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Desenho da autoria de Maria Beatriz Vieira, apresentado no concurso «Vou Desenhar a Minha Dor», promovido pela APED com o apoio da Bene Farmacêutica.

Esta iniciativa vai já na sua 17ª edição e visa contribuir para a sensibilização e educação do público, crianças e pais para a dor pediátrica, promovendo a melhoria continuada da comunicação e compreensão da dor na criança. O Concurso «Vou Desenhar a Minha Dor» convida todas as crianças hospitalizadas dos 6 aos 12 anos a terem no desenho uma expressão da sua dor. Na APED acreditamos que através do uso de uma linguagem criativa e ligada ao seu imaginário permitimos que a criança encontre um veículo mais natural, leve e próximo para dar voz à sua experiência da dor.

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Editorial

Editorial

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Está concluído e publicado o segundo volume de 2022 da revista Dor, o qual, apesar dos nossos esforços, não foi possível lançar mais cedo. Peço a todos os leitores, clínicos e cientistas que se interessam pela dor que contribuam para a publicação de trabalhos na nossa revista Dor, que é de todos nós. Enviem os vossos trabalhos, revisões e casos clínicos para a revista, porque esta depende da vitalidade das suas publicações. Uma forma de participar poderá ser com comunicações livres de trabalhos que sejam apresentados no próximo VIII Congresso da APED, a realizar em 20 e 21 de outubro na cidade do Porto. As melhores apresentações serão premiadas e depois os autores convidados a publicar esses estudos na revista, sob a forma de artigo. Cá esperamos pelos vossos trabalhos!

No primeiro artigo deste volume, de Marta Pires e Rita Frutuoso de Carvalho, são apresentados dois casos de dor neuropática refratária pós-mastectomia com necessidade de controlo da dor através da neurólise alcoólica de nervos intercostais. Nas situações apresentadas, os bloqueios fasciais não proporcionaram alívio analgésico adequado e a neuropatia estava claramente delimitada em termos de inervação sensitiva. Assim, estes pacientes foram considerados bons candidatos para realizar neurólise química alcoólica nos nervos afetados, com resultados iniciais satisfatórios. De notar que a crioablação é uma técnica alternativa, menos dolorosa e com menor risco do que aquele associado à dispersão do álcool. Nos casos apresentados, a crioablação não pôde ser utilizada como opção terapêutica devido à sua indisponibilidade na instituição. A neurólise alcoólica de nervos intercostais é uma técnica pouco documentada na literatura e os dois casos relatados mostram eficácia preliminar na paliação de dor refratária após cirurgia da mama.

No trabalho seguinte, de Ana Cristina Paredes e colaboradores, foi avaliado de que modo é que variáveis psicológicas negativas e positivas estão associadas à dor e incapacidade na osteoartrite. Foram recrutados sessenta e seis participantes com osteoartrite no joelho ou anca, e foi investigado o papel de variáveis psicológicas negativas (como catastrofização da dor, ansiedade e depressão) e positivas (como autoeficácia, otimismo e satisfação com a vida), por meio de testes de correlação e modelos de regressão linear hierárquica. A autoeficácia emergiu como a variável mais relevante nos modelos de regressão, acima de outras caraterísticas clínicas e psicológicas, mostrando a sua relevância para a experiência de dor crónica.

O terceiro trabalho apresenta a gestão clínica de um caso raro de rabdomiólise. Sylva El Kazma e colaboradores reportam a dor de um paciente submetido a uma cistectomia radical devido a um tumor invasivo da bexiga, que atinge o máximo de 10 na escala visual analógica e se torna muito difícil de controlar, com necessidade de abordagem multidisciplinar e analgesia multimodal.

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Ana Rita Arantes e colaboradores apresentam um estudo retrospetivo do protocolo introduzido no Hospital de Braga sobre a administração de cetamina oral no tratamento de dor oncológica refratária a terapêutica com opioide em altas doses e fármacos adjuvantes.

Em cinco doentes, a aplicação do protocolo de cetamina oral permitiu um controlo álgico eficaz e prolongado em três pacientes e redução de ≥ 50% na doce de opioide (em dois dos cinco doentes). Este estudo contribui para a aceitação da prescrição off-label da cetamina oral como um agente seguro e eficaz na abordagem da dor crónica oncológica refratária a analgesia com utilização de opioides.

"No último trabalho selecionado para este volume, Letícia Nóbrega e Rute Sampaio fazem uma revisão narrativa sobre as práticas de prescrição de opioides pelos médicos portugueses para tratar a dor crónica e a adesão dos doentes. Foram incluídos vinte e seis estudos na revisão, tendo sido verificado que o consumo de opioi des em Portugal é baixo, embora seja observada uma tendência crescente na sua administração. As autoras descrevem detalhadamente os estudos para melhor caraterização perante os leitores (catorze transversais, oito coortes, um estudo de validação, um estudo comparativo e dois artigos de opinião de peritos), incluindo os objetivos, fármacos usados, a aderência dos pacientes à medicação e os fatores que podem ter influenciado essa aderência. A adesão terapêutica dos doentes aos opioides para a dor crónica parece ser baixa, mas com tendência para aumentar e estar relacionada com crenças culturais entre doentes e médicos.

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CASOS CLÍNICOS

Neurólise alcoólica de nervos intercostais no tratamento de dor crónica após cirurgia mamária: relato de dois casos clínicos

Intercostal neurolysis with alcohol in the treatment of chronic pain after breast surgery: report of two clinical cases

Marta Rodrigues Pires[1] e Rita Sofia Frutuoso de Carvalho[2]*

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Resumo

A síndrome dolorosa pós-mastectomia é uma entidade classicamente descrita como dor neuropática localizada na região cirúrgica e área envolvente com duração superior a três meses. Apesar de o termo estar associado à mastectomia, qualquer cirurgia mamária é passível de desenvolver dor neuropática, incluindo os procedimentos menos invasivos. As opções terapêuticas apoiam-se em esquemas analgésicos com anticonvulsivantes e antidepressivos, tratamentos tópicos e, nos casos mais graves, a dor pode ser aliviada através de técnicas interventivas com bloqueios da parede torácica. Nos casos refratários, com dor neuropática localizada a dermátomos específicos, a neurólise química dos nervos intercostais dos territórios envolvidos é uma opção paliativa eficaz em doentes oncológicos. Os autores relatam dois casos clínicos de neurólise alcoólica de nervos intercostais para tratamento de dor neuropática após cirurgia mamária, nomeadamente tumorectomia alargada e mastectomia simples com exérese de gânglio sentinela. Em ambos os casos, a técnica foi realizada com administração de anestésico local e álcool 99% com apoio ecográfico a nível da linha axilar média. Após um período de agravamento transitório da dor, houve uma melhoria significativa da neuropatia com redução da necessidade de analgésicos. A neurólise alcoólica de nervos intercostais é uma técnica pouco documentada na literatura e os dois casos relatados mostram eficácia preliminar na paliação de dor refratária após cirurgia da mama.

Palavras-chave: *Neuropatia. Cirurgia mamária. Neurólise. Nervos intercostais.*

Abstract

Post-mastectomy pain syndrome is an entity classically described as neuropathic pain located in the surgical region and surrounding area lasting more than three months. Although the term is associated with mastectomy, any breast surgery is likely to develop neuropathic pain, including less invasive procedures. Therapeutic options are based on analgesic regimens with anticonvulsants and antidepressants, topical treatments and, in more severe cases, pain can be relieved through interventional techniques such as chest wall blocks. In refractory cases, with neuropathic pain localized to specific dermatomes, chemical neurolysis of the intercostal nerves is an effective palliative option in cancer patients. The authors report two clinical cases of alcohol neurolysis of intercostal nerves for the treatment of neuropathic pain after breast surgery, namely enlarged lumpectomy and simple mastectomy with sentinel node excision. In both cases, the technique was performed with the

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administration of local anesthetic and alcohol 99% with ultrasound guidance at the mid-axillary line. After a period of transient worsening of pain, there was a significant improvement in neuropathy with reduced need for analgesics. Alcohol neurolysis of intercostal nerves is a technique poorly documented in the literature and the two reported cases show preliminary efficacy in the palliation of refractory pain after breast surgery.

Keywords: *Neuropathy. Breast surgery. Neurolysis. Intercostal nerves.*

O tratamento da neoplasia da mama envolve atualmente diferentes abordagens cirúrgicas da mama e axila que vão desde a tumorectomia com excisão de gânglio sentinela até à mastectomia radical modificada com esvaziamento ganglionar axilar, podendo associar-se a radioterapia e/ou quimioterapia adjuvante[1].

A síndrome dolorosa pós-mastectomia é uma entidade classicamente descrita como dor neuropática localizada na região cirúrgica e área envolvente (mama, axila, parede torácica ântero-lateral, região proximal do braço) com duração superior a três meses[2]. Apesar do termo estar associado à mastectomia, qualquer cirurgia mamária é passível de desenvolver dor neuropática, incluindo os procedimentos menos invasivos[1].

Assim, a dor crónica após cirurgia mamária é uma complicação conhecida, com impacto negativo na qualidade de vida, que requer tratamento dirigido. As opções terapêuticas farmacológicas são limitadas e apoiam-se sobretudo em esquemas analgésicos com anticonvulsivantes e antidepressivos. Nos casos mais graves, a capsaicina e lidocaína tópicas promovem um alívio temporário dos sintomas[2]. Nos eventos de crise, técnicas interventivas com bloqueios da parede torácica (por exemplo, bloqueio paravertebral, bloqueio do plano eretor da espinha, bloqueio do plano do serrado, bloqueio dos ramos intercostais na linha axilar média [BRILMA]) são tratamentos eficazes, mas de duração variável que pode ir de semanas a meses.

A neurólise percutânea, química ou térmica, é uma técnica paliativa eficaz em doentes oncológicos com dor refratária. A neurólise química pode ser feita com fenol 3-20% ou álcool absoluto 95-100% e resulta em degeneração Walleriana, desnaturação de proteínas e necrose de coagulação do tecido nervoso. A neurólise alcoólica é preferível pela maior duração de ação mas pode causar um agravamento transitório da dor[3].

Os autores relatam dois casos clínicos de realização de neurólise alcoólica de nervos intercostais para tratamento de dor neuropática após cirurgia mamária. Os procedimentos realizados tiveram consentimento informado do doente assinado por escrito.

Caso 1

Doente do sexo feminino, com 69 anos de idade, submetida a tumorectomia alargada direita com alargamento de loca em dezembro de 2015, seguido de radioterapia adjuvante entre março e abril de 2016. A doente foi referenciada à Unidade de Dor em setembro de 2016 por dor constante do tipo picada na mama direita, com sensação de calor e irradiação para a região dorsal, de intensidade 7-8/10 na escala numérica de dor, tendo iniciado titulação oral com pregabalina. Na consulta de reavaliação, a pior queixa era uma área de dor neuropática extensa pré-torácica com DN4 7/10, não tendo tolerado a titulação de pregabalina por tonturas. Foi proposto um tratamento com capsaicina 8% tópica, em ambiente hospitalar, com melhoria reportada superior a 50%, mas ainda insuficiente, pelo que a doente recusou a repetição do tratamento. Por persistência de dor neuropática intensa, foram realizados, no total, sete bloqueios analgésicos da parede torácica (isto é, bloqueio do plano serrado anterior e BRILMA com anestésico local e corticoide) entre junho de 2017 e junho de 2022, com alívio da dor durante cerca de dois meses após cada procedimento. Durante este período esteve medicada com metamizol 575 mg tid, gabapentina 100 mg tid e emplastros de lidocaína 5%. Em julho de 2022, mantinha dor neuropática na parede torácica ântero-lateral à direita com alodinia a nível dos dermátomos T4-5 e, após confirmação com um bloqueio diagnóstico, foi realizada a neurólise alcoólica do 4.º e 5.º nervos intercostais direitos com apoio ecográfico a nível da linha axilar média com 4 ml de levobupivacaína 0,5% e 1 ml de álcool 99% em cada nível. A figura 1 apresenta uma imagem de ultrassonografia do 5.º espaço intercostal com identificação das estruturas anatómicas relevantes. O álcool deve ser administrado no ponto azul, que representa a localização do nervo intercostal. Após uma agudização transitória da dor com ardor e calor nos respetivos dermátomos, na reavaliação um mês após procedimento a doente apresentava-se assintomática, a tolerar palpação mamária, sem alodinia e sem necessidade de analgésicos orais. A dor inicial, ao 15.º dia e ao fim de um mês era 7/10, 4/10 (pela

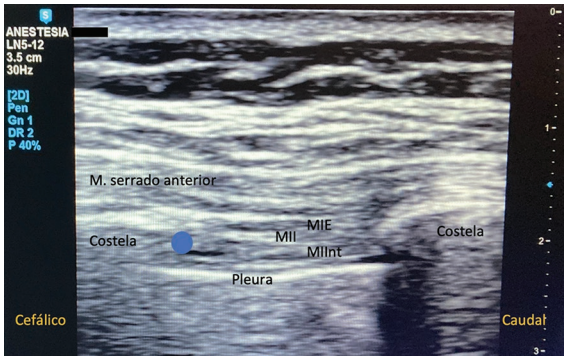

Figura 1. Ultrassonografia do 5.º espaço intercostal direito a nível da linha axilar média.
MIE: músculo intercostal externo; MII: músculo intercostal interno; MIInt: músculo intercostal íntimo.

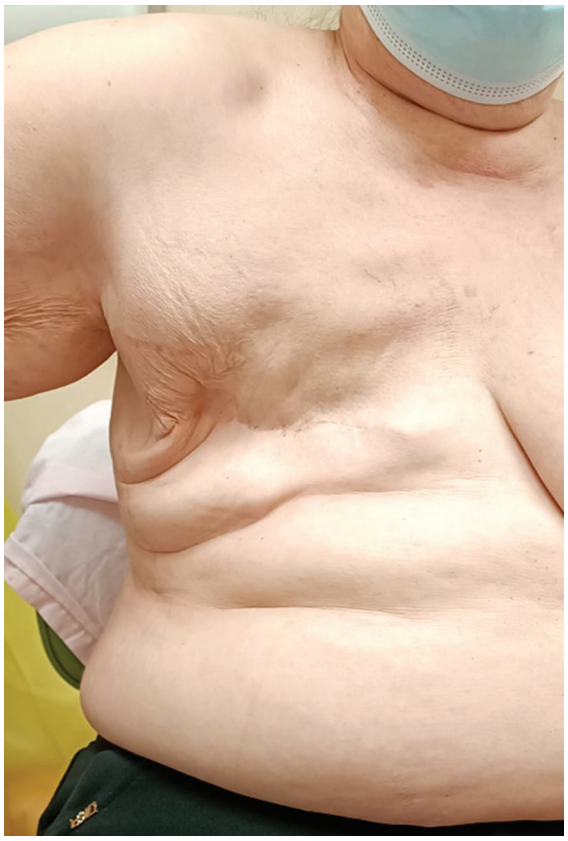

Figura 2. Cicatriz de mastectomia.

nevrite alcoólica) e 0/10, respetivamente. Após três meses de tratamento, a queixa mais valorizada pela doente foi uma dor residual na região supramamária, de caraterísticas nocicetivas, de provável origem musculoesquelética, numa doente que nunca fez reabilitação física pós-cirúrgica por dor neuropática intensa. Por este motivo, foi pedida a avaliação por Medicina Física e de Reabilitação.

