **Level I**). A comparison of demand dose-only PCEA, PCEA with a continuous infusion, and a continuous epidural infusion only during labour, showed that dose-only PCEA resulted in less total epidural dose compared with the other modalities; no differences were noted with respect to pain scores, motor block, duration of labour, number of staff interventions, delivery outcome, and maternal satisfaction score (Vallejo et al, 2007 **Level II**). However, a later systematic review of PCEA in labour analgesia concluded that the use of a continuous background epidural infusion combined with PCEA resulted in improved maternal analgesia and reduced unscheduled clinician interventions (Halpern & Carvalho 2009, **Level I**).

Single-injection intrathecal opioids were as effective as epidural local anaesthetics for the management of pain in early labour; there was increased pruritus but no effect on nausea or mode of delivery (Bucklin et al, 2002 **Level I**). Intrathecal opioids increased the risk of fetal bradycardia (NNH 28) and maternal pruritus (NNH 1.7) in comparison with non-intrathecal opioid analgesia (Mardirosoff et al, 2002 **Level I**). Continuous intrathecal infusion improved early analgesia with no differences in neonatal or obstetric outcomes, but more technical difficulties when compared with epidural administration (Arkoosh et al, 2008 **Level II**).

### **Other regional techniques in labour pain**

Paracervical block was more effective than IM opioids (Jensen et al, 1984 **Level II**) but required supplementation more frequently than epidural analgesia (Manninen et al, 2000 **Level II**) and was less effective than single-shot intrathecal analgesia (Junttila et al, 2009 **Level III-2**). Serious fetal complications may occur (Shnider et al, 1970), although this technique may have a role in hospitals without obstetric anaesthesia services (Levy et al, 1999 **Level III-2**) or in patients with contraindications for spinal techniques (Junttila et al, 2009 **Level III-2**).

### **Complementary and other methods of pain relief in labour**

Continuous or one-to-one support by a midwife or trained layperson during labour reduced analgesic use, operative delivery and dissatisfaction, especially if the support person was not a member of the hospital staff, was present from early labour, or if an epidural analgesia service was not available (Hodnett et al, 2007 **Level I**).

Non-pharmacological or complementary therapies may be used during labour. Acupuncture decreased the need for pain relief (RR 0.7; CI 0.49 to 1.0) and women taught self-hypnosis had reduced pharmacological requirements (RR 0.53; CI 0.36 to 0.79), a slight decrease in need for epidural analgesia (RR 0.30, CI 0.22 to 0.40), and increased satisfaction compared with controls (Smith et al, 2006 **Level I**). The efficacy of acupressure, aromatherapy, audio analgesia, relaxation or massage has not been established (Smith et al, 2006 **Level I**). TENS reduced reports of severe pain during labour, but a consistent reduction in pain scores or in requirements for other analgesia could not be confirmed (Dowswell et al, 2009 **Level I**). Few complementary therapies have been carefully studied in well-designed trials with clinically relevant outcomes, and sample sizes have been small (Smith et al, 2006 **Level I**).

## Pain after Caesarean section

After Caesarean section utilising epidural anaesthesia, epidural opioids were more effective than intermittent injections of parenteral opioids (ASA, 2007 **Level I**). Single-dose epidural morphine (particularly a slow-release formulation) (Carvalho et al, 2007 **Level II**) or intrathecal morphine (Girgin et al, 2008 **Level II**) reduced post Caesarean section analgesic requirements. The addition of clonidine to intrathecal hyperbaric bupivacaine improved early analgesia after Caesarean section, but did not reduce morphine consumption during the first 24 hours (van Tuijl et al, 2006 **Level II**).

Following Caesarean section under general anaesthesia, local anaesthetic wound infiltration reduced postoperative opioid requirements (Bamigboye & Justus, 2008 **Level II**), and bolus doses of local anaesthetic via an incisional catheter were as effective as epidural bolus doses (Ranta et al, 2006 **Level II**). Following Caesarean section under spinal anaesthesia, local anaesthetic transversus abdominus block reduced postoperative opioid requirements (McDonnell et al, 2008 **Level II**), but addition of a coxib had no advantage over intrathecal morphine alone (Carvalho et al, 2006 **Level II**). Local anaesthetic techniques (wound infiltration or catheter, ilio-inguinal/ilio-hypogastric block, transversus abdominus plane block) reduce opioid consumption following Caesarean section performed under general or regional anaesthesia, but the impact on opioid-related side-effects was not evaluated (Bamigboye & Hofmeyr, 2009 **Level I**).

Prior caesarean section is a risk factor for chronic pelvic pain (Latthe et al, 2006 **Level I**).

Persistent post-surgical pain has been reported in 6% to 12% of women following Caesarean section (Nikolajsen et al, 2004 **Level IV**), is likely to be neuropathic in nature and may be under-recognised (Gillett & Jones, 2009).

### Key messages

1. Epidural and combined spinal-epidural analgesia provide superior pain relief for labour and delivery compared with systemic analgesics (**S**) (**Level I** [Cochrane Review]).
2. Combined spinal-epidural in comparison with epidural analgesia reduces time to effective analgesia and increases the incidence of pruritus (**U**), does not increase maternal satisfaction (**R**), but increases the risk of urinary retention (**N**) (**Level I** [Cochrane Review]).
3. Epidural analgesia does not increase the incidence of Caesarean section or long-term backache (**S**) (**Level I** [Cochrane Review]).
4. Epidural analgesia is associated with increased duration of labour and increased rate of instrumental vaginal delivery (**S**) (**Level I** [Cochrane Review]).
5. Hypnosis used in labour reduces analgesic requirements (**S**) and improves satisfaction (**N**) (**Level I** [Cochrane Review]).
6. Acupuncture reduces analgesic requirements in labour (**U**) (**Level I** [Cochrane Review]).
7. TENS may reduce severe pain in labour but does not reliably reduce pain scores (**U**) or analgesic requirements (**N**) (**Level I** [Cochrane Review]).
8. Local anaesthetic wound infiltration and abdominal nerve blocks reduce opioid consumption following Caesarean section (**N**) (**Level I** [Cochrane Review]).
9. Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, operative delivery and dissatisfaction (**U**) (**Level I**).
10. There is no significant difference in any outcome between use of bupivacaine and ropivacaine for epidural labour analgesia (**U**) (**Level I**).



11. Patient-controlled epidural analgesia provides effective analgesia but optimal settings are not clear (**N**) (**Level I**).
12. Single-injection intrathecal opioids provide comparable early labour analgesia to epidural local anaesthetics with increased pruritus (**U**) (**Level I**).
13. Systemic opioids in labour increase the need for neonatal resuscitation and worsen acid-base status compared with regional analgesia (**U**) (**Level I**).
14. Nitrous oxide has some analgesic efficacy and is safe during labour (**U**) (**Level I**).

### 11.1.3 Pain management during lactation

A number of general principles apply when administering analgesic and antiemetic drugs for pain management during lactation:

- the choice of drugs should be based on knowledge of their potential impact on breastfeeding and on the breastfed infant secondary to transfer in human milk; and
- the lowest possible effective maternal dose of analgesic is recommended, breastfeeding is best avoided at times of peak drug concentration in milk, and the infant should be observed for effects of medication transferred in breast milk.

The effects of many analgesic and antiemetic drugs during lactation have not been adequately investigated, leaving clinical decisions to be made on evidence derived from pharmacokinetic or observational studies, case reports and anecdote. For most drugs, information on infant outcome is inadequate (based on single-dose or short-term administration or on case reports) or absent, so maternal consent is advisable and caution is warranted.

The principles of passage of drugs in human milk (Ito, 2000; Berlin & Briggs, 2005; Ilett & Kristensen, 2005) including drugs relevant to pain management (Rathmell et al, 1997; Spigset & Hagg, 2000; Bar-Oz et al, 2003) have been reviewed. The maternal plasma concentration, which is influenced by the dose and the ability of the mother to metabolise the drug, is an important determinant of drug levels in milk. High lipid solubility, low molecular weight, low protein binding and the unionised state favour secretion into breast milk. Most drugs have a milk-to-plasma ratio of 1 or less (Ito, 2000). The neonatal exposure is often 0.5% to 4% of the maternal dose, but infant drug metabolism may be impaired, and much of the data is from single maternal dose studies rather than chronic therapy (Berlin & Briggs, 2005). A safe level of infant exposure to a drug has been arbitrarily defined as no more than 10% of the therapeutic dose for infants (or the adult dose standardised by weight if the infant dose is not known) (Ito, 2000). Until about the third to fourth postpartum day only very small amounts of colostrum are secreted, so early breastfeeding is unlikely to pose a hazard, even from drugs administered in the peripartum period.

Lactating women having surgical procedures with general anaesthetic have been advised to discard their milk for 24 hours following the operation. Following single intraoperative doses of midazolam (2 mg), propofol (2.5 mg/kg), and fentanyl (100 mcg), less than 0.1% of the drugs were excreted into milk within 24 hours, suggesting that interruption of breastfeeding may not be required (Nitsun et al, 2006 **Level III-3**).

Drugs that might be prescribed during lactation have been categorised according to their risk for the baby. Some of the drugs that might be used in pain management are listed with comments in Table 11.3.

## **Paracetamol and non-steroidal anti-inflammatory drugs**

The weight-adjusted maternal dose of paracetamol transferred to the neonate was 1.85% (Notarianni et al, 1987). Although neonatal glucuronide conjugation may be deficient, the drug is considered safe as there have been no reports of adverse effects and levels in breast milk are a fraction of the recommended neonatal doses.

If an anti-inflammatory is required, nsNSAIDs are preferable to aspirin (Berlin & Briggs, 2005 **Level IV**). Despite similar proportional transfer as paracetamol, salicylates are eliminated slowly by the neonate, cause platelet dysfunction and have been associated with Reye's syndrome; aspirin in analgesic doses cannot be recommended as safe (Bar-Oz et al, 2003).

NsNSAIDs must be considered individually, but in general milk levels are low because they are weak acids and extensively plasma protein bound. In particular, ibuprofen has very low transfer (< 1% weight-adjusted maternal dose), is short acting, free of active metabolites and has the best documented safety (Ito, 2000). Diclofenac and ketorolac are minimally transported into breast milk and short-term or occasional use is compatible with breastfeeding. The safety of naproxen is less clear but it is also considered compatible (Rathmell et al, 1997).

Indomethacin (indometacin) has been associated with central maternal side effects, such as agitation and psychosis, in previously healthy postnatal women (Clunie et al, 2003 **Level IV**). Following a single 200 mg dose of celecoxib, less than 0.5% of the weight-adjusted maternal dose was present in breast milk, suggesting that breastfeeding during routine dosing poses minimal risk (Gardiner et al, 2006 **Level III-3**; Hale et al, 2004 **Level III-3**).

## **Opioids and tramadol**

With some provisos, the short-term use of opioids is generally considered safe during lactation (Ravin, 1995) as most opioids are secreted into breast milk in low doses.

An association between opioid exposure in breast milk and episodes of apnoea and cyanosis in infants has been described (Naumburg & Meny, 1988 **Level IV**), leading some to suggest that opioids should be avoided if the neonate experiences such events during the first week of life. Morphine has been recommended as the opioid of choice if potent analgesia is required in breastfeeding mothers (Ito, 2000 **Level IV**). About 6% of the weight-adjusted maternal dose of morphine is transferred in breast milk (Feilberg et al, 1989), but the oral bioavailability in the infant is low (about 25%), so only small amounts reach the infant. In mothers treated with IV PCA morphine for 48 hours following Caesarean section, levels of morphine and M6G were low in breast milk, suggesting minimal drug would be transferred to the neonate (Baka et al, 2002).

Pharmacokinetic studies also suggest the more lipophilic opioids such as fentanyl and alfentanil are unlikely to cause problems. Following a single dose of IV fentanyl, the weight-adjusted maternal dose received by the neonate was 3%, levels in colostrum became undetectable within several hours and the nursing infant appeared unaffected (Steer et al, 1992 **Level IV**).

Breastfed infants whose mothers received pethidine (meperidine) were less alert and oriented to auditory cues after Caesarean section than those of mothers receiving morphine (Wittels et al, 1997 **Level II**). As norpethidine (normeperidine) accumulates in breast milk with repeated use and has very slow neonatal elimination, pethidine use during breastfeeding is not recommended (Ito, 2000).

Codeine has a milk-to-plasma ratio of slightly more than 1 suggesting it is generally safe (Meny et al, 1993), but morphine toxicity and death has been reported in a breastfed neonate whose mother was an ultra-rapid metaboliser of codeine (Madadi et al, 2008 **Level IV**). A relationship between infant central nervous system (CNS) symptoms (decreased alertness, lethargy, poor

feeding) and maternal symptoms, codeine dose, and in some cases CYP2D6 phenotype, has been identified (Madadi et al, 2009 **Level III-3**).

As oxycodone is concentrated in human breast milk, and breastfed infants may receive >10% of a therapeutic dose, safety with repeated maternal dosing has been questioned (Ito, 2000). As a component of multimodal analgesia in the first 72 hours after Caesarean section, there may be minimal risk to breastfeeding infants as only a low volume of milk is ingested during this period (Seaton et al, 2007 **Level III-3**).

Use of tramadol (100 mg 6 hrly) on days 2 to 4 after Caesarean section was associated with a milk-to-plasma ratio of 2.2, a relative infant dose of 2.9%, and no detectable behavioural effects in the infants (Ilett et al, 2008 **Level III-2**). However, as with other drugs, these data cannot be directly extrapolated to long-term use at later postpartum stages when the volume of ingested milk is higher.

Methadone is considered compatible with breastfeeding. Plasma levels of methadone were low in infants of breastfeeding mothers on methadone maintenance programs, and no effect on infant neurobehavioural outcomes were found on days 3, 14 and 30 following birth (Jansson et al, 2008 **Level III-3**).

### **Other medications related to pain relief**

After epidural administration, local anaesthetics showed acceptable milk-to-plasma ratios of 1.1 for lignocaine (lidocaine) and 0.34 for bupivacaine (Ortega et al, 1999) and 0.25 for ropivacaine (Matsota et al, 2009), which are considered safe (Rathmell et al, 1997). Use of epidural analgesia (local anaesthetic ± fentanyl) during labour (Chang & Heaman, 2005 **Level III-3**) or as PCEA after Caesarean section (Matsota et al, 2009 **Level IV**) did not influence neurobehavioural scores in healthy term infants.

There is very little information about antiemetic use, and in almost all cases the manufacturers do not recommend their use during lactation (for recommendations see Table 11.3). Animal studies suggest possible CNS effects in the newborn, but human anecdotal experience is favourable.

In a single case report, the milk-to-plasma concentration of gabapentin was 0.86, the relative infant dose was 2.4%, and no adverse effects were noted in the infant. While suggestive of safety during lactation, a careful individual risk-benefit analysis was suggested (Kristensen et al, 2006 **Level IV**).

**Table 11.3 The breastfeeding patient and drugs used in pain management**

<b>Drug</b>	<b>Comments</b>
<b>Opioids</b>	
buprenorphine, codeine, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, pentazocine, tramadol	Safe to use occasional doses. Use repeated doses with caution, especially if infant is premature or <4 weeks old; monitor infant for sedation and other adverse effects
<b>Paracetamol</b>	Safe to use
<b>Aspirin</b>	Avoid due to theoretical risk of Reye's syndrome; ibuprofen is preferred
<b>Other NSAIDs</b>	
NsNSAIDs, Coxibs	Safe to use Limited data; appear safe
<b>Ketamine</b>	Limited data, avoid use

Drug	Comments
<b>Local anaesthetics</b>	
bupivacaine, cinchocaine, levobupivacaine lignocaine (lidocaine), mepivacaine, prilocaine, ropivacaine	Unlikely to cause problems
<b>Antidepressants</b>	
<i>SSRIs:</i>	
citalopram, fluvoxamine, paroxetine, sertraline	SSRIs are used in postnatal depression (some consider sertraline one of the preferred antidepressants in breastfeeding).
fluoxetine	Use an alternative SSRI because of fluoxetine's long half-life
<i>Tricyclic antidepressants (TCAs):</i>	
amitriptyline, clomipramine, dothiepin (dosulepin), doxepin, imipramine, nortriptyline, trimipramin	TCAs have been used to treat postnatal depression. Avoid doxepin if possible; a single case of neonatal respiratory depression has been reported
<i>Other antidepressants:</i>	
moclobemide	Appears to be safe; contact specialised information service
mirtazapine, venlafaxine	Contact specialised information service
<b>Anticonvulsants</b>	
carbamazepine	Safe to use; monitor infant for drowsiness and poor suckling
phenytoin sodium	May be used
sodium valproate	Should be safe to use
clonazepam	Risk of sedation in infant; contact specialised information service
gabapentin, tiagabine	Contact specialised information service
pregabalin	No data available
lamotrigine, topiramate	Excreted in breast milk; contact specialised information service
<b>Antiemetics, antinauseants</b>	
<i>Phenothiazines:</i>	
prochlorperazine	Safe to use
promethazine	Safe to use; however, may cause drowsiness or tiredness in mother
<i>Others:</i>	
dimenhydrinate	Safe to use
metoclopramide	Safe to use (used to stimulate lactation)
dolasetron, granisetron, ondansetron, tropisetron	Contact specialised information service; no data available, although 1 or 2 doses after delivery should not be a concern
domperidone	Used during first months of breastfeeding to stimulate lactation; mother may be less drowsy than with metoclopramide
hyoscine hydrobromide	Safe to use occasional doses

Drug	Comments
droperidol, haloperidol	Avoid if possible, or contact one of the pregnancy drug information centres; if used monitor infant for sedation

Source: Information taken with permission from *Australian Medicines Handbook 2009*.

### Key messages

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Prescribing medications during lactation requires consideration of possible transfer into breast milk, uptake by the baby and potential adverse effects for the baby; it should follow available prescribing guidelines (U).
- Local anaesthetics, paracetamol and several non-selective NSAIDs, in particular ibuprofen, are considered to be safe in the lactating patient (U).
- Morphine and fentanyl are considered safe in the lactating patient and are preferred over pethidine (U).

## 11.1.4 Pain management in the puerperium

Pain during the puerperium is common and of multiple aetiologies, most often being perineal or uterine cramping pain initially and breast pain from the fourth postpartum day. Women are often inadequately warned and remain ill informed of the best available treatments for postnatal pain. In the first 6 months postpartum, backache was reported by 44% of women and perineal pain by 21%, and many indicated they would have liked more help or advice (Brown & Lumley, 1998). Severe perineal and uterine pain limited mobility during maternal-infant bonding, and perineal trauma and pain was associated with delayed resumption of sexual relations after birth (Williams et al, 2007 **Level IV**). Breast, especially nipple, pain may result in abandonment of breastfeeding (Morland-Schultz & Hill, 2005).

### Perineal pain

A number of obstetric and surgical factors contribute to perineal pain following delivery. After adjusting for parity, perineal trauma, and length of labour, women with instrumented versus unassisted vaginal deliveries reported more perineal pain (Thompson et al, 2002 **Level IV**).

Restrictive use versus routine mediolateral episiotomy reduced the rate of episiotomy from 75% to 28% and reduced the risk of severe perineal trauma and the requirement for suturing, but did not influence the incidence or degree of perineal pain (Carroli & Mignini, 2009 **Level I**). In comparison with interrupted suturing methods, continuous suturing (particularly of all layers rather than skin only) was associated with reductions in pain and analgesic use (Kettle et al, 2007 **Level I**).

### Non-pharmacological treatments

There is only limited evidence to support the effectiveness of local cooling treatments (ice packs, cold gel pads, cold/iced baths) for relieving pain from perineal trauma sustained during childbirth, and pulsed electromagnetic energy was more effective than ice packs (East et al, 2007 **Level I**). Although improvement in perineal pain has been reported with ultrasound, there is insufficient evidence to fully evaluate efficacy (Hay-Smith, 2000 **Level I**).

For women without prior vaginal delivery, antenatal perineal massage (from 35 weeks gestation) reduced the incidence of perineal trauma requiring suturing (NNT 14; CI 9 to 35) and the requirement for episiotomy (NNT 23; CI 13 to 111), but values for NNT were high.

Effects on acute postpartum pain have not been reported, but a reduction in the incidence of pain at 3 months postpartum was reported in women who used antenatal massage and had previously given birth vaginally (Beckmann & Garrett, 2006 **Level I**).

### **Pharmacological treatments**

Paracetamol is moderately effective for perineal pain during the first 24 hours after birth. nsNSAID suppositories reduced perineal pain in the first 24 hours postpartum (Hedayati et al, 2003 **Level I**). Both oral celecoxib and diclofenac reduced perineal pain, with slight advantages of celecoxib for pain scores at rest and incidence of gastrointestinal symptoms (Lim et al, 2008 **Level II**).

Topical local anaesthetics (lignocaine, cinchocaine, pramoxine plus hydrocortisone preparations) and placebo did not improve pain relief in the 24 hours postpartum. One trial reported a reduction in supplemental analgesic requirements with epifoam (1% hydrocortisone and 1% pramoxine in mucoadhesive base). The use of systemic analgesics was not standardised across studies and may be a confounding factor (Hedayati et al, 2005 **Level I**). Following mediolateral episiotomy repair under epidural analgesia, a pudendal block with ropivacaine improved pain scores and reduced the proportion of women requiring additional analgesia (Aissaoui et al, 2008 **Level II**).

### **Breast pain**

Painful breasts are a common reason for ceasing breastfeeding (Morland-Schultz & Hill, 2005). Management is firstly directed toward remedying the cause, whether this is infant-related (incorrect attachment, sucking, oral abnormalities); lactation-related (breast engorgement, blocked ducts or forceful milk ejection); nipple trauma; dermatological or infective problems (Candida or mastitis); or other causes (Amir, 2003).

Nipple pain is experienced by 30% to 90% of women and tends to peak around the third day postpartum (Morland-Schultz & Hill, 2005). Topical agents (such as lanolin, wet compresses, hydrogel dressings, collagenase or dexpanthenol ointment) produce mild improvements in nipple pain, but no one agent was shown to be superior. Education in relation to proper breastfeeding technique is important for decreasing the incidence of nipple pain (Morland-Schultz & Hill, 2005 **Level I**).

Mastitis defined by at least two breast symptoms (pain, redness or lump) and at least one of fever or flu-like symptoms occurs in 17% to 33% of breastfeeding women, with most episodes occurring in the first 4 weeks (Amir et al, 2007 **Level IV**; Jahanfar et al, 2009 **Level I**). Infective mastitis is most commonly from *Staphylococcus aureus*, and non-infective mastitis is equally common. Currently, there is insufficient evidence to confirm efficacy for antibiotics in relieving symptoms, but only two trials met the inclusion criteria for analysis (Jahanfar et al, 2009 **Level I**).

Symptomatic therapies for breast engorgement have been inadequately investigated, but cabbage leaves and cabbage extract cream were no more effective than placebo (Snowden et al, 2001 **Level I**). Similarly, ultrasound was not effective and observed benefits may be due to the effect of radiant heat or massage (Snowden et al, 2001 **Level I**).

### **Uterine pain**

Uterine pain or 'after pains' often worsen with increasing parity, are experienced by most multiparous women, and result from the release of oxytocin from the posterior pituitary gland especially in response to breastfeeding. Lower abdominal pain may be mild to severe, accompanied by back pain and is described as throbbing, cramping and aching. Ergot alkaloids during the third stage of labour increased the requirement for analgesia for pain after birth due to persistent uterine contraction (RR 2.53; CI 1.34 to 4.78), but also decreased mean blood

loss and the incidence of postpartum haemorrhage compared with no uterotonic drugs (Liabsuetrakul et al, 2007 **Level I**).

Paracetamol and nsNSAIDs had similar efficacy for reducing uterine cramping pain and were modestly effective compared with placebo (Skovlund et al, 1991a **Level II**; Skovlund et al, 1991b **Level II**; Huang et al, 2002 **Level II**; Hsu et al, 2003 **Level II**).

High-intensity TENS was more effective than low-intensity TENS for postpartum uterine pain, but also produced more local discomfort (Olsen et al, 2007 **Level III-2**).

### Key messages

1. Routine episiotomy does not reduce perineal pain (**U**) (**Level I**).
2. Paracetamol and non-selective NSAIDs are effective in treating perineal pain after childbirth (**U**) (**Level I**).
3. Paracetamol and non-selective NSAIDs are equally but only modestly effective in treating uterine pain (**U**) (**Level II**).
4. Topical agents may improve nipple pain, but no one treatment is superior (**N**) (**Level I**).
5. There is only limited evidence to support the effectiveness of local cooling treatments in treatment of perineal pain after childbirth (**Q**) (**Level I**).
6. Topical local anaesthetic preparations are not effective for perineal pain after childbirth (**N**) (**Level I**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Pain after childbirth requires appropriate treatment as it coincides with new emotional, physical and learning demands and may trigger postnatal depression (**U**).
- Management of breast and nipple pain should target the cause (**U**).

## 11.2 THE OLDER PATIENT

The need to manage acute pain in the older patient is becoming more common as the population ages. Advances in anaesthetic and surgical techniques mean that increasingly older patients, including patients over 100 years old (Konttinen & Rosenberg, 2006), are undergoing more major surgery (Kojima & Narita, 2006). Medical conditions that are more common in older people may also lead to acute pain; these include acute exacerbations of arthritis, osteoporotic fractures of the spine, cancer and pain from other acute medical conditions including ischaemic heart disease, herpes zoster and peripheral vascular disease.

Factors that can combine to make effective control of acute pain in the older person more difficult than in younger patients include: a higher incidence of coexistent diseases and concurrent medications, which increases the risk of drug-drug and disease-drug interactions; age-related changes in physiology, pharmacodynamics and pharmacokinetics; altered responses to pain; and difficulties with assessment of pain, including problems related to cognitive impairment.



### 11.2.1 Pharmacokinetic and pharmacodynamic changes

The changes in physiology and effects on pharmacokinetics and pharmacodynamics in older people, and consequent alterations that might be required in some drug regimens are summarised in Table 11.4. The information in this table centres on opioids in view of their widespread use. The changes, the onset of which can be highly variable between individuals, are generally attributable to ageing alone but may be compounded by the higher incidence of degenerative and other concurrent diseases in older people.

**Table 11.4** Direction and approximate magnitude of physiological changes apparent in an older population (> 70 years) and the effects of individual changes on pharmacokinetic variables

Physiological process	Magnitude	Likely kinetic / dynamic consequence	Dose strategy
<i>Whole body</i>			
Cardiac output	↓ 0–20%	↓ central compartment volume ↑ peak concentration after bolus	<ul style="list-style-type: none"> <li>▪ smaller initial bolus dose</li> <li>▪ slower injection rate</li> </ul>
Fat	↑ 10–50% then ↓	Drug specific changes in distribution volume	<ul style="list-style-type: none"> <li>▪ drug specific – dose based on total body weight or lean body weight</li> </ul>
Muscle mass/ blood flow	↓ 20%		
Plasma volume	Little change		
Total body water	↓ 10%	↓ distribution volume (water-soluble drugs)	
Plasma albumin	↓ 20%	↑ free fraction of drug	<ul style="list-style-type: none"> <li>▪ potential for changes in clearance and oral bioavailability</li> <li>▪ potential for changes in cerebral effects</li> </ul>
Alpha 1 glycoprotein	↑ 30–50%	↔ hepatic clearance of high extraction drugs	
Drug binding	Drug specific	↑ hepatic clearance of low extraction drugs ↑ cerebral uptake of drug	
<i>Liver and gut</i>			
Liver size	↓ 25–40%	↓ hepatic clearance of high extraction drugs ↔ hepatic clearance of low extraction drugs	<ul style="list-style-type: none"> <li>▪ minimal effect on IV bolus dose</li> <li>▪ ↓ maintenance dose</li> <li>▪ potential for changes in oral bioavailability</li> </ul>
Hepatic blood flow	↓ 25–40%		
Phase I (eg oxidation)	↓ 25%	↓ hepatic clearance (some low extraction drugs)	
Phase II	Little change		

Physiological process	Magnitude	Likely kinetic / dynamic consequence	Dose strategy
<i>Kidney</i>			
Nephron mass	↓ 30%	↓ clearance (polar) drugs	<ul style="list-style-type: none"> <li>▪ ↓ maintenance dose (renally cleared drugs)</li> <li>▪ assume, and monitor for, accelerated accumulation of polar active (M6G) or toxic (M3G, norpethidine) metabolites</li> </ul>
Renal blood flow	↓ 10% / decade	Little effect on opioids (parent compound)	
Plasma flow at 80 years	↓ 50%	↓ clearance of some active metabolites (eg M6G)	
Glomerular filtration rate	↓ 30–50%		
Creatinine clearance	↓ 50–70%		
<i>CNS</i>			
Cerebral blood flow and metabolism	↓ 20%	↓ distribution to the CNS	<ul style="list-style-type: none"> <li>▪ little net effect on dose</li> </ul>
Cerebral volume	↓ 20%	↓ apparent volume in the CNS	
Active BBB transport (efflux)	↓ (drug specific)	↑ apparent volume in the CNS	<ul style="list-style-type: none"> <li>▪ ↓ bolus dose during titration</li> <li>▪ ↓ maintenance dose</li> </ul>
Pain threshold sensitivity	Little change	↑ apparent increase in CNS sensitivity	
Concentration response (opioids)	↑ 50% for some opioids	↑ response to opioids	<ul style="list-style-type: none"> <li>▪ ↓ bolus dose during titration</li> <li>▪ ↓ maintenance dose</li> </ul>

Note that the net effect of these changes in drug disposition may be minimal

M6G: morphine-6-glucuronide; M3G: morphine-3-glucuronide.

Source: Reproduced with kind permission from Macintyre & Upton, *Acute Pain Management in the Elderly Patient* Table 28.1, p 506 *Clinical Pain Management: Acute Pain*, Hodder Arnold.

Assessment of the pharmacodynamic changes associated with ageing is difficult. When such studies have been done with opioids, most have used a surrogate measure of effect other than clinical pain relief. For example, by studying the effects of fentanyl and alfentanil on the electroencephalogram (EEG) it was concluded that the pharmacokinetics were unaffected by age, but that the sensitivity of the brain to these opioids was increased by 50% in the older person (Scott & Stanski, 1987). Whether this can be attributed to changes in the number or function of opioid receptors in the CNS (in older rats there are fewer  $\mu$ - and  $\kappa$ -opioid receptors (Vuyk, 2003) or whether it is due to an increased penetration of opioids in the CNS is unclear. Some of the changes that may lead to increased drug sensitivity in the older patient are discussed below (see Section 11.2.2).

### 11.2.2 Physiology and perception of pain

Reviews by Gibson (Gibson, 2003), Gibson and Farrell (Gibson & Farrell, 2004) and Gagliese and Farrell (Gagliese & Farrell, 2005) summarise the age-related changes that occur in pain perception and the neurophysiology of nociception.

In general, in the nervous system of the older person, there are extensive alterations in structure, neurochemistry and function of both peripheral and central nervous systems, including neurochemical deterioration of the opioid and serotonergic systems. Therefore there may be changes in nociceptive processing, including impairment of the pain inhibitory system.

The peripheral nerves show a decrease in the density of both myelinated and, particularly, unmyelinated peripheral nerve fibres, an increase in the number of fibres with signs of damage or degeneration and a slowing of the conduction velocity; in rats, reductions in substance P, calcitonin gene-related peptide (CGRP) and somatostatin levels have been reported.

Similar structural and neurochemical changes have been noted in the CNS. In older humans there are sensory neuron degenerative changes and loss of myelin in the dorsal horn of the spinal cord as well as reductions in substance P, CGRP and somatostatin levels. Decreases in noradrenergic and serotonergic neurons may contribute to the impairment of descending inhibitory mechanisms and may underlie the decrease in pain tolerance seen in the older person (see below). Age-related loss of neurons and dendritic connections is seen in the human brain, particularly in the cerebral cortex including those areas involved in nociceptive processing; synthesis, axonal transport and receptor binding of neurotransmitters also change. Opioid receptor density is decreased in the brain but not in the spinal cord, and there may be decreases in endogenous opioids. However, the functional consequences of such age-related changes remains a subject of debate and recent functional MRI (fMRI) studies show more similarities than differences in the magnitude of activation in the brain response to acute noxious stimulation (Cole et al, 2008).

Variations in pain perception are best determined in controlled situations where severity of the noxious stimulus is standardised and mood is not an active variable. This can be done with experimental pain stimuli, or to a lesser extent, with standard medical procedures such as venipuncture and wound dressings.

The results of studies looking at the effects of experimental pain stimuli (brief noxious stimuli that do not result in tissue injury) on pain thresholds are conflicting and seem to depend on the type of stimulus used. In general, older people tend to have higher thresholds for thermal stimuli while results from mechanical stimulation are equivocal and there may be no change over the age groups with electrical stimuli (Gibson, 2003 **Level I**). The significance of these observations in the clinical setting, where pain is associated with tissue injury, remains uncertain although they could indicate some deficit in the early warning function of pain and narrow the gap between identification of the pain stimulus and recognition of a stimulus that might cause tissue injury (Gibson, 2006). For example, in patients with an acute myocardial infarction, greater intensity of chest pain was inversely correlated with lower pain threshold (Granot et al, 2007 **Level IV**); presentation and treatment of those patients with less pain may therefore be delayed.

Studies looking at age-related changes in pain tolerance are limited but, in general and using a variety of experimental pain stimuli, there is a reduced ability in older people to endure or tolerate strong pain (Gibson, 2003 **Level I**). This could mean that severe pain may have a greater impact on the more vulnerable older person.

Also noted have been significantly smaller increases in pain threshold following prolonged noxious stimulation and prolonged recovery from hyperalgesia (Zheng et al, 2000 **Level III-2**; Gibson, 2006). Using experimental pain stimuli it can be shown that the threshold for temporal summation is lower in the elderly (Gibson & Farrell, 2004). In subjects given trains of brief electrical stimuli of varying frequency, older subjects showed temporal summation at all frequencies of stimulation whereas summation was not seen at the lower frequencies in younger subjects (Farrell & Gibson, 2007 **Level III-2**). Temporal summation of thermal stimuli was increased in the older compared with younger subjects (Edwards & Fillingim, 2001 **Level III-2**; Lautenbacher et al, 2005 **Level III-2**) and more prolonged (Edwards & Fillingim, 2001 **Level III-2**), but temporal summation of pressure pain showed no age-related effects (Lautenbacher et al, 2005

**Level III-2).** After topical application of capsaicin, the magnitude and duration of primary hyperalgesia was similar on both older and younger subjects but secondary hyperalgesia (tenderness) resolved more slowly in older people (Zheng et al, 2000 **Level III-2**). The underlying reason for these findings is again that the older person may have impaired descending inhibitory mechanisms and a reduced capacity to down-regulate after sensitisation leading to prolonged recovery (Gagliese & Farrell, 2005).

### **Clinical implications**

There are a number of clinical reports, summarised by Gibson (Gibson, 2003 **Level IV**; Gibson, 2006 **Level IV**) and Pickering (Pickering, 2005 **Level IV**), suggesting that pain symptoms and presentation may change in the older patient; pain becomes a less frequent or less severe symptom of a variety of acute medical conditions. Examples of differences in reports of acute pain are commonly related to abdominal pain (eg associated with infection, peptic ulcer, cholecystitis, or intestinal obstruction) or chest pain (eg myocardial ischaemia or infarction; pneumonia) and are in general agreement with the experimental finding of increased pain thresholds in the older person.

Compared with the younger adult with the same clinical condition, the older adult may report less pain or atypical pain, report it later or report no pain at all. For example, in older patients, right upper quadrant or epigastric pain associated with cholecystitis may be absent in 85%; 30% of those with peptic ulcer disease and up to 90% with pancreatitis may have no abdominal pain; in those with advanced peritonitis pain may be a symptom in only 55%; and reports of atypical pain or absence of pain occur in up to 33% of older patients with an acute myocardial infarction and 50% with unstable angina (Pickering, 2005 **Level IV**).

Pain intensity after surgery may also be less. Older patients, matched for surgical procedure, reported less pain in the postoperative period: pain intensity decreased by 10% to 20% each decade after 60 years of age (Thomas et al, 1998 **Level III-2**). Older men undergoing prostatectomy reported less pain on a present pain intensity scale and McGill Pain Questionnaire (but not a visual analogue scale [VAS]) in the immediate postoperative period and used less PCA opioid than younger men undergoing the same procedure (Gagliese & Katz, 2003 **Level III-2**). In a study of pain following placement of an IV cannula (a relatively standardised pain stimulus), older patients reported significantly less pain than younger patients (Li et al, 2001 **Level IV**).

## **11.2.3 Assessment of pain**

### **Cognitive impairment**

Even though cognitively impaired patients are just as likely as cognitively intact patients of the same age to have painful conditions and illnesses, the number of pain complaints and reported pain intensity decrease with increasing cognitive impairment (Farrell et al, 1996; Herr et al, 2006). Reasons for this could include a diminished memory, impairment of capacity to report, or it could be that less pain is experienced (Farrell et al, 1996; Herr et al, 2006).

However, studies in patients with dementia suggest that they may not experience less pain. Functional MRI responses following mechanical pressure stimulation showed no evidence of diminished pain-related activity in patients with Alzheimer's disease compared with age-matched controls, indicating that pain perception and processing were not diminished in these patients (Cole et al, 2006 **Level III-2**).

Another study assessed the placebo component of analgesic therapies by looking at the effect of both 'overtly applied' and 'covertly applied' local anaesthetic on pain after venipuncture in patients with Alzheimer's disease; those patients with reduced Frontal Assessment Battery

scores (a measure of frontal executive function) had a reduced placebo component to their pain relief and dose increases were required to produce adequate analgesia (Benedetti et al, 2006 **Level III-2**).

Undertreatment of acute pain is more likely to occur in cognitively impaired patients (Feldt et al, 1998 **Level III-2**; Forster et al, 2000 **Level III-2**; Morrison & Siu, 2000 **Level III-2**).

A common form of acute cognitive impairment in the older patient is delirium or confusion, which is associated with increased postoperative morbidity, impaired postoperative rehabilitation and prolonged hospital stays (Bekker & Weeks, 2003; Bitsch et al, 2006; Fong et al, 2006; Greene et al, 2009 **Level III-3**). Delirium is more common during acute illnesses in the older person and occurs in up to 80% of older postoperative patients, depending on the type of surgery. A systematic review confirmed that postoperative cognitive dysfunction (POCD) is relatively common after non-cardiac surgery and that the older patient is particularly at risk (Newman et al, 2007 **Level I**).

Risk factors associated with the development of delirium include old age, infection, pre-existing dementia, pre-existing depression, hypoxaemia and reduced cerebral oxygen saturation, anaemia, drug withdrawal (eg alcohol, benzodiazepines), fluid and electrolyte imbalance, unrelieved pain and some drugs — for example, those with central anticholinergic activity (eg atropine, tricyclic antidepressants, major tranquilizers, some antiemetics), benzodiazepines, opioids, ketamine, oral hypoglycaemics, NSAIDs and anticonvulsants (Aakerlund & Rosenberg, 1994; Moore & O'Keeffe, 1999; Morrison et al, 2003 **Level III-2**; Alagiakrishnan & Wiens, 2004; Bitsch et al, 2006; Fong et al, 2006; Vaurio et al, 2006; Casati et al, 2007; Greene et al, 2009; Morimoto et al, 2009). While delirium is associated with early postoperative cognitive dysfunction, it may not have a long-term effect (Rudolph et al, 2008 **Level IV**).

## **Measurement of pain**

### ***Patient self-report measures of pain***

Unidimensional measures of pain intensity (see Section 2) are more commonly used to quantify pain in the acute pain setting than multidimensional measures. Unidimensional measures used in younger adult populations, and which have been shown to be appropriate for use in the older patient, include the verbal numerical rating scale (VNRS), Faces Pain Scales, verbal descriptor scale (VDS) and the numerical rating scale (NRS; a calibrated VAS), with more equivocal support for use of the VAS.

In a comparison of five pain scales — VAS, VNRS, NRS, VDS and FPS — in an experimental setting, all the scales could effectively discriminate different levels of pain sensation in older people. However the VDS was the most sensitive and reliable and considered to be the best choice in the older adult, including those with mild-to-moderate cognitive impairment, although it ranked second to the NRS for patient preference (Herr et al, 2004 **Level III-2**).

In a comparison of VAS, VDS and NRS, in younger and older patients using PCA after surgery, the NRS was also the preferred pain scale in both patient groups, with high reliability and validity, although the VDS also had a favourable and similar profile; use of the VAS in the older patients resulted in high rates of unscorable data and low validity (Gagliese et al, 2005 **Level III-2**).

Similarly, after a comparison of the Faces Pain Scale and Red Wedge Scale (RWS) in older patients (65 years or older) after cardiac surgery, when VAS and VDS were also measured in each patient, the VDS was shown to be the most reliable, followed by the RWS; the VAS was the least suitable (Pesonen et al, 2008 **Level III-1**). Using the same comparisons in patients aged 76 to 96 years with non-surgical pain that included an acute component, it was shown that those with normal cognitive function were able to use all four scales well, while only the VDS

(using familiar words such as none, slight, moderate, severe and unbearable) could be used with reasonable success in patients with mild, moderate and severe cognitive impairment (Pesonen et al, 2009 **Level III-2**). That the VDS may be of most use has been confirmed by other studies (Closs et al, 2004 **Level III-2**; Herr et al, 2004 **Level III-2**).

Self-assessment pain scales can be used reliably in most older patients with mild-to-moderate cognitive impairment, and in a significant number of patients with severe impairment, although a trial of different scales may be warranted (Pautex et al, 2005) and the patients may need more time to understand and respond to questions regarding pain (Gagliese & Melzack, 1997). Immediate reports of present pain may be reasonably accurate and as valid as those of cognitively intact patients, but recall of past pain is less likely to be as reliable (Herr et al, 2006).

### ***Other measures of pain***

Assessment of pain in non-communicative patients is more difficult. Behaviours such as restlessness, frowning, and grimacing or sounds such as grunting or groaning have been used in attempts to assess pain severity. In cognitively intact adults some of these behaviours have been shown to correlate reasonably well with patient self-report of pain (Bell, 1997). However, they may not always be valid indicators of pain in the non-verbal adult (Farrell et al, 1996) and can be difficult to interpret (Herr et al, 2006).

Observations of facial expressions and sounds may be accurate measures of the presence of pain but not pain intensity in patients with advanced dementia (Herr et al, 2006). More than 20 different observational pain assessment scales have been developed and used in patients with varying degrees of dementia. Examples include: Faces Pain Scales (Herr et al, 2004); Abbey Pain Scale (Abbey et al, 2004), Pain Assessment in Advanced Dementia (PAINAD, a simple, reliable and validated five-item observational tool) (Warden et al, 2003; Leong et al, 2006), Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) (Fuchs-Lacelle & Hadjistavropoulos, 2004) and Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale (MOBID) (Husebo et al, 2007). For a more detailed and critical review of 10 pain-assessment tools for use with non-verbal adults see Herr et al (Herr et al, 2006).

## **11.2.4 Drugs used in the management of acute pain in older people**

In general there is limited evidence about the use of analgesic medications in older patients; these patients, because of their age, comorbidities, or concurrent medications, are often specifically excluded from clinical trials. However, these factors will need to be taken into consideration when a choice of analgesic regimen is made.

While Sections 11.2.4 and 11.2.5 concentrate on the use of analgesic drugs and techniques in the older patient, as with other patients, physical and psychological strategies should also be employed.

### ***Non-selective non-steroidal anti-inflammatory drugs, coxibs and paracetamol***

Older patients are more likely to suffer adverse gastric and renal side effects following administration of nsNSAIDs and may also be more likely to develop cognitive dysfunction (Pilotto et al, 2003; Peura, 2004; Juhlin et al, 2005). In elderly (age over 65 years) medical inpatients, use of nsNSAIDs was a significant risk factor for renal function deterioration; other risk factors were loop diuretics, hypernatraemia and low serum albumin levels (Burkhardt et al, 2005).

Coxibs have a significantly lower incidence of upper gastrointestinal complications and have no antiplatelet effects, which might be of some advantage in the older patient; the risk of other adverse effects, including effects on renal function and exacerbation of cardiac failure,

are similar to nsNSAIDs (Argoff, 2005; Savage, 2005). Compared with paracetamol and placebo, administration of parexocib after orthopaedic surgery resulted in a significant but transient reduction in creatinine clearance at 2 hours; there was no difference at 4 and 6 hours (Koppert et al, 2006 **Level II**).

Longer-term use of high doses of both coxibs and nsNSAIDs (possibly apart from naproxen) appear to increase the risk of cardiovascular (CV) and cerebrovascular events and regular use of nsNSAIDs may interfere with the clinical benefits of low-dose aspirin (see Section 4.2). Extra precautions are therefore required in older patients.

There is no consistent evidence on the effect of ageing on clearance of paracetamol but there is probably no need to reduce the dose given in older people (Divoll et al, 1982; Miners et al, 1988; Bannwarth et al, 2001).

## **Opioids and tramadol**

Despite the age-related changes listed in Table 11.4, there may be few differences in fentanyl pharmacokinetics (Scott & Stanski, 1987) or the pharmacokinetics of morphine and oxycodone (Villesen et al, 2007) and buprenorphine (Kress, 2009) in the older patient.

After oral administration, the bioavailability of some drugs may be increased, leading to relatively higher blood concentrations (Mangoni & Jackson, 2004).

### **Opioid dose**

Older patients require less opioid than younger patients to achieve the same degree of pain relief (Macintyre & Jarvis, 1996 **Level IV**; Woodhouse & Mather, 1997 **Level IV**; Gagliese et al, 2000 **Level IV**; Upton et al, 2006), however, a large interpatient variability still exists and doses must be titrated to effect in all patients. The decrease is much greater than would be predicted by age-related alterations in physiology and seems to have a significant pharmacodynamic component (Macintyre & Upton, 2008).

In the clinical setting there is evidence of an age-related 2- to 4-fold decrease in morphine and fentanyl requirements (Macintyre & Jarvis, 1996 **Level IV**; Woodhouse & Mather, 1997 **Level IV**; Gagliese et al, 2000 **Level IV**). This is in agreement with the findings by Scott and Stanski (Scott & Stanski, 1987) that the sensitivity of the brain to fentanyl and alfentanil was increased by 50% in older people. It has been suggested that doses of fentanyl, sufentanil and alfentanil should all be reduced by up to 50% in older patients (Shafer, 1997); reductions in the doses of other opioids is also advised (Macintyre & Upton, 2008).

In patients over 75 years the elimination half-life of tramadol was slightly prolonged (Scott & Perry, 2000). Lower daily doses have been suggested (Barkin et al, 2005).

### **Opioid metabolites**

Reduced renal function in the older patient could lead to a more rapid accumulation of active opioid metabolites (eg M6G, M3G, hydromorphone-3-glucuronide, nordextropropoxyphene, norpethidine, desmethyl-tramadol) (see Section 4.1).

### **Side effects of opioids**

The fear of respiratory depression in older people, especially those with respiratory disease, often leads to inadequate doses of opioid being given for the treatment of their pain. However, as with other patients, significant respiratory depression can generally be avoided if appropriate monitoring (ie of sedation) is in place (see Section 4.1).

The incidence of nausea/vomiting and pruritus in the postoperative period lessens with increasing age (Quinn et al 1994). In older people, fentanyl may cause less postoperative cognitive dysfunction than morphine (Herrick et al, 1996 **Level II**) and less confusion (Narayanaswamy et al, 2006), although administration of an appropriate opioid medication is



often associated with higher levels of cognitive function compared with cognitive function if postoperative pain is undertreated (Lynch et al, 1998; Morrison & Siu, 2000). Herrick et al (Herrick et al, 1996 **Level II**) reported no statistically significant difference in the incidence of confusion, but the rates were 4.3% for patients given fentanyl and 14.3% for those receiving morphine. Pethidine was associated with a higher incidence of confusion compared with morphine (Adunsky et al, 2002 **Level III-3**) and a variety of other opioids (Morrison et al, 2003 **Level III-2**).

### **Local anaesthetics**

Age-related decreases in clearance of bupivacaine (Veering et al, 1987; Veering et al, 1991) and ropivacaine (Simon et al, 2006) have been shown. Older patients are more sensitive to the effects of local anaesthetic agents because of a slowing of conduction velocity in peripheral nerves and a decrease in the number of neurons in the spinal cord (Sadean & Glass, 2003).

### **Ketamine**

There are no good data on the need or otherwise to alter ketamine doses in the older patient. In aged animals, however, changes in the composition of the NMDA-receptor site and function have been reported (Clayton et al, 2002; Magnusson et al, 2002; Vuyk, 2003). Young and elderly rats, given the same dose of ketamine on a mg/kg basis showed similar EEG changes but these changes were quantitatively greater in the older rats (Fu et al, 2008). These data suggest that, apart from any pharmacokinetic changes, the older person may be more sensitive to the effects of ketamine and doses may need to be lower in this patient group.

### **Tricyclic antidepressants**

Clearance of tricyclic antidepressant (TCA) drugs may decrease with increasing patient age and lower initial doses are recommended in older people (Ahmad & Goucke, 2002). Older people may be particularly prone to the side effects of TCAs (Ahmad & Goucke, 2002; Fine, 2004) including sedation, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention and gait disturbances which may increase the risk of falls. Adverse effects appear to be most common with amitriptyline and nortriptyline may be preferred in this patient group (Ahmad & Goucke, 2002; Argoff, 2005; McGeeney, 2009). In addition, clinical conditions that may require TCAs to be administered with caution are more common in older people and include prostatic hypertrophy, narrow angle glaucoma, CV disease and impaired liver function; ECG abnormalities may be a contraindication to the use of TCAs in older people (Ahmad & Goucke, 2002).

### **Anticonvulsants**

As with TCAs, initial doses of anticonvulsant agents should be lower than for younger patients and any increases in dose should be titrated slowly (Ahmad & Goucke, 2002). As renal function declines with increasing age, elimination of gabapentin and pregabalin may be reduced and lower doses will be required (McGeeney, 2009).

The 'second generation' drugs such as gabapentin and topiramate may be less likely to result in adverse effects in the older patient (Argoff, 2005). The relatively high frequency of side effects such as somnolence and dizziness with pregabalin may be a problem in this group of patients (Guay, 2005). However, other features of gabapentin and pregabalin, such as a lower risk of drug-drug interactions, lower (less than 3%) protein binding, no hepatic metabolism and the lack of any need to monitor liver function and blood count on a regular basis, means that these drugs may be well-suited to the older patient population (McGeeney, 2009).

### 11.2.5 Patient-controlled analgesia

Many pharmacological and non-pharmacological treatments may be used in the management of acute pain in older people, either alone or in combination. However, differences between older and younger patients are more likely to be seen in treatments using analgesic drugs.

PCA is an effective method of pain relief in older people (Gagliese et al, 2000; Mann et al, 2000; Mann et al, 2003). Compared with younger patients (mean age 39 years), older patients (mean age 67 years) self-administered less opioid than the younger group, but there were no differences in pain relief, satisfaction with pain relief and level of control, or concerns about pain relief, adverse drug effects, risks of addiction or use of the equipment (Gagliese et al, 2000 **Level III-2**).

Compared with IM morphine analgesia in older men, PCA resulted in better pain relief, less confusion and fewer severe pulmonary complications (Egbert et al, 1990 **Level II**). In older patients PCA also resulted in significantly lower pain scores compared with intermittent SC morphine injections (Keita et al, 2003 **Level II**).

### 11.2.6 Epidural analgesia

In the general patient population epidural analgesia can provide the most effective pain relief of all analgesic therapies used in the postoperative setting (see Section 7.2). Older patients given PCEA (using a mixture of bupivacaine and sufentanil) had lower pain scores at rest and movement, higher satisfaction scores, improved mental status and more rapid recovery of bowel function compared with those using IV PCA (Mann et al, 2000 **Level II**). After hip fracture surgery, epidural analgesia with bupivacaine and morphine also provided better pain relief both at rest and with movement, but this did not lead to improved rehabilitation (Foss et al, 2005 **Level II**).

Older patients are more likely to have ischaemic heart disease and in such patients coronary blood flow may be reduced rather than increased in response to sympathetic stimulation. High thoracic epidural analgesia (TEA) also improved left ventricular function (Schmidt et al, 2005 **Level III-3**; Jakobsen et al, 2009 **Level III-3**) and myocardial oxygen availability (Lagunilla et al, 2006 **Level II**) in patients with ischaemic heart disease prior to coronary artery bypass surgery (CABG) surgery, and partly normalised myocardial blood flow in response to sympathetic stimulation (Nygard et al, 2005 **Level III-3**). However, epidural analgesia in patients undergoing CABG surgery has not been shown to improve ischaemic outcome (Barrington et al, 2005 **Level II**).

After a small study during and after surgery for hip fracture, older patients who had received epidural bupivacaine/fentanyl analgesia had significantly better pain relief than those who were given IM oxycodone; there was no difference in the number of patients who developed postoperative ischaemia or hypoxia, however the number of episodes and total duration of ischaemia in each patient was markedly greater in the oxycodone group (Scheinin et al, 2000 **Level II**).

Epidural morphine requirements decrease as patient age increases (Ready et al, 1987).

However, a comparison of fentanyl PCEA in patients aged over 65 years with those aged 20 to 64 years showed no difference in fentanyl requirements although pain relief on coughing (at 24 hours) was better in the older patient group; there was no difference in the incidence of pruritus (Ishiyama et al, 2007 **Level III-3**).

Age is also a determinant of the spread of local anaesthetic in the epidural space and the degree of motor blockade (Simon et al, 2002; Simon et al, 2004), thus smaller volumes will be needed to cover the same number of dermatomes than in a younger patient. When the same

volume of local anaesthetic was given, the concentration required to produce effective motor blockade decreased as patient age increased (Li et al, 2006 **Level III-1**). Combinations of a local anaesthetic and opioid are commonly used for epidural analgesia so it would seem reasonable to use lower infusion rates in older patients (Macintyre & Upton, 2008).

Older patients may be more susceptible to some of the adverse effects of epidural analgesia, including hypotension (Crawford et al, 1996; Simon et al, 2002; Veering, 2006).

### 11.2.7 Intrathecal opioid analgesia

Intrathecal morphine using a variety of doses provided more effective pain relief after major surgery compared with other opioid analgesia, although the risk of respiratory depression and pruritus was greater (Meylan et al, 2009 **Level I**). Advanced patient age is considered by some to be a risk factor for respiratory depression and it has been suggested that patients over the age of 70 years be monitored in an intensive care setting (Gwirtz et al, 1999 **Level IV**). However, others report that older patients (average age 69 years) given up to 200 mcg intrathecal morphine at the time of spinal anaesthesia for peripheral vascular and other surgery have been safely nursed on general wards by nursing staff who have received additional education and managed by an acute pain service (APS) according to strict guidelines (Lim & Macintyre, 2006 **Level IV**).

The 'optimal' dose of intrathecal morphine that should be given to older patients remains unknown and any evidence for the 'best' dose remains inconsistent. Intrathecal morphine doses of 200 mcg given in addition to general anaesthesia in older patients (average age 70 years) undergoing abdominal aortic surgery led to better postoperative analgesia and reduced postoperative analgesia requirements compared with those given general anaesthesia only; no conclusion could be made about adverse effects as total patients numbers were small (Blay et al, 2006 **Level II**).

A comparison of three doses of intrathecal morphine (50 mcg, 100 mcg and 200 mcg) given to older patients after hip surgery concluded that the 100 mcg dose provided the best balance between good pain relief and pruritus; there was no difference seen in the incidences of nausea and vomiting or respiratory depression (Murphy et al, 2003 **Level II**).

Use of intrathecal morphine in addition to IV PCA morphine after colorectal surgery led to better pain relief and lower PCA morphine requirements compared with PCA morphine alone, but sedation was increased and there were no differences in time to ambulation, duration of hospital stay or incidence of confusion (Beaussier et al, 2006 **Level II**).

### 11.2.8 Other regional analgesia

Possible advantages of regional blockade in older patients include a reduction in the incidence of side effects compared with central neuraxial blockade (Zaric et al, 2006 **Level II**). Patient outcome may also be improved when older patients receive regional rather than opioid analgesia after surgery. After fixation of a fractured hip, those who received patient-controlled femoral nerve analgesia in addition to regular paracetamol and metamizol were less likely to develop postoperative delirium, were able to sit at the bedside at an earlier stage, and required no SC morphine compared with those given just paracetamol and metamizol, 28% of whom required additional morphine analgesia (Rosario et al, 2008 **Level IV**).

The duration of action of sciatic nerve (Hanks et al, 2006 **Level III-2**) and brachial plexus blocks (Paqueron et al, 2002 **Level III-2**) is prolonged in the older patient.

In older (greater than 65 years of age) patients undergoing urological surgery via a flank incision, paravertebral blockade of the lumbar plexus using either ropivacaine or bupivacaine

has been shown to provide good analgesia with no changes in the patients' heart rate or blood pressure (Akin et al, 2005 **Level II**).

Unlike epidural analgesia, age did not influence the spread of bupivacaine in the thoracic paravertebral space (Cheema et al, 2003 **Level III-2**).

### Key messages

1. Experimental pain thresholds to a variety of noxious stimuli are altered in older people; there is also a reduction in tolerance to pain (**Q**) (**Level I**).
2. PCA and epidural analgesia are more effective in older people than conventional opioid regimens (**U**) (**Level II**).
3. Reported frequency and intensity of acute pain in clinical situations may be reduced in the older person (**U**) (**Level III-2**).
4. Common unidimensional self-report measures of pain can be used in the older patient in the acute pain setting; in the clinical setting, the verbal descriptor and numerical rating scales may be preferred (**S**) (**Level III-2**).
5. Undertreatment of acute pain is more likely to occur in cognitively impaired patients (**N**) (**Level III-2**).
6. There is an age-related decrease in opioid requirements; significant interpatient variability persists (**U**) (**Level IV**).
7. The use of nsNSAIDs and coxibs in older people requires extreme caution; paracetamol is the preferred non-opioid analgesic (**U**) (**Level IV**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- The assessment of pain and evaluation of pain relief therapies in the older patient may present problems arising from differences in reporting, cognitive impairment and difficulties in measurement (**U**).
- Measures of present pain may be more reliable than past pain, especially in patients with some cognitive impairment (**U**).
- The physiological changes associated with ageing are progressive. While the rate of change can vary markedly between individuals, these changes may decrease the dose (maintenance and/or bolus) of drug required for pain relief and may lead to increased accumulation of active metabolites (**U**).
- The age-related decrease in opioid requirements is related more to the changes in pharmacodynamics that accompany aging than to the changes in pharmacokinetics (**N**).

## 11.3 ABORIGINAL AND TORRES STRAIT ISLANDER PEOPLES

Aboriginal and Torres Strait Islander peoples are a heterogeneous group both in terms of their links to traditional cultural beliefs and links to the land, as well as in their degree of urbanisation and understanding of Western biomedical concepts. The appropriate assessment and treatment of pain in Aboriginal and Torres Strait Islander patients needs to take into account a number of factors including cultural and language differences between the patient and health care worker.

A study looking at issues associated with pain management in the palliative care setting in rural and remote Aboriginal peoples interviewed patients, carers, Aboriginal health care workers and other healthcare staff (McGrath, 2006 **Level IV**). While the focus was on palliative care, many of the conclusions and comments made can be extrapolated to pain management in general in this group of patients. The authors reported that Aboriginal patients may have a higher pain threshold and be less likely to complain of pain (particularly men, who may not want to appear weak by expressing their pain); there was also a fear of Western medicine. Pain may also be seen as a punishment for some misdeed (Honeyman & Jacobs, 1996 **Level IV**).

The prevalence of musculoskeletal pain in general (Vindigni et al, 2004 **Level IV**) and back pain specifically (Honeyman & Jacobs, 1996 **Level IV**) was reported to be high in non-urban Australian Aboriginal communities. However, it was uncommon for Aboriginal people to present with pain as a complaint and public expression of pain and illness behaviours were uncommon, including after painful injections in children and after acute injuries in adults (Vindigni et al, 2004 **Level IV**).

Aboriginal people may be reserved and unobtrusive when experiencing pain and health professionals may mistakenly label them as stoic (National Palliative Care Program, 2006). Such behaviour may lead to undertreatment of pain, and cultural issues, including marked shyness with strangers (especially where there is a gender difference), gratuitous concurrence (saying 'yes' to be polite), different health belief systems and language differences, may further complicate management (Howe et al, 1998 **Level IV**). Aboriginal people place a lot of importance on non-verbal communication so that words may be used only infrequently, they may avert their eyes or turn their head away when questions are asked, hide under a blanket or feign sleep (National Palliative Care Program, 2006).

Past unfortunate experiences with healthcare services can result in some not wishing to be cared for in an acute care hospital, even though their treatment requires admission. There may also be concerns about the use of morphine for the treatment of pain as some may believe that morphine hastens death and will therefore refuse to take pain relief medication; discussions with the patient as well as family may be required and a specific person (as well as the patient) may need to give consent before morphine is administered (National Palliative Care Program, 2006). Therefore, despite having significant pain, some Aboriginal patients may present late depending on access to health care facilities and attitudes to Western biomedical models of health care. Provision of quality analgesia requires sensitivity to cultural practices and beliefs, and behavioural expression of pain. Use of Aboriginal interpreters, health workers and liaison officers to assess pain is beneficial as in some cases English skills, although present, are limited and interpreters can help with non-verbal communication issues.

A study of Aboriginal women after surgery found that they had culturally appropriate ways of expressing and managing pain that were not well-understood by non-Aboriginal nurses (Fenwick & Stevens, 2004 **Level IV**). It was reported that the Aboriginal women were generally

silent about their pain even when asked, and that, in part at least, this arose from fear of pain (including its origin and significance in relation to themselves and the external world) and a belief that the nurses would know about the pain they were experiencing so that there was no need to tell them. In addition, access to appropriate pain relief may be more limited. In one Central Australian hospital, fewer Aboriginal patients were referred to the APS than non-Aboriginal patients, despite being the predominant patient group in that institution (Fenwick & Stevens, 2004).

Pain assessment by some conventional methods may not be appropriate. A verbal descriptor scale but not a numerical rating scale was a useful measure of pain (Sartain & Barry, 1999 **Level III-3**). This is consistent with the fact that specific numbers and numerical scales are not part of many Aboriginal language systems and more descriptive terms are used for quantification.

Aboriginal and Torres Strait Islander peoples can use PCA effectively if given adequate information about the technique. However, communication is often difficult and so techniques such as continuous opioid infusion techniques tend to be used more commonly in Aboriginal and Torres Strait Islander peoples than in other patient groups (Howe et al, 1998 **Level IV**). In addition, consent for invasive procedures such as epidural analgesia may be difficult to obtain; there may be communication difficulties or the patient may need to discuss the proposed consent with other members of the family.

Medical comorbidities such as renal impairment and diabetes are more common in Aboriginal and Torres Strait Islander peoples as well as New Zealand Maoris (Howe et al, 1998 **Level IV**; Bramley et al, 2004 **Level IV**; McDonald & Russ, 2003 **Level IV**). This may affect the choice of analgesics (see Section 11.6).

#### Key messages

1. The verbal descriptor scale may be a better choice of pain measurement tool than verbal numerical rating scales (**U**) (**Level III-3**).
2. Medical comorbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander peoples and New Zealand Maoris, and may influence the choice of analgesic agent (**U**) (**Level IV**).
3. Clinicians should be aware that pain may be under-reported by this group of patients (**U**) (**Level IV**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Communication may be hindered by social, language and cultural factors (**U**).
- Provision of quality analgesia requires sensitivity to cultural practices and beliefs, and behavioural expressions of pain (**N**).

## 11.4 DIFFERENT ETHNIC AND CULTURAL GROUPS

Australia is a culturally diverse nation with a relatively large immigrant population. In the 2006 Census, 71% of people were born in Australia and English was the only language spoken at home by 79% of these. The four most common languages used at home other than English were Chinese languages (2.3%), Italian (1.6%), Greek (1.3%) and Arabic (1.2%) (Australian Bureau of Statistics, 2006). In many other countries in the world there is also significant cultural and ethnic diversity.

There is a need to understand different cultures when considering pain assessment and management. This extends beyond the language spoken, because an individual's culture also influences their beliefs, expectations, methods of communication and norms of behaviour, as do the culture and attitudes of the health care provider (Green et al, 2003; Davidhizar & Giger, 2004). It is important for clinicians to be aware of both verbal and non-verbal indicators of pain and be sensitive to both emotive and stoic behaviours in an individual's response. Some cultural attitudes may limit pain-relief seeking behaviour. For example, it may be perceived by some patients as inappropriate to use a nurse's time to ask for analgesics or asking for pain relief may be seen as a weakness (Green et al, 2003).

Communication problems may make it difficult to adequately help non-English speaking patients with interactive pain management (eg PCA use, requesting analgesia when needed), gain consent for invasive analgesic techniques (eg epidural or plexus catheters) and assess their degree of pain (Howe et al, 1998 **Level IV**). When language is an obstacle, care should be used when enlisting non-professional interpreters to translate, because family members and friends of the patient may impose their own values when conveying the information to the clinician, and the patient may be reluctant to openly express themselves in front of people they know.

Cultural differences in response to pain in both the experimental and clinical settings have been reported. A review of studies investigating differences in responses to experimentally induced pain found that cultural differences influenced pain tolerance but not pain threshold, and concluded that intrinsic difficulties in the translation of pain descriptors between different cultures makes pain tolerance the more relevant pain measure (Zatzick & Dimsdale, 1990). In a comparison of experimental pain sensitivity in three ethnic groups, African Americans and Hispanic Americans showed a greater sensitivity to laboratory-evoked pain compared with non-Hispanic White Americans (Rahim-Williams et al, 2007 **Level III-2**). Similarly, African American women were more sensitive to ischaemic pain than non-Hispanic white women (Klatzkin et al, 2007 **Level III-2**). However, the implications of these results for the clinical setting are unclear.