Caso 2

Doente do sexo feminino, com 59 anos de idade, com antecedentes relevantes de diabetes *mellitus* tipo 2 e perturbação depressiva acompanhada em Psiquiatria. Foi submetida a mastectomia direita simples com exérese de gânglio sentinela em setembro de 2015, tendo realizado quimioterapia adjuvante entre outubro de 2015 e janeiro de 2016, seguida de hormonoterapia. Foi referenciada à Unidade de Dor em novembro de 2016 por dor neuropática intensa na região da cicatriz cirúrgica e dor de caraterísticas mistas na cintura escapular e membro superior direito, com limitação funcional, como mostra a figura 2. A dor foi descrita como do tipo facada e quantificada com intensidade 9/10 na escala numérica de dor. Foi instituído um esquema analgésico oral com tramadol, paracetamol e aplicação de capsaicina em creme na cicatriz, com melhoria ligeira da intensidade da dor. Em janeiro de 2017, foi realizado tratamento com capsaicina 8% tópica, em ambiente hospitalar, com diminuição da área dolorosa e menos episódios de dor intensa. Por manter ainda duas áreas de maior sensibilidade que impossibilitavam o uso de prótese, iniciou tapentadol oral, titulado até 100 mg bid. Perante a persistência de dor neuropática intensa, a doente recusou a repetição do tratamento com capsaicina 8% e optou-se pela realização de bloqueios analgésicos da parede torácica. Foram realizados, no total, 13 bloqueios analgésicos (isto é, bloqueio do plano serrado anterior, BRILMA e bloqueio do plano eretor da espinha com anestésico local e corticoide) entre junho de 2017 e novembro de 2021, com alívio da dor durante cerca de dois a três meses após cada procedimento. Durante este período, a doente estava medicada com oxicodona + naloxona 20 + 10 mg tid, pregabilina 100 mg id e tramadol orodispersível 50 mg SOS. Em julho de 2022, persistia dor do tipo picada e calor na região anterior da mastectomia, a nível dos dermátomos T4 e T5 e, após confirmação com um bloqueio diagnóstico, foi realizada a neurólise alcoólica do 5.º nervo intercostal direito com apoio ecográfico a nível da linha axilar média com 5 ml de levobupivacaína 0,5% e 1 ml de álcool 99%. A dor inicial, ao 15.º dia e ao fim de um mês era 9/10, 3/10 (pela nevrite alcoólica) e 0/10, respetivamente. Na reavaliação, um mês após procedimento, reportou melhoria significativa

com ardor transitório no dermátomo nos primeiros cinco dias. Por manter clínica de neuropatia no dermátomo T4, foi repetido o procedimento a nível do 4.º nervo intercostal direito em outubro de 2022, com melhoria dos sintomas sem necessidade de terapêutica analgésica oral de resgate três semanas após o procedimento, tendo sido mantido, um esquema analgésico com oxicodona + naloxona 20 + 10 mg tid e metamizol 575 mg SOS.

A neuropatia após cirurgia mamária pode levar à instalação de uma síndrome dolorosa incapacitante que impossibilita a reabilitação física pós-cirúrgica e à intolerância ao uso de prótese e roupa sobre a área afetada. Nos casos refratários à terapêutica farmacológica sistémica e tópica, os bloqueios fasciais podem conduzir a dessensibilização álgica ao longo do tempo e ter efeitos duradouros. Nos casos apresentados, a resposta analgésica aos bloqueios fasciais demonstrou-se insuficiente e a neuropatia era bem delimitada do ponto de vista de inervação sensitiva, o que tornou estes doentes bons candidatos para a realização de neurólise química alcoólica dos nervos envolvidos, com resultados iniciais satisfatórios. A relação risco-benefício desta técnica deve ser considerada tendo em conta as complicações possíveis de punção vascular, pneumotórax e, nos casos mais graves, dispersão do álcool para o espaço paravertebral e epidural com potenciais consequências neurológicas graves. Medidas como a punção guiada por ecografia e a nível da linha axilar média, mantendo o doente consciente e colaborante, aumentam a segurança do procedimento. A crioablação é uma técnica alternativa que utiliza temperaturas até -140 ºC para neuroablação, menos dolorosa e com menos riscos associados à dispersão do álcool[2]. Nos casos apresentados, a crioablação não foi uma opção terapêutica por ainda não estar disponível na instituição. A neurólise alcoólica de nervos intercostais é uma técnica pouco documentada na literatura e os dois casos relatados mostram eficácia preliminar na paliação de dor refratária após cirurgia da mama. A abordagem multidisciplinar decorrente da avaliação concomitante com a Medicina Física e de Reabilitação e Psiquiatria foi igualmente importante na orientação dos dois casos apresentados.

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ORIGINAL ARTICLE

Pain and disability in patients with osteoarthritis: the key role of self-efficacy

Dor e incapacidade em pacientes com osteoartrose: o papel da auto-eficácia

*Ana Cristina Paredes[1,2,3], Armando Almeida[1,2,3], and Patrícia R. Pinto[1,2,3]**

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Abstract

Osteoarthritis (OA) is a debilitating condition and better understood within a biopsychosocial framework. Psychological variables can influence disease experience and are amenable to change. This work explored how negative and positive psychological variables are associated with pain and disability in OA. Sixty-six participants with knee or hip OA (54.5% female; mean age 67.8 years) completed a sociodemographic, clinical, and psychological assessment. The role of negative (pain catastrophizing, anxiety, and depression) and positive (self-efficacy, optimism, and satisfaction with life) psychological variables was investigated using correlation tests and hierarchical linear regression models. Three separate models were created for each dependent variable (pain intensity and disability), controlling for sociodemographic, and clinical characteristics. Model 1 included negative variables, model 2 included positive variables, and model 3 combined the statistically significant variables in previous models. Variables associated with pain intensity were disability in model 1 (β = 0.264, p = 0.039) and self-efficacy in model 2 (β = –0.375, p = 0.017). Model 3 explained 21% of the variance in pain intensity, with self-efficacy being the only statistically significant variable (β = –0.380, p = 0.008). For disability, pain location (β = 0.293, p = 0.017), pain intensity (β = 0.244, p = 0.038), and depression (β = 0.290, p = 0.015) were statistically significant in model 1, along with self-efficacy in model 2 (β = –0.412, p = 0.003). Model 3 explained 34% of the variance in disability, with self-efficacy being the only statistically significant variable (β = –0.479, p = 0.001). Self-efficacy emerged as the most relevant variable in regression models, above other clinical and psychological characteristics. Promoting competency beliefs may be a useful strategy to improve pain and physical function in OA patients.

Keywords: *Osteoarthritis. Pain. Disability. Psychological variables. Self-efficacy.*

Resumo

A osteoartrose (OA) é uma doença incapacitante, que deve ser compreendida à luz do modelo biopsicossocial. As variáveis psicológicas podem influenciar a experiência da doença e são potencialmente modificáveis. Este estudo explorou a associação de variáveis psicológicas negativas e positivas, com dor e incapacidade na OA. Sessenta e seis participantes com OA no joelho ou anca (54.5% mulheres; idade média 67.8 anos) completaram avaliação sociodemográfica, clínica e psicológica. O papel das variáveis negativas (catastrofização da dor, ansiedade, depressão) e positivas (auto-eficácia, otimismo, satisfação com a vida) foi investigado com testes de correlação e regressões lineares hierárquicas. Foram criados três

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modelos para cada variável dependente (dor, incapacidade), controlando características demográficas e clínicas. O modelo 1 incluiu variáveis negativas, o modelo 2 variáveis positivas e o modelo 3 juntou as variáveis significativas dos modelos anteriores. As variáveis associadas com intensidade da dor foram a incapacidade, no modelo 1 (β = 0.264, p = 0.039), e a auto-eficácia no modelo 2 (β = –0.375, p = 0.017). O modelo 3 explicou 21% da variância da intensidade da dor, sendo a auto-eficácia a única variável significativa (β = –0.380, p = 0.008). Para a incapacidade, a localização (β = 0.293, p = 0.017), intensidade da dor (β = 0.244, p = 0.038) e depressão (β = 0.290, p = 0.015) foram significativas no modelo 1, e a auto-eficácia no modelo 2 (β = –0.412, p = 0.003). O modelo 3 explicou 34% da variância, sendo a auto-eficácia a única variável significativa (β = –0.479, p = 0.001). A auto-eficácia emergiu como a variável mais relevante nos modelos de regressão. Intervenções para promover crenças de autoconfiança poderão melhorar a dor e a funcionalidade dos pacientes com OA.

Palabras clave: *Osteoartrose. Dor. Incapacidade. Variáveis psicológicas. Auto-eficácia.*

Introduction

Osteoarthritis (OA) is a disease of the synovial joints that cause structural alterations in the articular cartilage, subchondral bone, synovium, capsule, periarticular muscles, supporting ligaments, and sensory nerve endings[1]. OA is the third most prevalent musculoskeletal disorder and the one with the greatest incidence increase in the past two decades[2]. According to the global burden of disease study, OA figures have grown by 113% from 1990 to 2019[3], accompanying worldwide trends of increasing life expectancy, obesity, and population aging[4,5].

Pain is a prevailing symptom in OA, along with functional limitations that make this condition a leading cause of disability[4,6]. OA is recognized as a major public health challenge, with high financial costs both for societies and individuals[5,7].

Pain experience in OA is complex and multifactorial, with the degree of radiographic damage being only weakly correlated with pain complaints and disability[8]. Indeed, OA outcomes can be best understood through a biopsychosocial framework. Pain and disability result from the multifactorial interplay between different factors, such as joint pathology, neurobiological mechanisms, demographics, psychological characteristics, and sociocultural influences[4,6]. However, research and treatment efforts are mostly focused on structural and pharmacological targets, which have proven insufficient for optimal symptom management[6].

In the realm of psychological variables, negative constructs such as depression, anxiety, and pain catastrophizing have been the focus of greater attention, with research being fairly consistent in pointing toward an association between psychological distress and pain reports[9]. For example, patients with anxiety and depression disorders are more likely to experience highly disabling pain[10]. Among OA patients, those with higher anxiety and depression are also more likely to report more intense pain[11,12], though the effects seem to be larger for anxiety[13]. Similar conclusions have been reached for disability outcomes, with higher distress being associated with more difficulties[11,12,14,15].

Pain catastrophizing is another psychological construct central to pain adaptation[16], which refers to exaggerated cognitive or emotional responses in face of actual or anticipated pain experiences[17]. Its role is supported by a robust body of evidence showing an association with pain and disability[11,12,18], independent of depression and anxiety levels[19-21].

Parallel to the exponential growth in research analyzing these negative psychological constructs, the past decades have seen increased interest in the role of positive psychological variables. More and more, these are being considered contributors to the well-being of individuals and societies[22]. For example, research with pain patients has shown that factors such as optimism, satisfaction with life, and self-efficacy (personal belief in the ability to succeed[23]) are associated with pain and disability outcomes[11,12,24,25]. These variables seem to be valuable resources to counter the effect of negative emotions associated with pain, and to improve pain coping[16].

Since psychological variables are amenable to change, it is crucial to understand and intervene in individual characteristics that can promote better outcomes. This work aimed to analyze how negative and positive psychological variables are associated with pain intensity and disability in patients with hip or knee OA.

Materials and methods

Procedure

This is a single-site and cross-sectional study conducted at Hospital of Braga (Portugal). The investigation followed international ethical guidelines for research involving humans and was approved by the Ethics Committees of University of Minho and Hospital of Braga.

Participants

The participants approached for this study were OA patients scheduled to have joint replacement surgery. Recruitment took place at the Orthopedics Unit during a presurgical appointment and the patients were invited to participate if the following inclusion criteria were met: (a) age over 50 years old; (b) diagnoses of knee or hip OA; and (c) ability to understand written information and give informed consent. Exclusion criteria were as follows: (a) severe neurologic, psychiatric, or organic diseases; and (b) contralateral knee or hip arthroplasty in the previous 6 months.

After accepting to participate, the informed consent form was signed by all participants.

Measures

Sociodemographic and Clinical Questionnaire (developed by the research team)

Sociodemographic information included sex, age, marital status, education, and employment. The clinical section evaluated pain characteristics and medical history.

Brief Pain Inventory (BPI)[26,27]

The BPI questionnaire evaluates pain intensity and interference. In this study, the pain "on the average" item was used as a measure of pain intensity. This question was answered according to an 11-point numerical rating scale (NRS; 0 = No pain; 10 = Worst pain imaginable).

Western Ontario and McMaster Osteoarthritis Index (WOMAC)[28]

WOMAC evaluates pain, stiffness, and disability in patients with knee or hip OA. Items are rated on a five-point Likert scale from 0 (no pain/stiffness/difficulty) to 4 (extreme pain/stiffness/difficulty). Each subscale score is the sum of all items, with higher scores indicating more pain, stiffness, and disability.

Hospital Anxiety and Depression Scale (HADS)[29]

HADS is a validated questionnaire to assess anxiety and depression in non-psychiatric clinical populations. It is composed of two subscales (anxiety and depression), with seven items each. Each item is answered on a four-point Likert scale, ranging from absence or few symptoms (lower scores) to severe symptomatology (higher scores).

Coping Strategies Questionnaire-Revised (CSQ-R)[30,31]

Pain catastrophizing was assessed using the corresponding subscale from the CSQ-R. It has six items that were rated using a five-point Likert scale (1=Never do that; 5=Always do that). The total score is the mean value of the answers to the six items and ranges from 1 to 5, with higher values indicating greater pain catastrophizing.

Pain Self-Efficacy Questionnaire (PSEQ)[32,33]

The PSEQ has ten items that evaluate confidence to engage in activities of daily living, despite pain. The answers are given according to a seven point scale, ranging from 0 (not at all confident) to 6 (completely confident). The total score is the sum of all items and varies from 0 to 60, with higher scores translating stronger self-efficacy beliefs.

Life Orientation Test-Revised (LOT-R)[34]

The LOT-R is composed of six items that derive an optimism score. These are answered according to a five-point Likert scale (0 = Strongly disagree; 4 = Strongly agree), resulting in a possible score that ranges from 0 to 24. Higher scores translate more optimistic expectations.

Satisfaction with Life Scale (SWLS)[35,36]

The SWLS is composed of five items. The Likert scale in the Portuguese version has five possible answers, ranging from 1 (strongly disagree) to 5 (strongly agree). The total score is the sum of all items and ranges from 1 to 25, with higher scores indicating higher satisfaction with life.

Statistical analysis

Data analyses were performed using IBM Statistical Package for the Social Sciences (SPSS), version 26 (Chicago, IL, USA). Participants' characteristics are expressed as absolute and relative frequencies for categorical data (n, %), or mean and standard deviation for continuous variables (M ± SD). The distribution

properties of continuous variables were analyzed through skewness (Sk) and kurtosis (Ku). Normality was assumed if Sk ± 2 and Ku ± 7[37]. Normality was guaranteed for all variables except pain duration, in which case non-parametric statistics was used.

Associations between study variables were analyzed using Pearson or Point-bisserial correlation test, according to the type of data. For non-normally distributed variables, the Spearman correlation test was used. Hierarchical linear regression analyses were used to explore positive and negative psychological variables associated with the selected dependent variables (DV): pain intensity (BPI pain on average) and disability (WOMAC). The models included those variables showing a statistical significant association with the DV in the previous correlation tests (statistical significance was set at $p < 0.05$ for all analyses). All models controlled for the influence of sex, which was included in the first block. The second block controlled for clinical variables (pain duration/location) and disability, and the third block included psychological variables. To analyze the differential role of positive versus negative variables, three different models were created for each DV: model 1 included negative psychological variables (pain catastrophizing, anxiety, and depression), model 2 included positive psychological variables (self-efficacy, optimism, and satisfaction with life), and model 3 (final model) included the statistically significant variables in models 1 and 2. All assumptions for performing regression analysis were met.

Results

This study included 66 OA patients, 36 (54.5%) women and 30 (45.5%) men. Mean age was 67.8 years old (SD = 7.3), with most participants being retired (72.8%). There was a wide variability in pain duration, ranging from 6 months to 3 years. The complete description of sociodemographic, clinical, and psychological characteristics is shown in table 1.

Table 2 shows the association of study variables with the two DVs. There was a statistically significant association of pain intensity with pain duration ($r = 0.250$, $p = 0.043$), disability ($r = 0.337$, $p = 0.006$), pain catastrophizing ($r = 0.356$, $p = 0.003$), depression ($r = 0.313$, $p = 0.011$), self-efficacy ($r = -0.468$, $p < 0.001$), and satisfaction with life ($r = -0.301$, $p = 0.014$).

Disability was significantly associated with pain location ($r = 0.303$, $p = 0.013$), pain intensity ($r = 0.337$, $p = 0.006$), depression ($r = 0.369$, $p = 0.002$), self-efficacy ($r = -0.571$, $p < 0.001$), and satisfaction with life ($r = -0.395$, $p = 0.001$).

Variables associated with pain intensity

Table 3 shows the final block of each hierarchical regression model considering pain intensity as DV. Disability and self-efficacy were significantly associated with pain intensity in the first (disability: $t = 2.112$, $p = 0.039$, $\beta = 0.264$) and second models (self-efficacy: $t = -2.466$, $p = 0.017$, $\beta = -0.375$). The final model was statistically significant ($F[4.61] = 5.340$, $p = 0.001$), with self-efficacy emerging as the only statistically significant variable ($t = -2.728$, $p = 0.008$, $\beta = -0.380$). This model explains 21% of the variance in pain intensity (Adj. $R^2 = 0.211$).

Variables associated with disability

Table 4 shows the final block of each hierarchical regression model considering disability as DV.

Statistically significant variables in model 1 were pain location ($t = 2.460$, $p = 0.017$, $\beta = 0.293$), pain intensity ($t = 2.118$, $p = 0.038$, $\beta = 0.244$), and depression ($t = 2.497$, $p = 0.015$, $\beta = 0.290$). In model 2, statistically significant variables were pain location ($t = 2.012$, $p = 0.049$, $\beta = 0.222$) and self-efficacy ($t = -3.115$, $p = 0.003$, $\beta = -0.412$). Thus, the final model included depression and self-efficacy, with the latter emerging as the only statistically significant variable ($t = -3.380$, $p = 0.001$, $\beta = -0.479$). This model explains 34% of the variance in disability (Adj. $R^2 = 0.343$).

Discussion

This work aimed to analyze the association of negative and positive psychological variables with pain intensity and disability in patients with OA. The results showed that pain and disability are associated with different negative (pain catastrophizing and depression) and positive (self-efficacy and satisfaction with life) psychological constructs. Among these, self-efficacy revealed the strongest association with the two outcomes. It also emerged as the only statistically significant variable in the final models, above other clinical and psychological characteristics. Pain-related self-efficacy translates a belief in the capacity to control pain, but also in the ability to maintain usual activities and manage negative emotions despite pain[38]. These beliefs are a relevant force behind

Table 1. Sociodemographic, clinical, and psychological characteristics of osteoarthritis patients

Variable [range]	Frequencies, n (%)/ minimum-maximum	Mean ± SD
Sex		
Female	36 (54.5)	
Male	30 (45.5)	
Age		67.82 ± 7.29
Marital status		
Married or living together	49 (74.2)	
Single, divorced or widowed	17 (25.8)	
Education		
No formal education	1 (1.5)	
1st-4th grade	45 (68.2)	
5th-10th grade	12 (18.2)	
High school or above	8 (12.1)	
Professional status		
Full-time job	6 (9.1)	
Unemployed	3 (4.5)	
Medical leave	6 (9.1)	
Retired	48 (72.8)	
Other income sources	3 (4.5)	
Pain location		
Knee	34 (51.5)	
Hip	32 (48.5)	
Pain duration (months)	6-372	60.59 ± 61.24
Pain intensity (BPI): [0-10]	2-10	5.11 ± 1.65
Disability (WOMAC): [0-68]	14-49	30.67 ± 9.45
Pain catastrophizing (CSQ-R): [1-5]	1-5	1.95 ± 1.04
Depression (HADS): [0-21]	0-14	3.88 ± 3.70
Anxiety (HADS): [0-21]	0-19	5.56 ± 5.04
Self-efficacy (PSEQ): [0-60]	4-60	36.94 ± 11.44
Optimism (LOT-R): [0-24]	3-24	15.80 ± 5.56
Satisfaction with Life (SWLS): [1-25]	5-25	17.53 ± 4.46

Categorical variables are presented as n (%) and continuous variables are presented as minimum, maximum and mean ± SD. The possible range of each questionnaire is indicated in square brackets. SD: standard deviation; BPI: Brief Pain Inventory; WOMAC: Western Ontario and McMaster Osteoarthritis Index; CSQ-R: Coping Strategies Questionnaire-Revised; HADS: Hospital Anxiety and Depression Scale; PSEQ: Pain Self-Efficacy Questionnaire; LOT-R: Life Orientation Test-Revised, SWLS: Satisfaction With Life Scale.

patients' actions, with the potential to influence how pain is experienced[23,39]. Accordingly, it has been demonstrated that patients with higher self-efficacy tend to report lower pain and improved physical function[12,14,40-43]. Beyond the results of individual studies, meta-analyses have also confirmed that self-efficacy is a robust correlate of functional impairment, emotional distress, and pain intensity in OA[39,44,45].

Different studies have shown that positive affect variables can influence mental health, physical functioning and activity levels[11,46]. For example, satisfaction with life influences the perception of health status, as demonstrated by the Portuguese National Health Survey[47]. Specifically for chronic pain, a recent cohort study confirmed that satisfaction with life was associated with disability in patients with knee pain[48]. Such results are corroborated by the present study, wherein significant correlations were also found between satisfaction with life and pain intensity and disability. Although satisfaction with life was not statistically significant in the regression models, focusing on positive resources seems to be a promising line of research to understand the outcomes of musculoskeletal disorders. This is a field with limited evidence that merits further investigation[48].

Table 2. Results of correlation tests between study variables

Variable	Correlation (r)	
	Pain intensity (BPI)	Disability (WOMAC)
Sex	0.134	–0.039
Age	–0.084	–0.057
Pain location	0.011	0.303*
Pain duration (months)	0.250*	0.114
Pain intensity (BPI)	1	0.337**
Disability (WOMAC)	0.337**	1
Pain catastrophizing (CSQ-R)	0.356**	0.180
Depression (HADS)	0.313*	0.369**
Anxiety (HADS)	0.108	0.228
Self-efficacy (PSEQ)	–0.468***	–0.571***
Optimism (LOT-R)	–0.176	–0.197
Satisfaction with life (SWLS)	–0.301*	–0.395***

*p < 0.05, **p < 0.01, ***p ≤ 0.001. Sex: male = 0, pain location: Knee = 0. BPI: Brief Pain Inventory; WOMAC: Western Ontario and McMaster Osteoarthritis Index; CSQ-R: Coping Strategies Questionnaire-Revised; HADS: Hospital Anxiety And Depression Scale, PSEQ: Pain Self-Efficacy Questionnaire; LOT-R: Life Orientation Test-Revised; SWLS: Satisfaction With Life Scale.

Pain catastrophizing was significantly associated with pain intensity in bivariate correlation, but became a non-significant variable in multivariate analysis. Instead, disability emerged as the only statistically significant predictor of pain intensity in model 1 (negative variables). Beyond statistical significance, it is interesting to note that the beta (β) values for the explanatory variables disability and pain catastrophizing are 0.26 and 0.27, respectively. Thus, the model corroborates the strong role of both variables to explain pain levels. The results for pain catastrophizing are also in line with the literature, which shows generally strong associations with pain intensity[11,12,18,19]. Yet, significant associations have also been reported between pain catastrophizing and disability[12,18-21], which was not corroborated in this research.

Surprisingly, optimism and anxiety were not associated with any of the outcomes. In fact, optimism has been strongly associated with pain in clinical and experimental settings and is considered a psychological variable related to a diminished experience of pain[49]. However, few studies assess optimism in OA patients and consider pain and disability as the main outcomes. According to the present findings, self-efficacy and satisfaction with life are positive psychological variables with a stronger influence on OA outcomes than optimism. However, these must be considered preliminary results to be explored in future studies with larger sample sizes and preferentially using longitudinal assessment.

Contrary to our results, anxiety has also been strongly associated with pain and disability in OA samples[11,15]. This is arguably because high-anxious patients may avoid movement and suffer greater physical deconditioning[13,50]. One possible explanation for the findings in this paper is the low levels of anxiety symptoms, with a mean score of 5.5 (out of a possible maximum of 21). However, it should be noted that depression levels were even lower (mean 3.9 score) and this variable reached statistical significance in bivariate and multivariate analyses. It can be hypothesized that higher anxiety scores are needed to influence pain outcomes, while lower depressive scores may already have an impact. Indeed, a systematic review concluded that the severity of depressive and anxious symptoms is associated with the degree of pain and disability[10]. It seems possible that symptom intensity should also be taken into account and different cutoffs might have to be considered for clinically relevant anxiety and depression in this context. The present results corroborate other studies showing the relevant role of depression for arthritis-related pain and disability[13,14,20,48], but fails to do so concerning the role of anxiety. Despite the amount of literature targeting these variables, their contribution to adverse pain events is not yet well understood and should be further explored[51].

Concerning pain-related characteristics, the analyses highlighted the role of pain location on disability levels, with hip OA patients reporting more difficulties. This may be due to a more restricted joint range of motion caused by hip than knee OA[52], which is an important determinant of disability[53]. Indeed, a systematic review of knee and hip research showed that the clinical presentation of symptoms may have some relevant differences between sites, which are worth considering when tailoring interventions to OA patients[52]. However, a recent large scale study reached different conclusions and pointed out that patients with knee or hip OA are "more alike than different"[54]. Nevertheless, the scarcity of comparative data available validates the pursuit of this line of research, to clarify potentially different mechanisms and improve treatment recommendations[52].

Table 3. Hierarchical linear regression model to predict pain intensity (BPI)

Variables	B	Beta (β)	t	p	Adjusted R^2	F	df	p
Negative variables (Model 1)								
Final block					0.170	3.662	5.60	**0.006**
Sex	0.187	0.057	0.484	0.630				
Pain duration	0.004	0.163	1.401	0.166				
Disability (WOMAC)	0.046	0.264	2.112	**0.039**				
Depression (HADS)	−0.002	−0.005	−0.028	0.978				
Pain catastrophizing (CSQ-R)	0.430	0.272	1.643	0.106				
Positive variables (Model 2)								
Final block					0.198	4.203	5.60	**0.002**
Sex	0.131	0.040	0.328	0.744				
Pain duration	0.005	0.174	1.524	0.133				
Disability (WOMAC)	0.016	0.090	0.644	0.522				
Self-efficacy (PSEQ)	−0.054	−0.375	−2.466	**0.017**				
Satisfaction with life (SWLS)	−0.004	−0.010	−0.074	0.942				
Final model (Model 3)								
Final block					0.211	5.340	4.61	**0.001**
Sex	0.140	0.043	0.371	0.712				
Pain duration	0.005	0.174	1.544	0.128				
Disability (WOMAC)	0.016	0.092	0.670	0.505				
Self-efficacy (PSEQ)	−0.055	−0.380	−2.728	**0.008**				

Sex: male = 0, bold: $p < 0.05$. WOMAC: Western Ontario and McMaster Osteoarthritis Index; HADS: Hospital Anxiety and Depression Scale; CSQ-R: Coping Strategies Questionnaire-Revised; PSEQ: Pain Self-Efficacy Questionnaire, SWLS: Satisfaction With Life Scale.

Table 4. Hierarchical linear regression model to predict disability (WOMAC)

Variables	B	Beta (β)	t	p	Adjusted R^2	F	df	p
Negative variables (Model 1)								
Final block					0.231	5.872	4.61	**< 0.001**
Sex	−0.149	−0.008	−0.065	0.948				
Pain location	5.488	0.293	2.460	**0.017**				
Pain intensity (BPI)	1.398	0.244	2.118	**0.038**				
Depression (HADS)	0.740	0.290	2.497	**0.015**				
Positive variables (Model 2)								
Final block					0.365	8.462	5.60	**< 0.001**
Sex	−1.989	−0.106	−0.922	0.360				
Pain location	4.173	0.222	2.012	**0.049**				
Pain intensity (BPI)	0.569	0.099	0.884	0.380				
Self-efficacy (PSEQ)	−0.341	−0.412	−3.115	**0.003**				
Satisfaction with life (SWLS)	−0.393	−0.185	−1.481	0.144				
Final model (Model 3)								
Final block					0.343	7.785	5.60	**< 0.001**
Sex	−1.280	−0.068	−0.599	0.551				
Pain location	4.017	0.214	1.906	0.061				
Pain intensity (BPI)	0.598	0.104	0.914	0.364				
Depression (HADS)	0.121	0.047	0.367	0.715				
Self-efficacy (PSEQ)	−0.395	−0.479	−3.380	**0.001**				

Sex: male = 0, pain location: Knee = 0, bold: $p < 0.05$. BPI: Brief Pain Inventory; HADS: Hospital Anxiety and Depression Scale; PSEQ: Pain Self-Efficacy Questionnaire; SWLS: Satisfaction With Life Scale.

Limitations

This study has some limitations that should be considered. Most importantly, the cross-sectional nature of the data does not allow for temporal associations between variables. This is most evident in the association between pain intensity and disability since these are significantly associated with one another in the regression models. More robust conclusions and cause-effect interpretations should be addressed in future studies with longitudinal assessment.

The sample in this study may not be representative of all OA patients since it included participants with end-stage OA with indication to undergo joint replacement. Furthermore, the relatively small sample size may have hindered statistical power and limited the ability to detect otherwise significant associations (type II error).

Conclusions

Taken together, the results support the relevance of a biopsychosocial and multidimensional approach to manage OA-related pain and disability[4,55]. Particularly, self-efficacy emerged as an important risk/protective factor[39,44,45], suggesting that interventions to promote competency beliefs can be a valuable tool to improve pain and physical function[56]. Such an approach has been analyzed in a few studies with promising results[57,58], but the overall evidence is still inconclusive and would benefit from more high-quality studies[59].

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Conflicts of interests

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Pain management and clinical considerations of a rare case of rhabdomyolysis caused by a hyperextension position after open radical cystectomy

Gestão da Dor e considerações clínicas de um caso raro de rabdomiólise causado pela posição de hiperextensão após Cistectomia radical aberta

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Abstract

Compartment syndrome (CS) is caused by an excessive increase in compartment intramuscular pressure, in which measurement is the reference diagnostic tool. We examine the case of a 44-year-old man with invasive bladder cancer who underwent an open radical cystectomy. After extubation, the patient is transferred from the operating room to the intermediate care unit, where he complains of severe lumbar pain on a visual analog scale of 10 that is unresponsive to opioids and is diagnosed with rhabdomyolysis due to CS. Multidisciplinary care and multi-modal analgesia approaches were used; no fasciotomy was performed; and a favorable outcome was achieved.

Keywords: *Cystectomy complications. Post-operative pain. Post-operative hyperkalemia. Severe muscular pain. Surgery position complications. Compartment syndrome.*

Resumo

A síndrome do Compartimento é causada por um excessivo aumento da pressão intramuscular, cuja medida é o padrão ouro para ferramenta diagnóstica. O caso em questão é um indivíduo do sexo masculino 44 anos com um cancer invasivo da bexiga que foi submetido à uma cistectomia radical aberta. Após extubação o doente é transferido da sala de operação para os cuidados semi-intensivos, queixando-se de dor lombar de intensidade severa, com escala analógica visual de 10, refratária ao uso de opióides, dor diagnosticada como rabdomiólise passiva devido à síndrome de compartimento lombar. Manejo multidisciplinar e analgesia multimodal foi usada e uma fasciotomia não foi necessária, permitindo um desfecho final favorável

Palavras-chaves: *Síndrome compartimental. Rabdomiólise. Manejo de dor. Posição de hiperextensão. Complicações de cistectomia.*

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Introduction

Compartment syndrome (CS) is a serious medical condition caused by rising pressure in and around muscles limiting then oxygen, blood, and nutrients to reach muscles and nerves leading to serious damage and possible death. Although acute CS is commonly assigned to trauma, it can have numerous causes. Positioning-related CS of the lower leg following long-duration gynecologic and urologic procedures is a rare complication. Rhabdomyolysis, limb loss, or even death may result from ineffective treatment.

Acute rhabdomyolysis is a syndrome characterized by a skeletal muscle lesion and subsequent release of contents into the circulatory system, which can cause potentially lethal complications such as myoglobinuria, electrolyte abnormalities like hyperkalemia, and acute kidney injury.

We examined the case of a 44-year-old male patient who underwent a radical cystectomy for high-grade urothelial carcinoma. This was complicated by massive rhabdomyolysis, which led to lumbar paraspinal CS and acute kidney injury.

Case report

A 44-year-old man was scheduled for an elective radical cystectomy with orthotopic neo bladder reconstruction by a Hautmann ileal neobladder for high-grade urothelial carcinoma "lymphoepithelioma-like" pT2 cN0 M0. His pre-operative anesthesia consultation revealed an American Society of Anesthesiologists physical status 2 with a body mass index of 33.3. His medical history included former tobacco use (45 packs/year) and spinal anesthesia for a transurethral bladder resection 2 months earlier. At the time of surgery, the patient received standard care and underwent four cycles of cisplatin and gemcitabine neoadjuvant chemotherapy.

The surgery was performed under general anesthesia. 30 min before incision, the patient received antibiotic prophylaxis with cefuroxime 1.5 g and metronidazole 500 mg.