A systemic review looked at the effect of patient race and ethnicity on pain assessment and management across a variety of clinical pain settings (Cintron & Morrison, 2006 **Level III-3**). Marked disparities in effective pain treatment were reported; African Americans and Hispanics were less likely to receive opioid analgesics, and were more likely to have their pain undertreated compared with white patients.

Differences have been reported in patients of different ethnic groups attending emergency departments and requiring analgesia. A review of the treatment of pain in United States emergency departments showed that opioid prescribing for pain-related visits increased over the period 1993 to 2005, but that white patients with pain were more likely than black, Hispanic or Asian patients to receive an opioid, and that these differences did not diminish over time (Pletcher et al, 2008 **Level III-3**). This disparity was reported for all types of pain visits, was more pronounced with increasing pain intensity, and was unaffected by adjustment for pain severity.

Prescription of PCA and PCA prescription details also varied with patient ethnicity (Ng et al, 1996 **Level III-3**; Salamonson & Everett, 2005 **Level III-3**), although the actual self-administered doses of opioid were similar (Ng et al, 1996 **Level IV**). After Caesarean section, significant ethnic group differences were noted in reported pain and morphine consumption; pain scores and morphine doses were higher in Indian patients compared with Chinese and Malay patients even after controlling for age, body mass index, and duration of operation (Tan et al, 2008 **Level III-2**).



Strategies used to facilitate cross-cultural pain education and management include bilingual handouts describing varying methods of pain control and VAS scales with carefully chosen anchor terms or the use of faces scales (see Section 2); the NRS, for example has been translated and validated in many languages (Davidhizar & Giger, 2004). A series of pain scales in a number of different languages has also been produced by the British Pain Society to assist in the assessment of people whose first language is not English and these are available on their website (British Pain Society, 2009).

While there is some evidence of differences in pain reports and analgesic use in different cultures or ethnic groups, it should not be used to stereotype patients or promote assumptions about differences in assessment and management of pain or response to pain therapies. Provision of effective analgesia requires sensitivity to a patient's cultural practices and beliefs, and their behavioural expression of pain. However, the large inter-individual differences in pain behaviours and analgesic requirements that exist in any patient group mean that pain is best assessed and managed on an individual basis rather than on the basis of what might be 'expected' in a patient from a particular cultural or ethnic background.

### Key messages

1. Disparities in assessment and effective treatment of pain exist across ethnic groups (**N**) (**Level III-3**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Ethnic and cultural background can significantly affect the ability to assess and treat acute pain (**U**).
- Multilingual printed information and pain measurement scales are useful in managing patients from different cultural or ethnic backgrounds (**U**).
- Differences between different ethnic and cultural groups should not be used to stereotype patients and lead to assumptions about responses to pain or pain therapies; pain assessment and management should be done on an individual patient basis (**N**).

## 11.5 THE PATIENT WITH OBSTRUCTIVE SLEEP APNOEA

Acute pain management in a patient with obstructive sleep apnoea (OSA) presents two main problems: choice of the most appropriate form of analgesia and the most suitable location in which to provide it. These difficulties arise primarily from the risk of exacerbating OSA by the administration of opioid analgesics.

Approximately one in five adults have at least mild OSA, one in fifteen have moderate or worse OSA and 75% to 80% of those who could benefit from treatment remain undiagnosed (Young et al, 2004). Therefore, many patients with undiagnosed OSA will have had treatment for acute pain without significant morbidity. This implies that the overall risk is quite low.

Despite the low risk, it has been reported that patients with OSA may be at increased risk of postoperative complications compared with other patients. However, it is possible that the risk lies more with the body size and build of the patient, especially those who are morbidly obese, rather than the fact they have a diagnosis of OSA (Loadsman 2009).

A significantly higher incidence of serious postoperative complications (including unplanned ICU admissions, reintubations, and cardiac events) and longer hospital stay after joint replacement surgery was reported in patients with OSA compared with matched controls

(Gupta et al, 2001 **Level III-3**). However, after outpatient surgery, a preoperative diagnosis of OSA was not associated with an increase in adverse events or unplanned hospital admission (Sabers et al, 2003 **Level III-3**).

Differences in the incidence of oxygen desaturation have also been reported. A study of 2467 patients used three different screening tools to determine if patients were at risk of OSA and reported an incidence of patients at high risk of OSA of between 28% and 33%, depending on the tool used; of the 416 patients consenting to the study, those identified as high risk were also more likely to develop postoperative complications (Chung, Yegneswaran et al, 2008 **Level III-2**). Similarly, screening of 2206 patients reported that 11% were at high risk of having OSA; data from 115 of these OSA-risk patients showed that they had a higher incidence of episodes of oxygen desaturation (Gali et al, 2007 **Level III-2**).

One of the main concerns in patients with OSA is that administration of opioids for the treatment of acute pain may lead to an increase in the number and severity of obstructive episodes and oxygen desaturation.

Opioid administration in the postoperative period is known to lead to episodes of pronounced oxygen desaturation while the patient is asleep, which are much more commonly a result of obstructive and central apnoea than a decrease in respiratory rate (Catley et al, 1985 **Level III-2**; Clyburn et al, 1990 **Level III-3**).

However, there remains a paucity of information regarding the effects of analgesics, including opioids, in the acute pain setting in patients with OSA, and therefore limited data on which to base recommendations for their postoperative care (Blake et al, 2008; Gross et al, 2006; Chung, Yuan et al, 2008).

A comparison of patients assessed (by history, body mass index and physical examination) to be at risk of having OSA ( $n = 33$ ) with control patients ( $n = 30$ ) has shown that patients classified as OSA risk have more obstructive events in the postoperative period (Blake et al, 2008 **Level III-2**). All patients were continuously monitored for 12 hours during the first postoperative night. Those classified as OSA risk had significantly more episodes of obstructive apnoea than control patients ( $39 \pm 22$  vs  $14 \pm 10$  events/ hour) and spent more time with oxygen saturation levels lower than 90% (Blake et al, 2008 **Level III-2**). There was no difference between the groups in the cumulative morphine dose over that time or frequency of central and mixed apnoeas (Blake et al, 2008 **Level III-2**). The correlation between a classification of high risk for OSA and a high number of oxygen desaturation each hour was also reported in patients monitored for 48 hours after surgery (Gali et al, 2009) **Level III-3**.

Evidence of the risks associated with analgesia and OSA is very limited. In a number of case reports, the use of opioid medications in patients with OSA appeared to be a common factor in most of the cases where complications, including death, have been reported following intermittent IM, patient-controlled IV and epidural analgesia (Reeder et al, 1991; VanDercar et al, 1991; Etches, 1994; Ostermeier et al, 1997; Cullen, 2001; Lofsky, 2002; Parikh et al, 2002). However, caution is required when interpreting these reports. Most of the cases involved what appear to be excessive opioid doses (eg excessive bolus dose or a background infusion with PCA) and/or inadequate monitoring for respiratory depression (eg it appeared here was an over-reliance on respiratory rate; sedation levels were not checked and/or increasing sedation was not recognised as an early indicator of respiratory depression) and/or protocol failures and/or concurrent administration of sedatives (Macintyre, 2005).

A report by an American Society of Anesthesiologists task force looking at the perioperative management of patients with OSA concluded that there was no good evidence that can be used to evaluate the effects of various postoperative analgesia techniques in patients with OSA (Gross et al, 2006) and no good comparisons between pure agonist opioids such as

morphine and tramadol or non-opioid analgesics. A small study in children undergoing adenotonsillectomy for OSA showed a trend to fewer episodes of postoperative desaturation in children given tramadol compared with morphine, but the difference was only significant for the second hour after surgery (Hullett et al, 2006 **Level II**). In patients with a body mass index of 28 or more and with signs or symptoms suggestive of OSA, there was no difference in the numbers of respiratory events (obstructive apnoeas, hypopnoeas or central apnoeas) in patients receiving IV morphine PCA and those receiving an 'opioid-sparing' analgesic regimen (IV tramadol PCA, parecoxib and 'rescue-only' morphine; however there was a correlation between more than 15 respiratory events/ hour and total morphine dose (Blake et al, 2009 **Level II**).

Expert opinion, however, consistently suggests that non-opioid analgesics and regional techniques should be considered, either as an alternative to opioids or to help limit the amount of opioid required (Benumof, 2001; Loadsman & Hillman, 2001; Gross et al, 2006; Chung, Yuan et al, 2008).

Morbid obesity is strongly associated with OSA (Young et al, 2004) and, using polysomnography, OSA was identified in 71% of patients presenting for bariatric surgery (Frey & Pilcher, 2003 **Level IV**). The use of PCA with appropriate bolus doses and monitoring in morbidly obese patients has been reported to be no less safe than regional or other systemic opioid analgesic techniques, although the studies lacked power (Kyzer et al, 1995 **Level II**; Choi et al, 2000 **Level IV**; Charghi et al, 2003 **Level IV**). In a comparison of morbidly obese patients, each of whom had a preoperative sleep study, with (n = 31) and without (n = 9) OSA undergoing laparoscopic bariatric surgery, episodes of postoperative hypoxaemia were frequent despite supplemental oxygen; there was no significant difference between OSA and non-OSA patients (Ahmad et al, 2008 **Level III-2**).

While oxygen therapy alone may not prevent the disruptions of sleep pattern or symptoms such as daytime somnolence and altered mental function that may occur in patients with OSA, it can reduce the likelihood of significant hypoxaemia (Phillips et al, 1990; Landsberg et al, 2001). As patients with OSA are more at risk of hypoxaemia after surgery or if given opioids, the use of supplemental oxygen would seem appropriate (Gross et al, 2006) despite concerns about reducing respiratory drive during the apnoeic periods (Lofsky, 2002).

The use of continuous positive airway pressure (CPAP) may help to reduce the postoperative risks and is recommended in patients with OSA (Benumof, 2001; Loadsman & Hillman, 2001). The effectiveness of CPAP (used appropriately) in the prevention of OSA in the postoperative setting is supported by case reports (Reeder et al, 1991; Rennotte et al, 1995; Mehta et al, 2000). Concerns about the risk of CPAP causing gastric distension and anastomotic leaks after upper GI surgery appear to be unfounded (Huerta et al, 2002 **Level III-2**).

The effective use of CPAP in the setting of acute pain management may require a higher level of supervision than that available in the general surgical ward; most reports of the successful use of postoperative CPAP utilise extended periods of high-dependency nursing (Reeder et al, 1991; Rennotte et al, 1995; Mehta et al, 2000).

Advice on the most appropriate environment for the care of OSA patients requiring analgesia is based on expert opinion only and suggests that the severity of OSA, efficacy of any current therapy, relevant comorbidities (eg cardiac) and the analgesia required be taken into consideration (Benumof, 2001; Loadsman & Hillman, 2001; Gross et al, 2006).

### Key messages

1. Patients with obstructive sleep apnoea may be at higher risk of complications after some types of surgery (**Q**).
2. Patients with obstructive sleep apnoea have an increased risk of obstructive episodes and desaturations (**N**) (**Level III-2**).
3. Morbidly obese patients undergoing bariatric surgery may be at increased risk of postoperative hypoxaemia independent of a diagnosis of obstructive sleep apnoea (**N**) (**Level III-2**).
4. Continuous positive airway pressure does not increase the risk of anastomotic leak after upper gastrointestinal surgery (**U**) (**Level III-2**).

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Management strategies that may increase the efficacy and safety of pain relief in patients with obstructive sleep apnoea include the provision of appropriate multimodal opioid-sparing analgesia, continuous positive airway pressure, monitoring and supervision (in a high-dependency area if necessary) and supplemental oxygen (**U**).

## 11.6 THE PATIENT WITH CONCURRENT HEPATIC OR RENAL DISEASE

The clinical efficacy of most analgesic drugs is altered by impaired renal or hepatic function, not simply because of altered clearance of the parent drug, but also through accumulation of toxic or therapeutically active metabolites. Some analgesic agents can aggravate pre-existing renal and hepatic disease, causing direct damage and thus altering their metabolism.

A brief summary of the effects that renal or hepatic disease may have on some of the drugs used in pain management, as well as alterations that might be required in analgesic drug regimens, is given in Tables 11.5 and 11.6.

### 11.6.1 Patients with renal disease

The degree to which analgesic drug regimens require alteration in patients with renal impairment depends largely on whether the drug has active metabolites that are dependent on the kidney for excretion or if the drug may further impair renal function.

There is some limited information about the ability of dialysis to clear the drugs and/or their metabolites. Molecules are more likely to be removed by dialysis if they have a low molecular weight, greater water solubility and lower volume of distribution; a higher degree of protein binding and use of lower-efficiency dialysis techniques will reduce removal (Dean, 2004).

The available data indicates the following (see Table 11.5 for references).

- Analgesics that exhibit the safest pharmacological profile in patients with renal impairment are alfentanil, buprenorphine, fentanyl, ketamine, paracetamol (except with compound analgesics) and sufentanil. None of these drugs delivers a high active metabolite load or has a significantly prolonged clearance.
- Oxycodone can usually be used without any dose adjustment in patients with renal impairment. Its metabolites do not appear to contribute to any clinical effect in patients with normal renal function.

- Amitriptyline, bupivacaine, levobupivacaine, lignocaine, ropivacaine, clonidine, gabapentin, codeine, hydromorphone, methadone, morphine and tramadol have been used in patients with renal disease but depending on the degree of impairment and, in the case of local anaesthetics, whether or not administration is prolonged, may require a reduction in dose. Levobupivacaine, with similar clearance mechanisms, and ropivacaine may be safer than bupivacaine because of a higher therapeutic ratio.
- NSAIDs (both nsNSAIDs and coxibs), dextropropoxyphene and pethidine should not be used in the presence of significant renal impairment.

### 11.6.2 Patients with hepatic disease

Not all patients with hepatic disease have impaired liver function. In patients with hepatic impairment, most analgesic drugs have reduced clearance and increased oral bioavailability, but the significance of these changes in the clinical setting has not been studied in depth. The available data indicates the following (see Table 11.6 for references).

- While there are limited data, dose adjustments are usually not required for alfentanil, buprenorphine, fentanyl, morphine, oxycodone and sufentanil.
- Tramadol may need to be given at lower doses.
- Methadone should be used with caution in the presence of severe liver disease because of the potential for greatly prolonged clearance.
- The clearance of local anaesthetics may be significantly impaired; doses may need to be decreased if use is prolonged.
- Carbamazepine and valproate should be avoided in patients with severe hepatic impairment.
- It may be wise to reduce the dose of paracetamol in patients with significant degrees of hepatic impairment.

#### Key messages

The following tick box  represents conclusions based on clinical experience and expert opinion.

- Consideration should be given to choice and dose regimen of analgesic agents in patients with hepatic and particularly renal impairment (**U**).

**Table 11.5 Analgesic drugs in patients with renal impairment**

Drug	Comments	Recommendations	References
NB doses must still be titrated to effect for each patient			
<b>Opioids</b>			
Alfentanil	No active metabolites 92% protein bound; increases in free fraction may result from alterations in protein binding	No dose adjustment required unless renal failure is severe	Craig & Hunter, 2008 Davies et al, 1996 Mercadante & Arcuri, 2004 Murtagh et al, 2007

<b>Drug</b>	<b>Comments</b>	<b>Recommendations</b>	<b>References</b>
		NB doses must still be titrated to effect for each patient	
Buprenorphine	Pharmacokinetics unchanged; predominantly biliary excretion of metabolites Pharmacokinetics also unchanged with dialysis	No dose adjustment required	Boger, 2006 Davies et al, 1996 Filitz et al, 2006 Hand et al, 1990 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004
Codeine	Accumulation of active metabolites can occur; prolonged sedation and respiratory arrest have been reported in patients with renal impairment No good data on removal by dialysis	Dose adjustment recommended or use an alternative opioid	AMH, 2008 Craig & Hunter, 2008 Davies et al, 1996 Dean, 2004 Mercadante & Arcuri, 2004
Dextro-propoxyphene	Accumulation of active metabolite (nordextropropoxyphene) can lead to CNS and cardiovascular system toxicity Blood concentrations not significantly changed during dialysis	Use of alternative agent recommended	AMH, 2008 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004 Murtagh et al, 2007
Dihydrocodeine	Metabolic pathway probably similar to codeine	Insufficient evidence: use not recommended	Craig & Hunter, 2008 Davies et al, 1996 Murtagh et al, 2007
Fentanyl	No active metabolites Not removed to any significant degree by dialysis	No dose adjustment required; may be used in patients with severe renal impairment	AMH, 2008 Craig & Hunter, 2008 Dean, 2004 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004 Murtagh et al, 2007
Hydromorphone	Neurotoxicity from accumulation of H3G possible H3G is effectively removed during dialysis	Dose adjustment recommended or use alternative opioid	AMH, 2008 Davison & Mayo, 2008 Dean, 2004 Mercadante & Arcuri, 2004

Drug	Comments	Recommendations	References
Methadone	<p>Methadone and its metabolites are excreted in urine and faeces; in anuric patients it may be mostly in faeces</p> <p>High protein binding, high volume of distribution and moderate water solubility would suggest that it is likely to be poorly removed by dialysis</p>	<p>NB doses must still be titrated to effect for each patient</p> <p>Dose adjustment may be required in severe renal impairment</p>	<p>AMH, 2008            Davies et al, 1996            Dean, 2004            Launay-Vacher et al, 2005            Lugo et al, 2005            Mercadante &amp; Arcuri, 2004            Murtagh et al, 2007</p>
Morphine	<p>Major metabolites M3G and M6G excreted via kidney and accumulate in renal impairment</p> <p>M6G is an opioid agonist that crosses the blood-brain barrier slowly; delayed sedation from M6G has been reported in renal failure</p> <p>Neurotoxicity from accumulation of M3G possible</p> <p>Oral administration results in proportionally higher metabolite load</p> <p>Morphine and its metabolites are cleared by most haemodialysis procedures but may not be significantly affected by peritoneal dialysis</p> <p>M6G also removed but slow diffusion from CNS delays response</p>	<p>Dose adjustment recommended or use alternative opioid</p>	<p>AMH, 2008            Angst et al, 2000            Craig &amp; Hunter, 2008            Davies et al, 1996            Dean, 2004            D'Honneur et al, 1994            Hanna et al, 1993            Launay-Vacher et al, 2005            Mercadante &amp; Arcuri, 2004            Pauli-Magnus et al, 1999            Richtsmeier et al, 1997</p>
Oxycodone	<p>The metabolite oxymorphone is active but plasma levels are normally negligible and therefore it has an insignificant clinical effect in patients with normal renal function</p> <p>Higher blood concentrations of oxycodone and metabolites with moderate to severe renal impairment; half life significantly increased in endstage renal disease</p> <p>Oxycodone and its metabolites are dialyzable</p>	<p>No dose adjustment required in most patients</p>	<p>AMH, 2008            Dean, 2004            Kalso, 2005            Lee et al, 2005            Riley et al, 2008</p>



Drug	Comments	Recommendations	References
		NB doses must still be titrated to effect for each patient	
Pethidine	Norpethidine is the only active metabolite and is renally excreted; it is dialyzable Accumulation of norpethidine can lead to neuroexcitation including seizures	Use of alternative agent recommended	AMH, 2008 Craig & Hunter, 2008 Davies et al, 1996 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004 Simopoulos et al, 2002
Sufentanil	Minimally active metabolite	No dose adjustment required	AMH, 2008 Davis et al, 1988 Murphy, 2005
Tramadol	Increased tramadol-like effects from active metabolite O-desmethyltramadol (M1) Tramadol is removed by dialysis	Dose adjustment recommended Use of alternative agent recommended with significant renal impairment	AMH, 2008 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004 MIMS, 2008
<b>Other drugs</b>			
Local anaesthetics	There may be no significant difference in plasma concentration of levobupivacaine, bupivacaine or ropivacaine in patients with chronic renal failure unless renal failure is severe, continuous infusions are used or repeated doses are used  Increases in free fraction may result from alterations in protein binding  Higher peak plasma concentrations of ropivacaine in uraemic patients but no difference in free fraction – uraemic patients have significantly higher alpha-1-acid glycoprotein plasma concentrations	Risk of toxicity may be affected by abnormalities in acid-base balance and/or potassium levels  Doses may need to be reduced if prolonged or repeated administration (eg continuous infusions)	AMH, 2008 Crews et al, 2002 De Martin et al, 2006 Jokinen, 2005 Rice et al, 1991
Paracetamol	Terminal elimination half-life may be prolonged Is dialysable	May need to increase dose interval if renal impairment is severe  Weak evidence that it may increase the rate of progression to chronic renal failure	AMH, 2008 Craig & Hunter, 2008 Launay-Vacher et al, 2005

Drug	Comments	Recommendations	References
		NB doses must still be titrated to effect for each patient	
NsNSAIDs and coxibs	Can affect renal function Behaviour during dialysis not clearly elucidated for most	Use with caution in patients with mild renal impairment and avoid in patients with severe renal impairment	Launay-Vacher et al, 2005
Clonidine	Half-life is increased in severe renal failure 50% metabolised by the liver; remained excreted unchanged by the kidney	Limited data; dose adjustment has been recommended	Khan et al, 1999 Lowenthal et al, 1993
Tricyclic antidepressants	Amitriptyline is metabolised in the liver to nortriptyline, the active agent Not significantly removed by dialysis	Limited data; metabolite accumulation may occur and increase the risk of side effects but little evidence to indicate need for dose reduction	Lieberman et al, 1985 Murphy, 2005 Dargan et al, 2005
Ketamine	Dehydronorketamine levels are increased but it has only 1% of potency of ketamine Ketamine is not removed well by dialysis	Limited data; probable that no dose adjustment is required	Koppel et al, 1990
Gabapentinoids	Gabapentin: impaired renal function results in reduced clearance in direct proportion to creatinine clearance; about 35% cleared by dialysis  Pregabalin: Impaired renal function results in reduced clearance in direct proportion to creatinine clearance; highly cleared by dialysis	Dose adjustment recommended on basis of creatinine clearance  Dose adjustment recommended on basis of creatinine clearance	AMH, 2008 Blum et al, 1994 Wong et al, 1995  AMH, 2008 Randinitis et al, 2003

**Table 11.6 Analgesic drugs in patients with hepatic impairment**

Drug	Comments	Recommendations	References
		NB doses must still be titrated to effect for each patient	
<b>Opioids</b>			
Alfentanil	No significant difference in half-life found in children undergoing liver transplant	Limited data: no dose adjustment required	Davis et al, 1989
Buprenorphine	Lower blood concentrations of buprenorphine and norbuprenorphine	Limited data: no dose adjustment required	Johnson et al, 2005

<b>Drug</b>	<b>Comments</b>	<b>Recommendations</b> NB doses must still be titrated to effect for each patient	<b>References</b>
Dextro-propoxyphene	Reduced oxidation leading to reduced clearance	Limited data: dose adjustment may be required	Tegeger et al, 1999
Fentanyl	Disposition appears to be unaffected	Limited data: no dose adjustment required	Tegeger et al, 1999
Methadone	Increased half-life but limited significance	Limited data: no dose adjustment required in chronic stable liver disease	Lugo et al, 2005 Novick et al, 1985
Morphine	Hepatic impairment does not appear to have a significant effect on morphine pharmacokinetics; even in patients with cirrhosis there is a large hepatic reserve for glucuronidation Blood concentrations of morphine but not morphine metabolites higher after liver resection; blood concentrations also higher in patients with liver cancer Increased oral bioavailability of morphine due to its normal high first pass metabolism when given via this route	In most patients no dose adjustment required	Kotb et al, 2005 Rudin et al, 2007
Oxycodone	Decreased oxycodone clearance with mild to moderate hepatic impairment	Limited data: no dose adjustment required in most patients	Kalso, 2005 Riley et al, 2008
Pethidine	Reduced clearance	Limited data: dose adjustment may be required; use not recommended	Tegeger et al, 1999
Sufentanil	No difference in clearance or elimination	No dose adjustment required	Chauvin et al, 1989 Tegeger et al, 1999
Tramadol	Reduced clearance	Limited data: dose adjustment may be required if impairment is severe	AMH, 2008 Tegeger et al, 1999 Kotb et al, 2008

Drug	Comments	Recommendations	References
		NB doses must still be titrated to effect for each patient	
<b>Other drugs</b>			
Local anaesthetics	Amide-type local anaesthetics undergo hepatic metabolism and clearance may be reduced in hepatic disease  Increased plasma concentrations of ropivacaine after continuous infusion but not single dose	Limited data: dose adjustment may be required with prolonged or repeated use	AMH, 2008 Bodenham & Park, 1990 Jokinen, 2005 Jokinen et al, 2007
Paracetamol	Metabolised in the liver; small proportion metabolised to the potentially hepatotoxic metabolite N-acetyl-p-benzoquinonemine. This is normally inactivated by hepatic glutathione.  Clearance is reduced	Commonly suggested that it should be used with caution or in reduced doses or frequency with active liver disease, alcohol-related liver disease and glucose-6-phosphate dehydrogenase deficiency  However, others report that it can be used safely in patients with liver disease and is preferred to NSAIDs, and that therapeutic doses of paracetamol, at least for short-term use, are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol	AMH, 2008 Benson et al, 2005 Graham et al, 2005 Zapater et al, 2004
Tricyclic antidepressants	Amitriptyline is metabolised in the liver to nortriptyline, the active agent	Reduce dose if hepatic impairment is severe	AMH, 2008
Carbamazepine	Transient rises in hepatic enzymes occur in 25%–61% of patients treated; has been reported to cause hepatic failure (rare)  Primarily metabolised in the liver	Dose adjustment may be required; use not recommended in severe hepatic impairment	Ahmed & Siddiqi, 2006 AMH, 2008
Valproate	Transient rises in hepatic enzymes occur in 10–15% of patients treated; has been reported to cause hepatic failure (rare)  Primarily metabolised in the liver	Dose adjustment may be required; use not recommended in severe hepatic impairment	Ahmed & Siddiqi, 2006 AMH, 2008

## 11.7 THE OPIOID-TOLERANT PATIENT

### 11.7.1 Definitions and clinical implications

Misunderstandings in the terminology related to addiction (see Section 11.8), tolerance, and physical dependence may confuse health care providers and lead to inappropriate and/or suboptimal acute pain management. Terms such as addiction, substance abuse, substance dependence and dependence are often used interchangeably. With this in mind, a consensus statement with agreed definitions for addiction, tolerance and physical dependence has been developed by the American Pain Society, the American Academy of Pain Medicine and the American Society of Addiction Medicine (AAPM et al, 2001).

**Table 11.7 Definitions for tolerance, physical dependence and addiction**

Tolerance (pharmacological)	A predictable physiological decrease in the effect of a drug over time so that a progressive increase in the amount of that drug is required to achieve the same effect. Tolerance develops to desired (eg analgesia) and undesired (eg euphoria, opioid-related sedation, nausea or constipation) effects at different rates.
Physical dependence	A physiological adaptation to a drug whereby abrupt discontinuation or reversal of that drug, or a sudden reduction in its dose, leads to a withdrawal (abstinence) syndrome. Withdrawal can be terminated by administration of the same or similar drug.
Addiction	A disease that is characterised by aberrant drug-seeking and maladaptive drug-taking behaviours that may include cravings, compulsive drug use and loss of control over drug use, despite the risk of physical, social and psychological harm. While psychoactive drugs have an addiction liability, psychological, social, environmental and genetic factors play an important role in the development of addiction. Unlike tolerance and physical dependence, addiction is not a predictable effect of a drug.
Pseudoaddiction	Behaviours that may seem inappropriately drug seeking but are a result of undertreatment of pain and resolve when pain relief is adequate.

Source: Adapted from Weissman & Haddox (1989), the Consensus statement from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine (2001), Alford et al (2006) and Ballantyne and LaForge (2007).

To the above list should be added opioid-induced hyperalgesia (OIH). Both acute and chronic administration of opioids given to treat pain may paradoxically lead to OIH, with reduced opioid efficacy and increased pain. For a more detailed discussion of opioid tolerance and OIH see Section 4.1.3.

#### ***Clinical implications of opioid tolerance and opioid-induced hyperalgesia***

The relative roles played by tolerance and OIH in the patient who is taking opioids on a long-term basis are unknown and both may contribute to increased pain (Angst & Clark, 2006; Chang et al, 2007). It is also possible that different opioids vary in their ability to induce OIH and tolerance (see Section 4.1.3 and below under Opioid Rotation).

There are some features of OIH that may help to distinguish it from pre-existing pain. With OIH, pain intensity may be increased above the level of the pre-existing pain; the distribution tends to be beyond that of the pre-existing pain as well as more diffuse; and quantitative

sensory testing (QST) may show changes in pain thresholds and tolerability (Chang et al, 2007). In the experimental setting, patients with opioid-managed (morphine or methadone) chronic non-cancer pain (Hay et al, 2009) and those in methadone maintenance programs (Compton et al, 2000 **Level III-2**; Doverty et al, 2001 **Level III-2**; Athanasos et al, 2006 **Level III-2**; Hay et al, 2009 **Level III-2**) have been shown, to be hyperalgesic when assessed with cold pressor testing but not with electrical pain stimuli. However, such testing is uncommon in the clinical setting.

The challenge faced by the clinician is that if inadequate pain relief is due to OIH, a reduction in opioid dose may help; if it is due to opioid tolerance, increased doses may provide better pain relief (Mao, 2008). There are case reports of patients with cancer and chronic non-cancer pain, taking high doses of opioid and who had developed OIH, whose pain relief improved following reduction of their opioid dose (Angst & Clark, 2006; Chang et al, 2007); there have been no such trials performed in the acute pain setting.

When a patient who has been taking opioids for a while (either legally prescribed or illicitly obtained) has new and ongoing tissue injury with resultant acute pain, a reasonable initial response to inadequate opioid analgesia, after an evaluation of the patient and in the absence of evidence to the contrary, is a trial of higher opioid doses (Chang et al, 2007). If the pain improves this would suggest that the inadequate analgesia resulted from tolerance; if pain worsens, or fails to respond to dose escalation, it could be a result of OIH (Chang et al, 2007). Fortunately, some of the strategies that may be tried in an attempt to attenuate opioid-tolerance in the acute pain setting may also moderate OIH (see below).

Other reasons for increased pain and/or increased opioid requirements should also be considered. These include acute neuropathic pain, pain due to other causes including postoperative complications, major psychological distress, and aberrant drug-seeking behaviours (see Section 11.8) (Macintyre & Schug, 2007).

### 11.7.2 Patient groups

Three main groups of opioid-tolerant patients/patients with OIH are encountered in surgical and other acute pain settings:

- patients with chronic cancer or non-cancer pain being treated with opioids, some of whom may exhibit features opioid addiction (see Section 11.8);
- patients with a substance abuse disorder either using illicit opioids or on an opioid maintenance treatment program (see Section 11.8); and
- patients who have developed acute opioid tolerance or OIH due to perioperative opioid administration, particularly opioids of high potency.

Recognition of the presence of opioid tolerance or OIH may not be possible if the patient's history is not available or accurate. If a patient is requiring much larger than expected opioid doses and other factors that might be leading to the high requirements have been excluded, opioid tolerance or OIH should be considered.

### 11.7.3 Management of acute pain

While the discussion below will focus on management of the opioid-tolerant patient, it is recognised that these patients may also have OIH.

Since 2004, a number of articles and chapters have been published outlining suggested strategies for the management of acute pain in the patient taking long-term opioids for both chronic non-cancer pain or because they have an addiction disorder and are in a drug treatment program (Carroll et al, 2004; Mitra & Sinatra, 2004; Kopf et al, 2005; Peng et al, 2005; Roberts & Meyer-Witting, 2005; Alford et al, 2006; Hadi et al, 2006; Mehta & Langford, 2006; Rozen &

DeGaetano, 2006; Basu et al, 2007; Ludlow et al, 2007; Macintyre & Schug, 2007; Roberts, 2008). However, evidence for the most appropriate management in these patients is very limited and the advice given in these papers remains based primarily on case series, case reports, expert opinion and personal experience.

In general, management of these patients should focus on:

- effective analgesia;
- use of strategies that may help to attenuate tolerance or OIH;
- prevention of withdrawal; and
- close liaison with other treating clinicians and specialist teams as required and appropriate discharge planning.

### **Effective analgesia**

It is known that opioid requirements are usually significantly higher in opioid-tolerant compared with opioid-naïve patients and that the interpatient variation in the doses needed is even greater. After a variety of surgical procedures, opioid-tolerant patients using PCA (Rapp et al, 1995 **Level III-2**) or epidural analgesia (de Leon-Casasola et al, 1993 **Level III-2**) required approximately three times the dose than their opioid-naïve counterparts. Opioid-tolerant patients with chronic pain also reported higher pain scores after surgery and their pain resolved more slowly compared with opioid-naïve patients (Chapman et al, 2009 **Level III-2**).

Opioid-tolerant patients reported higher pain scores (both resting and dynamic) and remained under the care of APSs longer than other patients (Rapp et al, 1995 **Level III-2**). Compared with opioid-tolerant patients with cancer pain, opioid-tolerant patients with non-cancer pain had higher rest and dynamic pain scores and required longer APS input, but there was no difference in opioid requirements (Rapp et al, 1995 **Level III-2**). In addition, staff relied more on functional measures of pain than on pain scores to assess pain intensity in these patients (Rapp et al, 1994 **Level IV**).

The incidence of opioid-induced nausea and vomiting may be lower in opioid-tolerant patients although the risk of excessive sedation/ respiratory depression may be higher (Rapp et al, 1995 **Level III-2**). An explanation to the patient of why good pain relief with opioids may be more difficult to obtain and why the dose that can safely be given will be limited by any onset of excessive sedation may be appropriate.

IV PCA is a useful modality for pain relief in opioid-tolerant patients, including those with an addiction disorder, provided that pain intensity and opioid consumption are carefully monitored and background requirements are provided if the patient cannot take their usual opioid; larger bolus doses will often be needed (Mitra & Sinatra, 2004; Macintyre & Schug, 2007). The size of an appropriate dose (on an individual patient basis) has been calculated by one group of investigators by using a preoperative fentanyl infusion until the patient's respiratory rate was lower than 5/minute; pharmacokinetic simulations were then used to predict the size of the PCA bolus dose and the rate of a background infusion that would be required for postoperative analgesia (Davis et al, 2005 **Level IV**). It may also be based on the dose of opioid the patient is already taking (Hadi et al, 2006; Macintyre & Schug, 2007). Regardless of the initial dose prescribed, subsequent doses will need to be titrated to effect for each patient.

Neuraxial opioids have been used effectively in opioid-tolerant patients; although higher doses may be required and may not result in an increase in adverse effects (de Leon-Casasola et al, 1993 **Level III-2**). Effective analgesia using intrathecal or epidural opioids will not necessarily prevent symptoms of opioid withdrawal (Carroll et al, 2004).



## **Attenuation of tolerance and opioid-induced hyperalgesia**

There are a number of strategies that may help attenuate opioid tolerance and OIH, at least to a certain degree. These include:

- use of NMDA- or opioid-receptor antagonists;
- opioid rotation; and
- other adjuvant drugs.

### **NMDA and opioid-receptor antagonists**

As noted in Section 4.1.3, the NMDA receptor is thought to be involved in the development of tolerance and OIH (Chang et al, 2007). In rodents, use of the NMDA-receptor antagonist ketamine has been shown to attenuate both the development of tolerance (Shimoyama et al, 1996; Laulin et al, 2002) and OIH (Laulin et al, 2002; Haugan et al, 2008).

Angst and Clark (Angst & Clark, 2006) summarised a number of RCTs that investigated the effects of a short remifentanyl infusion in volunteer subjects with pre-existing experimentally induced mechanical hyperalgesia; the use of remifentanyl was shown to aggravate hyperalgesia, the magnitude of the effect was directly related to the dose given, and coadministration of ketamine abolished the effect of remifentanyl. However, the evidence for the ability of ketamine to attenuate the acute tolerance and/or OIH seen after intraoperative use of remifentanyl infusions is conflicting, with both no benefit (Engelhardt et al, 2008 **Level II**) and prevention of OIH (Joly et al, 2005 **Level II**) shown. In patients taking opioids on a long-term basis, the administration of ketamine has been reported to lead to improved pain relief and reduced opioid requirements (Eilers et al, 2001; Sator-Katzenschlager et al, 2001; Mitra, 2008). After spinal fusion in opioid-tolerant patients, use of a continuous ketamine infusion resulted in significantly less pain but did not reduce PCA opioid requirements (Urban et al, 2008 **Level II**).

Similarly, in rodents, ultra low doses of naloxone have been shown to attenuate opioid tolerance (Crain & Shen, 1995; Crain & Shen, 2000; Wang et al, 2005). Clinical studies have concentrated on the effects of both naloxone and an opioid given acutely, with conflicting results; both improved postoperative pain and reduced opioid requirements and no differences in either have been reported (Angst & Clark, 2006; Sloan & Hamann, 2006). There was no analgesic benefit of adding naloxone to the PCA morphine solution (Sartain & Barry, 1999 **Level II**; Cepeda et al, 2002 **Level II**; Cepeda et al, 2004 **Level II**); in 'ultra low doses' but not in the higher dose studies, the incidence of nausea and pruritus was decreased (Cepeda et al, 2004 **Level II**). In the experimental pain setting in volunteers, the coadministration of ultra-low doses of naloxone to patients given buprenorphine significantly increased tolerance to cold pressor pain (La Vincente et al, 2008 **Level II**). There is no information about the effect of naloxone in patients taking opioids in the longer term.

Use over 3 months of a formulation combining oxycodone and ultra-low-dose naltrexone in the same tablet in patients with chronic pain, in comparison with oxycodone alone, showed that those given the combination had similar pain relief but with significantly smaller doses as well as less constipation, sedation, itching and physical dependence as assessed by a withdrawal scale (Webster et al, 2006 **Level II**).

### **Opioid rotation**

Opioid rotation is commonly used in the treatment of chronic non-cancer and cancer pain when a change to another opioid can improve analgesia and reduce side effects (Quigley, 2004; Mercadante & Arcuri, 2005; Angst & Clark, 2006). Opioid rotation (eg using an opioid that is different from the preadmission opioid) may also be of use in the acute pain setting (Hadi et al, 2006). The concept is based on the rationale that the different opioids do not act to the same degree on different opioid receptor subtypes and are metabolised differently, and also takes

advantage of the fact that cross-tolerance is likely to be incomplete (Jage, 2005; Mitra, 2008) and that the degree of OIH and tolerance appears to vary between opioids (see Section 4.1.3).

### **Other adjuvants**

In an experimental pain setting using intradermal electrical pain stimuli, parecoxib given before a remifentanyl infusion, but not if given during, was shown to modulate the hyperalgesia seen after withdrawal of the remifentanyl (Troster et al, 2006 **Level II**).

Intrathecal gabapentin has also been shown to attenuate opioid tolerance in rats (Lin et al, 2005), but there are no data from human studies.

### **Prevention of withdrawal**

Withdrawal from opioids is characterised by excitatory and autonomic symptoms including abdominal cramping, muscle aches and pain, insomnia, dysphoria, anxiety, restlessness, nausea and vomiting, diarrhoea, rhinorrhoea and sneezing, trembling, yawning, runny eyes and piloerection or 'gooseflesh' (Tetrault & O'Connor, 2008). The time of onset of withdrawal symptoms after cessation of the drug will depend on the duration of action of the opioid (Tetrault & O'Connor, 2008).

It should be prevented by maintenance of normal preadmission opioid regimens where possible (including, for patients undergoing surgery, on the day of their procedure), or appropriate substitutions with another opioid or the same opioid via another route (Carroll et al, 2004; Mitra & Sinatra, 2004; Macintyre & Schug, 2007). It is important to verify preadmission opioid doses, which may require contact with the patient's doctor, pharmacist or, where available, local regulatory authority. The use of additional unauthorised additional opioids (licit or illicit) or of lower doses than prescribed, may affect both pain relief and the risk of adverse effects.

While multimodal analgesic regimens (eg nsNSAIDs, paracetamol, ketamine, tramadol, regional analgesia) are of analgesic benefit, opioid-tolerant patients are at risk of opioid withdrawal if a purely non-opioid analgesic regimen or tramadol is used (Carroll et al, 2004; Mitra & Sinatra, 2004; Macintyre & Schug, 2007). For this reason opioid antagonists (naloxone, naltrexone) or mixed agonist-antagonists (eg buprenorphine, pentazocine) should be also avoided (unless the former are needed to treat respiratory depression) as their use may precipitate acute withdrawal reactions (Alford et al, 2006).

Use of intrathecal or epidural opioids will not necessarily prevent symptoms of opioid withdrawal and additional systemic opioids may be required (Carroll et al, 2004).

Clonidine, administered orally or parenterally, will aid in the symptomatic management of opioid withdrawal symptoms (Tetrault & O'Connor, 2008).

### **Management on discharge**

Discharge planning must take into account any regulatory requirements (eg the authority to prescribe an opioid may have be delegated to a particular physician only), the duration of use of any additional opioids prescribed for the short-term management of acute pain and the weaning of those drugs and, in a small of minority patients, the potential for prescribed opioids to be abused or misused. Appropriate use of non-opioid analgesics where possible, communication with the primary physician and health care professionals, and patient education and support must all be considered.

### Key messages

1. Opioid-tolerant patients report higher pain scores and have a lower incidence of opioid-induced nausea and vomiting (**U**) (**Level III-2**).
2. Ketamine improves pain relief after surgery in opioid-tolerant patients (**N**) (**Level II**).
3. Opioid-tolerant patients may have significantly higher opioid requirements than opioid-naive patients and interpatient variation in the doses needed may be even greater (**N**) (**Level III-2**).
4. Ketamine may reduce opioid requirements in opioid-tolerant patients (**U**) (**Level IV**).

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Usual preadmission opioid regimens should be maintained where possible or appropriate substitutions made (**U**).
- Opioid-tolerant patients are at risk of opioid withdrawal if non-opioid analgesic regimens or tramadol alone are used (**U**).
- PCA settings may need to include a background infusion to replace the usual opioid dose and a higher bolus dose (**U**).
- Neuraxial opioids can be used effectively in opioid-tolerant patients although higher doses may be required and these doses may be inadequate to prevent withdrawal (**U**).
- Liaison with all health care professionals involved in the treatment of the opioid-tolerant patient is important (**U**).
- In patients with escalating opioid requirements the possibility of the development of both tolerance and opioid-induced hyperalgesia should be considered (**N**).

## 11.8 THE PATIENT WITH AN ADDICTION DISORDER

An addiction disorder exists when the extent and pattern of substance use interferes with the psychological and sociocultural integrity of the person (see Table 11.7 above). For example, there may be recurring problems with social and personal interactions or with the legal system, recurrent failures to fulfil work or family obligations, or these patients may put themselves or others at risk of harm.

Use of the term addiction is recommended in the consensus statement from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine (AAPM et al, 2001), even though the alternative term substance dependence is used by other health organisations (Ballantyne & LaForge, 2007). This separates the behavioural component (addiction) from tolerance and physical dependence. The latter two factors are likely to exist if a patient is taking opioids long-term, but may not be present in all patients with an addiction disorder; it also reduces the risk of stigmatisation of patients who have a physical dependence because of long-term opioid therapy (Ballantyne & LaForge, 2007).

Effective management of acute pain in patients with an addiction disorder may be complex due to:

- psychological and behavioural characteristics associated with that disorder;
- presence of the drug (or drugs) of abuse;
- medications used to assist with drug withdrawal and/or rehabilitation;

- complications related to drug abuse including organ impairment and infectious diseases; and
- the presence of tolerance, physical dependence and the risk of withdrawal.

Evidence for the most appropriate management of acute pain in patients with an addiction disorder is limited and advice is based primarily on case series, case reports, expert opinion and personal experience.

Effective analgesia may be difficult, may be required for longer periods than in other patients (Rapp et al, 1995) and often requires significant deviations from 'standard' treatment protocols (Macintyre & Schug, 2007). In addition, ethical dilemmas can arise as a result of the need to balance concerns of undermedication against anxieties about safety and possible abuse or diversion of the drugs (Basu et al, 2007).

Identification of patients in whom there may be a risk of drug abuse is difficult. The ability of clinicians to predict which patients may misuse or abuse opioids is known to be poor (Jung & Reidenberg, 2007) and patient self-reports of drug use may not correlate with evidence from drug screens (Turk et al, 2008). Passik and Kirsh (Passik & Kirsh, 2008) recently reviewed a number of the screening tools that can be used to assess the risk of opioid abuse in patients given opioids for the management of chronic pain.

The first step in managing patients with an addiction disorder is identifying the problem, although obtaining an accurate history can sometimes be difficult. Polysubstance abuse is common and many of these patients will use drugs from different groups, the most common of which include CNS depressant drugs such as alcohol, opioids and benzodiazepines, or CNS-stimulant drugs including cocaine, amphetamines (amfetamines) and amphetamine-like drugs, cannabis and other hallucinogens. The group from which the drugs come determines their withdrawal characteristics (if any) and their interaction with acute pain therapy (Mitra & Sinatra, 2004; Peng et al, 2005). Patients should be asked about the route of administration used, as some may be injecting drugs intended for oral use. Confirmation of opioid doses should be sought where possible (Alford et al, 2006).

A number of centres worldwide monitor the use of illicit drugs on a regular basis, including prescription opioids. These include:

- in Australia, the National Drug and Alcohol Research Centre (NDARC) (see the section on Australian Drug Trends Series for Illicit Drug Reporting System [NDARC, 2009]);
- in New Zealand, the Centre for Social and Health Outcomes Research and Evaluation (SHORE) (see the section on the Illicit Drug Monitoring System [SHORE, 2009]);
- the surveillance systems set up by the National Health Service in the United Kingdom (see the section on Statistics of Drug Misuse [NHS, 2008]); and
- in the United States, the Substance Abuse and Mental Health Services of the US Department of Health and Human Services (SAMHSA, 2007), or other schemes specifically tracking prescription opioid abuse, such as Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) (Cicero et al, 2007).

Management of pain in patients with an addiction disorder should focus on:

- effective analgesia;
- use of strategies that may attenuate tolerance, and prevention of withdrawal (as outlined in Section 11.7);
- symptomatic treatment of affective disorders and behavioural disturbances; and
- the use of secure drug administration procedures.

Pain management in patients with an addiction disorder often presents significant challenges because of their fears of being stigmatised, concerns about inadequate pain relief, past experiences, expectations, and responses to interventions (Roberts, 2008). Inappropriate behaviours can be prevented to a significant extent by the development of a respectful, honest and open approach to communication and, as with all other patients, an explanation of treatment plans and the fact that complete relief of pain may not be a realistic goal, as well as involvement of the patient in the choice of plan (within appropriate boundaries) (Roberts, 2008).

In all cases, close liaison with other treating clinicians and drug and alcohol services is required. This is especially important if additional opioids are thought to be needed for pain relief for a limited period after discharge, or if any alteration has been made, after consultation with the relevant services, to methadone or buprenorphine doses while in hospital. In many countries regulatory requirements will dictate that only one physician has the authority to prescribe for these patients. However, restricted use of additional opioids after discharge may be possible in some circumstances. For example, it could be arranged for the patient to also pick up a limited and progressively decreasing number of tablets each day or every other day, along with their usual methadone or buprenorphine (Peng et al, 2005).

### 11.8.1 Management of acute pain in pregnant patients with an addiction disorder

The majority of women with an addiction disorder are of child bearing age; 0.76% of all births at one institution were to women using opioids and 0.42% to those using amphetamines (Ludlow et al, 2007). The management of acute pain in pregnant patients with an addiction disorder must take into account treatment of the mother as well as possible effects on the child, both before and after birth. Identification of these patients during pregnancy allows time to plan for appropriate management — but this is not always possible. Poor antenatal care is more common in these patients as are other factors related to their use of drugs such as respiratory infections, endocarditis, untreated cellulitis and abscesses, HIV/AIDS and hepatitis (Ludlow et al, 2007). For a detailed review of the anaesthetic issues in these patients see Ludlow et al (Ludlow et al, 2007).

It has been suggested that pregnant patients taking methadone as part of a drug-dependence treatment program should receive whatever dose is needed to prevent heroin use, and that the dose may need to be increased in the third trimester because the physiological changes associated with pregnancy can alter the pharmacokinetics of the drug (Ludlow et al, 2007). Additional opioid will be required for any postoperative pain, as with any opioid-tolerant patient, and the infant will require high-level neonatal care because of the risk of withdrawal (Ludlow et al, 2007; Jones et al, 2008). Opioid requirements during labour may not be significantly increased although methadone-maintained patients in this study did have higher pain scores (Meyer et al, 2007). Those taking buprenorphine will also have higher opioid requirements after surgery, and the newborn is still at risk (albeit maybe a lower risk) of withdrawal (Ludlow et al, 2007); again, opioid requirements during labour may not be increased (Jones et al, 2008). Both methadone and buprenorphine should be continued without interruption or, if the patient cannot take oral medications, then an alternative route (or opioid) should be used (Jones et al, 2008). Opioid requirements and the risk of withdrawal — for the patient and the infant — will also be higher in patients still taking heroin prior to delivery (Ludlow et al, 2007). For further information on maternal and neonatal outcomes see Section 11.1.3.

Opioid requirements in those addicted to substances other than opioids should be similar to other patients.

## 11.8.2 CNS depressant drugs

Although not inevitable, abuse of CNS-depressant drugs (eg opioids, alcohol) is often associated with physical dependence and the development of tolerance (see Section 11.7). Withdrawal from CNS-depressant drugs produces symptoms of CNS and autonomic hyperexcitability, the opposite of the effects of the CNS-depressant drugs themselves.

### Opioids

Opioid abuse not only involves the use of heroin but also legally prescribed opioids or prescription opioids illegally obtained. The number of prescriptions for opioids continues to increase in many countries and along with this the incidence of abuse of these drugs (Cicero et al, 2007; Katz et al, 2007). Illicitly obtained prescription opioids now account for a large proportion of all opioids used by patients with an addiction disorder (NDARC, 2009), in some instances exceeding the use of heroin (Fischer et al, 2006; Katz et al, 2007).

Not all aberrant drug behaviours indicate opioid addiction. Those that may include unsanctioned dose escalations, 'lost' or 'stolen' medications, obtaining the drugs from a number of different prescribers, polysubstance abuse, use of opioids obtained illicitly, and forging prescriptions (Turk et al, 2008), or other features listed under the definition of addiction in Table 11.7 above. Other aberrant behaviours may indicate problematic opioid use caused by a variety of factors other than addiction (Ballantyne & LaForge, 2007).

In general, when opioids are used in the short term to treat acute pain, they are usually effective and the risk of abuse is considered to be very small, although there are no accurate data and the exact incidence is unknown (Wasan et al, 2006). This may not be the case when these drugs are used in the management of chronic non-cancer pain, where long-term use of opioids may not provide as effective pain relief and the risk of abuse of the drugs may be higher (Ballantyne & LaForge, 2007; Chou et al, 2009; RACP et al, 2009). Both patients with chronic pain and those with an addiction disorder have a high rate of psychiatric comorbidities (such as anxiety, depression and personality disorders) and patients with chronic pain may therefore be more at risk of developing behavioural problems associated with opioid use (Ballantyne & LaForge, 2007).

A large survey, to which over 9000 patients with chronic non-cancer pain responded (a 64% response rate), found that users of prescription opioids had higher rates of opioid and non-opioid illicit drug misuse and alcohol abuse compared with those not using prescription opioids (Edlund et al, 2007 **Level III-2**). However, it is difficult to get accurate information on the rate of opioid addiction in chronic pain patients, especially as a variety of definitions are used that may not differentiate between problematic drug use and true addiction (Ballantyne & LaForge, 2007). The prevalence of addiction in chronic pain patients prescribed opioids is reported to range from 0% to 50% (Hojsted & Sjogren, 2007 **Level IV**). Others have reported that, on the basis of urine toxicology, up to 30% to 40% of patients prescribed opioids for the management of their chronic pain misuse those drugs (Turk et al, 2008 **Level IV**).

More recently, focus has turned to the use of 'abuse deterrent' formulations; strategies that are being assessed include the use of technologies that prevent the release of active opioid when tablets are crushed or attempts are made to extract the drugs by other means, and combination of the opioid with an opioid antagonist such as naloxone (Katz et al, 2007). Suboxone® is a trade name for a combination formulation of buprenorphine and naloxone, now commonly used in opioid-addiction treatment programs (see below).

## **Alcohol and benzodiazepines**

There is no cross-tolerance between opioids and alcohol or benzodiazepines and there is therefore no pharmacological reason to use higher than 'standard' initial opioid doses in patients with an alcohol or benzodiazepine addiction.

Alcohol and/or benzodiazepine abuse is relatively common and prevention of withdrawal should be a clinical priority in all patients. If benzodiazepines are administered for the treatment of withdrawal signs and symptoms, patient sedation levels must be monitored, especially if they are receiving concurrent opioids. Excessive sedation will limit the amount of opioid than can safely be given.

## **Cannabinoids**

Evidence supporting the effectiveness of cannabinoids in the management of acute pain is mixed (see Section 4.3.8). Although anecdotal reports suggest higher opioid doses may be required for the management of acute pain in patients who are heavy users of cannabinoids there is no published information to support this.

### **11.8.3 CNS stimulant drugs**

Abuse of CNS-stimulant drugs (eg cocaine, amphetamines, ecstasy) is associated with a psychological rather than physical dependence and only a low degree of tolerance; these drugs do not exhibit any cross-tolerance with opioids, and while behavioural and autonomic effects are seen during acute exposure, withdrawal symptoms are predominantly affective rather than physical.

Although cocaine and ecstasy (N-Methyl-3,4-methylenedioxyamphetamine or MDMA) are known to enhance the analgesic effects of morphine in animals (Kauppila et al, 1992; Gatch et al, 1999; Nencini et al, 1988), there are currently no data from human studies. In experimental pain settings, subjects taking ecstasy have been shown to have a reduced pain tolerance (O'Regan & Clow, 2004 **Level III-2**) and those taking cocaine reduced cold-pressor pain thresholds (Compton, 1994 **Level III-2**). There are no data from the clinical setting of any difference in opioid requirements compared from patients who do not use these drugs.

Withdrawal from methamphetamines is characterised by increases in sleepiness and appetite that can last for a few days; the severity of sleepiness correlated with amount used (calculated by cost per month) and length of regular use (McGregor et al, 2005).

### **11.8.4 Drugs used in the treatment of addiction disorders**

#### **Methadone**

Methadone is a long-acting opioid agonist used in the management of patients with an opioid addiction. It is usually given once a day, which is often enough to suppress symptoms of opioid withdrawal; the duration of any analgesic effect from the dose is likely to be much shorter (Alford et al, 2006; Basu et al, 2007). Dividing the daily dose on a temporary basis (eg giving the methadone in two equal doses twice a day) may allow some of the analgesic effect to be seen. In the acute pain setting methadone should be continued, where possible, as usual at the same dose. If there is any doubt about the dose (for example, there is a suspicion that the patient is diverting part or the entire prescribed amount), it may be prudent to give part of the reported dose and repeat this over the day if needed and if the patient is not sedated (Peng et al, 2005). If the patient is unable to take methadone by mouth, substitution with parenteral methadone or other opioids will be required in the short term (Mitra & Sinatra, 2004). Parenteral methadone doses should be based on half to two-thirds of the oral maintenance



dose and can be given in equal divided doses by SC or IM injection 2 to 4 times daily (Alford et al, 2006) or by continuous infusion.

### **Buprenorphine**

Buprenorphine is a partial opioid agonist used in the treatment of opioid addiction and is commonly prescribed in doses of 8 to 32 mg (Roberts & Meyer-Witting, 2005). Administered sublingually, it has a mean terminal half-life of 28 hours (Johnson et al, 2005). It is usually given once every day or two, which again is often enough to suppress symptoms of opioid withdrawal; like methadone the duration of any analgesic effect from the dose is likely to be much shorter (Alford et al, 2006). Preparations that combine buprenorphine and naloxone (poorly absorbed by the sublingual route) are available (Harris et al, 2004). The addition of naloxone to buprenorphine is said to reduce potential parenteral abuse of the drug (Johnson et al, 2005).

While patients in methadone maintenance programs have been shown to be hyperalgesic when assessed with cold pressor testing (Compton et al, 2000 **Level III-2**; Doverty et al, 2001 **Level III-2**; Athanasos et al, 2006 **Level III-2**), much less information is available for the effects of experimental pain stimuli in patients in buprenorphine maintenance programs. In a very small study comparing methadone-maintained (n = 5) and buprenorphine-maintained (n = 7) subjects with opioid-naive controls, both methadone-maintained and buprenorphine-maintained were more sensitive to cold-pressor pain than the controls although to a lesser degree in those taking buprenorphine (Compton et al, 2001 **Level III-2**). In opioid-naive subjects, administration of buprenorphine resulted in decreased hyperalgesia following transcutaneous pain stimuli compared with those given a placebo, suggesting that unlike morphine and methadone, buprenorphine may exert an antihyperalgesic effect (Koppert et al, 2005 **Level III-2**). There are no good data on which to base the management of patients on buprenorphine maintenance programs requiring pain relief. If shorter-acting opioid agonists will be required, a decision needs to be made whether or not to continue buprenorphine. Suggestions for management vary from withholding the buprenorphine and substituting an alternative opioid (eg methadone), to continuing the buprenorphine as usual (Roberts & Meyer-Witting, 2005; Alford et al, 2006). However, in practice, there appears to be little problem if the buprenorphine is continued and acute pain managed with the combination of a short-acting pure opioid agonist as well as other multimodal analgesic strategies (Macintyre & Schug, 2007). As with methadone, dividing the daily doses on a temporary basis may take advantage of the analgesic properties of the buprenorphine (Alford et al, 2006).

Close liaison with all treating clinicians and drug and alcohol services should occur. If buprenorphine has been ceased, its reintroduction should be managed in consultation with the prescribing practitioner.

### **Naltrexone**

Naltrexone is a pure opioid antagonist used in the management of patients with opioid or alcohol addiction. The usual oral maintenance dose is up to 25 to 50 mg daily; long acting implantable pellets are also available in some countries (Roberts & Meyer-Witting, 2005; Vickers & Jolly, 2006). Orally administered, naltrexone has an apparent half-life of about 14 hours and binds to opioid receptors for over 24 hours following a single dose (Vickers & Jolly, 2006), which can create difficulties in the acute pain setting.

It has been recommended that, where possible, naltrexone be stopped for at least 24 hours before surgery (Mitra & Sinatra, 2004; Vickers & Jolly, 2006). In these patients and in patients requiring surgery within this 24-hour period, multimodal analgesic regimens (eg NSAIDs, paracetamol, ketamine, tramadol and regional analgesia) should also be employed.

There is experimental evidence of  $\mu$ -opioid receptor upregulation following antagonist withdrawal (Millan et al, 1988) and abrupt discontinuation of naltrexone may therefore lead to a period of increased opioid sensitivity (Vickers & Jolly, 2006). As the effect of naltrexone diminishes after it has been ceased, the amount of opioid required to maintain analgesia may also need to be decreased in order to avoid signs of excessive opioid dose (in particular, respiratory depression).

Reintroduction of naltrexone should be done in consultation with the prescribing practitioner.

### 11.8.5 Recovering patients

Patients in drug treatment programs or in drug-free recovery may be concerned about the risk of relapse if they are given opioids for the management of their acute pain. However, there is no evidence that the use of opioids to treat acute pain increases the rate of relapse; a more likely trigger is unrelieved pain (Alford et al, 2006). Effective communication and planning, the use of multimodal analgesic strategies, reassurance that the risk of reversion to an active addiction disorder is small, and information that ineffective analgesia can paradoxically lead to relapses in recovering patients, are important and help avoid under treatment (Mitra & Sinatra, 2004).

#### Key messages

The following tick boxes  represent conclusions based on clinical experience and expert opinion.

- Naltrexone should be stopped at least 24 hours prior to elective surgery (U).
- Patients who have completed naltrexone therapy should be regarded as opioid naive; in the immediate post-treatment phase they may be opioid-sensitive (U).
- Maintenance methadone regimens should be continued where possible (U).
- Buprenorphine maintenance may be continued; if buprenorphine is ceased prior to surgery conversion to an alternative opioid is required (U).
- There is no cross-tolerance between central nervous system stimulants and opioids (U).

## REFERENCES

- Aakerlund LP & Rosenberg J (1994) Postoperative delirium: treatment with supplementary oxygen. *Br J Anaesth* **72**(3): 286–90.
- AAPM, APS & ASAM (2001) *Consensus statement from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine: Definitions related to the use of opioids for the treatment of pain*. Accessed January 2009.
- Abbey J, Piller N, De Bellis A et al (2004) The Abbey pain scale: a 1-minute numerical indicator for people with end-stage dementia. *Int J Palliat Nurs* **10**(1): 6–13.
- Abenhaim HA & Fraser WD (2008) Impact of pain level on second-stage delivery outcomes among women with epidural analgesia: results from the PEOPLE study. *Am J Obstet Gynecol* **199**(5): 500 e1–6.
- Abrao KC, Francisco RP, Miyadahira S et al (2009) Elevation of uterine basal tone and fetal heart rate abnormalities after labor analgesia: a randomized controlled trial. *Obstet Gynecol* **113**(1): 41–7.
- Adunsky A, Levy R, Heim M et al (2002) Meperidine analgesia and delirium in aged hip fracture patients. *Arch Gerontol Geriatr* **35**(3): 253–9.
- Ahmad M & Goucke CR (2002) Management strategies for the treatment of neuropathic pain in the elderly. *Drugs Aging* **19**(12): 929–45.
- Ahmed SN & Siddiqi ZA (2006) Antiepileptic drugs and liver disease. *Seizure* **15**(3): 156–64.

- Ahmad S, Nagle A, McCarthy RJ et al (2008) Postoperative hypoxemia in morbidly obese patients with and without obstructive sleep apnea undergoing laparoscopic bariatric surgery. *Anesth Analg* **107**(1): 138–43.
- Aissaoui Y, Bruyere R, Mustapha H et al (2008) A randomized controlled trial of pudendal nerve block for pain relief after episiotomy. *Anesth Analg* **107**(2): 625–9.
- Akin S, Aribogan A, Turunc T et al (2005) Lumbar plexus blockade with ropivacaine for postoperative pain management in elderly patients undergoing urologic surgeries. *Urol Int* **75**(4): 345–9.
- Alagiakrishnan K & Wiens CA (2004) An approach to drug induced delirium in the elderly. *Postgrad Med J* **80**(945): 388–93.
- Alano MA, Ngougma E, Ostrea EM, Jr. et al (2001) Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. *Pediatrics* **107**(3): 519–23.
- Alford DP, Compton P & Samet JH (2006) Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med* **144**(2): 127–34.
- AMH (2008) *Australian Medicines Handbook*. Adelaide, Australian Medicines Handbook Pty Ltd.
- Amir LH (2003) Breast pain in lactating women—mastitis or something else? *Aust Fam Physician* **32**(3): 141–5.
- Amir LH, Forster DA, Lumley J et al (2007) A descriptive study of mastitis in Australian breastfeeding women: incidence and determinants. *BMC Public Health* **7**: 62.
- Angst MS, Buhner M & Lotsch J (2000) Insidious intoxication after morphine treatment in renal failure: delayed onset of morphine-6-glucuronide action. *Anesthesiology* **92**(5): 1473–6.
- Angst MS & Clark JD (2006) Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* **104**(3): 570–87.
- Anim-Somuah M, Smyth R & Howell C (2005) Epidural versus non-epidural or no analgesia in labour. *Cochrane Database Syst Rev*(4): CD000331.
- Argoff CE (2005) Pharmacotherapeutic options in pain management. *Geriatrics Suppl*: 3–9.
- Arkoosh VA, Palmer CM, Yun EM et al (2008) A randomized, double-masked, multicenter comparison of the safety of continuous intrathecal labor analgesia using a 28-gauge catheter versus continuous epidural labor analgesia. *Anesthesiology* **108**(2): 286–98.
- ASA (2007) Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. *Anesthesiology* **106**(4): 843–63.
- Aslan E & Fynes M (2007) Symphysial pelvic dysfunction. *Curr Opin Obstet Gynecol* **19**(2): 133–9.
- Athanasos P, Smith CS, White JM et al (2006) Methadone maintenance patients are cross-tolerant to the antinociceptive effects of very high plasma morphine concentrations. *Pain* **120**(3): 267–75.
- Atienzar MC, Palanca JM, Torres F et al (2008) A randomized comparison of levobupivacaine, bupivacaine and ropivacaine with fentanyl, for labor analgesia. *Int J Obstet Anesth* **17**(2): 106–11.
- Australian Bureau of Statistics (2006) *Census data*. <http://abs.gov.au/websitedbs/D3310114.nsf/home/Census+data> Australian Bureau of Statistics. Accessed March 2009.
- Baka NE, Bayoumeu F, Boutroy MJ et al (2002) Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. *Anesth Analg* **94**(1): 184–7.
- Bakstad B, Sarfi M, Welle-Strand GK et al (2009) Opioid Maintenance Treatment during Pregnancy: Occurrence and Severity of Neonatal Abstinence Syndrome. A National Prospective Study. *Eur Addict Res* **15**(3): 128–34.
- Ballantyne JC & LaForge KS (2007) Opioid dependence and addiction during opioid treatment of chronic pain. *Pain* **129**(3): 235–55.
- Bamigboye AA & Justus HG (2008) Ropivacaine abdominal wound infiltration and peritoneal spraying at cesarean delivery for preemptive analgesia. *Int J Gynaecol Obstet* **102**(2): 160–4.
- Bamigboye AA & Hofmeyr GJ (2009) Local anaesthetic wound infiltration and abdominal nerves block during caesarean section for postoperative pain relief. *Cochrane Database Syst Rev*(3): CD006954.