For anesthesia induction, we used lidocaine 1% 50 mg, propofol 1% 300 mg, sufentanil 20 mcg, and rocuronium 50 mg. Anesthesia was maintained with desflurane 7% (MAC 1.0) and multimodal analgesia provided using continuous infusions of lidocaine (2 mg/kg/h), ketamine (0.15 mg/kg/h), and dexmedetomidine (0.4 mcg/kg/h). The surgical procedure lasted 6 hours and estimated blood loss was about 400 mL. During surgery, vital signs were stable, especially blood pressure and O_2 Saturation.

This surgery required special positioning so the patient was placed in the hyperextended supine position with the iliac crest located just below the fulcrum of the operating table.

Post-operative pain was anticipated by placing a pain-relieving device (Pain Buster) which consists of a catheter with multiple aligned holes linked to a pump containing ropivacaine 0.2% (7mL/h) for a spread of the local anesthetic to ensure proper, continuous, and sufficient post-operative wound infiltration in the abdominal compartment.

The surgery went uncomplicated, and the patient was transferred to intermediate care for post-operative care. In the immediate post-operative period, the patient described severe lumbar pain (visual analog scale 10/10). Laboratory results (Table 1) revealed an increase in creatine kinase (15351 UI/L) in the absence of lactate and a 32% increase in basal creatinine (117 mmol/L) in the presence of hyperkalemia (5.8 mmol/L). The first hypothesis was poor controlled pain, this idea was reinforced considering laparotomy incision. However, uncontrolled severe pain was persistent and an abdominopelvic CT scan was done at D1 showing no signs of ischemia or a herniated disk.

Intravenous patient-controlled analgesia was used to titrate morphine, but the results were insufficient. Then, we administered an infusion of fentanyl 50 μg/h and ketamine 20 mg/h, tizanidine 6 mg daily (3 mg twice a day orally), clonidine 90 μg twice daily intravenously, magnesium 3 g once daily intravenously, and lorazepam 1 mg once daily orally. In addition, hypnosis and physiotherapy sessions once daily were also applied.

Four days later (D4), the pain was uncontrollable and persistent despite these treatments. We performed abdominal and lumbar magnetic resonance imaging, which revealed muscular edema that affected the paraspinal muscles down to the dermis and roots of the gluteal muscles (Fig. 1A and B).

Imaging and an increase in compartment pressure (measured at 27 mmHg and a delta pressure of 43 mmHg at D5 by a handheld manometer device) resulting from prolonged hyperextension under general anesthesia confirmed the presence of CS with rhabdomyolysis. Due to the delayed diagnosis and the risk of infection, a fasciotomy was not performed. References values are showed in table 2.

The implementation of an insulin-glucose protocol and hyperhydration resulted in the normalization of serum potassium and kidney function. In addition, the evolution of creatine kinase was positive, and the patient was pain-free after multimodal analgesia at D5.

Table 1. D0 (day of the surgery) to D11 laboratory results

	D0	D1	D3	D4	D7	D8	D9	D11
Hgb (g/L)	114	107	77	77	76	78	77	77
WBC (×10^9/L)	17	13	10.2	9.4	6.9	7.4	8.5	8.2
Platelet count (×10^9/L)	250	248	167	215	350	427	520	522
Na (mmol/L)	139	136		133	140	138	137	138
K (mmol/L)	5.8	5.9	3.9	4.1	3.9	4	3.9	4.7
Creatinine (µmol/L)	117	123		237	123	120	129	87
Creatine-kinase MB (UI/L)	15351	33400	20386	14712		4363	2718	
C reactive protein (mg/L)	10.6			260	93.4		53.1	26.1
ASAT (UI/L)		754		487		166	121	
ALAT (UI/L)		251		355		220	157	
Gamma GT (UI/L)		103						

Table 2. Reference values - Compartment pressures

Normal (mmHg)	0-10	
Elevated (mmHg)	20-30	Conservative treatment
Emergency (mmHg)	> 30	Emergent fasciotomy

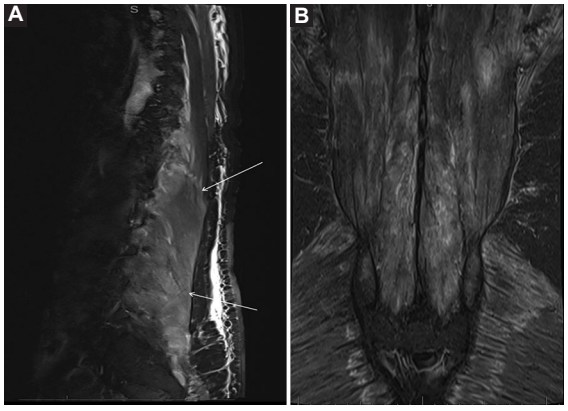

Figure 1. Thoracolumbar magnetic resonance imaging with sequence T2 STIR with fat saturation showing a marked diffuse hypersignal "edema" of paraspinal muscles. **A:** parasagittal view. **B:** anterior view; white arrows: edema of paraspinal muscles.

Discussion

CS is caused by abnormal increases in intra-compartmental pressures within a non-expandable fascial space. It was described after prolonged elevation of the lower limbs during surgical procedures in the lithotomy position and many other positions, such as the hyperextended position used during open cystectomy. The incidence of CS after major pelvic surgery in the lithotomy position has been estimated to be 1 in 3500 cases, but it may be higher in urological surgery (Simms and Terry, 2004)[1]. The incidence of cystectomy surgery in a non-lithotomy position has not, however, been documented in the literature. CS is caused by a prolonged decrease in perfusion pressure within a group of muscles as a result of an increase in compartment pressure. Reduced perfusion pressure results in tissue ischemia. Ischemia can be followed by reperfusion, causing subsequent capillary leakage and tissue edema. The result is a vicious cycle of tissue edema and further impairment of perfusion. When compartment pressure exceeds 50 mmHg for more than four hours, irreversible neuromuscular damage occurs.[2]

Risk factors for the development of CS include intraoperative hypotension, blood loss/hypovolemia, peripheral vascular disease, prolonged operation (more than four hours), muscular calves, and high body mass index (> 25 kg/m^2). Our patient had two risk factors at the time of surgery: a prolonged operation and a high body mass (33.3 kg/m^2). Anesthetists should be aware that any degree of head-down Trendelemburg tilt may increase compartment pressures. Nevertheless, at the present, no consistent data is available indicating which degree of inclination should be considered harmful or

safe. A delay in diagnosing a CS may be associated with a worse prognosis and can lead to death. CS is a rare post-operative complication and lack of staff awareness may have contributed to this delay, and all staff involved in the perioperative and post-operative care of such patients must have a low index of suspicion for the development of CS.[3]

In our case report, magnetic resonance imaging provided a definitive diagnosis only 5 days after extubation and measurement of compartment pressure due to uncontrolled pain. A previous negative CT for CS should not be considered the gold standard for diagnosis.

The patient also developed acute kidney injury (Kidney Disease: Improving Global Out-Comes II Classification) due to rhabdomyolysis. Possible post-renal acute kidney failure may also be responsible for kidney injury. A temporary nephrostomy that was difficult to flush was reported by paramedical staff. After correcting all of these factors, the patient's renal function returned to normal 10 days after being discharged from intermediate care. This patient was sent for rehabilitation and discharged days later without any lasting effects.

Conclusion

CS requires a high level of clinical suspicion and, if untreated, can result in permanent injury or death[4]. Our case is exceptional due to a position that is poorly described in the literature, and its outcome was positive. The use of hydraulic stirrups for operating table may allow for simple and minimally disruptive position changes during procedures, such as changing position during a cystectomy and then lowering the patient at the end of the procedure. Medical staff must be aware of the clinical presentation, treatment, and outcome.

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ORIGINAL ARTICLE

Introdução da cetamina oral no controlo da dor crónica oncológica refratária: a nossa experiência.

Introduction of oral ketamine in refractory chronic cancer pain management: our experience.

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Resumo

O uso off-label da cetamina com o intuito analgésico na área dor crónica é cada vez mais aceite. No entanto, em muitas instituições, representa uma estratégia reservada apenas a casos refratários. Em 2020, foi introduzido no Hospital de Braga um protocolo que visa a administração de cetamina oral no tratamento de dor crónica oncológica refratária à terapêutica com opioide em altas doses e fármacos adjuvantes. Foi realizado um estudo retrospetivo dos casos clínicos em que foi aplicado o referido protocolo, entre janeiro de 2020 e junho de 2021, com base nos registos clínicos disponíveis. O objetivo foi avaliar a eficácia e a tolerância da administração de cetamina por via oral na dor crónica oncológica refratária, tendo em conta a obtenção de controlo álgico, redução no consumo de opioide e ocorrência de eventos adversos. O protocolo foi aplicado a cinco doentes, durante intervalos de tempo compreendidos entre 18 e 81 dias. Todos os doentes apresentavam dor crónica oncológica refratária, cuja neoplasia se apresentava em estádio 4. A aplicação do protocolo de cetamina oral permitiu um controlo álgico eficaz e sustentado em 60% (3 em 5) dos doentes e uma redução de 50-75% na dose de opioide em 40% (2 em 5) dos doentes, para uma dose média efetiva de 2 mg/kg/dia (0,5-2,9 mg/kg/dia). A utilização off-label de cetamina oral revelou-se um agente seguro e eficaz na abordagem da dor crónica oncológica refratária. A sua utilização por via oral potenciou o seu uso a longo prazo, minimizando a necessidade e duração de internamento hospitalar.

Palavras-chave: *Dor crónica oncológica. Cetamina oral.*

Abstract

The off-label use of ketamine for analgesic purposes in chronic pain is increasingly accepted. However, in many institutions, it represents a strategy reserved only for refractory cases. In 2020, a protocol for the administration of oral ketamine in the treatment of chronic cancer pain refractory to high-dose opioid therapy and adjuvant drugs was introduced at Hospital de Braga. A retrospective study of clinical cases in which the aforementioned protocol was applied, between January 2020 and June 2021, based on available clinical records. The objective was to evaluate the efficacy and tolerance of oral ketamine administration in refractory chronic cancer pain, considering the achievement of pain control, reduction in opioid consumption and occurrence of adverse events. The protocol was applied to 5 patients, during 18 to 81 days. All patients had refractory chronic cancer pain, whose cancer was in Stage 4. The application of the oral ketamine protocol allowed an effective and

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sustained pain control in 60% (3 out of 5) of the patients and a 50-75% reduction in opioid dose in 40% (2 out of 5) of patients, for a mean effective dose of 2mg/kg/day (0.5-2.9mg/kg/day). In this retrospective case series, the off-label use of oral ketamine proved to be a safe and effective agent in the management of refractory chronic cancer pain. Its oral use potentiated its long-term use, minimizing the need and duration of hospital stay.

Keywords: *Chronic cancer pain. Oral ketamine.*

Introdução

A dor crónica é uma entidade complexa que apresenta desafios constantes na sua abordagem clínica. A dor crónica não controlada condiciona uma diminuição da funcionalidade e qualidade de vida dos doentes. Nestes casos, a cetamina oral tem sido usada com alguma eficácia, apesar de não existirem estudos aleatorizados a comprová-lo [1,2]. O uso *off-label* da cetamina com o intuito analgésico na área dor crónica é cada vez mais aceite, representando, contudo, uma estratégia reservada a casos refratários[3,4].

A cetamina é um anestésico geral dissociativo derivado da fenciclidina que exerce uma variedade ampla de efeitos clínicos dose-dependentes: indução/manutenção anestésica, analgesia, antidepressivo e psicomimético. O seu principal mecanismo de ação é desempenhado através do antagonismo não competitivo dos recetores inotrópicos de glutamato N-metil-D-aspartato (NMDA), através do qual desempenha ação analgésica e anestésica. No entanto, estão descritas outras vias de ação alternativas, apresentando interação com recetores dopaminérgicos, serotoninérgicos e opioides, entre outros[5].

As propriedades analgésicas da cetamina, quando administrada em doses subanestésicas, são tema de investigação há várias décadas. Os recetores NMDA, descritos como a principal via de ação, estão também envolvidos na transmissão e modulação da dor, contribuindo para a sensibilização central e desenvolvimento de dor crónica[6]. Além disso, a ação da cetamina noutros recetores como os muscarínicos, nicotínicos e opioides potencia as vias antinociceptivas endógenas, como a via inibitória descendente, conferindo-lhe propriedades analgésicas[1,4]. Os estudos existentes sugerem que a utilização de cetamina no tratamento da dor crónica se pode refletir na diminuição da avaliação da intensidade da dor e num efeito poupador de opioide[4,5,7]. No entanto, a evidência existente é ainda insuficiente, pelo que é frequentemente encarada como fármaco de terceira linha no tratamento da dor, estando reservada para doentes com níveis elevados de intensidade de dor em muitas instituições[2].

Numa perspetiva farmacocinética, a cetamina é uma molécula hidro e lipossolúvel, o que permite a sua administração por várias vias de administração (via endovenosa, oral, intranasal e sublingual, entre outras). No que concerne a via oral, quando comparada com a via endovenosa, a cetamina apresenta baixa biodisponibilidade devido ao extenso metabolismo hepático de primeira passagem de que é alvo[6]. No entanto, o seu principal metabolito, a norcetamina é uma molécula ativa e parece contribuir para o efeito analgésico e uma duração de ação mais prolongada (4 a 6 horas)[1]. Apesar de requerer doses substancialmente mais altas, a via oral tem demonstrado providenciar analgesia eficaz, possibilitando o tratamento em regime de ambulatório[5]. Não existe ainda formulação oral aprovada, mas a solução oral pode ser preparada através da diluição da solução parentérica em sumo de fruta, de forma a mascarar o sabor amargo[3].

No que concerne ao perfil de efeitos adversos, a cetamina estimula o sistema nervoso simpático, provocando elevação da pressão arterial e frequência cardíaca. Estão ainda associados ao seu uso, distúrbios cognitivos (alteração da perceção das cores, alterações da memória e atenção) e adição psicológica. A sua administração a longo prazo parece estar associada a patologia da bexiga como cistite e espessamento da parede vesical[6].

Neste artigo, apresentamos uma série de casos clínicos, referente à introdução de um protocolo de administração de cetamina oral no Hospital de Braga, destinado a doentes com dor crónica oncológica refratária.

Métodos

O estudo foi aprovado pela Comissão de Ética do Hospital de Braga a 10 de novembro de 2021 (referência n.º 155_2021). Foi realizado um estudo retrospetivo observacional entre janeiro de 2020 e junho de 2021. Foram incluídos todos os doentes com dor crónica oncológica refratária a quem foi aplicado o protocolo de administração de cetamina por via oral em vigor no Hospital de Braga. Todos os doentes foram seguidos através de consultas presenciais e/ou telefónicas e

respetivo registo em processo clínico, realizados pelos médicos da Unidade de Dor Crónica (UDC) do Hospital de Braga.

O objetivo do estudo foi avaliar a eficácia e tolerância da administração de cetamina por via oral na dor crónica oncológica refratária, tendo em conta a obtenção de controlo álgico, redução no consumo de opioide e ocorrência de eventos adversos.

Protocolo

Em janeiro de 2020, foi aprovado no Hospital de Braga o protocolo específico "Cetamina no tratamento de dor crónica refratária", indicado para o tratamento de dor crónica oncológica refratária à terapêutica com opioide em altas doses e fármacos adjuvantes.

O protocolo define o início do tratamento em regime de internamento, com perfusão endovenosa (0,05 mg/kg/h, com titulação gradual até um máximo de 0,4 mg/kg/h) ou por via subcutânea (0,1 mg/kg/h com titulação até 0,8 mg/kg/h), em simultâneo com perfusão titulada de morfina endovenosa, para um controlo álgico ótimo. A esta prescrição deve associar-se haloperidol (1 mg, 12/12 h) ou uma benzodiazepina, para redução dos efeitos psicomiméticos. Perante a previsibilidade de alta hospitalar e se for considerada benéfica a continuação do tratamento com cetamina por via oral, a transição para esta via é iniciada com uma redução de 25-50% da dose endovenosa ou subcutânea. Assim, a transição para a via oral é habitualmente iniciada com recurso a uma dose de 10-25 mg, *per os,* 6/6 h, com titulações de 5-10 mg até obtenção do efeito desejado. A aplicação do protocolo implica a monitorização diária da qualidade analgésica e efeitos laterais, feita pelos elementos da UDC durante o período de internamento do doente.