- Bannwarth B, Pehourcq F, Lagrange F et al (2001) Single and multiple dose pharmacokinetics of acetaminophen (paracetamol) in polymedicated very old patients with rheumatic pain. *J Rheumatol* **28**(1): 182–4.
- Bar-Oz B, Bulkowstein M, Benyamini L et al (2003) Use of antibiotic and analgesic drugs during lactation. *Drug Saf* **26**(13): 925–35.
- Barkin RL, Barkin SJ & Barkin DS (2005) Perception, assessment, treatment, and management of pain in the elderly. *Clin Geriatr Med* **21**(3): 465–90.
- Barrington MJ, Kluger R, Watson R et al (2005) Epidural anesthesia for coronary artery bypass surgery compared with general anesthesia alone does not reduce biochemical markers of myocardial damage. *Anesth Analg* **100**(4): 921–8.
- Basu S, Bruce RD, Barry DT et al (2007) Pharmacological pain control for human immunodeficiency virus-infected adults with a history of drug dependence. *J Subst Abuse Treat* **32**(4): 399–409.
- Beaussier M, Weickmans H, Parc Y et al (2006) Postoperative analgesia and recovery course after major colorectal surgery in elderly patients: a randomized comparison between intrathecal morphine and intravenous PCA morphine. *Reg Anesth Pain Med* **31**(6): 531–8.
- Beckmann MM & Garrett AJ (2006) Antenatal perineal massage for reducing perineal trauma. *Cochrane Database Syst Rev*(1): CD005123.
- Bekker AY & Weeks EJ (2003) Cognitive function after anaesthesia in the elderly. *Best Pract Res Clin Anaesthesiol* **17**(2): 259–72.
- Bell ML (1997) Postoperative pain management for the cognitively impaired older adult. *Semin Perioper Nurs* **6**(1): 37–41.
- Benedetti F, Arduino C, Costa S et al (2006) Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. *Pain* **121**(1-2): 133–44.
- Benson GD, Koff RS & Tolman KG (2005) The therapeutic use of acetaminophen in patients with liver disease. *Am J Ther* **12**(2): 133–41.
- Benumof JL (2001) Obstructive sleep apnea in the adult obese patient: implications for airway management. *J Clin Anesth* **13**(2): 144–56.
- Berlin CM & Briggs GG (2005) Drugs and chemicals in human milk. *Semin Fetal Neonatal Med* **10**(2): 149–59.
- Bitsch MS, Foss NB, Kristensen BB et al (2006) Acute cognitive dysfunction after hip fracture: frequency and risk factors in an optimized, multimodal, rehabilitation program. *Acta Anaesthesiol Scand* **50**(4): 428–36.
- Blake DW, Chia PH, Donnan G et al (2008) Preoperative assessment for obstructive sleep apnoea and the prediction of postoperative respiratory obstruction and hypoxaemia. *Anaesth Intensive Care* **36**(3): 379–84.
- Blake DW, Yew CY, Donnan GB et al (2009) Postoperative analgesia and respiratory events in patients with symptoms of obstructive sleep apnoea. *Anesth Intensive Care* **37**(accepted for publication).
- Blay M, Orban JC, Rami L et al (2006) Efficacy of low-dose intrathecal morphine for postoperative analgesia after abdominal aortic surgery: a double-blind randomized study. *Reg Anesth Pain Med* **31**(2): 127–33.
- Blum RA, Comstock TJ, Sica DA et al (1994) Pharmacokinetics of gabapentin in subjects with various degrees of renal function. *Clin Pharmacol Ther* **56**(2): 154–9.
- Bodenham A & Park GR (1990) Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation. *Br J Anaesth* **64**(4): 436–41.
- Boger RH (2006) Renal impairment: a challenge for opioid treatment? The role of buprenorphine. *Palliat Med* **20** (Suppl 1): s17–23.
- Borg-Stein J & Dugan SA (2007) Musculoskeletal disorders of pregnancy, delivery and postpartum. *Phys Med Rehabil Clin N Am* **18**(3): 459–76.
- Bramley D, Hebert P, Jackson R et al (2004) Indigenous disparities in disease-specific mortality, a cross-country comparison: New Zealand, Australia, Canada, and the United States. *N Z Med J* **117**(1207): U1215.

- British Pain Society (2009) *Pain scales in multiple languages*. [http://www.britishpainsociety.org/pub\\_pain\\_scales.htm](http://www.britishpainsociety.org/pub_pain_scales.htm) British Pain Society. Accessed April 2009.
- Brown S & Lumley J (1998) Maternal health after childbirth: results of an Australian population based survey. *Br J Obstet Gynaecol* **105**(2): 156–61.
- Bucklin BA, Chestnut DH & Hawkins JL (2002) Intrathecal opioids versus epidural local anesthetics for labor analgesia: a meta-analysis. *Reg Anesth Pain Med* **27**(1): 23–30.
- Burkhardt H, Bruckner D & Gladisch R (2005) Risk factors of worsening renal function in hospitalized elderly patients. *J Nephrol* **18**(2): 166–73.
- Carroli G & Mignini L (2009) Episiotomy for vaginal birth. *Cochrane Database Syst Rev*(1): CD000081.
- Carroll IR, Angst MS & Clark JD (2004) Management of perioperative pain in patients chronically consuming opioids. *Reg Anesth Pain Med* **29**(6): 576–91.
- Carvalho B, Chu L, Fuller A et al (2006) Valdecoxib for postoperative pain management after cesarean delivery: a randomized, double-blind, placebo-controlled study. *Anesth Analg* **103**(3): 664–70.
- Carvalho B, Roland LM, Chu LF et al (2007) Single-dose, extended-release epidural morphine (DepoDur) compared to conventional epidural morphine for post-cesarean pain. *Anesth Analg* **105**(1): 176–83.
- Carvalho B (2008) Respiratory depression after neuraxial opioids in the obstetric setting. *Anesth Analg* **107**(3): 956–61.
- Casati A, Fanelli G, Pietropaoli P et al (2007) Monitoring cerebral oxygen saturation in elderly patients undergoing general abdominal surgery: a prospective cohort study. *Eur J Anaesthesiol* **24**(1): 59–65.
- Catley DM, Thornton C, Jordan C et al (1985) Pronounced, episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* **63**(1): 20–8.
- Cepeda MS, Africano JM, Manrique AM et al (2002) The combination of low dose of naloxone and morphine in PCA does not decrease opioid requirements in the postoperative period. *Pain* **96**(1-2): 73–9.
- Cepeda MS, Alvarez H, Morales O et al (2004) Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. *Pain* **107**(1-2): 41–6.
- Chang G, Chen L & Mao J (2007) Opioid tolerance and hyperalgesia. *Med Clin North Am* **91**(2): 199–211.
- Chang ZM & Heaman MI (2005) Epidural analgesia during labor and delivery: effects on the initiation and continuation of effective breastfeeding. *J Hum Lact* **21**(3): 305–14.
- Chapman CR, Donaldson G, Davis J et al (2009) Postoperative pain patterns in chronic pain patients: a pilot study. *Pain Med* **10**(3): 481–7.
- Charghi R, Backman S, Christou N et al (2003) Patient controlled i.v. analgesia is an acceptable pain management strategy in morbidly obese patients undergoing gastric bypass surgery. A retrospective comparison with epidural analgesia. *Can J Anaesth* **50**(7): 672–8.
- Chauvin M, Ferrier C, Haberer JP et al (1989) Sufentanil pharmacokinetics in patients with cirrhosis. *Anesth Analg* **68**(1): 1–4.
- Cheema S, Richardson J & McGurgan P (2003) Factors affecting the spread of bupivacaine in the adult thoracic paravertebral space. *Anaesthesia* **58**(7): 684–7.
- Choi YK, Brolin RE, Wagner BK et al (2000) Efficacy and safety of patient-controlled analgesia for morbidly obese patients following gastric bypass surgery. *Obes Surg* **10**(2): 154–9.
- Chou R, Fanciullo GJ, Fine PG et al (2009) Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* **10**(2): 113–30.
- Chung F, Yegneswaran B, Liao P et al (2008) Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. *Anesthesiology* **108**(5): 822–30.
- Chung SA, Yuan H & Chung F (2008) A systemic review of obstructive sleep apnea and its implications for anesthesiologists. *Anesth Analg* **107**(5): 1543–63.
- Cicero TJ, Dart RC, Inciardi JA et al (2007) The development of a comprehensive risk-management program for prescription opioid analgesics: researched abuse, diversion and addiction-related surveillance (RADARS). *Pain Med* **8**(2): 157–70.

- Cintron A & Morrison RS (2006) Pain and ethnicity in the United States: A systematic review. *J Palliat Med* **9**(6): 1454–73.
- Clayton DA, Grosshans DR & Browning MD (2002) Aging and surface expression of hippocampal NMDA receptors. *J Biol Chem* **277**(17): 14367–9.
- Closs SJ, Barr B, Briggs M et al (2004) A comparison of five pain assessment scales for nursing home residents with varying degrees of cognitive impairment. *J Pain Symptom Manage* **27**(3): 196–205.
- Clunie M, Crone LA, Klassen L et al (2003) Psychiatric side effects of indomethacin in parturients. *Can J Anaesth* **50**(6): 586–8.
- Clyburn PA, Rosen M & Vickers MD (1990) Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block. *Br J Anaesth* **64**(4): 446–9.
- Cole LJ, Farrell MJ, Duff EP et al (2006) Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease. *Brain* **129**(Pt 11): 2957–65.
- Cole LJ, Farrell MJ, Gibson SJ et al (2008) Age-related differences in pain sensitivity and regional brain activity evoked by noxious pressure. *Neurobiol Aging*. (Epub June 2008)
- Comparative Obstetric Mobile Epidural Trial (COMET) Study Group U (2001) Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet* **358**(9275): 19–23.
- Compton MA (1994) Cold-pressor pain tolerance in opiate and cocaine abusers: correlates of drug type and use status. *J Pain Symptom Manage* **9**(7): 462–73.
- Compton P, Charuvastra VC, Kintaudi K et al (2000) Pain responses in methadone-maintained opioid abusers. *J Pain Symptom Manage* **20**(4): 237–45.
- Compton P, Charuvastra VC & Ling W (2001) Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. *Drug Alcohol Depend* **63**(2): 139–46.
- Craig RG & Hunter JM (2008) Recent developments in the perioperative management of adult patients with chronic kidney disease. *Br J Anaesth* **101**(3): 296–310.
- Crain SM & Shen KF (1995) Ultra-low concentrations of naloxone selectively antagonize excitatory effects of morphine on sensory neurons, thereby increasing its antinociceptive potency and attenuating tolerance/dependence during chronic cotreatment. *Proc Natl Acad Sci U S A* **92**(23): 10540–4.
- Crain SM & Shen KF (2000) Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. *Pain* **84**(2-3): 121–31.
- Crawford ME, Moiniche S, Orbaek J et al (1996) Orthostatic hypotension during postoperative continuous thoracic epidural bupivacaine-morphine in patients undergoing abdominal surgery. *Anesth Analg* **83**(5): 1028–32.
- Crews JC, Weller RS, Moss J et al (2002) Levobupivacaine for axillary brachial plexus block: a pharmacokinetic and clinical comparison in patients with normal renal function or renal disease. *Anesth Analg* **95**(1): 219–23.
- Cullen DJ (2001) Obstructive sleep apnea and postoperative analgesia—a potentially dangerous combination. *J Clin Anesth* **13**(2): 83–5.
- D'Honneur G, Gilton A, Sandouk P et al (1994) Plasma and cerebrospinal fluid concentrations of morphine and morphine glucuronides after oral morphine. The influence of renal failure. *Anesthesiology* **81**(1): 87–93.
- Dargan PI, Colbridge MG & Jones AL (2005) The management of tricyclic antidepressant poisoning: the role of gut decontamination, extracorporeal procedures and Fab antibody fragments. *Toxicol Rev* **24**(3): 187–94.
- Davidhizar R & Giger JN (2004) A review of the literature on care of clients in pain who are culturally diverse. *Int Nurs Rev* **51**(1): 47–55.
- Davies G, Kingswood C & Street M (1996) Pharmacokinetics of opioids in renal dysfunction. *Clin Pharmacokinet* **31**(6): 410–22.
- Davis JJ, Swenson JD, Hall RH et al (2005) Preoperative "fentanyl challenge" as a tool to estimate postoperative opioid dosing in chronic opioid-consuming patients. *Anesth Analg* **101**(2): 389–95.



- Davis PJ, Stiller RL, Cook DR et al (1988) Pharmacokinetics of sufentanil in adolescent patients with chronic renal failure. *Anesth Analg* **67**(3): 268–71.
- Davis PJ, Stiller RL, Cook DR et al (1989) Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. *Anesth Analg* **68**(5): 579–83.
- Davison SN & Mayo PR (2008) Pain management in chronic kidney disease: the pharmacokinetics and pharmacodynamics of hydromorphone and hydromorphone-3-glucuronide in hemodialysis patients. *J Opioid Manag* **4**(6): 335–6.
- de Leon-Casasola OA, Myers DP, Donaparthi S et al (1993) A comparison of postoperative epidural analgesia between patients with chronic cancer taking high doses of oral opioids versus opioid-naïve patients. *Anesth Analg* **76**(2): 302–7.
- De Martin S, Orlando R, Bertoli M et al (2006) Differential effect of chronic renal failure on the pharmacokinetics of lidocaine in patients receiving and not receiving hemodialysis. *Clin Pharmacol Ther* **80**(6): 597–606.
- Dean M (2004) Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* **28**(5): 497–504.
- Divoll M, Abernethy DR, Ameer B et al (1982) Acetaminophen kinetics in the elderly. *Clin Pharmacol Ther* **31**(2): 151–6.
- Doverly M, White JM, Somogyi AA et al (2001) Hyperalgesic responses in methadone maintenance patients. *Pain* **90**(1-2): 91–6.
- Dowswell T, Bedwell C, Lavender T et al (2009) Transcutaneous electrical nerve stimulation (TENS) for pain relief in labour. *Cochrane Database Syst Rev*(2): CD007214.
- East CE, Begg L, Henshall NE et al (2007) Local cooling for relieving pain from perineal trauma sustained during childbirth. *Cochrane Database Syst Rev*(4): CD006304.
- Edlund MJ, Sullivan M, Steffick D et al (2007) Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med* **8**(8): 647–56.
- Edwards RR & Fillingim RB (2001) Effects of age on temporal summation and habituation of thermal pain: clinical relevance in healthy older and younger adults. *J Pain* **2**(6): 307–17.
- Ee CC, Manheimer E, Pirootta MV et al (2008) Acupuncture for pelvic and back pain in pregnancy: a systematic review. *Am J Obstet Gynecol* **198**(3): 254–9.
- Egbert AM, Parks LH, Short LM et al (1990) Randomized trial of postoperative patient-controlled analgesia vs intramuscular narcotics in frail elderly men. *Arch Intern Med* **150**(9): 1897–903.
- Eilers H, Philip LA, Bickler PE et al (2001) The reversal of fentanyl-induced tolerance by administration of "small-dose" ketamine. *Anesth Analg* **93**(1): 213–4.
- Elden H, Hagberg H, Olsen MF et al (2008) Regression of pelvic girdle pain after delivery: follow-up of a randomised single blind controlled trial with different treatment modalities. *Acta Obstet Gynecol Scand* **87**(2): 201–8.
- Engelhardt T, Zaarour C, Naser B et al (2008) Intraoperative low-dose ketamine does not prevent a remifentanil-induced increase in morphine requirement after pediatric scoliosis surgery. *Anesth Analg* **107**(4): 1170–5.
- Etches RC (1994) Respiratory depression associated with patient-controlled analgesia: a review of eight cases. *Can J Anaesth* **41**(2): 125–32.
- Farid WO, Dunlop SA, Tait RJ et al (2008) The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: review of human and animal data. *Curr Neuropharmacol* **6**(2): 125–50.
- Farrell M & Gibson S (2007) Age interacts with stimulus frequency in the temporal summation of pain. *Pain Med* **8**(6): 514–20.
- Farrell MJ, Katz B & Helme RD (1996) The impact of dementia on the pain experience. *Pain* **67**(1): 7–15.
- Feilberg VL, Rosenborg D, Broen Christensen C et al (1989) Excretion of morphine in human breast milk. *Acta Anaesthesiol Scand* **33**(5): 426–8.
- Feldt KS, Ryden MB & Miles S (1998) Treatment of pain in cognitively impaired compared with cognitively intact older patients with hip-fracture. *J Am Geriatr Soc* **46**(9): 1079–85.



- Fenwick C & Stevens J (2004) Post operative pain experiences of central Australian aboriginal women. What do we understand? *Aust J Rural Health* **12**(1): 22–7.
- Filitz J, Griessinger N, Sittl R et al (2006) Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. *Eur J Pain* **10**(8): 743–8.
- Fine PG (2004) Pharmacological management of persistent pain in older patients. *Clin J Pain* **20**(4): 220–6.
- Fischer B, Rehm J, Patra J et al (2006) Changes in illicit opioid use across Canada. *CMAJ* **175**(11): 1385.
- Flink IK, Mroczek MZ, Sullivan MJ et al (2009) Pain in childbirth and postpartum recovery: the role of catastrophizing. *Eur J Pain* **13**(3): 312–6.
- Fong HK, Sands LP & Leung JM (2006) The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesth Analg* **102**(4): 1255–66.
- Forster MC, Pardiwala A & Calthorpe D (2000) Analgesia requirements following hip fracture in the cognitively impaired. *Injury* **31**(6): 435–6.
- Foss NB, Kristensen MT, Kristensen BB et al (2005) Effect of postoperative epidural analgesia on rehabilitation and pain after hip fracture surgery: a randomized, double-blind, placebo-controlled trial. *Anesthesiology* **102**(6): 1197–204.
- Frey WC & Pilcher J (2003) Obstructive sleep-related breathing disorders in patients evaluated for bariatric surgery. *Obes Surg* **13**(5): 676–83.
- Fu Y, Guo L, Zhang J et al (2008) Differential effects of ageing on the EEG during pentobarbital and ketamine anaesthesia. *Eur J Anaesthesiol* **25**(10): 826–33.
- Fuchs-Lacelle S & Hadjistavropoulos T (2004) Development and preliminary validation of the pain assessment checklist for seniors with limited ability to communicate (PACSLAC). *Pain Manag Nurs* **5**(1): 37–49.
- Gagliese L & Melzack R (1997) Chronic pain in elderly people. *Pain* **70**(1): 3–14.
- Gagliese L, Jackson M, Ritvo P et al (2000) Age is not an impediment to effective use of patient-controlled analgesia by surgical patients. *Anesthesiology* **93**(3): 601–10.
- Gagliese L & Katz J (2003) Age differences in postoperative pain are scale dependent: a comparison of measures of pain intensity and quality in younger and older surgical patients. *Pain* **103**(1–2): 11–20.
- Gagliese L & Farrell MJ (2005) The neurobiology of aging, nociception and pain: an integration of animal and human experimental evidence. In: *Pain in older persons. Progress in Pain Research and Management* edn. Gibson SJ and Weiner DK (eds). Seattle, IASP Press.
- Gagliese L, Weizblit N, Ellis W et al (2005) The measurement of postoperative pain: a comparison of intensity scales in younger and older surgical patients. *Pain* **117**(3): 412–20.
- Gali B, Whalen FX, Jr., Gay PC et al (2007) Management plan to reduce risks in perioperative care of patients with presumed obstructive sleep apnea syndrome. *J Clin Sleep Med* **3**(6): 582–8.
- Gali B, Whalen FX, Schroeder DR et al (2009) Identification of patients at risk for postoperative respiratory complications using a preoperative obstructive sleep apnea screening tool and postanesthesia care assessment. *Anesthesiology* **110**(4): 869–77.
- Gardiner SJ, Doogue MP, Zhang M et al (2006) Quantification of infant exposure to celecoxib through breast milk. *Br J Clin Pharmacol* **61**(1): 101–4.
- Gatch MB, Negus SS & Mello NK (1999) Antinociceptive effects of cocaine in rhesus monkeys. *Pharmacol Biochem Behav* **62**(2): 291–7.
- Gibson SJ (2003) Pain and aging: the pain experience over the adult life span. In: *Proceedings of the 10th World Congress on Pain. Progress in Pain Research and Management* edn. Dostrovsky JO, Carr DB and Koltzenburg M (eds). Seattle, IASP Press. 24: 767–90.
- Gibson SJ & Farrell M (2004) A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. *Clin J Pain* **20**(4): 227–39.
- Gibson SJ (2006) Older people's pain. *Pain: Clinical Updates (IASP)* **14**(3).
- Gillett WR & Jones D (2009) Chronic pelvic pain in women: role of the nervous system. *Expert Rev Obstet Gynecol* **4**(2): 149–63.

- Girgin NK, Gurbet A, Turker G et al (2008) Intrathecal morphine in anesthesia for cesarean delivery: dose-response relationship for combinations of low-dose intrathecal morphine and spinal bupivacaine. *J Clin Anesth* **20**(3): 180–5.
- Goodman SR, Smiley RM, Negron MA et al (2009) A randomized trial of breakthrough pain during combined spinal-epidural versus epidural labor analgesia in parous women. *Anesth Analg* **108**(1): 246–51.
- Graham GG, Scott KF & Day RO (2005) Tolerability of paracetamol. *Drug Saf* **28**(3): 227–40.
- Granot M, Khoury R, Berger G et al (2007) Clinical and experimental pain perception is attenuated in patients with painless myocardial infarction. *Pain* **133**(1-3): 120–7.
- Green CR, Anderson KO, Baker TA et al (2003) The unequal burden of pain: confronting racial and ethnic disparities in pain. *Pain Med* **4**(3): 277–94.
- Greene NH, Attix DK, Weldon BC et al (2009) Measures of executive function and depression identify patients at risk for postoperative delirium. *Anesthesiology* **110**(4): 788–95.
- Gross JB, Bachenberg KL, Benumof JL et al (2006) Practice guidelines for the perioperative management of patients with obstructive sleep apnea: a report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology* **104**(5): 1081–93.
- Guay DR (2005) Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? *Am J Geriatr Pharmacother* **3**(4): 274–87.
- Gupta RM, Parvizi J, Hanssen AD et al (2001) Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: a case-control study. *Mayo Clin Proc* **76**(9): 897–905.
- Gutke A, Ostgaard HC & Oberg B (2008) Association between muscle function and low back pain in relation to pregnancy. *J Rehabil Med* **40**(4): 304–11.
- Gwartz KH, Young JV, Byers RS et al (1999) The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. *Anesth Analg* **88**(3): 599–604.
- Hadi I, Morley-Forster PK, Dain S et al (2006) Brief review: Perioperative management of the patient with chronic non-cancer pain: [Article de synthèse court: Prise en charge périopératoire des patients souffrant de douleur chronique non cancéreuse]. *Can J Anaesth* **53**(12): 1190–99.
- Hale TW, McDonald R & Boger J (2004) Transfer of celecoxib into human milk. *J Hum Lact* **20**(4): 397–403.
- Halpern SH & Walsh V (2003) Epidural ropivacaine versus bupivacaine for labor: a meta-analysis. *Anesth Analg* **96**(5): 1473–9.
- Halpern SH & Carvalho B (2009) Patient-controlled epidural analgesia for labor. *Anesth Analg* **108**(3): 921–8.
- Hand CW, Sear JW, Uppington J et al (1990) Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. *Br J Anaesth* **64**(3): 276–82.
- Hanks RK, Pietrobon R, Nielsen KC et al (2006) The effect of age on sciatic nerve block duration. *Anesth Analg* **102**(2): 588–92.
- Hanna MH, D'Costa F, Peat SJ et al (1993) Morphine-6-glucuronide disposition in renal impairment. *Br J Anaesth* **70**(5): 511–4.
- Harney D & Patijn J (2007) Meralgia paresthetica: diagnosis and management strategies. *Pain Med* **8**(8): 669–77.
- Harris DS, Mendelson JE, Lin ET et al (2004) Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone: lack of dose proportionality. *Clin Pharmacokinet* **43**(5): 329–40.
- Haugan F, Rygh LJ & Tjolsen A (2008) Ketamine blocks enhancement of spinal long-term potentiation in chronic opioid treated rats. *Acta Anaesthesiol Scand* **52**(5): 681–7.
- Hay-Smith EJ (2000) Therapeutic ultrasound for postpartum perineal pain and dyspareunia. *Cochrane Database Syst Rev*(2): CD000495.

- Hay JL, White JM, Bochner F et al (2009) Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. *J Pain* **10**(3): 316–22.
- Hedayati H, Parsons J & Crowther CA (2003) Rectal analgesia for pain from perineal trauma following childbirth. *Cochrane Database Syst Rev*(3): CD003931.
- Hedayati H, Parsons J & Crowther CA (2005) Topically applied anaesthetics for treating perineal pain after childbirth. *Cochrane Database Syst Rev*(2): CD004223.
- Herr K, Bjoro K & Decker S (2006) Tools for assessment of pain in nonverbal older adults with dementia: a state-of-the-science review. *J Pain Symptom Manage* **31**(2): 170–92.
- Herr KA, Spratt K, Mobily PR et al (2004) Pain intensity assessment in older adults: use of experimental pain to compare psychometric properties and usability of selected pain scales with younger adults. *Clin J Pain* **20**(4): 207–19.
- Herrick IA, Ganapathy S, Komar W et al (1996) Postoperative cognitive impairment in the elderly. Choice of patient-controlled analgesia opioid. *Anaesthesia* **51**(4): 356–60.
- Hill D (2008) Remifentanyl in obstetrics. *Curr Opin Anaesthesiol* **21**(3): 270–4.
- Hodnett ED, Gates S, Hofmeyr GJ et al (2007) Continuous support for women during childbirth. *Cochrane Database Syst Rev*(3): CD003766.
- Hojsted J & Sjogren P (2007) Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain* **11**(5): 490–518.
- Honeyman PT & Jacobs EA (1996) Effects of culture on back pain in Australian aboriginals. *Spine* **21**(7): 841–3.
- Howe PW, Condon JR & Goodchild CS (1998) Anaesthesia for aboriginal Australians. *Anaesth Intensive Care* **26**(1): 86–91.
- Hsu HW, Cheng YJ, Chen LK et al (2003) Differential analgesic effect of tenoxicam on the wound pain and uterine cramping pain after cesarean section. *Clin J Pain* **19**(1): 55–8.
- Huang YC, Tsai SK, Huang CH et al (2002) Intravenous tenoxicam reduces uterine cramps after Cesarean delivery. *Can J Anaesth* **49**(4): 384–7.
- Huerta S, DeShields S, Shpiner R et al (2002) Safety and efficacy of postoperative continuous positive airway pressure to prevent pulmonary complications after Roux-en-Y gastric bypass. *J Gastrointest Surg* **6**(3): 354–8.
- Hullett BJ, Chambers NA, Pascoe EM et al (2006) Tramadol vs morphine during adenotonsillectomy for obstructive sleep apnea in children. *Paediatr Anaesth* **16**(6): 648–53.
- Husebo BS, Strand LI, Moe-Nilssen R et al (2007) Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale (MOBID): development and validation of a nurse-administered pain assessment tool for use in dementia. *J Pain Symptom Manage* **34**(1): 67–80.
- Ilett KF & Kristensen JH (2005) Drug use and breastfeeding. *Expert Opin Drug Saf* **4**(4): 745–68.
- Ilett KF, Paech MJ, Page-Sharp M et al (2008) Use of a sparse sampling study design to assess transfer of tramadol and its O-desmethyl metabolite into transitional breast milk. *Br J Clin Pharmacol* **65**(5): 661–6.
- Isenor L & Penny-MacGillivray T (1993) Intravenous meperidine infusion for obstetric analgesia. *J Obstet Gynecol Neonatal Nurs* **22**(4): 349–56.
- Ishiyama T, Iijima T, Sugawara T et al (2007) The use of patient-controlled epidural fentanyl in elderly patients. *Anaesthesia* **62**(12): 1246–50.
- Ito S (2000) Drug therapy for breast-feeding women. *N Engl J Med* **343**(2): 118–26.
- Jage J (2005) Opioid tolerance and dependence -- do they matter? *Eur J Pain* **9**(2): 157–62.
- Jahanfar S, Ng CJ & Teng CL (2009) Antibiotics for mastitis in breastfeeding women. *Cochrane Database Syst Rev*(1): CD005458.
- Jakobsen CJ, Nygaard E, Norrild K et al (2009) High thoracic epidural analgesia improves left ventricular function in patients with ischemic heart. *Acta Anaesthesiol Scand* **53**(5): 559–64.
- Jansson LM, Choo R, Velez ML et al (2008) Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics* **121**(1): 106–14.
- Jensen F, Qvist I, Brocks V et al (1984) Submucous paracervical blockade compared with intramuscular meperidine as analgesia during labor: a double-blind study. *Obstet Gynecol* **64**(5): 724–7.

- Johnson RE, Fudala PJ & Payne R (2005) Buprenorphine: considerations for pain management. *J Pain Symptom Manage* **29**(3): 297–326.
- Jokinen MJ (2005) The pharmacokinetics of ropivacaine in hepatic and renal insufficiency. *Best Pract Res Clin Anaesthesiol* **19**(2): 269–74.
- Jokinen MJ, Neuvonen PJ, Lindgren L et al (2007) Pharmacokinetics of ropivacaine in patients with chronic end-stage liver disease. *Anesthesiology* **106**(1): 43–55.
- Joly V, Richebe P, Guignard B et al (2005) Remifentanyl-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* **103**(1): 147–55.
- Jones HE, Martin PR, Heil SH et al (2008) Treatment of opioid-dependent pregnant women: clinical and research issues. *J Subst Abuse Treat* **35**(3): 245–59.
- Juhlin T, Bjorkman S & Hoglund P (2005) Cyclooxygenase inhibition causes marked impairment of renal function in elderly subjects treated with diuretics and ACE-inhibitors. *Eur J Heart Fail* **7**(6): 1049–56.
- Jung B & Reidenberg MM (2007) Physicians being deceived. *Pain Med* **8**(5): 433–7.
- Junttila EK, Karjalainen PK, Ohtonen PP et al (2009) A comparison of paracervical block with single-shot spinal for labour analgesia in multiparous women: a randomised controlled trial. *Int J Obstet Anesth* **18**(1): 15–21.
- Kalso E (2005) Oxycodone. *J Pain Symptom Manage* **29**(5 Suppl): S47–56.
- Kalus SM, Kornman LH & Quinlivan JA (2008) Managing back pain in pregnancy using a support garment: a randomised trial. *BJOG* **115**(1): 68–75.
- Katz NP, Adams EH, Benneyan JC et al (2007) Foundations of opioid risk management. *Clin J Pain* **23**(2): 103–18.
- Kauppila T, Mecke E & Pertovaara A (1992) Enhancement of morphine-induced analgesia and attenuation of morphine-induced side-effects by cocaine in rats. *Pharmacol Toxicol* **71**(3 Pt 1): 173–8.
- Keita H, Geachan N, Dahmani S et al (2003) Comparison between patient-controlled analgesia and subcutaneous morphine in elderly patients after total hip replacement. *Br J Anaesth* **90**(1): 53–7.
- Kettle C, Hills RK & Ismail KM (2007) Continuous versus interrupted sutures for repair of episiotomy or second degree tears. *Cochrane Database Syst Rev*(4): CD000947.
- Khan ZP, Ferguson CN & Jones RM (1999) alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia* **54**(2): 146–65.
- Khooshideh M & Shahriari A (2009) A comparison of tramadol and pethidine analgesia on the duration of labour: a randomised clinical trial. *Aust N Z J Obstet Gynaecol* **49**(1): 59–63.
- Klatzkin RR, Mechlin B, Bunevicius R et al (2007) Race and histories of mood disorders modulate experimental pain tolerance in women. *J Pain* **8**(11): 861–8.
- Kojima Y & Narita M (2006) Postoperative outcome among elderly patients after general anaesthesia. *Acta Anaesthesiol Scand* **50**(1): 19–25.
- Konttinen N & Rosenberg PH (2006) Outcome after anaesthesia and emergency surgery in patients over 100 years old. *Acta Anaesthesiol Scand* **50**(3): 283–9.
- Kopf A, Banzhaf A & Stein C (2005) Perioperative management of the chronic pain patient. *Best Pract Res Clin Anaesthesiol* **19**(1): 59–76.
- Koppel C, Arndt I & Ibe K (1990) Effects of enzyme induction, renal and cardiac function on ketamine plasma kinetics in patients with ketamine long-term analgesedation. *Eur J Drug Metab Pharmacokinet* **15**(3): 259–63.
- Koppert W, Ihmsen H, Korber N et al (2005) Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain* **118**(1-2): 15–22.
- Koppert W, Frotsch K, Huzurudin N et al (2006) The effects of paracetamol and parecoxib on kidney function in elderly patients undergoing orthopedic surgery. *Anesth Analg* **103**(5): 1170–6.
- Koren G, Florescu A, Costei AM et al (2006) Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother* **40**(5): 824–9.
- Kotb HI, El-Kady SA, Emara SE et al (2005) Pharmacokinetics of controlled release morphine (MST) in patients with liver carcinoma. *Br J Anaesth* **94**(1): 95–9.

- Kotb HI, Fouad IA, Fares KM et al (2008) Pharmacokinetics of oral tramadol in patients with liver cancer. *J Opioid Manag* **4**(2): 99–104.
- Kress HG (2009) Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain* **13**(3): 219–30.
- Kristensen JH, Ilett KF, Hackett LP et al (2006) Gabapentin and breastfeeding: a case report. *J Hum Lact* **22**(4): 426–8.
- Kyzer S, Ramadan E, Gersch M et al (1995) Patient-Controlled Analgesia Following Vertical Gastroplasty: a Comparison with Intramuscular Narcotics. *Obes Surg* **5**(1): 18–21.
- La Vincente SF, White JM, Somogyi AA et al (2008) Enhanced buprenorphine analgesia with the addition of ultra-low-dose naloxone in healthy subjects. *Clin Pharmacol Ther* **83**(1): 144–52.
- Lagunilla J, Garcia-Bengochea JB, Fernandez AL et al (2006) High thoracic epidural blockade increases myocardial oxygen availability in coronary surgery patients. *Acta Anaesthesiol Scand* **50**(7): 780–6.
- Landsberg R, Friedman M & Ascher-Landsberg J (2001) Treatment of hypoxemia in obstructive sleep apnea. *Am J Rhinol* **15**(5): 311–3.
- Latthe P, Mignini L, Gray R et al (2006) Factors predisposing women to chronic pelvic pain: systematic review. *BMJ* **332**(7544): 749–55.
- Laulin JP, Maurette P, Corcuff JB et al (2002) The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. *Anesth Analg* **94**(5): 1263–9.
- Launay-Vacher V, Karie S, Fau JB et al (2005) Treatment of pain in patients with renal insufficiency: the World Health Organization three-step ladder adapted. *J Pain* **6**(3): 137–48.
- Lautenbacher S, Kunz M, Strate P et al (2005) Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain* **115**(3): 410–8.
- Lee MA, Leng ME & Cooper RM (2005) Measurements of plasma oxycodone, noroxycodone and oxymorphone levels in a patient with bilateral nephrectomy who is undergoing haemodialysis. *Palliat Med* **19**(3): 259–60.
- Leo S & Sia AT (2008) Maintaining labour epidural analgesia: what is the best option? *Curr Opin Anaesthesiol* **21**(3): 263–9.
- Leong IY, Chong MS & Gibson SJ (2006) The use of a self-reported pain measure, a nurse-reported pain measure and the PAINAD in nursing home residents with moderate and severe dementia: a validation study. *Age Ageing* **35**(3): 252–6.
- Levy BT, Bergus GR, Hartz A et al (1999) Is paracervical block safe and effective? A prospective study of its association with neonatal umbilical artery pH values. *J Fam Pract* **48**(10): 778–84.
- Li DK, Liu L & Odouli R (2003) Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* **327**(7411): 368.
- Li SF, Greenwald PW, Gennis P et al (2001) Effect of age on acute pain perception of a standardized stimulus in the emergency department. *Ann Emerg Med* **38**(6): 644–7.
- Li Y, Zhu S, Bao F et al (2006) The effects of age on the median effective concentration of ropivacaine for motor blockade after epidural anesthesia with ropivacaine. *Anesth Analg* **102**(6): 1847–50.
- Liabsuetrakul T, Choobun T, Peeyanjarassri K et al (2007) Prophylactic use of ergot alkaloids in the third stage of labour. *Cochrane Database Syst Rev*(2): CD005456.
- Lieberman JA, Cooper TB, Suckow RF et al (1985) Tricyclic antidepressant and metabolite levels in chronic renal failure. *Clin Pharmacol Ther* **37**(3): 301–7.
- Lim PC & Macintyre PE (2006) An audit of intrathecal morphine analgesia for non-obstetric postsurgical patients in an adult tertiary hospital. *Anaesthesia and Intensive Care* **34**(6): 776–81.
- Lim SS, Tan PC, Sockalingam JK et al (2008) Oral celecoxib versus oral diclofenac for post-perineal repair analgesia after spontaneous vaginal birth: a randomised trial. *Aust N Z J Obstet Gynaecol* **48**(1): 71–7.
- Lin JA, Lee MS, Wu CT et al (2005) Attenuation of morphine tolerance by intrathecal gabapentin is associated with suppression of morphine-evoked excitatory amino acid release in the rat spinal cord. *Brain Res* **1054**(2): 167–73.
- Loadsman JA & Hillman DR (2001) Anaesthesia and sleep apnoea. *Br J Anaesth* **86**(2): 254–66.

- Loadman J A (2009) Preoperative screening for obstructive sleep apnoea – are we losing sleep over nothing. *Anaesth Intensive Care* **37**(5): 720–725.
- Lofsky A (2002) Sleep apnea and narcotic postoperative pain medication morbidity and mortality risk. *Anesthesia Patient Safety Foundation Newsletter* **17**: 24.
- Lowenthal DT, Saris SD, Paran E et al (1993) The use of transdermal clonidine in the hypertensive patient with chronic renal failure. *Clin Nephrol* **39**(1): 37–43.
- Ludlow J, Christmas T, Paech MJ et al (2007) Drug abuse and dependency during pregnancy: anaesthetic issues. *Anaesth Intensive Care* **35**(6): 881–93.
- Lugo RA, Satterfield KL & Kern SE (2005) Pharmacokinetics of methadone. *J Pain Palliat Care Pharmacother* **19**(4): 13–24.
- Lynch EP, Lazor MA, Gellis JE et al (1998) The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg* **86**(4): 781–5.
- Macintyre PE (2005) Intravenous patient-controlled analgesia: one size does not fit all. *Anesthesiol Clin North America* **23**(1): 109–23.
- Macintyre PE & Jarvis DA (1996) Age is the best predictor of postoperative morphine requirements. *Pain* **64**(2): 357–64.
- Macintyre PE & Schug SA (2007) *Acute pain management: a practical guide*. London, Elsevier.
- Macintyre PE & Upton R (2008) Acute pain management in the elderly patient. In: *Clinical Pain Management: Acute Pain* 2nd edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
- Madadi P, Shirazi F, Walter FG et al (2008) Establishing causality of CNS depression in breastfed infants following maternal codeine use. *Paediatr Drugs* **10**(6): 399–404.
- Madadi P, Ross CJ, Hayden MR et al (2009) Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* **85**(1): 31–5.
- Magnusson KR, Nelson SE & Young AB (2002) Age-related changes in the protein expression of subunits of the NMDA receptor. *Brain Res Mol Brain Res* **99**(1): 40–5.
- Mangoni AA & Jackson SH (2004) Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* **57**(1): 6–14.
- Mann C, Pouzeratte Y, Boccarda G et al (2000) Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* **92**(2): 433–41.
- Mann C, Pouzeratte Y & Eledjam JJ (2003) Postoperative patient-controlled analgesia in the elderly: risks and benefits of epidural versus intravenous administration. *Drugs Aging* **20**(5): 337–45.
- Manninen T, Aantaa R, Salonen M et al (2000) A comparison of the hemodynamic effects of paracervical block and epidural anesthesia for labor analgesia. *Acta Anaesthesiol Scand* **44**(4): 441–5.
- Mao J (2008) Opioid-induced hyperalgesia. *Pain: Clinical Updates (IASP)* **16**(2).
- Mardirosoff C, Dumont L, Boulvain M et al (2002) Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. *BJOG* **109**(3): 274–81.
- Marucci M, Cinnella G, Perchiazzi G et al (2007) Patient-requested neuraxial analgesia for labor: impact on rates of cesarean and instrumental vaginal delivery. *Anesthesiology* **106**(5): 1035–45.
- Matsota PK, Markantonis SL, Fouteri MZ et al (2009) Excretion of ropivacaine in breast milk during patient-controlled epidural analgesia after cesarean delivery. *Reg Anesth Pain Med* **34**(2): 126–9.
- McDonald SP & Russ GR (2003) Current incidence, treatment patterns and outcome of end-stage renal disease among indigenous groups in Australia and New Zealand. *Nephrology (Carlton)* **8**(1): 42–8.
- McDonnell JG, Curley G, Carney J et al (2008) The analgesic efficacy of transversus abdominis plane block after cesarean delivery: a randomized controlled trial. *Anesth Analg* **106**(1): 186–91.
- McGeeney BE (2009) Pharmacological management of neuropathic pain in older adults: an update on peripherally and centrally acting agents. *J Pain Symptom Manage* **38**(2 Suppl): S15–27.
- McGrath P (2006) 'The biggest worry...': research findings on pain management for Aboriginal peoples in Northern Territory, Australia. *Rural Remote Health* **6**(3): 549.
- McGregor C, Srisurapanont M, Jittiwutikarn J et al (2005) The nature, time course and severity of methamphetamine withdrawal. *Addiction* **100**(9): 1320–9.



- Mehta V & Langford RM (2006) Acute pain management for opioid dependent patients. *Anaesthesia* **61**(3): 269–76.
- Mehta Y, Manikappa S, Juneja R et al (2000) Obstructive sleep apnea syndrome: anesthetic implications in the cardiac surgical patient. *J Cardiothorac Vasc Anesth* **14**(4): 449–53.
- Meny RG, Naumburg EG, Alger LS et al (1993) Codeine and the breastfed neonate. *J Hum Lact* **9**(4): 237–40.
- Mercadante S & Arcuri E (2004) Opioids and renal function. *J Pain* **5**(1): 2–19.
- Mercadante S & Arcuri E (2005) Hyperalgesia and opioid switching. *Am J Hosp Palliat Care* **22**(4): 291–4.
- Meyer M, Wagner K, Benvenuto A et al (2007) Intrapartum and postpartum analgesia for women maintained on methadone during pregnancy. *Obstet Gynecol* **110**(2 Pt 1): 261–6.
- Meylan N, Elia N, Lysakowski C et al (2009) Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth* **102**(2): 156–67.
- Millan MJ, Morris BJ & Herz A (1988) Antagonist-induced opioid receptor up-regulation. I. Characterization of supersensitivity to selective mu and kappa agonists. *J Pharmacol Exp Ther* **247**(2): 721–8.
- MIMS (2008) *MIMS Annual 2008*, MediMedia Australia Pty Ltd.
- Miners JO, Penhall R, Robson RA et al (1988) Comparison of paracetamol metabolism in young adult and elderly males. *Eur J Clin Pharmacol* **35**(2): 157–60.
- Minozzi S, Amato L, Vecchi S et al (2008) Maintenance agonist treatments for opiate dependent pregnant women. *Cochrane Database Syst Rev*(2): CD006318.
- Mitra S & Sinatra RS (2004) Perioperative management of acute pain in the opioid-dependent patient. *Anesthesiology* **101**(1): 212–27.
- Mitra S (2008) Opioid-induced hyperalgesia: pathophysiology and clinical implications. *J Opioid Manag* **4**(3): 123–30.
- Moore AR & O'Keefe ST (1999) Drug-induced cognitive impairment in the elderly. *Drugs Aging* **15**(1): 15–28.
- Morimoto Y, Yoshimura M, Utada K et al (2009) Prediction of postoperative delirium after abdominal surgery in the elderly. *J Anesth* **23**(1): 51–6.
- Morland-Schultz K & Hill PD (2005) Prevention of and therapies for nipple pain: a systematic review. *J Obstet Gynecol Neonatal Nurs* **34**(4): 428–37.
- Morrison RS & Siu AL (2000) A comparison of pain and its treatment in advanced dementia and cognitively intact patients with hip fracture. *J Pain Symptom Manage* **19**(4): 240–8.
- Morrison RS, Magaziner J, Gilbert M et al (2003) Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* **58**(1): 76–81.
- Murphy EJ (2005) Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. *Anaesth Intensive Care* **33**(3): 311–22.
- Murphy PM, Stack D, Kinirons B et al (2003) Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. *Anesth Analg* **97**(6): 1709–15.
- Murtagh FE, Chai MO, Donohoe P et al (2007) The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother* **21**(2): 5–16.
- Narayanaswamy M, Smith J & Spralja A (2006) Choice of opiate and incidence of confusion in elderly postoperative patients. *Annual Scientific Meeting of the Australian and New Zealand Society of Anaesthetists*. Adelaide, Australia.
- National Palliative Care Program (2006) *Providing culturally appropriate palliative care to Aboriginal people in South Australia: Resource Kit*  
<http://www.pallcare.asn.au/aboriginalcaresa.php> Department of Health, Government of South Australia. Accessed June 2009.
- Naumburg EG & Meny RG (1988) Breast milk opioids and neonatal apnea. *Am J Dis Child* **142**(1): 11–2.



- NDARC (2009) *National Alcohol and Drug Research Centre: Australian Drug Trends Series*. <http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/page/National+Reports>. Accessed February 2009.
- Nencini P, Woolverton WL & Seiden LS (1988) Enhancement of morphine-induced analgesia after repeated injections of methylenedioxymethamphetamine. *Brain Res* **457**(1): 136–42.
- Newman S, Stygall J, Hirani S et al (2007) Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology* **106**(3): 572–90.
- Ng B, Dimsdale JE, Rollnik JD et al (1996) The effect of ethnicity on prescriptions for patient-controlled analgesia for post-operative pain. *Pain* **66**(1): 9–12.
- NHS (2008) *Drug Misuse*. <http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles/drug-misuse>. Accessed March 2009.
- Nicolet J, Miller A, Kaufman I et al (2008) Maternal factors implicated in fetal bradycardia after combined spinal epidural for labour pain. *Eur J Anaesthesiol* **25**(9): 721–5.
- Niederhoff H & Zahradnik HP (1983) Analgesics during pregnancy. *Am J Med* **75**(5A): 117–20.
- Nielsen GL, Skriver MV, Pedersen L et al (2004) Danish group reanalyses miscarriage in NSAID users. *BMJ* **328**(7431): 109.
- Nikolajsen L, Sorensen HC, Jensen TS et al (2004) Chronic pain following Caesarean section. *Acta Anaesthesiol Scand* **48**(1): 111–6.
- Nitsun M, Szokol JW, Saleh HJ et al (2006) Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* **79**(6): 549–57.
- Notarianni LJ, Oldham HG & Bennett PN (1987) Passage of paracetamol into breast milk and its subsequent metabolism by the neonate. *Br J Clin Pharmacol* **24**(1): 63–7.
- Novick DM, Kreek MJ, Arns PA et al (1985) Effect of severe alcoholic liver disease on the disposition of methadone in maintenance patients. *Alcohol Clin Exp Res* **9**(4): 349–54.
- Nygaard IH, Valbo A, Pethick SV et al (2008) Does oral magnesium substitution relieve pregnancy-induced leg cramps? *Eur J Obstet Gynecol Reprod Biol* **141**(1): 23–6.
- Nygaard E, Kofoed KF, Freiberg J et al (2005) Effects of high thoracic epidural analgesia on myocardial blood flow in patients with ischemic heart disease. *Circulation* **111**(17): 2165–70.
- O'Regan MC & Clow A (2004) Decreased pain tolerance and mood in recreational users of MDMA. *Psychopharmacology (Berl)* **173**(3–4): 446–51.
- Olsen MF, Elden H, Janson ED et al (2007) A comparison of high- versus low-intensity, high-frequency transcutaneous electric nerve stimulation for painful postpartum uterine contractions. *Acta Obstet Gynecol Scand* **86**(3): 310–4.
- Orlikowski CE, Dickinson JE, Paech MJ et al (2006) Intrapartum analgesia and its association with postpartum back pain and headache in nulliparous women. *Aust N Z J Obstet Gynaecol* **46**(5): 395–401.
- Ortega D, Viviand X, Lorec AM et al (1999) Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. *Acta Anaesthesiol Scand* **43**(4): 394–7.
- Ostensen ME & Skomsvoll JF (2004) Anti-inflammatory pharmacotherapy during pregnancy. *Expert Opin Pharmacother* **5**(3): 571–80.
- Ostermeier AM, Roizen MF, Hautkappe M et al (1997) Three sudden postoperative respiratory arrests associated with epidural opioids in patients with sleep apnea. *Anesth Analg* **85**(2): 452–60.
- Paqueron X, Boccara G, Bendahou M et al (2002) Brachial plexus nerve block exhibits prolonged duration in the elderly. *Anesthesiology* **97**(5): 1245–9.
- Parikh SN, Stuchin SA, Maca C et al (2002) Sleep apnea syndrome in patients undergoing total joint arthroplasty. *J Arthroplasty* **17**(5): 635–42.
- Passik SD & Kirsh KL (2008) Screening for opioid abuse potential. *Pain: Clinical Updates (IASP)* **16**(7).
- Pauli-Magnus C, Hofmann U, Mikus G et al (1999) Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* **14**(4): 903–9.
- Pautex S, Herrmann F, Le Lous P et al (2005) Feasibility and reliability of four pain self-assessment scales and correlation with an observational rating scale in hospitalized elderly demented patients. *J Gerontol A Biol Sci Med Sci* **60**(4): 524–9.

- Peng PW, Tumber PS & Gourlay D (2005) Review article: perioperative pain management of patients on methadone therapy. *Can J Anaesth* **52**(5): 513–23.
- Pennick VE & Young G (2007) Interventions for preventing and treating pelvic and back pain in pregnancy. *Cochrane Database Syst Rev*(2): CD001139.
- Persky V, Piorkowski J, Hernandez E et al (2008) Prenatal exposure to acetaminophen and respiratory symptoms in the first year of life. *Ann Allergy Asthma Immunol* **101**(3): 271–8.
- Pesonen A, Suojaranta-Ylinen R, Tarkkila P et al (2008) Applicability of tools to assess pain in elderly patients after cardiac surgery. *Acta Anaesthesiol Scand* **52**(2): 267–73.
- Pesonen A, Kaupilla T, Tarkkila P et al (2009) Evaluation of easily applicable pain measurement tools for the assessment of pain in demented patients. *Acta Anaesthesiol Scand* **53**(5): 657–64.
- Peura DA (2004) Prevention of nonsteroidal anti-inflammatory drug-associated gastrointestinal symptoms and ulcer complications. *Am J Med* **117 Suppl 5A**: 63S–71S.
- Phillips BA, Schmitt FA, Berry DT et al (1990) Treatment of obstructive sleep apnea. A preliminary report comparing nasal CPAP to nasal oxygen in patients with mild OSA. *Chest* **98**(2): 325–30.
- Pickering G (2005) Age differences in clinical pain states. In: *Pain in Older Persons. Progress in Pain Research and Management* edn. Gibson SJ and Weiner DK (eds). Seattle, IASP Press.
- Pilotto A, Franceschi M, Leandro G et al (2003) The risk of upper gastrointestinal bleeding in elderly users of aspirin and other non-steroidal anti-inflammatory drugs: the role of gastroprotective drugs. *Aging Clin Exp Res* **15**(6): 494–9.
- Pletcher MJ, Kertesz SG, Kohn MA et al (2008) Trends in opioid prescribing by race/ethnicity for patients seeking care in US emergency departments. *JAMA* **299**(1): 70–8.
- Quigley C (2004) Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev*(3): CD004847.
- RACP, FPM, RACGP et al (2009) *Prescription Opioid Policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use*. <http://www.racp.edu.au/index.cfm?objectid=49F4E2A9-2A57-5487-D0597D1ED8218B61>. Accessed March 2009.
- Rahim-Williams FB, Riley JL, 3rd, Herrera D et al (2007) Ethnic identity predicts experimental pain sensitivity in African Americans and Hispanics. *Pain* **129**(1-2): 177–84.
- Randinitis EJ, Posvar EL, Alvey CW et al (2003) Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol* **43**(3): 277–83.
- Ranta PO, Ala-Kokko TI, Kukkonen JE et al (2006) Incisional and epidural analgesia after caesarean delivery: a prospective, placebo-controlled, randomised clinical study. *Int J Obstet Anesth* **15**(3): 189–94.
- RANZCOG, ANZCA, RACGP et al (March 2009) *Position Statement on the Provision of Obstetric Anaesthesia and Analgesia Services*. <http://www.ranzcog.edu.au/publications/statements/wpi14.pdf>. Accessed April 2009.
- Rapp SE, Wild LM, Egan KJ et al (1994) Acute pain management of the chronic pain patient on opiates: a survey of caregivers at University of Washington Medical Center. *Clin J Pain* **10**(2): 133–8.
- Rapp SE, Ready LB & Nessly ML (1995) Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review. *Pain* **61**(2): 195–201.
- Rathmell JP, Viscomi CM & Ashburn MA (1997) Management of nonobstetric pain during pregnancy and lactation. *Anesth Analg* **85**(5): 1074–87.
- Ravin DS (1995) Narcotic analgesics and breastfeeding. *J Hum Lact* **11**(1): 47–50.
- Ready LB, Chadwick HS & Ross B (1987) Age predicts effective epidural morphine dose after abdominal hysterectomy. *Anesth Analg* **66**(12): 1215–8.
- Rebordosa C, Kogevinas M, Horvath-Puho E et al (2008) Acetaminophen use during pregnancy: effects on risk for congenital abnormalities. *Am J Obstet Gynecol* **198**(2): 178 e1–7.
- Rebordosa C, Kogevinas M, Sorensen HT et al (2008) Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. *Int J Epidemiol* **37**(3): 583–90.
- Rebordosa C, Kogevinas M, Bech BH et al (2009) Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes. *Int J Epidemiol*. **38**(3): 706–14.

- Reeder MK, Goldman MD, Loh L et al (1991) Postoperative obstructive sleep apnoea. Haemodynamic effects of treatment with nasal CPAP. *Anaesthesia* **46**(10): 849–53.
- Rennotte MT, Baele P, Aubert G et al (1995) Nasal continuous positive airway pressure in the perioperative management of patients with obstructive sleep apnea submitted to surgery. *Chest* **107**(2): 367–74.
- Reynolds F, Sharma SK & Seed PT (2002) Analgesia in labour and fetal acid-base balance: a meta-analysis comparing epidural with systemic opioid analgesia. *BJOG* **109**(12): 1344–53.
- Rice AS, Pither CE & Tucker GT (1991) Plasma concentrations of bupivacaine after supraclavicular brachial plexus blockade in patients with chronic renal failure. *Anaesthesia* **46**(5): 354–7.
- Richtsmeier AJ, Jr., Barnes SD & Barkin RL (1997) Ventilatory arrest with morphine patient-controlled analgesia in a child with renal failure. *Am J Ther* **4**(7-8): 255–7.
- Riley J, Eisenberg E, Muller-Schwefe G et al (2008) Oxycodone: a review of its use in the management of pain. *Curr Med Res Opin* **24**(1): 175–92.
- Roberts DM & Meyer-Witting M (2005) High-dose buprenorphine: perioperative precautions and management strategies. *Anaesth Intensive Care* **33**(1): 17–25.
- Roberts LJ (2008) The opioid-tolerant patient, including those with a substance abuse disorder. In: *Clinical Pain Management: Acute Pain* edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
- Rosario ED, Esteve N, Sernandez MJ et al (2008) Does femoral nerve analgesia impact the development of postoperative delirium in the elderly? A retrospective investigation. *Acute Pain* **10**: 59–64.
- Rosen MA (2002) Nitrous oxide for relief of labor pain: a systematic review. *Am J Obstet Gynecol* **186**(5 Suppl Nature): S110–26.
- Rozen D & DeGaetano NP (2006) Perioperative management of opioid-tolerant chronic pain patients. *J Opioid Manag* **2**(6): 353–63.
- Rudin A, Lundberg JF, Hammarlund-Udenaes M et al (2007) Morphine metabolism after major liver surgery. *Anesth Analg* **104**(6): 1409–14.
- Rudolph JL, Marcantonio ER, Culley DJ et al (2008) Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia* **63**(9): 941–7.
- Sabers C, Plevak DJ, Schroeder DR et al (2003) The diagnosis of obstructive sleep apnea as a risk factor for unanticipated admissions in outpatient surgery. *Anesth Analg* **96**(5): 1328–35.
- Sadean MR & Glass PS (2003) Pharmacokinetics in the elderly. *Best Pract Res Clin Anaesthesiol* **17**(2): 191–205.
- Salamonson Y & Everett B (2005) Demographic disparities in the prescription of patient-controlled analgesia for postoperative pain. *Acute Pain*(7): 21–6.
- SAMHSA (2007). <http://oas.samhsa.gov/NSDUHLatest.htm>. Accessed March 2009.
- Sartain JB & Barry JJ (1999) The impact of an acute pain service on postoperative pain management. *Anaesth Intensive Care* **27**(4): 375–80.
- Sator-Katzenschlager S, Deusch E, Maier P et al (2001) The long-term antinociceptive effect of intrathecal S(+)-ketamine in a patient with established morphine tolerance. *Anesth Analg* **93**(4): 1032–4.
- Savage R (2005) Cyclo-oxygenase-2 inhibitors: when should they be used in the elderly? *Drugs Aging* **22**(3): 185–200.
- Sax TW & Rosenbaum RB (2006) Neuromuscular disorders in pregnancy. *Muscle Nerve* **34**(5): 559–71.
- Scheinin H, Virtanen T, Kentala E et al (2000) Epidural infusion of bupivacaine and fentanyl reduces perioperative myocardial ischaemia in elderly patients with hip fracture—a randomized controlled trial. *Acta Anaesthesiol Scand* **44**(9): 1061–70.
- Schmidt C, Hinder F, Van Aken H et al (2005) The effect of high thoracic epidural anesthesia on systolic and diastolic left ventricular function in patients with coronary artery disease. *Anesth Analg* **100**(6): 1561–9.
- Scott JC & Stanski DR (1987) Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* **240**(1): 159–66.

- Scott LJ & Perry CM (2000) Tramadol: a review of its use in perioperative pain. *Drugs* **60**(1): 139–76.
- Seaton S, Reeves M & McLean S (2007) Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: relationships between maternal plasma, breast milk and neonatal plasma levels. *Aust N Z J Obstet Gynaecol* **47**(3): 181–5.
- Shafer SL (1997) Pharmacokinetics and pharmacodynamics of the elderly. In: *Geriatric anaesthesiology* edn. McKleskey C (eds). Baltimore, Williams and Wilkins.
- Sharpe C & Kuschel C (2004) Outcomes of infants born to mothers receiving methadone for pain management in pregnancy. *Arch Dis Child Fetal Neonatal Ed* **89**(1): F33–6.
- Shimoyama N, Shimoyama M, Inturrisi CE et al (1996) Ketamine attenuates and reverses morphine tolerance in rodents. *Anesthesiology* **85**(6): 1357–66.
- Shnider SM, Asling JH, Holl JW et al (1970) Paracervical block anesthesia in obstetrics. I. Fetal complications and neonatal morbidity. *Am J Obstet Gynecol* **107**(4): 619–25.
- SHORE (2009) *Illicit drug monitoring system*. [http://www.shore.ac.nz/projects/idms\\_study.htm](http://www.shore.ac.nz/projects/idms_study.htm). Accessed March 2009.
- Simmons SW, Cyna AM, Dennis AT et al (2007) Combined spinal-epidural versus epidural analgesia in labour. *Cochrane Database Syst Rev*(3): CD003401.
- Simon MJ, Veering BT, Stienstra R et al (2002) The effects of age on neural blockade and hemodynamic changes after epidural anesthesia with ropivacaine. *Anesth Analg* **94**(5): 1325–30.
- Simon MJ, Veering BT, Stienstra R et al (2004) Effect of age on the clinical profile and systemic absorption and disposition of levobupivacaine after epidural administration. *Br J Anaesth* **93**(4): 512–20.
- Simon MJ, Veering BT, Vletter AA et al (2006) The effect of age on the systemic absorption and systemic disposition of ropivacaine after epidural administration. *Anesth Analg* **102**(1): 276–82.
- Simopoulos TT, Smith HS, Peeters-Asdourian C et al (2002) Use of meperidine in patient-controlled analgesia and the development of a normeperidine toxic reaction. *Arch Surg* **137**(1): 84–8.
- Skovlund E, Fyllingen G, Landre H et al (1991a) Comparison of postpartum pain treatments using a sequential trial design. I. Paracetamol versus placebo. *Eur J Clin Pharmacol* **40**(4): 343–7.
- Skovlund E, Fyllingen G, Landre H et al (1991b) Comparison of postpartum pain treatments using a sequential trial design: II. Naproxen versus paracetamol. *Eur J Clin Pharmacol* **40**(6): 539–42.
- Slade P (2006) Towards a conceptual framework for understanding post-traumatic stress symptoms following childbirth and implications for further research. *J Psychosom Obstet Gynaecol* **27**(2): 99–105.
- Sloan P & Hamann S (2006) Ultra-low-dose opioid antagonists to enhance opioid analgesia. *J Opioid Manag* **2**(5): 295–304.
- Smith CA, Collins CT, Cyna AM et al (2006) Complementary and alternative therapies for pain management in labour. *Cochrane Database Syst Rev*(4): CD003521.
- Snowden HM, Renfrew MJ & Woolridge MW (2001) Treatments for breast engorgement during lactation. *Cochrane Database Syst Rev*(2): CD000046.
- Spigset O & Hagg S (2000) Analgesics and breast-feeding: safety considerations. *Paediatr Drugs* **2**(3): 223–38.
- Steer PL, Biddle CJ, Marley WS et al (1992) Concentration of fentanyl in colostrum after an analgesic dose. *Can J Anaesth* **39**(3): 231–5.
- Stuber KJ & Smith DL (2008) Chiropractic treatment of pregnancy-related low back pain: a systematic review of the evidence. *J Manipulative Physiol Ther* **31**(6): 447–54.
- Tan EC, Lim Y, Teo YY et al (2008) Ethnic differences in pain perception and patient-controlled analgesia usage for postoperative pain. *J Pain* **9**(9): 849–55.
- Taylor RN & Sonson RD (1986) Separation of the pubic symphysis. An underrecognized peripartum complication. *J Reprod Med* **31**(3): 203–6.
- Tegeger I, Lotsch J & Geisslinger G (1999) Pharmacokinetics of opioids in liver disease. *Clin Pharmacokinet* **37**(1): 17–40.
- Tetrault JM & O'Connor PG (2008) Substance abuse and withdrawal in the critical care setting. *Crit Care Clin* **24**(4): 767–88.

- TGA (1999) *Therapeutics Goods Administration: Prescribing in Pregnancy*. www.tga.gov.au/docs/html/medpreg.htm. Accessed April 2009.
- Thomas T, Robinson C, Champion D et al (1998) Prediction and assessment of the severity of post-operative pain and of satisfaction with management. *Pain* **75**(2-3): 177–85.
- Thompson JF, Roberts CL, Currie M et al (2002) Prevalence and persistence of health problems after childbirth: associations with parity and method of birth. *Birth* **29**(2): 83–94.
- Troster A, Sittl R, Singler B et al (2006) Modulation of remifentanyl-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. *Anesthesiology* **105**(5): 1016–23.
- Tuckey JP, Prout RE & Wee MY (2008) Prescribing intramuscular opioids for labour analgesia in consultant-led maternity units: a survey of UK practice. *Int J Obstet Anesth* **17**(1): 3–8.
- Turk DC, Swanson KS & Gatchel RJ (2008) Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain* **24**(6): 497–508.
- Upton RN, Semple TJ, Macintyre PE et al (2006) Population pharmacokinetic modelling of subcutaneous morphine in the elderly. *Acute Pain* **8**(3): 109–16.
- Urban MK, Ya Deau JT, Wukovits B et al (2008) Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. *HSS J* **4**(1): 62–5.
- Vallejo MC, Ramesh V, Phelps AL et al (2007) Epidural labor analgesia: continuous infusion versus patient-controlled epidural analgesia with background infusion versus without a background infusion. *J Pain* **8**(12): 970–5.
- Van Diver T & Camann W (1995) Meralgia paresthetica in the parturient. *Int J Obstet Anesth* **4**(2): 109–12.
- van Slobbe AM, Bohnen AM, Bernsen RM et al (2004) Incidence rates and determinants in meralgia paresthetica in general practice. *J Neurol* **251**(3): 294–7.
- van Tuijl I, van Klei WA, van der Werff DB et al (2006) The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section: a randomized controlled trial. *Br J Anaesth* **97**(3): 365–70.
- VanDercar DH, Martinez AP & De Lisser EA (1991) Sleep apnea syndromes: a potential contraindication for patient-controlled analgesia. *Anesthesiology* **74**(3): 623–4.
- Vaurio LE, Sands LP, Wang Y et al (2006) Postoperative delirium: the importance of pain and pain management. *Anesth Analg* **102**(4): 1267–73.
- Veering BT, Burm AG, van Kleef JW et al (1987) Epidural anesthesia with bupivacaine: effects of age on neural blockade and pharmacokinetics. *Anesth Analg* **66**(7): 589–93.
- Veering BT, Burm AG, Vletter AA et al (1991) The effect of age on systemic absorption and systemic disposition of bupivacaine after subarachnoid administration. *Anesthesiology* **74**(2): 250–7.
- Veering BT (2006) Hemodynamic effects of central neural blockade in elderly patients. *Can J Anaesth* **53**(2): 117–21.
- Vickers AP & Jolly A (2006) Naltrexone and problems in pain management. *BMJ* **332**(7534): 132–3.
- Villesen HH, Banning AM, Petersen RH et al (2007) Pharmacokinetics of morphine and oxycodone following intravenous administration in elderly patients. *Ther Clin Risk Manag* **3**(5): 961–7.
- Vindigni D, Griffen D, Perkins J et al (2004) Prevalence of musculoskeletal conditions, associated pain and disability and the barriers to managing these conditions in a rural, Australian Aboriginal community. *Rural Remote Health* **4**(3): 230.
- Vleeming A, Albert HB, Ostgaard HC et al (2008) European guidelines for the diagnosis and treatment of pelvic girdle pain. *Eur Spine J* **17**(6): 794–819.
- Volmanen P, Akural E, Raudaskoski T et al (2005) Comparison of remifentanyl and nitrous oxide in labour analgesia. *Acta Anaesthesiol Scand* **49**(4): 453–8.
- Volmanen P, Sarvela J, Akural EI et al (2008) Intravenous remifentanyl vs. epidural levobupivacaine with fentanyl for pain relief in early labour: a randomised, controlled, double-blinded study. *Acta Anaesthesiol Scand* **52**(2): 249–55.
- Vuyk J (2003) Pharmacodynamics in the elderly. *Best Pract Res Clin Anaesthesiol* **17**(2): 207–18.