A preparação da solução oral de cetamina usada no domicílio é realizada pela farmácia hospitalar (concentração de 10 mg/ml), com estabilidade prevista de 10 dias. Para o domicílio deve ser também prescrita uma benzodiazepina pelas razões acima descritas. Inicialmente é realizado um contacto telefónico diário após a alta hospitalar para monitorização dos efeitos terapêuticos e efeitos laterais da terapêutica em curso. Alcançado o controlo satisfatório da dor, o contacto passa a ser realizado duas vezes por semana.

Estão definidas as seguintes contraindicações à aplicação do protocolo: elevação da pressão intracraniana, instabilidade tensional, hipertensão arterial, delírio, história recente de convulsões ou epilepsia não controlada e história de psicose.

Resultados

Até à data de 30 de junho de 2021, o protocolo específico "Cetamina no tratamento de dor crónica refratária" foi aplicado a cinco doentes, sendo que um deles ainda mantinha o protocolo em ambulatório. Todos os doentes, com idades compreendidas entre os 9 e os 69 anos, sofriam de dor crónica oncológica refratária, cuja neoplasia se apresentava em estádio 4. De acordo com os registos clínicos, todos os doentes apresentavam dor severa classificada entre 8-9/10, na escala numérica. As caraterísticas dos doentes incluídos estão descritas na tabela 1.

De acordo com o previsto, todos os doentes iniciaram o protocolo em regime de internamento. Apresentaram um tempo médio de internamento de 26 dias (8-51 dias). De notar que o doente 3 registou três internamentos hospitalares, totalizando 44 dias de internamento.

Os doentes iniciaram o protocolo através de perfusão de cetamina endovenosa, com doses entre os 0,05 mg/kg/h e os 0,2 mg/kg/h, a par com perfusão de morfina endovenosa (67-500 mg/dia), com posterior titulação para obtenção de controlo álgico ótimo. A transição para cetamina oral foi efetuada nos cinco doentes. Em quatro doentes (doentes 1, 2, 3 e 4), a transição visou possibilitar a continuidade do protocolo em ambulatório, tendo sido efetuada entre o 5.° e o 11.° dia de internamento (Fig. 1). Tal foi acompanhado de uma rotação do opioide endovenoso para fentanil transdérmico (75-125 mcg/h), em função do consumo total diário de morfina.

Em 60% dos doentes foi possível obter um controlo álgico descrito como "bom/satisfatório" em diário clínico, não existindo, no entanto, registo da intensidade da dor em todos os doentes. Dos quatro doentes com alta para o ambulatório, três mantiveram o controlo da dor de forma sustentada, sem necessidade de novos internamentos para controlo álgico, com recurso a uma dose efetiva média de 2 mg/kg por dia (0,5-2,9 mg/kg/dia).

Em 40% dos doentes, foi possível diminuir a dose de opioide em 50-75%. À data de admissão o doente 1 estava medicado com fentanil transdérmico 100 μg/h e teve alta medicado com 25 μg/h. Por sua vez, o doente 4 estava medicado com fentanil transdérmico 250 μg/h e teve alta medicado com 125 μg/h, sendo que posteriormente foi reduzido para 100 μg/h.

Relativamente ao doente 3, no primeiro internamento este doente teve alta contra o parecer da UDC, cotando a dor em 6/10, com recurso a 2-5 SOS de morfina diários. O doente realizou o tratamento com cetamina oral 40 mg *per* os, 6/6h (160 mg/dia), durante 24 dias em ambulatório, período durante o qual necessitou de

Tabela 1. Caraterização dos doentes incluídos

Doente	Género	Idade	Neoplasia	Estádio oncológico	SMD na admissão	Duração do protocolo	Controlo álgico
1	Masculino	69 anos	Carcinoma de células renais	4	8/10	60 dias	Bom controlo álgico
2	Feminino	9 anos	Sarcoma de Ewing	4	8/10	18 dias	Bom controlo álgico
3	Masculino	60 anos	Adenocarcinoma do pâncreas	4	9/10	81 dias	Controlo parcial/não sustentado
4	Masculino	60 anos	Colangiocarcinoma intra-hepático	4	9/10	79 dias (ainda em curso)	Bom controlo álgico
5	Feminino	50 anos	Adenocarcinoma do pulmão	4	8/10	51 dias	Controlo parcial/não sustentado

SMD: *Score* máximo de dor.

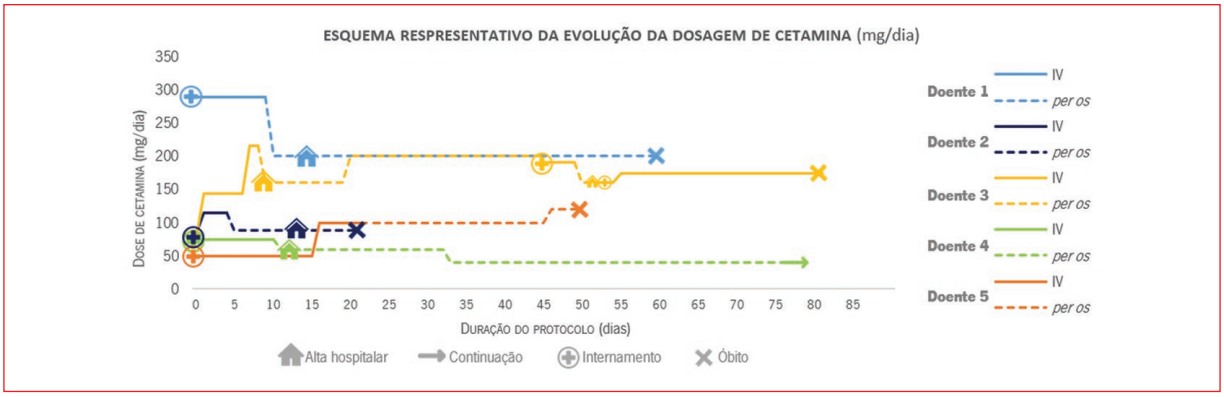

Figura 1. Esquema representativo da evolução da dosagem de cetamina.

ajustes subsequentes na medicação: subida na dose de cetamina oral no 20.° dia do protocolo, para 200 mg/dia, assim como escalada na dose de opioide (fentanil transdérmico de 100 mcg/h para 125 mcg/h associado a morfina de ação rápida 20 mg em SOS que o doente fazia de 4/4 h à data do reinternamento). Foi novamente internado no 45.° dia do protocolo por dor não controlada. Neste internamento, foi reiniciada a perfusão endovenosa de cetamina (192 mg/dia) e realizada rotação do opioide transdérmico para morfina endovenosa (130 mg/dia). A transição para cetamina oral (160 mg/dia) foi novamente executada ao 5.° dia de internamento e o doente teve alta para o domicílio ao 8.° dia, com dor controlada (cotava a dor em 2/10, com necessidade de 2 SOS de morfina/dia). Contudo, o doente retornou ao hospital no dia seguinte por dor não controlada (dor 8/10), tendo reiniciado perfusão de cetamina (174 mg/dia) e morfina endovenosa, que manteve até à data do óbito, no 81.° dia do protocolo (26.° dia de internamento).

Na doente 5, tal como protocolado, a introdução da cetamina endovenosa (50 mg/dia) ocorreu em associação com a perfusão de morfina endovenosa (500 mg/dia). A transição para cetamina oral (100 mg/dia), em associação com perfusão de morfina subcutânea (350 mg/dia), foi efetuada ao 23.º dia por dificuldade em manter acessos venosos patentes. Embora tenha sido possível obter controlo álgico em algumas fases do internamento, não se revelou um controlo álgico sustentado, o que motivou dois ajustes da dose de cetamina, conforme representado na figura 1. À data de óbito, encontrava-se medicada com cetamina oral (120 mg/dia) e morfina subcutânea (500 mg/dia).

Relativamente aos efeitos adversos, apenas o doente 4 demonstrou efeitos adversos relacionados com a estratégia adotada, referindo sonolência, o que motivou a descida da dose de fentanil transdérmico, numa primeira avaliação, e posteriormente uma descida na dose de cetamina oral de 15 mg 6/6h para 10 mg 6/6h. Não foram reportados efeitos psicomiméticos, sendo que todos os

doentes realizaram profilaxia, com recurso a um agente antipsicótico (haloperidol) ou benzodiazepínico por descrição do médico que implementou o protocolo.

Discussão

Durante muito tempo a cetamina foi usada primariamente como anestésico dissociativo e, em alguns países, como analgésico no Serviço de Urgência. Ao longo dos últimos anos, este agente tem vindo a ganhar terreno na abordagem clínica de patologias como a depressão, abuso de substâncias e a dor crónica refratária. De acordo com a experiência da nossa instituição, ainda que muito limitada, a aplicação do protocolo de cetamina oral em doentes com dor crónica oncológica refratária permitiu um controlo álgico eficaz e sustentado em 60% dos doentes e uma redução de 50-75% na dose de opioide em 40% dos doentes.

A evidência clínica existente até à data sugere que a cetamina possa desempenhar um papel benéfico na abordagem de dor crónica refratária associado a um perfil de toxicidade limitado. Todavia, de acordo com a revisão Cochrane mais recente, conduzida por Bell et al. em 2017, a evidência existente para recomendar a cetamina como terapia adjuvante na dor crónica oncológica é ainda insuficiente[2].

Num estudo retrospetivo conduzido por Marchetti et al. foi avaliada uma amostra de 55 doentes submetida a um protocolo de cetamina oral para o tratamento de dor crónica refratária (não oncológica)[4]. A aplicação do protocolo resultou numa taxa de eficácia de 44% e uma redução de 40% na intensidade da dor referida pelos doentes, para uma dose efetiva média de 2 mg/kg/dia[4]. O perfil de segurança apresentado pela cetamina oral permitiu inclusive que o protocolo praticado nesta instituição pudesse ser aplicado exclusivamente em ambulatório, sem necessidade de internamento para indução com cetamina endovenosa. Na nossa série de casos, verificámos uma taxa de eficácia superior (60%) para uma dose média efetiva de 2 mg/kg/dia, sobreponível à verificada por Marchetti et al., ainda que não comparável pelas distintas etiologias da dor.

Por sua vez, no estudo de Hardy et al., que incluiu 185 doentes com dor crónica oncológica, a cetamina demonstrou um melhor perfil analgésico em doentes com avaliação superior da intensidade de dor no início do protocolo, mas não foi clinicamente significativo[8]. Este estudo demonstrou um efeito placebo importante ao administrar cetamina subcutânea num regime de escalada terapêutica de cinco dias, associada a uma taxa de efeitos adversos significativamente acrescida[8]. No entanto, o estudo é criticado pela utilização de doses superiores de cetamina (100-500 mg/dia) às utilizadas noutros estudos, numa escalada terapêutica rápida[2]. Na série de casos agora descrita, verificámos doses diárias inferiores (40-288 mg/dia) às deste estudo, o que poderá ter contribuído para o melhor perfil de segurança verificado.

A dor crónica oncológica apresenta uma fisiopatologia complexa, envolvendo vários mecanismos de dor. O antagonismo dos recetores NMDA desempenhado pela cetamina parece favorecer a diminuição do componente neuropático associado à dor oncológica, assim como pode reduzir a tolerância à terapêutica opioide, aumentando ou restabelecendo o efeito analgésico da mesma[2,5]. De facto, em dois dos cinco doentes apresentados nesta série de casos, foi possível obter uma redução de 50-75% da terapêutica opioide, comparando a dose prévia à admissão e a dose prescrita à data da alta. Também no estudo realizado por Marchetti et al. se verificou uma redução na dose de terapêutica opioide em 62% dos doentes[4].

Além da redução do consumo de opioide, a magnitude de redução da dor é apontada como um dos principais resultados a avaliar. Nesta série de casos não nos foi possível verificar a taxa de redução na quantificação da dor, uma vez que a maioria dos registos de avaliação da dor durante a aplicação do protocolo foi qualitativa, omitindo uma avaliação quantitativa.

A utilização de cetamina oral por longos períodos aparenta ser segura e bem tolerada. Todavia, os efeitos adversos da utilização de cetamina a longo prazo são ainda pouco estudados e carecem de evidência científica sustentada[9]. Na presente série de casos, com a utilização de cetamina por períodos de 18-81 dias, apenas um doente referiu a ocorrência de efeitos adversos, relatando sonolência, que motivou inicialmente um ajuste da terapia opioide e posteriormente redução na dose de cetamina oral, com resolução do sintoma referido e manutenção do controlo álgico. Não foram reportados outros efeitos adversos, nomeadamente efeitos psicomiméticos, insuficiência renal, cistite ou hepatotoxicidade. Estes resultados diferem dos resultados apresentados por Marchetti et al. em que metade (51%) dos doentes apresentou algum efeito adverso, ainda que a sua ocorrência apenas tenha determinado a suspensão em oito doentes, de um total de 55. Verificaram ainda que a ocorrência de efeitos adversos foi menor nos

casos em que estava associada terapia opioide. A ocorrência de efeitos adversos não demonstrou correlação com nenhuma outra variável estudada[4].

Este estudo inclui uma pequena amostra de doentes, o que representa a sua grande limitação, refletindo uma amostra de doentes oncológicos em fase paliativa. Assim, no futuro, será importante sensibilizar e formar as equipas envolvidas no tratamento da patologia oncológica para a referenciação de doentes à UDC, a fim de poder beneficiar um maior número de pacientes. O facto de se tratar de um estudo retrospetivo observacional constitui outra importante limitação, na medida em que os dados registados em processo clínico não foram estandardizados. Será importante a uniformização dos registos clínicos, procurando registar um maior número de variáveis de forma consistente e contínua ao longo da aplicação do protocolo.

Conclusão

A cetamina tem vindo a ganhar relevância em várias áreas da prática clínica, e apresenta um papel promissor no tratamento da dor crónica refratária. Nesta série retrospetiva de casos, a utilização *off-label* de cetamina oral revelou-se um agente seguro e eficaz na abordagem da dor crónica oncológica refratária. A sua utilização por via oral potenciou o seu uso a longo prazo, minimizando a necessidade e duração de internamento. Foi, por isso, possível que três dos cinco doentes continuassem o tratamento da dor crónica oncológica refratária em ambulatório, sem necessidade de novos internamentos.

Declaração de contributo de autores

Todos os autores contribuíram igualmente para a realização do trabalho, revisão crítica do manuscrito, redação final e aprovação da versão a ser publicada.

Conflitos de interesse

O autor declara não ter conflitos de interesse relacionados com o presente trabalho.

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NARRATIVE REVIEW ARTICLE

Medical prescription practices and patients' adherence to chronic pain treatment with opioids in Portugal

Práticas de prescrição médica e adesão à terapêutica da dor crónica com opioides em Portugal

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Abstract

Some countries, like the United States of America, witnessed a rise in opioid prescriptions for chronic pain (CP) treatment and opioid-related deaths. This generates concerns and raises questions on whether the same can be happening in Portugal. Little research is available regarding opioid prescription practices and patients' adherence to them in the country. This narrative review aims to describe Portuguese physicians' opioid prescription practices for managing CP and patients' adherence to them. A digital literature research was carried out from September 20, 2022, to January 8, 2023, in seven electronic databases (b-on, EBSCO, PubMed, Scopus, USC Libraries, VHL, and Web of Science) and on the websites of Associação Portuguesa Para o Estudo da Dor and International Association for the Study of Pain. Twenty-six studies were included in this review (14 cross-sectional studies, eight cohort studies, one validation study, one comparative study, and two experts' opinions). Opioid consumption in Portugal is low, but an ascending tendency has been occurring and requires further investigation and monitoring. Studies show that Portuguese physicians typically resort to tramadol as a weak opioid and to fentanyl, buprenorphine, tapentadol, and morphine as strong opioids. Patients' therapeutic adherence to opioids for CP seems low and is related to cultural misconceptions among patients and physicians. Up-to-date investigation is needed as there is a lack of research in these fields of knowledge in the country.