- Wang HY, Friedman E, Olmstead MC et al (2005) Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbetagamma signaling. *Neuroscience* **135**(1): 247–61.
- Warden V, Hurley AC & Volicer L (2003) Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. *J Am Med Dir Assoc* **4**(1): 9–15.
- Wasan AD, Correll DJ, Kissin I et al (2006) Iatrogenic addiction in patients treated for acute or subacute pain: a systematic review. *J Opioid Manag* **2**(1): 16–22.
- Webster LR, Butera PG, Moran LV et al (2006) Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. *J Pain* **7**(12): 937–46.
- Williams A, Herron-Marx S & Carolyn H (2007) The prevalence of enduring postnatal perineal morbidity and its relationship to perineal trauma. *Midwifery* **23**(4): 392–403.
- Winklbaur B, Jung E & Fischer G (2008) Opioid dependence and pregnancy. *Curr Opin Psychiatry* **21**(3): 255–9.
- Wittels B, Glosten B, Faure EA et al (1997) Postcesarean analgesia with both epidural morphine and intravenous patient-controlled analgesia: neurobehavioral outcomes among nursing neonates. *Anesth Analg* **85**(3): 600–6.
- Wong CA, McCarthy RJ, Sullivan JT et al (2009) Early compared with late neuraxial analgesia in nulliparous labor induction: a randomized controlled trial. *Obstet Gynecol* **113**(5): 1066–74.
- Wong MO, Eldon MA, Keane WF et al (1995) Disposition of gabapentin in anuric subjects on hemodialysis. *J Clin Pharmacol* **35**(6): 622–6.
- Woodhouse A & Mather LE (1997) The influence of age upon opioid analgesic use in the patient-controlled analgesia (PCA) environment. *Anaesthesia* **52**(10): 949–55.
- Wunsch MJ, Stanard V & Schnoll SH (2003) Treatment of pain in pregnancy. *Clin J Pain* **19**(3): 148–55.
- Yeo ST, Holdcroft A, Yentis SM et al (2007) Analgesia with sevoflurane during labour: ii. Sevoflurane compared with Entonox for labour analgesia. *Br J Anaesth* **98**(1): 110–5.
- Young T, Skatrud J & Peppard PE (2004) Risk factors for obstructive sleep apnea in adults. *JAMA* **291**(16): 2013–6.
- Zapater P, Lasso de la Vega MC, Horga JF et al (2004) Pharmacokinetic variations of acetaminophen according to liver dysfunction and portal hypertension status. *Aliment Pharmacol Ther* **20**(1): 29–36.
- Zaric D, Boysen K, Christiansen C et al (2006) A comparison of epidural analgesia with combined continuous femoral-sciatic nerve blocks after total knee replacement. *Anesth Analg* **102**(4): 1240–6.
- Zatzick DF & Dimsdale JE (1990) Cultural variations in response to painful stimuli. *Psychosom Med* **52**(5): 544–57.
- Zelop CM (2008) Is it time to re-evaluate our use of acetaminophen in certain sub-groups of pregnant women? *J Matern Fetal Neonatal Med* **21**(11): 761–2.
- Zheng Z, Gibson SJ, Khalil Z et al (2000) Age-related differences in the time course of capsaicin-induced hyperalgesia. *Pain* **85**(1-2): 51–8.

# APPENDIX A

---

## THE WORKING PARTY, CONTRIBUTORS AND MEMBERS OF THE MULTIDISCIPLINARY CONSULTATIVE COMMITTEE

### Working party

---

#### Editors

---

Assoc Prof Pam Macintyre (senior editor)	Director, Acute Pain Service Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine Royal Adelaide Hospital and University of Adelaide Adelaide South Australia
---	---

---

Professor Stephan Schug	Chair of Anaesthesiology, Pharmacology and Anaesthesiology Unit School of Medicine and Pharmacology, University of Western Australia Director of Pain Medicine, Royal Perth Hospital Perth Western Australia
-------------------------	---

---

Assoc Prof David A Scott	Head, Acute Pain Service Deputy Director, Department of Anaesthesia St. Vincent's Hospital Melbourne Victoria
--------------------------	---

---

Dr Suellen Walker	Clinical Senior Lecturer and Honorary Consultant in Paediatric Anaesthesia and Pain Medicine Portex Unit: Pain Research and Department of Anaesthesia UCL Institute of Child Health and Great Ormond St Hospital NHS Trust London United Kingdom
-------------------	--

---

Dr Eric Visser	Specialist in Pain Medicine and Anaesthesia Fremantle Hospital, Joondalup Health Campus and Mercy Medical Centre (Mt Lawley), Western Australia.
----------------	---

---

#### Editorial Advisory Group

---

Dr Douglas Justins	Dean Faculty of Pain Medicine of the Royal College of Anaesthetists London United Kingdom
--------------------	--

---

Professor Karen Grimmer-Somers	Director, Centre for Allied Health Evidence University of South Australia Adelaide South Australia
--------------------------------	---

---



## Contributors

Contributor	Affiliation
Assoc. Prof Franz Babl	Consultant Paediatric Emergency Physician Department of Emergency Medicine Royal Children's Hospital, Melbourne and University of Melbourne Melbourne Victoria
Dr Michael Barrington	Staff Anaesthetist Department of Anaesthesia St Vincent's Hospital Melbourne Victoria
Dr Melanie Benson	Palliative Medicine Physician Palliative Care Service Alfred Health Melbourne Victoria
Assoc Prof Duncan Blake	Specialist Anaesthetist Dept of Anaesthesia and Pain Management, Royal Melbourne Hospital Department of Pharmacology, University of Melbourne Melbourne Victoria
Dr Meredith Borland	Emergency Physician Clinical Senior Lecturer University of Western Australia Princess Margaret Hospital for Children Perth Western Australia
Dr George Chalkiadis	Head, Children's Pain Management Service Staff Anaesthetist, Royal Children's Hospital Clinical Associate Professor, University of Melbourne Melbourne Victoria
Dr Phoon P Chen	Consultant Department Anaesthesiology & Operating Services Alice Ho Miu Ling Nethersole Hospital & North District Hospital Hong Kong
Assoc Prof Katherine Clark	The Cunningham Centre for Palliative Care, The University of Notre Dame Australia Sydney New South Wales
Dr Julia Coldrey	Consultant Anaesthetist Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine Royal Adelaide Hospital Adelaide South Australia

<b>Contributor</b>	<b>Affiliation</b>
Assoc Prof John Collins	Department Pain Medicine and Palliative Care Children's Hospital at Westmead Sydney New South Wales Australia
Assoc Prof Tomas Corcoran	School of Medicine and Pharmacology University of Western Australia Director of Research, Department of Anaesthesia and Pain Medicine Royal Perth Hospital Perth Western Australia
Dr Elizabeth Cotterell	Paediatric Emergency Physician Staff Specialist, Children's Emergency Sydney Children's Hospital, Randwick New South Wales
Professor Michael Cousins	Professor and Director Pain Management Research Institute Royal North Shore Hospital Sydney New South Wales
Dr Meredith Craigie	Senior Consultant Department of Anaesthesia and Pain Medicine Flinders Medical Centre, Bedford Park South Australia
Dr Andrew Davidson	Consultant Anaesthetist Department of Anaesthesia and Pain Medicine Royal Children's Hospital Melbourne Victoria
Assoc Prof Robert Delcanho	School of Medicine and Dentistry University of Western Australia Perth Western Australia
Assoc Prof Steven Doherty	Emergency Department Tamworth Rural Referral Hospital Tamworth New South Wales
Dr Bronwen Evans	Consultant Anaesthetist Department of Anaesthesia and Pain Medicine Western Health, Melbourne Victoria
Professor Julia Fleming	Director, Professor Tess Cramond Multidisciplinary Pain Centre Royal Brisbane and Womens' Hospital Brisbane Queensland

<b>Contributor</b>	<b>Affiliation</b>
Dr Ray Garrick	Consultant Neurologist Adjunct Associate Professor of Medicine University of Notre Dame Australia St Vincent's Hospital Darlinghurst New South Wales
Professor Stephen Gibson	Deputy Director National Ageing Research Institute Director of Research Caulfield Pain Management and Research Centre Victoria
Dr C Roger Goucke	Senior Staff Specialist Anaesthesia and Pain Medicine Sir Charles Gairdner Hospital Clinical Associate Professor University of Western Australia Perth Western Australia
Assoc Prof Hugh Grantham	Executive Director Clinical Services SA Ambulance Service Adelaide South Australia
Dr Paul Gray	Senior Staff Specialist The Professor Tess Cramond Multidisciplinary Pain Centre Royal Brisbane and Women's Hospital Brisbane Queensland
Dr Barry Gunn	Emergency Physician Department of Emergency Medicine Western Health Footscray Victoria
Dr Richard Halliwell	Department of Anaesthesia Westmead Hospital Clinical Senior Lecturer, Discipline of Anaesthesia Sydney Medical School, University of Sydney Sydney New South Wales
Dr Malcolm Hogg	Head of Pain Services Dept of Anaesthesia and Pain Management Royal Melbourne Hospital Parkville Victoria
Dr Steve Jones	Consultant Anaesthetist Waikato Hospital Hamilton New Zealand

<b>Contributor</b>	<b>Affiliation</b>
Professor Peter C A Kam	Nuffield Professor of Anaesthetics, University of Sydney, Department of Anaesthetics Royal Prince Alfred Hospital Camperdown, Sydney New South Wales
Professor Anne-Maree Kelly	Director, Joseph Epstein Centre for Emergency Medicine Research Western Health, Footscray, Victoria
Dr Daniel J Lee	Consultant Physician in Rehabilitation and Pain Medicine Dept of Anaesthesia and Pain Management Royal Melbourne Hospital Parkville Victoria
Dr Edward Murphy	Specialist Anaesthetist Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine Royal Adelaide Hospital and University of Adelaide Adelaide South Australia
Dr David Murrell	Senior Staff Specialist Department of Anaesthesia, The Children's Hospital at Westmead Sydney New South Wales
Assoc Prof Michael K Nicholas	Director, ADAPT Pain Management Programme Pain Management and Research Centre University of Sydney at Royal North Shore Hospital St Leonards New South Wales
Dr Irene Ng	Staff Anaesthetist Department of Anaesthesia and Pain Management The Royal Melbourne Hospital Parkville Victoria
Dr David Olive	Consultant Anaesthetist Department of Anaesthesia St. Vincent's Hospital Melbourne Victoria
Dr Greta Palmer	Clinical Associate Professor Dept of Anaesthesia and Pain Management Royal Children's and Royal Melbourne Hospitals and University of Melbourne Melbourne Victoria

<b>Contributor</b>	<b>Affiliation</b>
Dr Tim Pavy	Head, Department of Anaesthesia and Pain Medicine King Edward Memorial Hospital for Women Senior Clinical Lecturer, School of Medicine and Pharmacology University of Western Australia Subiaco Western Australia
Dr Lindy Roberts	Anaesthetist and Pain Specialist Departments of Anaesthesia and Pain Management Sir Charles Gairdner Hospital Perth Western Australia
Assoc Prof Philip Siddall	Pain Management Research Institute University of Sydney Royal North Shore Hospital Sydney New South Wales
Professor Edward A Shipton	Academic Head: Department of Anaesthesia University of Otago, Christchurch New Zealand
Dr Brian Spain	Consultant Anaesthetist Department of Anaesthesia Royal Darwin Hospital Darwin Northern Territory
Dr Kian Hian Tan	Director Pain Management Centre Consultant Anaesthesiologist Department of Anaesthesiology Singapore General Hospital Singapore
Dr Jane Trinca	Barbara Walker Centre for Pain Management St Vincents Hospital, Melbourne Acute Pain Service Department of Anaesthesia, Austin Health, Heidelberg Victoria
Dr Maggie Wong	Consultant Anaesthetist Department of Anaesthesia Royal Women's Hospital, Melbourne St Vincent's Hospital, Melbourne Victoria
<b>Technical editors</b>	
Elizabeth Hall	Ampersand Health Science Writing
Jenny Ramson	Ampersand Health Science Writing

## Multidisciplinary consultative committee

Area of expertise	Member	Affiliation
Clinical Pharmacology	Professor Paul Rolan	Discipline of Pharmacology University of Adelaide Adelaide South Australia
Aboriginal and Torres Strait Islander Liaison	Judith Deane-Freeman	Acting Aboriginal Health Nurse Aboriginal and Torres Strait Islander Liaison Unit Royal Adelaide Hospital Adelaide South Australia
Australian Medicines Handbook	Louise Quinn	Editor Australian Medicines Handbook Pty Ltd Adelaide South Australia
Burns Surgery	Dr John E Greenwood AM	Director, Burns Unit Royal Adelaide Hospital Adelaide South Australia
Cardiology	Dr Dale Ashby	Consultant Cardiologist Cardiovascular Investigation Unit Royal Adelaide Hospital Adelaide South Australia
Chiropractic	Dr Keith Charlton	Forest Lake Chiropractic Forest Lake Queensland
Chiropractic	Assoc Prof Philip S Bolton	School of Biomedical Sciences & Pharmacy Faculty of Health University of Newcastle Callaghan, NSW
Colorectal Surgery	Dr Michelle Thomas	Consultant Colorectal Surgeon Department of Surgery Royal Adelaide Hospital North Terrace Adelaide South Australia
Community representative	Helen Maxwell Wright	Community Representative Melbourne Victoria
Complementary Medicine	Dr Caroline Smith	Associate Professor Centre for Complementary Medicine Research The University of Western Sydney New South Wales

<b>Area of expertise</b>	<b>Member</b>	<b>Affiliation</b>
Drug and Alcohol and Addiction Medicine	Dr Matt Gaughwin	Drug and Alcohol Resource Unit Drug and Alcohol Services South Australia Royal Adelaide Hospital Adelaide South Australia
General Practice	Professor Nicholas Glasgow	Dean Medicine and Health Sciences College of Medicine Biology and Environment Australian National University Canberra Australian Capital Territory
Medical Oncology	Professor Dorothy MK Keefe	Cancer Council SA Professor of Cancer Medicine University of Adelaide Adelaide South Australia
Neurosurgery	Professor Nigel Jones	Professor Nigel Jones Consultant Neurosurgeon Calvary Wakefield Hospital and Dept Surgery (Neurosurgery) University of Adelaide Adelaide South Australia
Neurosurgery	A/Prof Leigh Atkinson	Pain Medicine Specialist and Neurosurgeon Princess Alexandra Hospital Brisbane Queensland
Nursing	Ms Fran Bermingham	CPC, Acute Pain Service Flinders Medical Centre Adelaide South Australia
Nursing	Ms Julie Lanzendorfer	Clinical Practice Consultant Acute Pain Service Royal Adelaide Hospital Adelaide South Australia
Obstetrics and Gynaecology	Professor Wayne Gillett	Associate Professor Department of Women's and Children's Health University of Otago Dunedin New Zealand
Orthopaedic Surgery	Dr Owen Williamson	Adjunct Senior Lecturer Department of Epidemiology and Preventive Medicine, Monash University Melbourne Victoria



<b>Area of expertise</b>	<b>Member</b>	<b>Affiliation</b>
Osteopathy	Dr Nick Penny	Dr J Nick Penney The Osteopath P/L Maroochydore Queensland On behalf of the Australian Osteopathic Association
Pharmacology	Professor Maree Smith	Director, Centre for Integrated Preclinical Drug Development Professor of Pharmacy, The University of Queensland St Lucia Campus Brisbane Queensland
Pharmacy	Stephanie Wiltshire	Senior Pharmacist Royal Adelaide Hospital Adelaide South Australia
Physiotherapy	Professor Tony Wright	School of Physiotherapy Curtin University of Technology Perth Western Australia
Psychiatry	Dr Faiz Noore	Consultant Psychiatrist and Specialist in Pain Medicine Department of Anaesthesia and Pain Management The Nepean Hospital Penrith New South Wales
Rehabilitation Medicine	Dr Carolyn Arnold	Clinical Director Caulfield Pain Management & Research Centre Alfred Health Melbourne Victoria
Rheumatology	Assoc Prof Milton Cohen	Consultant Physician in Rheumatology and Pain Medicine Departments of Rheumatology and Pain Medicine St Vincent's Hospital Sydney New South Wales
Rural and Remote Medicine	Dr John Hadok	Clinical Director, Mater Immediate Medical Service Senior Medical Officer, Emergency Department, Mackay Base Hospital Mackay Queensland

<b>Area of expertise</b>	<b>Member</b>	<b>Affiliation</b>
Specific Statistical Issues (Expert External Consultant)	Professor Paul Myles	Director, Department of Anaesthesia and Perioperative Medicine Alfred Hospital and Monash University Melbourne Victoria
Thoracic Surgery	Mr Craig Jurisevic	Cardiothoracic Surgical Consultant Cardiothoracic Surgical Department Royal Adelaide Hospital Adelaide South Australia

# APPENDIX B

---

## PROCESS REPORT

This is the third edition of the document *Acute Pain Management: Scientific Evidence*. The first edition was written by a multidisciplinary committee headed by Professor Michael Cousins and published by the National Health and Medical Research Council (NHMRC) in 1999. The second edition was written by multiple contributors and a working party chaired by Dr Pam Macintyre. It was approved by the NHMRC and published by the Australian and New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPM) in 2005. It was also endorsed by other major organisations – the International Association for the Study of Pain (IASP), the Royal College of Anaesthetists (United Kingdom), the Australasian Faculty of Rehabilitation Medicine, the Royal Australasian College of Physicians, the Royal Australasian College of Surgeons, the Royal Australian and New Zealand College of Psychiatrists and the Australian Pain Society – and recommended to its members by the American Academy of Pain Medicine.

In accord with the NHMRC requirement that guidelines should be revised as further evidence accumulates, and as there has been a continuing and large increase in the quantity of information available about acute pain management, it was seen as timely to reassess the available evidence. ANZCA and the FPM therefore again took responsibility as an ‘external body’ for revising and updating the document – this third edition.

Since the second edition was published in 2005, a sizeable amount of new evidence relating to the management of acute pain has been published. The aim of this third edition is, as with the first two editions, to combine a review of the best available evidence for acute pain management with current clinical and expert practice, rather than to formulate specific clinical practice recommendations. Accordingly, the document aims to summarise, in a concise and easily readable form, the substantial amount of evidence currently available for the management of acute pain in a wide range of patients and acute pain settings using a variety of treatment modalities. It aims to assist those involved in the management of acute pain with the best current (up to August 2009) evidence-based information.

It is recognised that while knowledge of current best evidence is important, it plays only a part in the management of acute pain for any individual patient and more than evidence is needed if such treatment is to be effective.

Evidence-based medicine has been defined as ‘the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients’ and that it must ‘integrate research evidence, clinical expertise and patient values’ (Sackett et al, 1996). Therefore evidence, clinical expertise and, importantly, patient participation (ie including the patient as part of the treating and decision-making team, taking into account their values, concerns and expectations) are required if each patient is to get the best treatment. The information provided in this document is not intended to over-ride the clinical expertise of health care professionals. There is no substitute for the skilled assessment of each individual patient’s health status, circumstances and perspectives, which health care practitioners will then use to help select the treatments that are relevant and appropriate to that patient.

This report provides examples of the decision-making processes that were put in place to deal with the plethora of available evidence under consideration.

## Development process

A working party was convened to coordinate and oversee the development process. An editorial subgroup of the working party (Assoc Prof Pam Macintyre, Prof Stephan Schug, Assoc Prof David Scott, Dr Eric Visser and Dr Suellen Walker) coordinated the development process and edited and/or wrote the sections. The working party also included Dr Douglas Justins (Dean of the Faculty of Pain Medicine, Royal College of Anaesthetists in the United Kingdom) and Prof Karen Grimmer-Somers from the University of South Australia, who had been the NHMRC-appointed Guidelines Assessment Register representative for the second edition and provided expert advice on the use of evidence-based findings and the application of NHMRC criteria for this edition.

A large panel of contributors was appointed to draft sections of the document and a multidisciplinary consultative committee was chosen to review the early drafts of the document and contribute more broadly as required. A list of panel members is attached in Appendix A, together with a list of contributing authors and working party members.

Structures and processes for the revised edition were developed, and within these frameworks contributors were invited to review the evidence and submit content for specific sections according to their area of expertise. All contributors were given instructions about the process of the literature search and the requirements for submission of their section, referred to the website of the NHMRC document *How to use the evidence: assessment and application of scientific evidence* (2000), and directed to the ANZCA website for copies of the second edition of the document as well as an update that was published in 2007.

Members of the editorial subgroup of the working party were responsible for the initial editing of each section, the evaluation of the literature submitted with the contributions and checking for further relevant references. In a series of meetings the working party compiled and edited an initial draft. Once the draft of the document had been prepared, it was sent to all contributors for comment as well as members of the multidisciplinary panel, before being redrafted for public consultation. For the second and subsequent drafts the working party had the assistance of technical editors experienced in NHMRC requirements and processes. To ensure general applicability, there was a very wide range of experts on the contributor and multidisciplinary committee, including medical, nursing, allied health and complementary medicine clinicians and consumers – see Appendix A.

The third edition of *Acute Pain Management: Scientific Evidence* is based on the NHMRC's recommendations for guideline development. That is, this review of the best available evidence for acute pain management focuses on improving patient outcomes, is based on the best evidence available, includes statements concerning the strength of levels of evidence underpinning recommendations, and uses a multidisciplinary approach involving all stakeholders (including consumers).

A companion document for consumers – *Managing Acute Pain: a Guide for Patients* – was prepared after publication of the second edition of *Acute Pain Management: Scientific Evidence* and approved by the NHMRC in December 2005 (ANZCA & FPM 2005).

Consideration is being given to revision of this consumer document.

### Competing interests

Conflicts of interest were managed by each of the five editors responsible for writing the content of the document by completing an International Journal of Medical Editors *Conflict of Interest (ICMJE) Uniform Disclosure Form for Potential Conflicts of Interest*. Copies of these statements were forwarded to the NHMRC. No disclosures of interests were requested from

contributors. Contributors conducted searches and summarised the new literature, and had no influence on the content or the decisions on inclusion or exclusion of material.

## Review of the evidence

This document is a revision of the second edition of *Acute Pain Management: Scientific Evidence* published in 2005. Therefore most of the new evidence included in the third edition has been published from January 2005 onwards. Evidence-based guidelines have been published in the areas of acute back and musculoskeletal pain, and recommendations relevant to the management of acute pain were drawn directly from these.

### Levels of evidence

Levels of evidence were documented according to the NHMRC designation (NHMRC 1999) and, as for the second edition of this document, clinical practice points have been added.

#### Levels of evidence

- I Evidence obtained from a systematic review of all relevant randomised controlled trials.
- II Evidence obtained from at least one properly designed randomised controlled trial
- III-1 Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
- III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-controlled studies or interrupted time series with a control group
- III-3 Evidence obtained from comparative studies with historical control, 2 or more single-arm studies, or interrupted time series without a parallel control group
- IV Evidence obtained from case series, either post-test or pre-test and post-test

#### Clinical practice points

- Recommended best practice based on clinical experience and expert opinion

## Key messages

These levels of evidence were also used for the Key Messages. However, it was felt that there should be an indication of how the Key Messages in this third edition related to those in the previous edition. The system used by Johnston et al (Johnston et al, 2003) to reflect the implications of new evidence on clinical recommendations was therefore reviewed and adapted. The letters N, U, S, W, Q and R were used in the Key Messages to indicate New, Unchanged, Strengthened, Weakened, Qualified and Reversed respectively – see table below.

#### Review and Revision of Key Messages

<b>New</b>	New evidence leads to new key message(s).
<b>Unchanged</b>	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged.
<b>Strengthened</b>	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged or expanded. The level of evidence and/or content of the key message in the original report has been strengthened to reflect this additional evidence.
<b>Weakened</b>	The new evidence is inconsistent with the data used to inform the original key message(s). However, the new evidence does not alter the key message but weakens the level of evidence.

<b>Qualified</b>	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged but applicability may be limited to specific patient groups/ circumstances.
<b>Reversed</b>	The new evidence is inconsistent with the data used to inform the original key message(s). The strength of the new evidence alters the conclusions of the original document.
<b>NB</b>	Clinical and scientific judgment informed the choices made by the Working Party members; there was no mandatory threshold of new evidence (e.g. number of studies, types of studies, magnitude of statistical findings) that had to be met before classification to categories occurred.  The first letter of each of the words ( <b>N</b> ew, <b>U</b> nchanged etc) were used to denote the changes (if any) from the last edition of this document.

An example of the use of this system is taken from the Key Messages in Section 7.1 – Patient-controlled analgesia.

### Key Messages

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**S**) (**Level I** [Cochrane review]).
2. Opioid administration by IV PCA leads to higher opioid consumption (**R**), a higher incidence of pruritus (**R**), and no difference in other opioid-related adverse effects (**S**) or hospital stay (**S**) compared with traditional methods of intermittent parenteral opioid administration (**Level I** [Cochrane review]).
3. In settings where there are high nurse-patient ratios there may be no difference in effectiveness of PCA and conventional parenteral opioid regimens (**N**) (**Level I**).
4. Patient preference for intravenous PCA is higher when compared with conventional regimens (**U**) (**Level I**).

Where the new evidence led to reversal of a conclusion and Key Message, this was noted in the text. For the example above this appeared in the text as:

**Note: reversal of conclusion**

This partly reverses the Level 1 conclusion in the previous edition of this document; earlier meta-analyses had reported no difference in opioid consumption or opioid-related adverse effects

Key messages were based on the highest levels of evidence available. Key messages referring to information extracted from Cochrane meta-analyses were marked ‘**Level I** [Cochrane Review]’, and these were listed first.

### Search strategies

Searches of the electronic databases Medline or PubMed, Embase and Cochrane were conducted for each of the main topics included in the review. Searches were limited to articles concerning humans published mainly in English, and literature published between January 2005 and August 2009 was highlighted. One of the members of the working party, who is fluent in German, translated key texts written in German, which were highlighted during the search. These texts were used for validation purposes only. The initial searches were inevitably broad, given the very wide scope of the topic. ‘Pain’, ‘acute pain’, ‘postoperative pain’ or ‘analgesia’ was searched with the key headings of the various sections and subsections of the

document such as ‘neuropathic’, ‘patient-controlled’, ‘epidural’, ‘paracetamol’ and so on. For drugs and techniques a search was also made for ‘efficacy’ and ‘complications’. Hand searches were also conducted of a large range of relevant journals from 2005 onwards and bibliographies of relevant papers were checked.

### **Preferred evidence**

A review of acute pain management requires a broad focus on a range of topics (eg postoperative pain, musculoskeletal pain, migraine, pain associated with spinal cord injury etc). This broad focus inevitably produces a very large number of research publications. In order to provide the best information and to inform best practice, it was important to concentrate on the highest ranked, highest quality evidence available.

*Secondary evidence:* High quality systematic reviews of randomised-controlled trials (NHMRC **Level I**) were the preferred evidence source. This approach was efficient as many high quality systematic reviews of specific aspects of acute pain management have already been undertaken by the Cochrane Collaboration and other reputable evidence-synthesis groups (such as members of the Oxford Pain Group). Systematic reviews that included non-randomised controlled studies were assigned the level of evidence of their component studies, as outlined in the NHMRC designation of evidence levels (NHMRC 1999) (see below).

*Primary evidence:* Where **Level I** reviews were not available, the next preferred level of evidence was single randomised controlled trials (NHMRC **Level II**). Where these were not available, other experimental evidence or case series were accepted as the best available evidence by the guideline developers (reflecting NHMRC **Level II** and **Level IV**). According to NHMRC guidelines (NHMRC 1999), **Level IV** evidence is obtained from case series, either post-test or pre-test and post-test; the levels refer to evidence about interventions. Publications describing results of audits or papers that were comprehensive clinical reviews, for example, were also included as **Level IV** evidence.

*Expert opinion:* In the few instances where no relevant published evidence was available, expert opinion was included as the best available information.

*Other evidence types:* Not all evidence relating to the management of acute pain is intervention-based. In a number of instances, best practice has been derived from record audit, quality processes or single case reports.

*Examples of evidence level decision-making:* For examples of the decisions that were made about assigning levels to low quality evidence where there was limited evidence available, see the table below.

---

#### **Examples of decisions made assigning levels to evidence of lower quality**

---

Systematic reviews of articles including those with the lowest level of evidence designated as <b>Level III-2</b> were cited as <b>Level III-2</b>	A systematic review looking at the benefits or otherwise of preoperative education for orthopaedic patients highlighted the difficulties of comparing studies of variable methodological quality (Johansson et al 2005)
Evidence from audits or case series that directly affects patient safety cited as <b>Level IV</b>	The amount of morphine a patient requires is better predicted by their age rather than weight (adds to safety of prescribing) (Macintyre & Jarvis 1996) The routine use of a continuous infusion with patient-controlled analgesia (PCA) markedly increases the risk of respiratory depression (Schug & Torrie 1993) Delays in the diagnosis and treatment of an epidural abscess in a patient

---



	with neurological signs greatly increases the risk of an incomplete recovery (Davies et al 2004)
Evidence from a single case report or letter that <i>directly affects patient safety</i> cited as <b>Level IV</b>	Electrical corruption of PCA pumps resulting in uncontrolled delivery of syringe contents (Notcutt et al 1992) The need for antisiphon valves when using PCA in order to prevent inadvertent delivery of an excessive dose of opioid (Kwan 1995)

## Quality scoring

Where Cochrane reviews or reviews from other reputable sources were available, no additional methodological quality evaluation was undertaken, and what was available in the review was accepted as the quality scoring for these guidelines. For the remaining systematic reviews containing controlled trials (**Level I**) and primary RCT evidence (**Level II**), methodological quality was evaluated using a purpose-built system, which identified studies that were subsequently included in the review. The purpose-built criteria included the presence of a CONSORT diagram (Moher et al 2001), explicit inclusion and exclusion criteria, sound description of the intervention and clear outcome measures. No quality evaluation was undertaken for lower ranked evidence (**Level III** and **Level IV**), when this was the highest available level of evidence. Thus this document is underpinned by the highest level, highest methodological quality evidence available for each review question.

## Conflicting evidence

If evidence was consistent, the most recent, highest level and highest quality references were used. If it was conflicting, the same approach was taken (identifying highest level, highest quality evidence) however examples were given of differences within the literature so that readers could appreciate the ongoing debate. In some instances, particularly in acute pain management in various patient populations, evidence was limited to case reports only, which was made clear in the document as the best available evidence in this instance.

## Management of retracted publications

In May 2009, two editorials (Shafer et al 2009; White et al 2009) were published in *Anesthesia and Analgesia* giving details of 21 publications that had been retracted by a number of journals because of allegations of scientific fraud. The editorial by Shafer (Shafer et al 2009) contains a list of the retracted articles. This list can also be found at <http://www.aeditor.org/HWP/Retraction.Notice.pdf>.

The position of the journal was that unretracted articles ‘remain part of the unimpeached literature, at least for now’. In a companion editorial White et al (White et al 2009) reviewed both the retracted and unimpeached literature, ‘distinguishing our understandings that remain fully supported from those that are no longer supported by the unimpeached literature.’ Also in May 2009, Eisenach (Eisenach 2009) the editor of *Anesthesiology*, presented a graph of numbers of citations of retracted and unretracted articles affected by this issue and called for research re-examining the conclusions of the retracted articles.

A July 2009 editorial by Neal (Neal 2009) described contact with ‘the lead or high ranking authors’ of six original articles and one review article in that editor’s journal and which had not been retracted. These articles are listed in this editorial. He concluded that ‘Based on the attestations of the involved coauthors and the investigations of the Chief Academic Officer of Baystate Medical Center, the Editorial Board of *Regional Anesthesia and Pain Medicine* is comfortable recommending that practitioners continue to make clinical decisions based on the information contained within the seven below cited articles.’

Of the references listed in the May 2009 retraction notice (Shafer 2009), four were included in the second edition of *Acute Pain Management: Scientific Evidence* along with a further two publications that were not included in this list of retractions.

There are no precedents for how best to manage a problem such as this. However, the editors responsible for the development of this third edition of *Acute Pain Management: Scientific Evidence* decided against including any publications by the individuals affected by these retractions when listed as first author on the papers. An assessment was made of each of the meta-analyses that cited affected articles. This was based upon the other papers included in these meta-analyses, other supporting evidence and independent consideration by an expert in biostatistics. In some cases, although cited, the affected references were not actually included in the meta-analysis performed. In other cases, assessment indicated that the strength of the evidence may be reduced because of the inclusion of affected publications.

Following the consensus that appeared to rapidly emerge among editors of the leading peer-reviewed journals in anaesthesiology and pain medicine despite initial concerns about meta-analyses that included this work (White et al 2009), the editors of the third edition of *Acute Pain Management: Scientific Evidence* felt that indiscriminately omitting all meta-analyses purely on the basis of inclusion of one or two of those papers would be to deny inclusion of some important credible information in the document. Indeed, the purpose of meta-analysis is to aggregate results from the literature as a whole, thereby diluting the impact of any one specific study.

Just prior to finalisation of this third edition of *Acute Pain Management: Scientific Evidence*, an article was published in *Anesthesiology* in December 2009 (Marret et al, 2009) which examined in detail the effect that excluding data obtained from the retracted articles would have on the results of 14 systematic reviews (six quantitative and eight qualitative) in which they were cited. Marret et al (Marret et al, 2009) reanalysed the data after excluding results from affected articles and concluded that withdrawal of these articles did not alter the conclusions of five out of the six quantitative reviews (meta-analyses): the sixth meta-analysis has not been included in *Acute Pain Management: Scientific Evidence*. Thus there was agreement with the assessments that had already made about the validity of these meta-analyses which included the retracted articles. Marret et al (Marret E et al, 2009) concluded that meta-analyses were 'vulnerable' if data from retracted studies made up more than 30% of the total.

A footnote has been added to the relevant sections indicating the systematic reviews (quantitative and qualitative) that includes affected articles along with a summary of the effect, if any, on the results obtained. Also, specific note has been made in the text of the third edition of *Acute Pain Management: Scientific Evidence* where retraction of the affected papers involved key messages that were published in the second edition. Should additional information become available it will be added as needed before publication of this document. Information that comes to light after publication will be posted as appropriate on the *Acute Pain Management: Scientific Evidence* website.

## Cost analyses

The area of acute pain management remains remarkably deficient in research on costs and cost-benefit. Where this information was available it was reported. One obvious example is the costs associated with the adverse effects of treatment. Information to assist clinicians to better manage both pain and some of the adverse effects of treatment, as well as better individualise treatment for each patient, may assist in minimising such costs. This is again noted as an area warranting further research.

## Public consultation

Following acceptance of the draft by the contributors and the multidisciplinary committee, its availability was advertised in a national newspaper. The public consultation period was from August 10<sup>th</sup> to September 10<sup>th</sup> 2009. The draft was made available on a website ([www.acutepain.org.au](http://www.acutepain.org.au)) and Colleges of many of the contributors and multidisciplinary consultative committee members were notified of the availability of the draft and asked to disseminate this information to their members.

The public was invited to provide comments on the draft and 15 submissions and comments were received from the following individuals.

### Submissions

Name	Affiliation
Dr Dan Carr	Tufts Medical Center and Tufts University School of Medicine Boston United States
Dr Steven Fowler	The Alfred Melbourne Victoria
Dr Michael Fredrickson	Department of Anaesthesiology The University of Auckland New Zealand
Dr Roger Graham	Department of Anaesthetics Liverpool Hospital New South Wales
Dr Donal Harney	Mercy University Hospital Cork Ireland
Dr John Martin	Cairns Anaesthetics Group, Cairns Private Hospital, Cairns Base Hospital, Atherton District Memorial Hospital Cairns Queensland
Dr John Quintner	Fremantle Hospital Western Australia
Dr Jason Ray	The Professor Tess Cramond Multidisciplinary Pain Centre, Royal Brisbane and Women's Hospital and Axxon Health, Mater Private Clinic South Brisbane Queensland
Dr Siva Senthuran	Dept of Intensive Care Medicine Royal Brisbane Hospital Herston Queensland
Dr Craig Surtees	Consultant Anaesthetist Palmerston North Hospital Southern Cross / Aorangi Hospitals Palmerston North New Zealand

Name	Affiliation
Simon van Rysewyk	School of Philosophy University of Tasmania Tasmania
Dr John Williamson	Retired anaesthetist Adelaide South Australia

### Comments

Name	Affiliation
Dr David Butler	Dept of Anaesthesia Fremantle Hospital Western Australia
Dr Donald Johnson	NHS Lothian United Kingdom
Dr Michael Duncan	Guys' and St Thomas' NHS Foundation Trust London United Kingdom

### Topics raised

The main topics raised in these submissions and comments related to:

- use of pethidine in acute pain management;
- effect of lignocaine on postoperative outcome;
- continuous peripheral nerve blockade;
- definition of pain;
- problems of ongoing opioid prescriptions;
- use of coxibs after surgery;
- aspects of pain-related physiology;
- psychological aspects of acute pain; and
- complications after central neuraxial blockade.

### Implementation, dissemination and revision

The Australian and New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPM) will be responsible for the dissemination, implementation, and updating of this document. The document will be available on the internet (formatted to allow for downloading and printing) as well as in hard copy. ANZCA will distribute hard copies to all its members and trainees and to all contributors and multidisciplinary consultative committee members. ANZCA will also notify the Colleges of all contributors and multidisciplinary consultative committee members of the availability of the document and ask them to disseminate the information to their members. In addition, information will be sent to all national and international organisations that endorse this document for distribution to their members. This is further expected to heighten awareness of its availability. The document will also be promoted at relevant professional meetings and conferences and by editorials in professional journals.

The ANZCA working party responsible for this document will continue to monitor the literature relevant to acute pain management. As new evidence becomes available, further revision will be required. Unless earlier revision is indicated, it is anticipated that the document will be revised again in 2014.

## Areas identified as requiring further research

As in the second edition of this document, the Working Party identified the same areas that warrant urgent further research using appropriate research approaches. These relate primarily to:

1. The management (including pain assessment and education) of acute pain in specific patient groups including:
  - elderly patients;
  - patients who are cognitively impaired;
  - patients requiring prehospital analgesia;
  - patients from difference cultural and ethnic backgrounds;
  - Aboriginal and Torres Strait Islander peoples;
  - patients with obstructive sleep apnoea;
  - patients who are opioid-tolerant;
  - patients with a opioid addiction disorder; and
  - patients with or at risk of persistent postoperative pain.

The only area in which research had improved was in children.

2. Issues of cost and cost-effectiveness.

The NHMRC is encouraged to fund primary research projects that will address this current lack of evidence.

## References

- Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2005) *Managing acute pain: a guide for patients*. <http://www.anzca.edu.au/resources/books-and-publications/ManagingAcutePain.pdf>.
- Davies DP, Wold RM, Patel RJ et al (2004) The clinical presentation and impact of diagnostic delays on emergency department patients with spinal epidural abscess. *J Emerg Med* **26**: 285–91.
- Eisenach JC (2009) Data fabrication and article retraction: how not to get lost in the woods. *Anesthesiology* **110**(5): 955–6.
- Johansson K, Nuutila L, Virtanen H et al (2005) Preoperative education for orthopaedic patients: systematic review. *J Adv Nurs* **50**: 212–23.
- Johnston M, Brouwers M, Browman G (2003) Keeping cancer guidelines current: results of a comprehensive prospective literature monitoring strategy for twenty clinical practice guidelines. *International Journal of Technology Assessment in Health Care* **19**: 646–655.
- Kwan A (1995) Overdose of morphine during PCA. *Anaesthesia* **50**: 919.
- Macintyre PE & Jarvis DA (1996) Age is the best predictor of postoperative morphine requirements. *Pain* **64**: 357–64.
- Marret E, Elia N, Dahl JB et al (2009) Susceptibility to fraud in systematic reviews. *Anesthesiology* **111**: 1279–89.
- Moher D, Schulz KF, Altman DG (2001) CONSORT. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *Ann Intern Med* **134**(8): 657–62.
- Neal JM (2009) Retraction. *Reg Anesth Pain Med* **34**(4): 385.

NHMRC (1999) *A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines*. National Health and Medical Research Council, Canberra.

<http://www.nhmrc.gov.au/publications/synopses/cp30syn.htm>

Notcutt WG, Knowles P, Kaldas R (1992) Overdose of opioid from patient-controlled analgesia pumps. *Br J Anaesth* **69**: 95–97.

Sackett DL, Rosenberg WM, Gray JA et al (1996) Evidence based-medicine: what it is and what it isn't. *BMJ* **312**: 71–2.

Schug SA & Torrie JJ (1993) Safety assessment of postoperative pain management by an acute pain service. *Pain* **55**: 387–91.

Shafer SL (2009) Tattered threads. *Anesth Analg* **108**:1361–3.

White PF, Kehlet H & Liu S (2009) Perioperative analgesia: what do we still know? *Anesth Analg* **108**: 1364–7.

# ABBREVIATIONS AND ACRONYMS

---

5HT	5-hydroxytryptamine (serotonin)
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotrophic hormone
ADEC	Australian Drug Evaluation Committee
ADH	antidiuretic hormone
ADLs	activities of daily living
AERD	aspirin-exacerbated respiratory disease
AIDS	acquired immunodeficiency syndrome
ALA	aminolaevulinic acid
ALCAR	acetyl-L-carnitine
AMPA	$\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
ANZCA	Australia and New Zealand College of Anaesthetists
APS	acute pain service
ARAC	Australasian Regional Anaesthesia Collaboration
ASA	American Society of Anesthesiologists
ASIC	acid-sensing ion channel
ATP	adenosine triphosphate
BDNF	brain-derived neurotrophic factor
BK	bradykinin
CABG	coronary artery bypass graft
CAMs	complementary or alternative medicines
CCL3	chemokine (C-C motif) ligand 3
CGRP	calcitonin gene-related peptide
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
CI	confidence interval
CNS	central nervous system
COMT	catechol-O-methyltransferase
COX-2	cyclo-oxygenase-2
CPAP	continuous positive airway pressure
CPNB	continuous peripheral nerve blockade
CPSP	chronic postsurgical pain
CR	controlled-release
CRIES	Cries, Requires oxygen, Increased vital signs, Expression, Sleeplessness
CRPS	chronic regional pain syndrome
CSE	combined spinal epidural
CSF	cerebrospinal fluid
CV	cardiovascular



CYP	cytochrome P450
DIS	daily interruption of sedation
DNA	deoxyribonucleic acid
DNIC	diffuse noxious inhibitory control
DRASIC	subtype of acid sensing ion channel
DRG	dorsal root ganglia
DSP	distal symmetrical polyneuropathy
DVT	deep vein thrombosis
EBP	epidural blood patch
ECF	extracellular fluid
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyelograph
EREM	extended-release epidural morphine
FAS	Functional Activity Scale
FBT	fentanyl buccal tablets
FDA	Food and Drugs Administration
FFA	free fatty acid
FLACC	Faces, Legs, Activity, Cry and Consolability
fMRI	functional magnetic resonance imaging
FPM	Faculty of Pain Medicine
g	gram
GCH1	guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
H3G	hydromorphone-3-glucuronide
HIV	human immunodeficiency virus
HP $\beta$ CD	hydroxypropyl beta-cyclodextrin
HSAN	hereditary sensory and autonomic neuropathy
HSN	hereditary sensory neuropathy
HZ	herpes zoster
IASP	International Association for the Study of Pain
ICF	intracellular fluid
ICU	intensive care unit
ICV	intracerebroventricular
iGluR	ionotropic glutamate receptor
IL	interleukin
IM	intramuscular
IN	intranasal
INN	International Non-proprietary Name

INR	International Normalised Ratio
IR	immediate-release
IV	intravenous
IVRA	intravenous regional anaesthesia
LMWH	low molecular weight heparin
LTP	long-term potentiation
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MAM	monoacetylmorphine
MAOI	monoamine oxidase inhibitor
MC1R	melanocortin-1 receptor
mcg	microgram
MEDD	morphine equivalent daily dose
mg	milligram
mGluR	metabotropic glutamate receptor
mL	millilitre
MLAC	minimum local anaesthetic concentration
mm	millimetre
MOBID	Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale
MOR	mu-opioid receptor
MRI	magnetic resonance imaging
MS	methionine synthetase
N <sub>2</sub> O	nitrous oxide
NAS	neonatal abstinence syndrome
NCA	nurse-controlled analgesia
NCCPC-PV	Non-Communicating Children's Pain Checklist — postoperative version
NCCPC-R	Non-Communicating Children's Pain Checklist
NDARC	National Drug and Alcohol Research Centre
NFCS	Neonatal Facial Coding Scale
ng	nanogram
NHMRC	National Health and Medical Research Council
NIPS	Neonatal Infant Pain Scale
NK1	neurokinin-1
NMDA	N-methyl-D-aspartate
NNH	number-needed-to-harm
NNT	number-needed-to-treat
NO	nitric oxide
NRS	numerical rating scale
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug

nsNSAID	non-selective non-steroidal anti-inflammatory drug
OIH	opioid-induced hyperalgesia
OR	odds ratio
OSA	obstructive sleep apnoea
OTC	over-the-counter
OTFC	oral transmucosal fentanyl citrate
P <sub>2</sub> X <sub>3</sub>	purinergic receptor subtype
PACSLAC	Pain Assessment Checklist for Seniors with Limited Ability to Communicate
PACU	postanaesthesia care unit
PAINAD	Pain Assessment in Advanced Dementia
PAR	proteinase-activated receptor
PCA	patient-controlled analgesia
PCEA	patient-controlled epidural analgesia
PCINA	patient-controlled intranasal analgesia
PCRA	patient-controlled regional analgesia
PCS	Pain Catastrophising Scale
PCTS	patient-controlled transdermal system
PDPH	post-dural puncture headache
PG-BA	polyethylene glycol and benzyl alcohol
PGE <sub>2</sub>	prostaglandin E2
PGH	prostaglandin endoperoxide
PGI <sub>2</sub>	prostacyclin
PHN	post-herpetic neuralgia
PIPP	premature infant pain profile
PNB	peripheral nerve block
PNS	peripheral nerve stimulator
POCD	postoperative cognitive dysfunction
PONV	postoperative nausea and vomiting
PPI	proton pump inhibitor
PPP	Paediatric Pain Profile
PPPM	Parents Postoperative Pain Measure
PTA	Polymyxin E, tobramycin and amphotericin B
QOL	quality of life
QST	quantitative sensory testing
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
RCT	randomised controlled trial
rESS	revised Edmonton Staging System
RNA	ribonucleic acid
RR	relative risk
RVM	rostromedial medulla

RWS	Red Wedge Scale
SACD	subacute combined degeneration
SC	subcutaneous
SCI	spinal cord injury
SF-36	Short Form 36 of Medical Outcomes Study
SHORE	Social and Health Outcomes Research and Evaluation
SIP	Sickness Impact Profile
SL	sublingual
SNP	single nucleotide polymorphism
SPID	summed pain intensity difference
SR	slow-release
SSRI	selective serotonin reuptake inhibitor
SUNCT	Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing
TCA	tricyclic antidepressant
TdP	Torsades de Points
TEA	thoracic epidural analgesia
TENS	transcutaneous electrical nerve stimulation
THC	tetrahydrocannabinol
T <sub>max</sub>	time to reach maximum serum concentration
TNF	tumour necrosis factor
TNS	Transient Neurological Symptoms
TOTPAR	total pain relief
TRP	transient receptor potential
TTH	tension-type headaches
US	ultrasound
USP	United States Pharmacopeia
VAS	visual analogue scale
VDS	verbal descriptor scale
VNRS	verbal numerical rating scale
VPL	ventral posterolateral nucleus of the thalamus
VPM	ventral posteromedial nucleus of the thalamus
VR	virtual reality
VZV	varicella-zoster virus
WMD	weighted mean difference

# INDEX

- abdominal migraine ..... 252
- abdominal pain ..... 250–52, 291
- Aboriginal and Torres Strait Islander peoples ... 408–9
- acetaminophen ..... See paracetamol
- acupressure ..... 227
- acupuncture ..... 227
- acute pain settings ..... 8–9
- acute rehabilitation ..... 20
- addiction disorder ..... 427–33
- adjuvant drugs ..... 79–96, 131–36
  - adrenaline ..... 132
  - alpha-2 agonists ..... 92, 131–32
  - anticonvulsants ..... 89–90
  - antidepressants ..... 87–89
  - bisphosphonates ..... 93
  - botulinum toxin A ..... 135–36
  - calcitonin ..... 92
  - cannabinoids ..... 93–94
  - complementary and alternative medicines ..... 96
  - glucocorticoids ..... 94–95
  - ketamine ..... 133
  - magnesium ..... 135
  - membrane stabilisers ..... 91
  - methoxyflurane ..... 82
  - midazolam ..... 134
  - neostigmine ..... 134–35
  - nitrous oxide ..... 79–83
  - NMDA-receptor antagonists ..... 83–86
  - patient-controlled analgesia ..... 173–75
- adrenaline ..... 132
  - neuraxial ..... 132
  - peripheral ..... 133
  - topical ..... 133
- after pains ..... See uterine pain
- allodynia 4, 34, 69, 83, 84, 85, 91, 201, 244, 245, 254, 336
- alpha-2 agonists ..... 92, 131–32
  - intra-articular ..... 132
  - neuraxial ..... 131
  - plexus block ..... 132
  - regional anaesthesia ..... 132
- amantadine ..... 86
- analgesic ‘rebound’ headache ..... 270
- anticonvulsants ..... 89–90
  - lactation ..... 393
  - older patients ..... 404
  - pregnancy ..... 385
- antidepressants ..... 87–89
  - lactation ..... 393
  - older patients ..... 404
  - pregnancy ..... 384
- antiemetics
  - lactation ..... 393
  - pregnancy ..... 386
- antiviral agents ..... 253
- anxiety .. 8, 9, 35, 46, 62, 96, 175, 176, 224, 226, 228, 247, 251, 280, 293, 297, 343, 344, 345, 346
- anxiolytics ..... 297
- aspirin
  - adverse effects ..... 74
  - children ..... 349
  - lactation ..... 392
  - pregnancy ..... 384
- aspirin-exacerbated respiratory disease ..... 75, 78
- assessment ..... See pain assessment
- attention ..... 7
- attentional techniques ..... 223–24
- back pain ..... 46, 73, 88, 96, 138, 162, 228, 248–49
  - pregnancy ..... 382
- beliefs ..... 7
- biliary colic ..... 60, 251, 291
- bisphosphonates ..... 93, 283
- blood sampling, neonates ..... 343
- bone marrow aspiration, children ..... 344
- botulinum toxin A ..... 135–36
- breast pain ..... 395
- buccal route ..... 162–63
- buprenorphine ..... 55
- burn injury pain ..... 245–48
  - children ..... 344
  - non-pharmacological management ..... 247
  - procedural pain ..... 246–47

burns dressings, children .....	344	cognitive-behavioural interventions.....	224–26
Caesarean section .....	389	complementary and alternative medicines .....	96
calcitonin .....	92	continuous peripheral nerve blockade .....	195–99
cancer pain .....	280–86	lower limb .....	196
bone involvement.....	283–84	needle and catheter localising .....	198
breakthrough pain .....	281–82	patient-controlled .....	199
children.....	361–62	thoracic.....	198
interventional therapies .....	285	upper limb .....	195
malignant bowel obstruction.....	284	cooling, postoperative .....	228
postoperative and procedural .....	282	corticosteroids .....	136–37
principles of management .....	281	children.....	352
scope.....	280–81	neuraxial.....	136
cannabinoids .....	93–94	peripheral .....	136
cannulation, children .....	343	topical.....	137
cannulation, neonates.....	343	coxibs .....	75–78
carbamazepine.....	89	adverse effects .....	76
cardiac effects of opioids .....	64	children.....	349–50
cardiac pain .....	255–56, 298	efficacy .....	76
caudal analgesia		intramuscular .....	158
children.....	357	intravenous .....	156
chest drain removal, children.....	344	older patients .....	402
children		oral .....	154–55
analgesic agents.....	347–53	pregnancy.....	384
cancer pain .....	361	subcutaneous .....	158
procedural pain .....	361–62	cranial neurosurgery.....	241–43
treatment-related pain .....	362	dental pain .....	273
central neural blockade .....	357–61	dextromethorphan .....	85
cognitive impairment.....	339–42	dextropropoxyphene .....	57
consequences of early pain .....	336	diamorphine .....	57
developmental neurobiology .....	335	dihydrocodeine .....	57
immunisation pain .....	345	drug metabolism.....	23–24
nurse-controlled analgesia .....	354–55	dysmenorrhoea.....	73, 252
observational and behavioural measures.....	338	education .....	45–47
opioid infusions .....	353	patients .....	45–46
pain assessment .....	336–42	staff .....	46–47
pain assessment, neonates.....	337–38	elderly patients.....	<i>See</i> older patients
patient-controlled analgesia.....	354	emergency department .....	290–94
peripheral nerve blocks .....	355–57	non-pharmacological management .....	293
procedural pain.....	342–47	procedural pain in children .....	345–47
procedural pain, neonates.....	343	systemic analgesics .....	290–91
self report .....	338–39	epidural abscess.....	187
chronic pain, progression to.....	12, 9–12	epidural analgesia.....	182–90
circumcision .....	356	adjuvant drugs.....	185
cluster headache .....	267	adverse effects .....	186–89
codeine.....	56	children.....	358
metabolism.....	23		

drugs used .....	184–85
efficacy .....	182–84
labour .....	192, 387
older patients .....	405
patient-controlled .....	185–86
epidural haematoma .....	187, 193
epinephrine .....	<i>See</i> adrenaline
ergot derivatives .....	264
ethnic and cultural groups .....	409–11
Faces Pain Scale .....	340
fentanyl .....	57
fracture pain, children .....	345
gabapentin .....	89, 90
gastrointestinal motility, impaired .....	67
glucocorticoids .....	94–95
Guillain-Barre syndrome .....	288–89
haematological disorders .....	256–59
haemophilia .....	258–59
head and neck surgery .....	357
head injury .....	298
headache	
complementary and alternative medicines and therapies .....	270
opioids .....	271
substance withdrawal .....	270
tension-type .....	260
healing touch .....	228
heat .....	228
hepatic disease .....	415–21
herniotomy .....	237
herpes zoster .....	253–55
HIV pain .....	278–80
hydromorphone .....	58
hyperalgesia .....	4, 34, 68
hyperbaric oxygen therapy .....	265
hypnosis .....	222
hypotension .....	188
hysterectomy .....	237
immunisation pain .....	345
inguinal hernia repair .....	356
injury response .....	15–16
intensive care .....	286–89
Guillain-Barre syndrome .....	288–89
non-pharmacological measures .....	287
pain assessment .....	287
pharmacological treatment .....	287–88
procedural pain .....	289
intra-articular analgesia .....	199–200
intramuscular route .....	157–58
coxibs .....	158
nsNSAIDs .....	158
opioids .....	157–58
tramadol .....	157–58
intranasal route .....	160–62
intrathecal analgesia .....	190–93
adjuvant drugs .....	192
children .....	360
drugs used .....	190–92
labour .....	192
local anaesthetics .....	190
older patients .....	406
opioids .....	190–92
intravenous route .....	155–56
coxibs .....	156
nsNSAIDs .....	156
opioids .....	155–56
paracetamol .....	156
tramadol .....	155–56
irritable bowel syndrome .....	251
ketamine .....	83–85, 133
emergency department .....	291
lactation .....	392
neuraxial .....	133
older patients .....	404
prehospital analgesia .....	297
sublingual .....	163
labour pain .....	386–88
laceration repair, children .....	345
lactation .....	390–94
lamotrigine .....	90
learning .....	7
local anaesthetic	
with opioids .....	122
local anaesthetics	
children .....	343
epidural .....	122, 184
intrathecal analgesia .....	190



lactation.....	393	OTC analgesics.....	262
long duration.....	121–23	pregnancy and breastfeeding.....	266
older patients.....	404	simple analgesics.....	262
peripheral.....	123	tramadol.....	264
pregnancy.....	384	triptans.....	263
short duration.....	121	millimetre wave therapy.....	228
topical application.....	200–201	morphine.....	58
toxicity.....	124–25	mucositis.....	276, 362
loss of pain sensation.....	22	multiple sclerosis.....	272
lumbar puncture, children.....	344	musculoskeletal pain.....	249–50
lumbar puncture, neonates.....	343	nasogastric tube insertion, children.....	344
magnesium.....	86	nausea and vomiting.....	65
malignant bowel obstruction.....	284	neostigmine.....	134–35
manual therapies.....	228	neuraxial blockade.....	193–94
massage therapies.....	228	neurological disorders.....	272–73
mastectomy.....	237	neurological injury.....	186
mastitis.....	395	neuropathic pain.....	6, 233
measurement.....	See pain measurement	nitrous oxide.....	79–83
medical pain.....	280	emergency department.....	291
abdominal.....	250–52	prehospital analgesia.....	296
cardiac.....	255–56	toxicity.....	80
haemophilia.....	258–59	NMDA-receptor antagonists.....	83–86
headache.....	260–72	non-English speaking patients.....	See ethnic and cultural groups
herpes zoster.....	253–55	NSAIDs.....	137–38
neurological disorders.....	272–73	emergency department.....	291
orofacial.....	273	lactation.....	391, 392
porphyrias.....	259	metabolism.....	24
sickle cell disease.....	256–58	peripheral.....	137
memantine.....	86	prehospital analgesia.....	297
membrane stabilisers.....	91	preventive analgesia.....	14
memory.....	7	topical.....	137
meperidine.....	See pethidine	nsNSAIDs.....	73–75
meralgia paresthetica.....	382	adverse effects.....	74
methadone.....	58	children.....	348–49
metabolism.....	24	efficacy.....	73
methoxyflurane.....	82	intramuscular.....	158
prehospital analgesia.....	296	intravenous.....	156
midazolam.....	134	older patients.....	402
migraine.....	261–67, 292	oral.....	154–55
antiemetics.....	265	pregnancy.....	381, 384
children.....	266	rectal.....	158
ergot derivatives.....	264	subcutaneous.....	158
menstruation.....	266	obstructive sleep apnoea.....	411
opioids.....	264	ocular examination, neonates.....	343

older patients .....	396–407	orofacial pain .....	273
analgesic agents.....	402	otitis media .....	275, 352
assessment of pain .....	400–402	outcome measures .....	40–42
pharmacokinetic and pharmacodynamic changes .....	397–98	adverse symptoms and events.....	41
physiology of pain.....	398–400	emotional functioning .....	41
opioid tolerance .....	422–27	pain.....	40
opioids.....	55–71	oxycodone.....	59
adverse effects.....	62–70	pain	
children .....	350–52	adverse physiological effects.....	16–18
choice.....	55	adverse psychological effects.....	21
controlled-release.....	154	effects on injury-induced organ dysfunction .....	19
dose .....	61–62	functional impact .....	38
emergency department.....	290	physiology .....	1–6
epidural.....	128, 184	psychological aspects .....	6–9
immediate-release.....	153	pain assessment.....	34–35
inhaled .....	163	children.....	336–42
intramuscular.....	157–58	neonates.....	337–38
intranasal.....	161	older patients .....	400–402
intrathecal.....	126	pain coping strategies.....	225
intrathecal analgesia.....	190–92	pain history .....	35
intravenous.....	155–56	pain measurement.....	35–39, <i>See also</i> outcome measures
continuous.....	156	categorical scales.....	36
intermittent.....	155	children.....	338–39
lactation.....	391, 392	multidimensional measures .....	38–39
neuraxial .....	126–29	numerical scales .....	37
older patients.....	403	older patients .....	401
oral.....	153–54	patients with special needs .....	39
patient-controlled analgesia .....	172–73	unidimensional measures .....	36–38
peripheral .....	131–32	pain pathways.....	1–6
pregnancy .....	381, 384	pain perception.....	1–6
prehospital analgesia.....	295	pain transmission.....	3
preventive analgesia .....	14	pancreatitis .....	251
rectal.....	158	paracetamol.....	71–72
subcutaneous.....	157–58	adverse effects .....	72
sublingual.....	162	children.....	347–48
transdermal .....	159–60	efficacy .....	71
with local anaesthetic.....	184	intravenous .....	156
with local anaesthetics .....	122	lactation.....	391, 392
oral route .....	150–55	older patients .....	402
coxibs.....	154–55	oral .....	155
nsNSAIDs.....	154–55	pregnancy.....	381, 384
opioids .....	153–54	prehospital analgesia .....	297
paracetamol.....	155	rectal .....	159
tramadol .....	153–54	paroxysmal hemicrania.....	268
oral ulceration.....	276	patient-controlled analgesia.....	171–81
organisational requirements.....	47–50		
acute pain services .....	48–50		
general.....	48		

adjuvant drugs .....	173–75	pelvic girdle pain .....	382
background infusion .....	176	symphyseal diastasis .....	382
bolus dose .....	175	prehospital analgesia .....	294–98
complications .....	177–78	assessment .....	295
dose limits .....	176	non-pharmacological management .....	297–98
efficacy .....	171–72	regional .....	297
equipment .....	178–79	systemic .....	295–97
intranasal .....	176	preventive analgesia .....	12–15
loading dose .....	176	procedural pain	
lockout interval .....	175	children .....	342–47, 361–62
older patients .....	405	intensive care .....	289
opioids .....	172–73	neonates .....	343
oral .....	176	patients with cancer .....	282
patient factors .....	179–80	pruritus .....	67
staff factors .....	180	psychological interventions .....	221–26
subcutaneous .....	176	attentional techniques .....	223–24
transdermal .....	177	children .....	346
percutaneous vertebroplasty .....	284	cognitive-behavioural interventions .....	224–26
perineal pain .....	394	information provision .....	221–22
peripheral nociceptors .....	1	stress and tension reduction .....	222–23
pethidine .....	60, <i>See</i> meperidine	puerperium .....	394
pharyngitis .....	274	radiotherapy .....	283
phenytoin .....	90	rectal route .....	158–59
porphyrias .....	259	nsNSAIDs .....	158
postamputation pain .....	234–36	opioids .....	158
postdural puncture headache .....	188, 268–70	paracetamol .....	159
postherpetic neuralgia .....	253–55	regional analgesia .....	193–95
postoperative pain .....	233–43	anticoagulation .....	193–94, 201
cranial neurosurgery .....	241–43	infection .....	202
day-stay or short-stay surgery .....	238–41	nerve injury .....	201
neuropathic pain .....	233	neuraxial blockade .....	193–94
postamputation pain .....	234–36	peripheral blockade .....	195
postherniotomy pain syndrome .....	237	plexus blockade .....	195
posthysterectomy pain syndrome .....	237	safety .....	201–3
postmastectomy pain syndrome .....	237	toxicity .....	202
post-thoracotomy pain syndrome .....	236	relaxation .....	222
poststroke pain .....	273	renal colic .....	73, 250
pre-emptive analgesia .....	12–15	renal disease .....	414–15
pregabalin .....	89, 90	respiratory depression .....	63, 188
pregnancy .....	381–90	sickle cell disease .....	256–58
back pain .....	382	sinusitis .....	275
labour pain .....	386–88	sodium valproate .....	89, 90
meralgia paresthetica .....	382	spinal cord injury pain .....	243–45
nsNSAIDs .....	381	static magnet therapy .....	228
opioids .....	381	status migrainosus .....	265
paracetamol .....	381		

subcutaneous route .....	157–58	metabolism.....	24
coxibs.....	158	older patients .....	403
nsNSAIDs.....	158	oral .....	153–54
opioids .....	157–58	prehospital analgesia .....	295
tramadol .....	157–58	subcutaneous .....	157–58
sublingual route .....	162–63	transcranial magnetic stimulation .....	228
SUNCT .....	268	transcutaneous electrical nerve stimulation ..	226–27
symphyseal diastasis .....	382	transdermal route.....	159–60
TENSSee transcutaneous electrical nerve stimulation		opioids.....	159–60
tension-type headache.....	260	other drugs.....	160
thoracotomy.....	236	transmucosal routes .....	159–64
thought processes.....	7	trigeminal autonomic cephalalgia.....	267
tolerance .....	68	trigeminal neuralgia.....	273
tonsillectomy.....	74, 275–76, 347, 348, 352, 357	triptans.....	263
tramadol.....	60	urethral catheterisation, children.....	344
children.....	350–52	urinary retention.....	67
controlled-release.....	154	urine sampling, neonates .....	343
emergency department.....	291	uterine pain.....	395
immediate-release.....	153	venipuncture, children.....	343
intramuscular.....	157–58	wound infiltration .....	200
intravenous.....	155–56	wounds .....	293
lactation.....	391		



Australian Government  
National Health and  
Medical Research Council

N H M R C



ANZCA

AUSTRALIAN AND NEW ZEALAND  
COLLEGE OF ANAESTHETISTS



FPM

FACULTY OF PAIN MEDICINE  
ANZCA