Keywords: *Chronic pain. Opioid prescription. Therapeutic adherence. Portugal.*

Resumo

Em alguns países, como os Estados Unidos da América, verificou-se um aumento da prescrição de opioides para o tratamento da dor crónica e das mortes decorrentes da sua utilização. Este facto levanta preocupações e questões sobre se o mesmo poderá estar a acontecer em Portugal. A investigação sobre as práticas de prescrição de opioides e respetiva adesão dos doentes no país é escassa. Esta revisão narrativa pretende descrever as práticas de prescrição de opioides pelos médicos portugueses para tratar a dor crónica e a adesão dos doentes. A pesquisa bibliográfica foi realizada entre 20 de Setembro de 2022 e 8 de Janeiro de 2023 em sete bases de dados eletrónicas (b-on, EBSCO, PubMed, Scopus, USC Libraries, VHL e Web of Science) e nos websites da Associação Portuguesa Para o Estudo da Dor e da Associação Internacional para o Estudo da Dor. Vinte e seis estudos foram incluídos nesta revisão (catorze transversais, oito coortes, um estudo de validação, um estudo comparativo e dois artigos de opinião de peritos). O consumo de opioides em Portugal é baixo, mas uma tendência ascendente tem sido observada, requerendo investigação e monitorização. Os estudos mostram

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que os médicos portugueses recorrem tipicamente ao tramadol como opioide fraco e ao fentanilo, buprenorfina, tapentadol e morfina como opioides fortes. A adesão terapêutica dos doentes aos opioides para a dor crónica parece ser baixa e estar relacionada com crenças culturais entre doentes e médicos. É necessária investigação atualizada face à escassez de informação nestes domínios de conhecimento no país.

Palavras chave: *Dor crónica. Prescrição de opioides. Adesão terapêutica. Portugal.*

Introduction

According to the 11th revision of the International Classification of Diseases (ICD-11) by the World Health Organization (WHO), chronic pain (CP) is defined as pain that persists or recurs for longer than 3 months[1], a definition also used by the International Association for the Study of Pain (IASP). It affects an estimated 20% of people worldwide[2] and, according to Azevedo et al.[3], 36.7% of the Portuguese population. Pain is an unpleasant and debilitating syndrome with the potential to negatively affect physical and psychological health, as well as patients' professional, familiar, and social life, thus resulting in the loss of life quality[3,4]. However, the Pain in Europe Survey, which occurred in 2003 and included 15 European countries and Israel, depicted extensive undertreatment of pain[5,6]. Consequently, strategies for CP management are of the highest need and importance.

Pharmacotherapy is one of the possible approaches to the management of CP, namely, using opioids. In 1986, the WHO proposed an analgesic ladder to guide physicians in providing adequate pain relief for cancer pain patients[7]. Over the years, its use has been extended to chronic non-cancer pain[7]. The ladder consists of three steps: the first step corresponds to mild pain, for which non-opioid analgesics (non-steroidal anti-inflammatory drugs [NSAIDs] – or acetaminophen) should be used with or without pharmacological adjuvants (antidepressants, anticonvulsants, topical anesthetics, corticosteroids, bisphosphonates, cannabinoids, etc.); the second step refers to moderate pain, for which weak opioids (e.g., hydrocodone, codeine and tramadol) should be used with or without pharmacological adjuvants and non-opioid analgesics; the third step targets severe pain, for which strong opioids (e.g., morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, and oxymorphone) should be used with or without pharmacological adjuvants and non-opioid analgesics[7]. Despite these recommendations, opioid prescription is heterogeneous around the world.

The United States of America (USA) are well-known for facing an "opioid epidemic"[8]. Around the 1990s, it was brought up to public attention that pain was being undertreated in the country, which led to a significant rise in the rate of opioid prescriptions[9]. The first wave of the USA opioid crisis consisted mainly of addiction to prescription opioids and opioids diverted to non-medical use[9]. Later, heroin gradually took over due to its lower cost and higher availability, initiating the second wave and increasing heroin overdose deaths by 2010[10]. The third wave came around 2013/2014[10], consisting of illicit synthetic opioids, mainly illicitly manufactured fentanyl and fentanyl analogues[11]. In 2017, overdose deaths caused by prescription opioids and heroin began to decline[11]. In contrast, those associated with fentanyl (and its analogues) continued to escalate, making them a current and emergent problem in the USA and other parts of the world[11].

Europe has also been witnessing an increase in opioid prescriptions since 2009[12] (mainly tramadol, fentanyl and oxycodone)[10], yet prescription rates are still much lower than in the USA[12]. Overdose deaths are seven times more common in the USA than in Western Europe[13]. Some authors have even come up with the terms "opioid-phobia"[14] or "morphinophobia" to describe "a set of false beliefs concerning the negative effects of morphine in the management of pain, an inappropriate attitude of professionals in the pain management due to a lack of knowledge, a philosophical opposition to the prescription and the use of morphine in pain management"[15]. Nonetheless, Europe is quite heterogeneous, with countries exhibiting significantly higher opioid-related deaths than others[12]. That said, Portugal has an estimated opioid prescription rate of 4% for CP, contrary to 15-30% in other Western countries[16]. Opioid consumption in Portugal is among the lowest in Western Europe[17]. Around 2007, this was thought to be attributable to cultural, regulatory, and economic obstacles[18]. Nevertheless, around 2013, the scenario was equivalent despite the achievement of no substantial legal or financial impediments regarding opioid prescription[19].

However, CP management goes beyond opioid prescription practices. Effective opioid treatment of CP requires patients' therapeutic adherence. According to the WHO's Adherence to Long-term Therapies Project, a global initiative launched in 2001, adherence to long-term therapy can be defined as "the extent to which a

person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health-care provider"[20]. The new Taxonomy describes medication adherence as "the process by which patients take their medications as prescribed" according to three phases: initiation, implementation, and discontinuation[21]. Poor therapeutic adherence is the primary cause for suboptimal clinical benefit, namely, CP relief[20]. Many factors can influence therapeutic adherence and some authors have suggested strategies to improve it[22].

In Portugal, there is little updated information about medically prescribed opioids, including data about the prescription of the most recent formulations[23]. There is even scarcer information about patients' therapeutic adherence to CP treatment with opioids. Understanding patients' adherence and its predictors is of great clinical importance for physicians and other health-care professionals to better approach and manage CP. Thus, the main objective of this review is to describe, on the one hand, Portuguese physicians' opioid prescription practices for the management of CP and, on the other hand, patients' adherence to them. A secondary objective is to reflect on the factors influencing patients' therapeutic adherence.

Methods

This narrative review was conducted to summarize the evidence about medical opioid prescription and patients' therapeutic adherence to opioid medication for CP management in Portugal.

Setting and design

This is a narrative review of medical opioid prescription practices for the management of CP and patients' adherence to them.

Search strategy

A digital literature research was conducted from September 20, 2022, to January 8, 2023. Seven electronic databases were searched: b-on, EBSCO, PubMed, Scopus, USC Libraries, VHL, and Web of Science. A search for information was also conducted on the websites of *Associação Portuguesa para o Estudo da Dor* (*APED*) and IASP. Two queries were used, one for medical opioid prescription practices for managing CP and the other for patient adherence to that treatment (Appendix 1).

Eligibility criteria and selection process

Eligibility criteria were publications about medical opioid prescription practices for managing CP and/or patients' adherence to opioid treatment of CP, both of which about the scenario in Portugal (mainland and/or islands); publications written in English or Portuguese. There were no restrictions on the publication period. This review was conducted according to the Scale for the Assessment of Narrative Review Articles (SANRA) (Table 1 and Appendix 2).

The initial search identified 3301 records. After the remotion of duplicates (n = 137), 3164 articles were screened for abstract and 3140 were removed for not meeting eligibility criteria. A total of 24 publications underwent full-text screening, three of which were excluded for not meeting eligibility criteria. Relevant literature from the APED website was included in the study (n = 2). Relevant studies identified on PubMed during research for the introduction section were included in the study (n = 3). A total of 26 articles were selected for this review (Fig. 1).

Results and discussion

The literature that met the eligibility criteria comprises 14 cross-sectional studies, eight cohort studies (five prospective and three retrospective), one validation study, one comparative study, and two experts' opinions (Table 2). Twenty-three studies describe opioid prescription[3,4,6,16-19,23-38] (see studies 1-5, 7-21, 24-26; Table 2), three describe therapeutic adherence[15,34,39] (see studies 6, 18, 22; Table 2) and four describe factors that can influence adherence[15,22,25,39] (see studies 4, 6, 22, 23; Table 2). No study describes all three outcomes (prescription, adherence, and factors influencing adherence).

We are not aware of a study that provides a comprehensive overview of Portuguese physicians' opioid prescription practices for the management of CP and how and why patients adhere to them. This review addresses that void and highlights the lack of current evidence about opioid prescriptions in primary care and patients' therapeutic adherence behaviors.

Opioid prescription practices for CP management

Opioid consumption in Portugal is one of the lowest in Europe[22]. By the early 2000s and among nine European countries, Portugal exhibited one of the lowest consumption

Table 1. Application of the Scale for the Assessment of Narrative Review Articles (SANRA) (see Appendix 2)

1. Justification of the article's importance for the readership	This item was accomplished in Category 2 as it is illustrated in: – Page 6 (Paragraph 3): "In Portugal, there is little updated information about medically prescribed opioids, including data about the prescription of the most recent formulations[23]. There is even scarcer information about patients' therapeutic adherence to CP treatment with opioids. Understanding patients' adherence and its predictors is of great clinical importance for physicians and other health-care professionals to better approach and manage CP." – Page 8 (Paragraph 4): "We are not aware of a study that provides a comprehensive overview of Portuguese physicians' opioid prescription practices for the management of CP and how and why patients adhere to them. This review addresses that void and highlights the lack of current evidence about opioid prescriptions in primary care and patients' therapeutic adherence behaviors."
2. Statement of concrete aims or formulation of questions	This item was accomplished in Category 2 as it is illustrated in Page 6 (Paragraph 3): "Thus, the main objective of this review is to describe, on the one hand, Portuguese physicians' opioid prescription practices for the management of CP and, on the other hand, patients' adherence to them. A secondary objective is to reflect on the factors influencing patients' therapeutic adherence."
3. Description of the literature search	This item was accomplished in Category 2 as it is illustrated in: – Page 7 (Paragraph 4): "Two queries were used, one for medical opioid prescription practices for managing CP and the other for patient adherence to that treatment (Appendix 1)." – Page 7 (Paragraph 5): "Eligibility criteria were publications about medical opioid prescription practices for managing CP and/or patients' adherence to opioid treatment of CP, both of which about the scenario in Portugal (mainland and/or islands); publications written in English or Portuguese. There were no restrictions on the publication period." – Page 8 (Paragraph 3): "The literature that met the eligibility criteria comprises 14 cross-sectional studies, eight cohort studies (five prospective and three retrospective), one validation study, one comparative study, and two experts' opinions (Table 2)."
4. Referencing	This item was accomplished in Category 2 as it is exemplified in Page 4 (Paragraph 1): "According to the 11th revision of the International Classification of Diseases-11 by the World Health Organization, CP is defined as pain that persists or recurs for longer than 3 months[1], a definition also used by the International Association for the Study of Pain (IASP). It affects an estimated 20% of people worldwide[2] and, according to Azevedo *et al.*[3], 36.7% of the Portuguese population."
5. Scientific reasoning	This item was accomplished in Category 2 as it is exemplified in: – Page 10 (Paragraph 2): "A prospective cohort study developed in *Instituto Português de Oncologia do Porto Francisco Gentil*, a cancer center in the North of Portugal, verified that among eighty-four cancer pain patients with metastatic bone disease, 45 were prescribed analgesic drugs: 24 were treated with tramadol, ten with tramadol and acetaminophen, eight with morphine, three with transdermal fentanyl, and two with transdermal buprenorphine[35]." – Page 14 (Paragraph 3): "The study consisted of a prospective cohort in five pain clinics in Área Metropolitana do Porto[39]. It observed that, among the patients that responded to all assessments (n = 562), 49% still adhered to their pharmacological CP treatment at the end of the 1-year follow-up period[39]."
6. Appropriate presentation of data	This item was accomplished in Category 2 as it is exemplified in: – Page 9 (Paragraph 3): "At the time, according to a cross-sectional study, opioid analgesics were used by 4.37% (95% CI = 3.44-5.54%) of Portuguese CP patients – 4.20% were weak opioids and 0.17% were strong opioids[3]." – Page 10 (paragraph 1): "Regarding CP patients with and without cancer-related pain, the prevalence of opioid consumption was, respectively, 10.13% (95% CI = 3.78-24.46%) – weak opioids 7.44%, strong opioids 2.69% – and 4.24% (95% CI = 3.31-5.41%) – weak opioids 4.13%, strong opioids 0.10%[3]."

CI: confidence interval; CP: chronic pain.

of opioids, namely, tramadol, morphine, and fentanyl[24]. Furthermore, while most European countries registered increased opioid sales, Portugal revealed stability of all opioid purchase data[24].

Opioid prescription has suffered several changes throughout the years. By the early 2000s, Portuguese physicians had to go through numerous steps to prescribe opioids[18]. More specifically, prescriptions should be made on particular forms, in triplicate, and were of a different color; they were sometimes difficult to obtain; in private practices, physicians had to pay for the prescription forms themselves; they required the fulfillment of a substantial amount of information about the prescriber and the patient; prescriptions' expiration date was of 10 days and they could only include two boxes of each opioid[18]. In addition, opioid analgesics were 40% reimbursable, the lowest value in Europe at that time, regardless of the pain cause[18]. One can speculate that these regulatory and economic obstacles explain the low opioid prescription rates in Portugal. Later, in 2013,

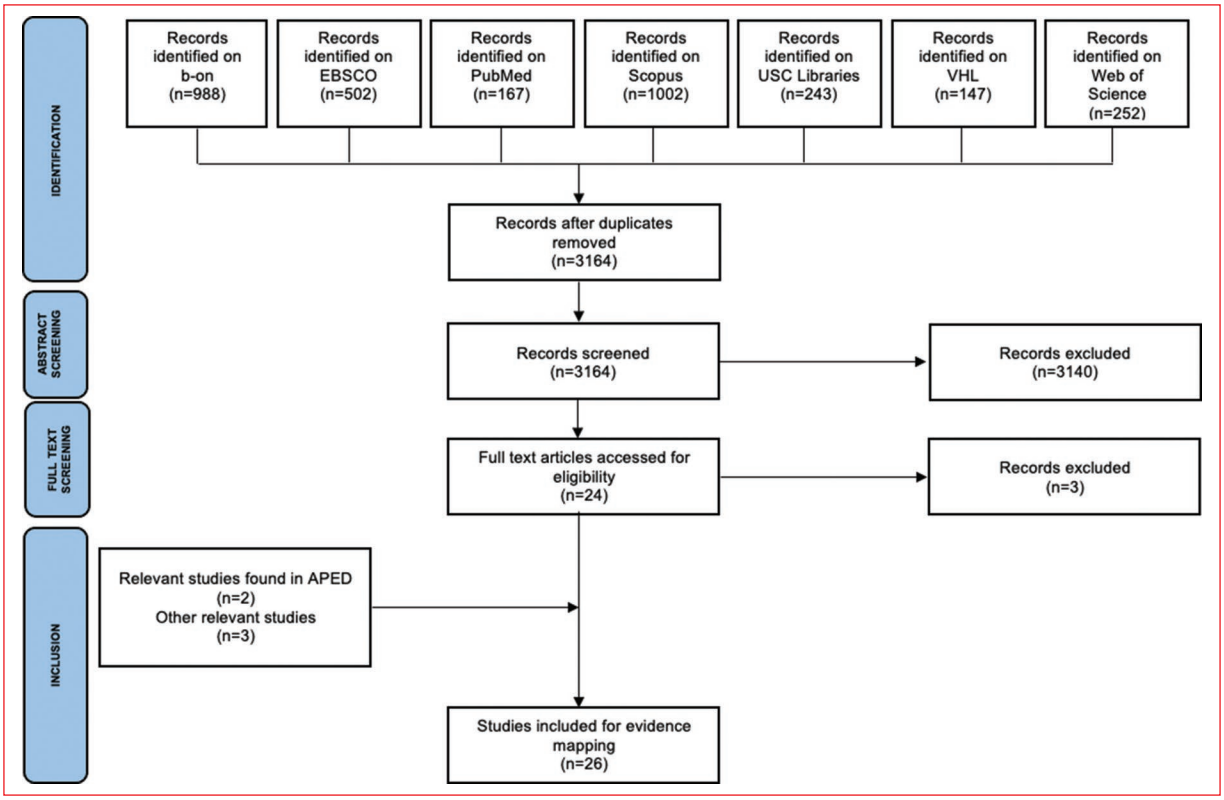

Figure 1. Flow diagram of the literature selection (adapted from the PRISMA 2020 Guideline[45]).

these barriers had already been surpassed as there was no need to fulfill particular prescription forms and the Government funded 90%-95% of the price of most opioids for cancer patients[17,19]. At the time, according to a cross-sectional study, opioid analgesics were used by 4.37% (95% confidence interval [CI] = 3.44-5.54%) of Portuguese CP patients – 4.20% were weak opioids and 0.17% were strong opioids[3]. Regarding CP patients with and without cancer-related pain, the prevalence of opioid consumption was, respectively, 10.13% (95% CI = 3.78-24.46%) – weak opioids 7.44%, strong opioids 2.69% – and 4.24% (95% CI = 3.31-5.41%) – weak opioids 4.13%, strong opioids 0.10% (3). Concerning Portuguese patients with active chronic low back pain (CLBP; n = 1487), a cross-sectional study revealed that 1.6% (95% CI = 0.9-2.2%) consumed opioids[31].

Regarding opioid types, Reis-Pina et al.[17] stated that the opioids most used in Portugal to manage CP were, respectively, fentanyl, hydromorphone, and morphine. In contrast, a prospective and cohort study of four North Portuguese multidisciplinary pain clinics found buprenorphine and tapentadol as the step three most prescribed drugs for chronic non-cancer pain[34]. A prospective and cohort study developed in *Instituto Português de Oncologia do Porto Francisco Gentil*, a cancer center in the North of Portugal, verified that among 84 cancer pain patients with metastatic bone disease, 45 were prescribed analgesic drugs: 22 were treated with tramadol, ten with tramadol and acetaminophen, eight with morphine, three with transdermal fentanyl, and two with transdermal buprenorphine[35]. According to a study of patients that visited the CP Unit of *Centro Hospitalar e Universitário de São João* (n = 98), in the North region of Portugal, tapentadol (27.6%), tramadol (26.5%), fentanyl (13.3%), and buprenorphine (10.2%) were the most used formulations[37]. Regarding these data, there seems to be a preference for prescribing tramadol as a Step 2 weak opioid. As to step three, strong opioids, there appears to be a tendency towards prescribing fentanyl, buprenorphine, tapentadol, and morphine. In other words, of the strong opioids available in Portugal, oxycodone is the only formulation which does not seem to be used regularly. These findings are in line with the increased prescription of tramadol and fentanyl in Europe[10], yet contrast with a USA cross-sectional study in which oxycodone, hydrocodone, and fentanyl were the most used formulations in health systems[40].

Table 2. Description of the twenty-six articles included in this review

	Study (year)	Study design	Objective	Prescription	Adherence	Factors that can influence adherence
1	De Conno et al.	Cross-sectional study	Evaluation of the sales trend of four opioids as an indicator of opioid consumption in nine European countries in 2001, 2002, and 2003	Portugal reported one of the lowest consumptions of morphine, fentanyl, and tramadol and showed stability of all opioid purchase data	Not mentioned	Not mentioned
2	26 experts (2006)	Experts' opinion	To identify legal, regulatory, cultural, and economic factors that prevent effective treatment of CP using opioids	In Portugal, prescription forms for strong opioids are different from those for other medicines; private doctors must pay for the forms themselves; triplicate forms must be filled in; prescription forms are of a different color; the reimbursement rate for strong opioids is 40%	Not mentioned	Not mentioned
3	Beubler et al.	Comparative study	To compare prescribing policies for opioids in Austria, Israel, and Portugal	In Portugal, opioids must be prescribed on particular forms, in triplicate; the forms have a different color from average prescriptions, can be challenging to obtain and require much information about the patient and the doctor; the prescriptions are only valid for 10 days and can include only two packs per drug; the reimbursement of opioids in Portugal is low (40%)	Not mentioned	Not mentioned
4	Carneiro et al.	Cross-sectional study	To understand health-care professionals' attitudes (physicians and nurses) in an internal medicine nursery of a Portuguese hospital	About 38% of the respondents did not consider major opioids adequate for the treatment of moderate-intensity pain	Not mentioned	The practice of a patient-centered medicine, rather than centered on the physician, brings several advantages, namely, a greater adherence to treatment
5	Tiago et al.	Cross-sectional study	To analyze general practitioners' attitudes toward the prescription of strong opioids to treat chronic non-oncologic pain	Two-thirds (66.9%) of the respondents (n = 154) classified their attitude as favorable toward the prescription of strong opioids; Abusive behaviors were considered probable for 43.2% of physicians, whereas 39.2% of them considered addictive behaviors probable	Not mentioned	Not mentioned

(Continues)

Table 2. Description of the twenty-six articles included in this review *(continued)*

	Study (year)	Study design	Objective	Prescription	Adherence	Factors that can influence adherence
6	Verloo et al.	Cross-sectional study	To compare the use of morphine as perceived by the general population (GP) and healthcare professionals (HP; physicians and nurses) in the region of Beira Interior	Not mentioned	Men are less prone to use morphine as an analgesic than women; The older the respondents, the more false beliefs exist about morphine use; Morphinophobia was highest among little-educated older men living in rural areas	The reasons for not using morphine are: for GP (n = 194), its use means advanced disease (56.0%), risk of addiction (50.0%) and legal requirements (49.7%); for HP (n = 412) it means legal risks (56.3%) and adverse side effects such as somnolence-sedation (30.5%)
7	Figueiredo et al.	Cross-sectional study	To record the analgesic prescription performed by Portuguese rheumatologists	The prescription of acetaminophen and tramadol had a prevalence of 23.4% and 8.5%, respectively (n = 94)	Not mentioned	Not mentioned
8	Johnson et al.	Cross-sectional study	To assess the challenges of chronic non-malignant pain (CNMP) in primary care in Europe	Of the patients with CNMP seen by the physicians (n = 1309), 40% were managed without opioids, 40% used weak opioids only, 11% used strong opioids only, and 9% used both strong and weak opioids	Not mentioned	Not mentioned
9	Azevedo et al.	Cross-sectional study	To describe the prevalence and factors associated with opioid use in subjects with CP in Portugal	The prevalence of opioid use by subjects with CP was 4.37%; in subjects presenting CP with and without cancer, it was 10.13% and 4.24%, respectively	Not mentioned	Not mentioned
10	Gonçalves et al.	Cross-sectional study	To study the prevalence, intensity and treatment of pain in Portuguese palliative care teams	164 patients were included in the study; tramadol was the only opioid for mild-to-moderate pain used in 15% of the patients; opioids most used for moderate-to-intense pain were morphine (45%), fentanyl (20%), and buprenorphine (17%); oxycodone is not available in Portugal; methadone is only licensed for drug addiction treatment and is available for pain relief in only a few hospitals	Not mentioned	Not mentioned

(Continues)

Table 2. Description of the twenty-six articles included in this review *(continued)*

	Study (year)	Study design	Objective	Prescription	Adherence	Factors that can influence adherence
11	Pina et al.	Cross-sectional study	To describe the characteristics of cancer pain and determine the correlates and predictors of initial pain intensity when patients were referred to a cancer pain clinic in Portugal	The initial median morphine equivalent daily dose was 30 mg, which is very low and suggestive of opioid underuse	Not mentioned	Not mentioned
12	Meireles et al.	Cross-sectional study	To characterize the treatment of CP in primary care, assess opioid prescription and determine the reasons for non-prescription	65 questionnaires were obtained; the most used drug classes are weak opioids (93.8%), simple analgesics (76.9%), and NSAIDs (75.4%); tapentadol and fentanyl were the most prescribed strong opioids; 75.4% of the respondents frequently deal with CP patients but only 26.1% always/ almost always prescribe strong opioids, while 50.8% reported prescribing them sometimes	Not mentioned	Not mentioned
13	Gouveia et al.	Cross-sectional study	To characterize the intake profile of pain-relief drugs in the adult Portuguese population with active CLBP	Among the population with active CLBP (n = 1487), the prevalence of opioid use was 1.6%; most subjects with severe pain were in the first step of the WHO analgesic ladder	Not mentioned	Not mentioned
14	Reis-Pina et al.	Cross-sectional study	To determine the adequacy of cancer-related pain management in a specialized Lisbon pain clinic of the Portuguese Cancer Institute	The study had 371 participants; although 20.8% of the patients rated their pain as severe, only 11.7% were prescribed a strong opioid; for analgesia, no opioid was prescribed for 11.3% of the patients	Not mentioned	Not mentioned
15	Reis-Pina et al.	Experts' opinion	Not mentioned	In Portugal, not considering methadone, use was 84.27 morphine equivalents (ME): morphine (4.46 ME), oxycodone (1.06 ME), fentanyl (70.94 ME), hydromorphone (7.26 ME) and pethidine (0.55 ME); in Portugal, most of the methadone is used for medication-assisted treatment of opioid dependence syndrome	Not mentioned	Not mentioned

(Continues)

Table 2. Description of the twenty-six articles included in this review *(continued)*

	Study (year)	Study design	Objective	Prescription	Adherence	Factors that can influence adherence
16	Reis-Pina et al.	Prospective and cohort study	To determine, among other aspects, changes in the level of opioid consumption between baseline and the time of achieving stable pain control in a Portuguese cohort of patients with cancer pain	There was a doubling in the median morphine equivalent daily dose to 60 mg	Not mentioned	Not mentioned
17	Veiga et al.	Prospective and cohort study	To describe the trends and patterns of opioid therapy over 2 years of follow-up in a cohort of chronic non-cancer pain patients	The cohort comprised 674 patients; opioid prescriptions at baseline had a prevalence of 59.6%; At 24 months, opioid prescription prevalence was 74.3%; buprenorphine and tapentadol were the most prevalent strong opioids prescribed	Most opioid users (71%) maintained their prescription during the 2-year follow-up; Regarding medical opioid prescription, opioid discontinuation was very low (1%)	Not mentioned
18	Veiga et al.	Prospective and cohort study	To assess long-term opioid effectiveness in chronic non-cancer pain patients	The cohort consisted of 674 patients; the rate of prescription opioid use was 59.7% at baseline and increased to 70.3% over 2 years; Buprenorphine and tapentadol were the most prescribed strong opioids	Not mentioned	Not mentioned
19	Vieira et al.	Prospective and cohort study	To characterize pain and survival in a cohort of patients with cancer and bone metastasis who were treated with intravenous bisphosphonates	Among patients with severe pain (n = 29), 17.2% were treated with strong opioids; In a sample of n = 84, tramadol was used to treat 22 patients, ten patients were treated with tramadol with acetaminophen, eight patients were treated by morphine sustained release and five with a transdermal patch	Not mentioned	Not mentioned
20	Ferraz Gonçalves et al.	Retrospective and cohort study	To review the use of alfentanil in palliative care	Opioids most used before alfentanil were morphine and transdermal fentanyl; The rescue opioids were morphine in 66% of the cases, alfentanil in 20% and fentanyl in 4%	Not mentioned	Not mentioned

(Continues)

Table 2. Description of the twenty-six articles included in this review *(continued)*

	Study (year)	Study design	Objective	Prescription	Adherence	Factors that can influence adherence
21	Mendes-Morais et al.	Validation study	To translate, adapt and validate the COMM questionnaire to be used in CP patients in the Portuguese population	The most used opioids among the patients (n = 98) were tapentadol (27.6%), tramadol (26.5%), fentanyl (13.3%) and buprenorphine (10.2%)	Not mentioned	Not mentioned
22	Sampaio et al.	Prospective and cohort study	Understanding and describing non-adherence from the perspective of CP patients during a 1-year follow-up study	Not mentioned	Of the 562 patients who responded to all assessments during follow-up, 49% were adherent after 1 year of general CP treatment (not specifically with opioids)	Regarding opioids, the reasons for patient non-adherence were perceived side effects and delayed start
23	Antunes et al.	Cross-sectional study	To assess and characterize CP in patients who visit Portuguese primary care units	Not mentioned	Not mentioned	Psychological support could help manage CP patients' expectations, increasing treatment adherence; Introducing support for non-pharmacological strategies could improve patient functionality and treatment satisfaction; Effective communication will improve physicians' ability to identify a suitable treatment regimen to which the patients will adhere
24	Caldeira et al.	Retrospective and cohort study	Characterize the prescribing patterns of opioids in the Health Administrative Region of Lisbon and Tagus Valley	The prescription of opioid drugs has increased by approximately 50% over 4 years in ambulatory care; Tramadol, buprenorphine and tapentadol were the top three opioid drugs used in 2017; The opioids with the most significant absolute increase in this period were tramadol, tapentadol, and codeine	Not mentioned	Not mentioned

(Continues)

Table 2. Description of the twenty-six articles included in this review *(continued)*

	Study (year)	Study design	Objective	Prescription	Adherence	Factors that can influence adherence
25	Paulino et al.	Cross-sectional study	To establish Portuguese critical care practices regarding analgesia, sedation and delirium	Survey (n = 117): Opioids were the most used analgesics (94%) Point prevalence study (n = 192): Acetaminophen was the first option, followed by opioids – fentanyl (21.3%), morphine (9.2%), tramadol (7.9%), and remifentanil (4.2%)	Not mentioned	Not mentioned
26	Peralta et al.	Retrospective and cohort study	To evaluate the prescribing pattern in a Portuguese palliative care unit at two different time points: on admission and the day of death	From a sample of 115 patients, opioids were the most prescribed drugs both at admission (73.0%) and on the day of death (82.6%), with a statistically significant increase (p = 0.013; significance level of 5%)	Not mentioned	Not mentioned

NSAIDs: nonsteroidal anti-inflammatory drugs; CP: chronic pain; CLBP: chronic low back pain.

Looking into the context of intensive care units (ICUs), in a cross-sectional study, Portuguese ICU physicians (n = 117) fulfilled an online survey between September 2016 and April 2017[38]. They reported opioids (94%) and acetaminophen (77%) as the most prescribed drugs for pain relief in their clinical practice[38]. Yet, a point prevalence study (n = 192) carried out in seventeen adult Portuguese ICUs in 2018 showed a reversal of this pattern, with acetaminophen being the first option (34.6%), followed by opioids (fentanyl 21.3%; morphine 9.2%; tramadol 7.9%; and remifentanil 4.2%)[38].

Focusing on palliative care units (PCUs), a cross-sectional study of ten Portuguese palliative care teams and 164 patients showed that non-opioid analgesics were used by 49% of the patients (acetaminophen 37%; NSAIDs 12%); weak opioids were used by 15% of the patients, with tramadol being the only one used; strong opioids were used by 87% of the patients (morphine 45%; fentanyl 20%; buprenorphine 19%; hydromorphone 1%; alfentanil 1%; and methadone 1%)[19]. Similarly, a retrospective and cohort study (n = 115) between August 2017 and December 2018 in a PCU located in the North of Portugal, Braga, observed that opioids were the most prescribed drugs both at admission (73.0%) and on the day of death (82.6%)[4]. Looking at ICUs and PCUs alone, there seems to be a higher prevalence of opioid prescriptions, which is unsurprising as these physicians deal with moderate and severe pain daily. It is possible to observe that tramadol remains the preferred step two weak opioid, while morphine and fentanyl are the step three strong opioids of choice. It should be noted that tramadol is the only weak opioid sold separately from other opioid formulations in Portugal, which can explain these findings regarding step two opioid prescription[41].

Following the overview of opioid prescription in specialized pain centers, it is relevant to understand the opioid prescription scenario in general practice and ambulatory care. A cross-sectional study developed in Bragança, a district in the North of Portugal, observed that, among 65 general practitioners (specialists and residents), the pharmacological classes most prescribed for CP management were weak opioids (93.8%), acetaminophen (76.9%), and NSAIDs (75.4%)[30]. Furthermore, strong opioids were reported to be prescribed by 50.8% of the respondents[30]. Tapentadol and fentanyl were the most prescribed strong opioids[30]. Other findings were obtained in a retrospective and cohort study of ambulatory patients in the region of Lisboa e Vale do Tejo, where tramadol, buprenorphine, and tapentadol were the most used opioids[23]. It is important to note that, among our results, only one study targets general practitioners' opioid prescription practices[30]. This prevents us from drawing robust conclusions and does not allow us to understand primary care opioid prescription practices nationally. As primary care is the main gateway to

healthcare, comprehending opioid prescription practices in this context is crucial to better understanding the Portuguese reality.

The analysis of opioid prescription patterns raised concerns about the undertreatment of CP in Portugal[30,31,35]. Among the 65 general practitioners of the previously mentioned study in Bragança, 75.4% reported dealing frequently with uncontrolled CP, yet 26.1% stated prescribing strong opioids "always" or "almost always" and 50.8% reported prescribing them "sometimes"[30]. Furthermore, 23.1% of the respondents "rarely" or "never" prescribe strong opioids[30]. In the study of Portuguese patients with active CLBP, 42.2% reported severe pain and 47.0% moderate pain, of which 17.2% and 2.0% were taking pain-relief drugs, respectively[31]. In a prospective and cohort study, other authors observed that 5 (17.2%) out of 29 cancer patients that reported severe pain were receiving treatment with strong opioids[35]. Hence, there seems to be some reluctance in prescribing opioids for cancer and non-cancer pain. On the other hand, there appears to be an under-application of the WHO analgesic ladder. The study on active CLBP mentioned above observed that most individuals under pain-relief drugs were on the first step of the ladder, regardless of pain intensity[31]. We believe that this needs to be acknowledged to reduce CP's impact on patients' lives.

Concerns were also raised over a possible increasing trend in opioid prescriptions. A prospective and cohort study (n = 674) referred previously, published in 2019, observed an opioid prescription increase over the 2-year follow-up period[34]. Opioid prescription raised from 59.6% (strong opioids 13.0%) at baseline to 74.0% at the end of follow-up (strong opioids 31.0%)[34]. Hence, there is a chance of a growing opioid prescription trend for CP management in Portugal. Nevertheless, other explanations are plausible, such as the fact that participants were recruited at specialized centers for pain management[34]. Thus, understanding if this growth occurs outside of specialized pain centers is highly relevant. According to a previously mentioned retrospective and cohort study of ambulatory patients in the region of Lisboa e Vale do Tejo, opioid prescriptions increased by 50% between 2013 and 2017[23]. The authors suggested that health conditions potentially causative of pain had not risen in the same magnitude and alerted for a need to carefully monitor this tendency and reflect on whether it can have a national dimension[23]. Our results did not find a study which described the evolution of opioid prescription rates in primary care. This should be further investigated to comprehend better whether Portugal is on the verge of an "opioid epidemic" like the USA[8].

Therapeutic adherence to opioids for CP management

Therapeutic adherence intimately relates to a patient's active behavior toward managing his illness[39]. This concept can be particularly challenging when applied to patients with chronic conditions, where CP is included in the study, since it implies maintenance over a potentially very long and continuous period. Improving adherence is possibly the best investment to address chronic conditions effectively[20]. Furthermore, CP management often involves a combination of therapeutic interventions, where pharmacological treatment is frequently a central pillar[42].

In Portugal, as in Europe and the rest of the world, there is a lack of research on adherence to pharmacotherapy for CP. Notwithstanding, this is a crucial scope of action since some interventions, such as regular follow-ups and monitoring for adherence, proved to enhance medication-taking behaviors in chronic opioid therapy[43]. According to a previously referred prospective and cohort study, most opioid users (71%) maintained their prescription at the end of the 2-year follow-up period, despite non-significant improvement in clinical outcomes[34]. The authors also observed that opioid discontinuation was as low as 1%[34]. It is essential to highlight that this study measured adherence through the prescriber's scope and, thus, did not evaluate patients' therapeutic adherence. Our results found only one study which conducted a therapeutic adherence analysis[39]. The study consisted of a prospective cohort in five pain clinics in Área Metropolitana do Porto[39]. It observed that, among the patients that responded to all assessments (n = 562), 49% still adhered to their pharmacological CP treatment at the end of the 1-year follow-up period[39]. The study found a non-adherence rate of almost 37% on day 7, which rose to 47% in the 6th month and 51% in the 12th month[39]. Nonetheless, the study did not detail the non-adherence rate for opioid medication. However, the authors observed that the reasons for non-adherence to opioids perceived by CP patients were side effects and delayed start[39]. Characterizing the non-adherence rate to prescribed opioids is relevant in further investigations since it will provide a comparison point for the future and allow the evaluation and monitoring of potential implemented strategies to improve therapeutic adherence. Moreover, further research is needed to describe whether Portugal implements such procedures.

Factors that can influence therapeutic adherence

Understanding the motivations for non-adherent behaviors among CP patients undergoing opioid treatment is of substantial relevance so that they can be addressed. In general, side effects, long therapy durations, frequent dosing and complex regimen (e.g., multiple drugs and schedules) are associated with poor patient adherence[20]. Apart from these factors, a reflection on whether patients' and physicians' beliefs toward opioid therapy for CP influence therapeutic adherence is appropriate. A cross-sectional study compared the perception of the general population (n = 194) and health-care professionals (n = 412) of Beira Interior, North-eastern Portugal, toward the use of morphine[15]. For the general population, the word "morphine" first stands for "drugs", while for health-care professionals it first stands for "analgesic"[15]. The general population who do not use morphine believe that its use means advanced disease (56.1%), risk of addiction (50.0%), and legal requirements (49.7%)[15]. As for health-care professionals, the reasons for not using morphine were legal risks (56.3%) and adverse side effects such as somnolence or sedation (30.5%)[15]. Nonetheless, it is essential to emphasize that these findings cannot be generalized for other opioids. Other authors stated that patients and some physicians believe opioids should only be used in desperate cases, namely, close to death[18]. The authors attributed physicians' concerns to fear of addiction and respiratory depression and highlighted that cultural changes take a long time and effort to be accomplished[18]. False beliefs can be dangerous and prevent physicians from prescribing opioids and patients from adhering to them, which may result in improper management of CP. Portuguese final-year medical students and residents considered education on CP insufficient, namely, regarding opioid prescription[44]. Therefore, there seems to be a need for information campaigns targeting the general population[15] and to reinforce the pre-graduate medical curriculum[44] on CP management with opioids to enhance therapeutic adherence.

There is a study in which strategies to improve CP patients' therapeutic adherence were suggested by the authors Vrijens et al.[22]. They raised the possibility that introducing psychological support would help manage patients' expectations and, thus, promote adherent behaviours[22]. Moreover, reinforcing non-pharmacological approaches could improve functionality and overall treatment satisfaction[22] and further research is relevant to understand whether this can decrease the susceptibility of non-adherent behaviors. In addition, they stressed the value of effective patient-physician communication so that physicians can not only identify patients suffering from CP, which can be challenging due to its subjective nature, but also so that they can accurately identify the treatment regimen to which each specific patient will most likely adhere[22].

Limitations

This review was conducted with a systematic approach, followed a pre-defined methodology and attempted to obtain all relevant studies on opioid prescription and therapeutic adherence in Portugal. Notwithstanding, it must be interpreted according to its limitations. First, there is a lack of research on opioid prescriptions for CP management in Portugal. The scarcity is even more significant regarding patients' therapeutic adherence, making it difficult to draw robust conclusions. Second, the inclusion criteria for this review did not address study type or validity. Therefore, there is a high potential for bias. Third, several studies in this review lack confidence intervals accompanying the respective effect sizes.

Conclusion

Opioid consumption in Portugal remains low compared to other countries worldwide, but an ascending tendency has slowly been occurring over the years and requires further investigation and monitoring. Portuguese physicians' opioid prescription practices for CP are heterogeneous. Still, they tend to resort to tramadol as a Step 2 weak opioid. Regarding Step 3 strong opioids, fentanyl, buprenorphine, tapentadol, and morphine are the most used formulations, raising the possibility of oxycodone being the least used formulation of the strong opioids available in Portugal. However, current data are needed. As to therapeutic adherence to opioids, there is a lack of research in the field and most of the existing records are outdated. However, it seems low and related to cultural misconceptions that have persisted throughout the years among patients and physicians. Finally, it is essential to stress Portugal's need for better training of medical students and physicians on the adequate and safe management of pain and the use of opioids. It is also relevant that more up-to-date investigation is conducted in both these fields of knowledge.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflicts of interest

The authors declare no conflicts of interest.

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APPENDICES

Appendix 1. Queries

b-on

- AB (adherence OR compliance OR use OR usage OR discontinuation) AND AB pain AND AB (opioid OR opiate) AND (Portugal OR Portuguese)
- AB (prescription OR prescribing OR prescribe OR use OR usage OR using OR manage OR managing OR management) AND AB pain AND AB (opioid OR opiate) AND (Portugal OR Portuguese)

EBSCO

- AND adherence OR compliance OR use OR usage OR discontinuation Abstract AND pain Abstract AND opioid OR opiate Abstract AND Portugal OR Portuguese AllFields
- AND prescription OR prescribing OR prescribe OR use OR usage OR using OR manage OR managing OR management Abstract AND pain Abstract AND opioid OR opiate Abstract AND Portugal OR Portuguese AllFields

PubMed

- (((adherence[Title/Abstract] OR compliance[Title/Abstract] OR use[Title/Abstract] OR usage[Title/Abstract] OR discontinuation[Title/Abstract]) AND (pain[Title/Abstract])) AND (opioid[Title/Abstract] OR opiate[Title/Abstract])) AND (Portugal OR Portuguese) AND (English[Filter] OR Portuguese[Filter])
- (((prescription[Title/Abstract] OR prescribing[Title/Abstract] OR prescribe[Title/Abstract] OR use[Title/Abstract] OR usage[Title/Abstract] OR using[Title/Abstract] OR manage[Title/Abstract] OR managing[Title/Abstract] OR management[Title/Abstract]) AND (pain[Title/Abstract])) AND (opioid[Title/Abstract] OR opiate[Title/Abstract])) AND (Portugal OR Portuguese) AND (English[Filter] OR Portuguese[Filter])

Scopus

- (TITLE-ABS-KEY(adherence OR compliance OR use OR usage OR discontinuation) AND TITLE-ABS-KEY(pain) AND TITLE-ABS-KEY(opioid OR opiate) AND ALL(Portugal OR Portuguese)) AND (LIMIT-TO (LANGUAGE,"English") OR LIMIT-TO (LANGUAGE, "Portuguese"))
- (TITLE-ABS-KEY(prescription OR prescribing OR prescribe OR use OR usage OR using OR manage OR managing OR management) AND TITLE-ABS-KEY(pain) AND TITLE-ABS-KEY(opioid OR opiate) AND ALL(Portugal OR Portuguese)) AND (LIMIT-TO (LANGUAGE,"English") OR LIMIT-TO (LANGUAGE, "Portuguese"))

USC Libraries

- Subject contains adherence OR compliance OR use OR usage OR discontinuation AND Subject contains pain AND Subject contains opioid OR opiate AND Any field contains Portugal OR Portuguese
- Subject contains prescription OR prescribing OR prescribe OR use OR usage OR using OR manage OR managing OR management AND Subject contains pain AND Subject contains opioid OR opiate AND Any field contains Portugal OR Portuguese

VHL

- (adherence OR compliance OR use OR usage OR discontinuation) AND (pain) AND (opioid OR opiate) AND (af:(Portugal OR Portuguese)) AND (la:("en" OR "pt"))
- (prescription OR prescribing OR prescribe OR use OR usage OR using OR manage OR managing OR management) AND (pain) AND (opioid OR opiate) AND (af:(Portugal OR Portuguese)) AND (la:("en" OR "pt"))

Web of Science

- (((TS=(adherence OR compliance OR use OR usage OR discontinuation)) AND TS=(pain)) AND TS=(opioid OR opiate)) AND ALL=(Portugal OR Portuguese) and English or Portuguese (Languages)
- (((TS=(prescription OR prescribing OR prescribe OR use OR usage OR using OR manage OR managing OR management)) AND TS=(pain)) AND TS=(opioid OR opiate)) AND ALL=(Portugal OR Portuguese) and English or Portuguese (Languages)

Appendix 2. Reporting guidelines

Scale for the Assessment of Narrative Review Articles – SANRA

Please rate the quality of the narrative review article in question, using categories 0–2 on the following scale. For each aspect of quality, please choose the option which best fits your evaluation, using categories 0 and 2 freely to imply general low and high quality. These are not intended to imply the worst or best imaginable quality.

1) Justification of the article's importance for the readership

The importance is not justified. — 0
The importance is alluded to, but not explicitly justified. — 1
The importance is explicitly justified. — 2

2) Statement of concrete aims or formulation of questions

No aims or questions are formulated. — 0
Aims are formulated generally but not concretely or in terms of clear questions. — 1
One or more concrete aims or questions are formulated. — 2

3) Description of the literature search

The search strategy is not presented. — 0
The literature search is described briefly. — 1
The literature search is described in detail, including search terms and inclusion criteria. — 2

4) Referencing

Key statements are not supported by references. — 0
The referencing of key statements is inconsistent. — 1
Key statements are supported by references. — 2

5) Scientific reasoning

(e.g., incorporation of appropriate evidence, such as RCTs in clinical medicine)

The article's point is not based on appropriate arguments. — 0
Appropriate evidence is introduced selectively. — 1
Appropriate evidence is generally present. — 2

6) Appropriate presentation of data

(e.g., absolute vs relative risk; effect sizes without confidence intervals)

Data are presented inadequately. — 0
Data are often not presented in the most appropriate way. — 1
Relevant outcome data are generally presented appropriately. — 2

Sumscore

SANRA - Scale

SANRA – explanations and instructions

This scale is intended to help editors assess the quality of a narrative review article based on formal criteria accessible to the reader. It cannot cover other elements of editorial decision making such as degree of originality, topicality, conflicts of interest or the plausibility, correctness or completeness of the content itself. SANRA is an instrument for editors, authors, and reviewers evaluating individual manuscripts. It may also help editors to document average manuscript quality within their journal and researchers to document the manuscript quality, for example in peer review research. Using only three scoring options, 0, 1 and 2, SANRA is intended to provide a swift and pragmatic sum score for quality, for everyday use with real manuscripts, in a field where established quality standards have previously been lacking. It is not designed as an exact measurement of the quality of all theoretically possible manuscripts. For this reason, the extreme values (0 and 2) should be used relatively freely and not reserved only for perfect or hopeless articles.

We recommend that users test-rate a few manuscripts to familiarize themselves with the scale, before using it on the intended group of manuscripts. Ratings should assess the totality of a manuscript, including the abstract. The following comments clarify how each question is designed to be used.

Item 1 – Justification of the article's importance for the readership

Justification of importance for the readership must be seen in the context of each journal's readership.
Consider how well the manuscript outlines the clinical problem and highlights unanswered questions or evidence gaps – thoroughly (2), superficially (1), or not at all (0).

Item 2 – Statement of concrete/specific aims or formulation of questions

A good paper will propose one or more specific aims or questions which will be dealt with or topics which will be reviewed. Please rate whether this has been done thoroughly and clearly (2), vaguely or unclearly (1), or not at all (0).

Item 3 – Description of the literature search

A convincing narrative review will be transparent about the sources of information on which the text is based. Please rate the degree to which you think this has been achieved. To achieve a rating of 2, it is not necessary to describe the literature search in as much detail as for a systematic review (searching multiple databases, including exact descriptions of search history, flowcharts, etc.), but it is necessary to specify search terms, and the types of literature included. A manuscript which only refers briefly to its literature search would score 1, while one not mentioning its methods would score 0.

Item 4 – Referencing

No manuscript references all statements. However, those that are essential for the arguments of the manuscript – "key statements" – should be backed by references in all or almost all cases. Exceptions could reasonably be made for rating purposes where a key statement has uncontroversial face-validity, such as "Diabetes is among the commonest causes of chronic morbidity worldwide." Please rate the completeness of referencing: for most or all relevant key statements (2), inconsistently (1), sporadically (0).

Item 5 – Scientific reasoning

The item describes the quality of the scientific point made. A convincing narrative review presents evidence for key arguments. It should mention study design (randomized controlled trial, qualitative study, etc), and where available, levels of evidence. Please rate whether you feel this has been done thoroughly (2), superficially (1), or hardly at all (0). Unlike item 6, which is concerned with the selection and presentation of concrete outcome data, this item relates to the use of evidence and of types of evidence in the manuscript's arguments.

Item 6 – Appropriate presentation of data:

This item describes the correct presentation of data central to the article's argument. Which data are considered relevant varies from field to field. In some areas relevant data would be absolute rather than relative risks or clinical versus surrogate or intermediate endpoints. These outcomes must be presented correctly. For example, it is appropriate that effect sizes are accompanied by confidence intervals. Please rate how far the paper achieves this – thoroughgoingly (2), partially (1), or hardly at all (0). Unlike item 5, which relates to the use of evidence and of types of evidence in the manuscript's arguments, this item is concerned with the selection and presentation of concrete outcome data.

SANRA—explanations and instructions document