PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
MESTRADO EM CIÊNCIAS DA SAÚDE

MARIA CAROLINA RODRIGUES SALINI

PREVALÊNCIA DO USO E PRESCRIÇÃO DE ANALGÉSICOS OPIOIDES PARA IDOSOS COM DOR CRÔNICA NÃO ONCOLÓGICA: UMA REVISÃO SISTEMÁTICA COM META-ANÁLISE

Presidente Prudente, SP
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Prof. Dr. Crystian Bitencourt Soares de Oliveira

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Aos vinte e seis dias do mês de março do ano de dois mil e vinte e cinco, às vinte horas, o(a) Prof(a). Dr(a). Crystian Bitencourt Soares de Oliveira, orientador(a) do(a) mestrando(a) **MARIA CAROLINA RODRIGUES SALINI**, fez a abertura da sessão de arguição da Defesa Pública de Dissertação de Mestrado do Programa de Pós-Graduação em Ciências da Saúde - Área de Concentração: Ciências da Saúde, por sistema on-line. Na condição de Presidente da Banca Examinadora, procedeu a chamada dos membros indicados e aprovados pelo Colegiado do Programa de Pós-Graduação em Ciências da Saúde, para compor a mesa, com os seguintes doutores: Francis Lopes Pacagnelli – Unoeste/Universidade do Oeste Paulista e Gustavo Carvalho Machado - The University of Sydney. Iniciados os trabalhos, a Presidência declarou para o conhecimento dos membros da Banca e do(a) Candidato(a), as normas que regem a defesa pública e definiu a ordem a ser seguida pelos examinadores para a arguição. A seguir o(a) candidato(a) passou a apresentação de sua dissertação intitulada: **"PREVALÊNCIA DO USO E PRESCRIÇÃO DE ANALGÉSICOS OPIOIDES PARA IDOSOS COM DOR CRÔNICA NÃO ONCOLÓGICA: UMA REVISÃO SISTEMÁTICA COM META-ANÁLISE"**. Encerrada a defesa, procedeu-se ao julgamento, cujo resultado foi:

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DEDICATÓRIA

A minha mãe, Luciane, cuja presença, mesmo na ausência, continua a iluminar meu caminho. Seu amor, força e ensinamentos foram e sempre serão a base de minhas conquistas. Embora não tenha podido compartilhar comigo este momento, sei que cada palavra escrita aqui carrega um pouco do que aprendi com ela. Seu exemplo de determinação e humildade segue vivo em mim, e este trabalho é, em parte, fruto do seu legado. Com eterno amor e saudade.

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Aos colaboradores internos: Rubens V. C. Vidal e Guilherme H. D. Grande, da Faculdade de Medicina da Universidade do Oeste Paulista. E, aos colaboradores externos: Stephanie Mathieson, Gustavo C. Machado, e, Christopher G. Maher, da Universidade de Sydney, Austrália.

“Conheça todas as teorias, domine
todas as técnicas, mas, ao tocar uma alma humana,
seja apenas outra alma humana”.
(Carl Jung)

RESUMO

Prevalência do uso e prescrição de analgésicos opioides para idosos com dor crônica não oncológica: uma revisão sistemática com meta-análise

Introdução: A dor crônica não oncológica é um problema comum entre idosos. Embora os opioides sejam comumente prescritos para tratar dor crônica não oncológica, esse medicamento fornece apenas benefícios limitados com altas chances de danos sérios. Assim, o objetivo desta revisão sistemática foi estimar a proporção de uso e prescrição de opioides entre idosos com dor crônica não oncológica. ***Métodos:*** As buscas foram realizadas identificando os estudos elegíveis incluídos em duas revisões sistemáticas publicadas recentemente, realizando a *backward citation* destes e atualizando as buscas, no período de outubro de 2018 até junho de 2024. Foram incluídos estudos observacionais que investigaram a proporção de uso e prescrições de opioides em uma amostra representativa de idosos (60 anos ou mais) com dor crônica não oncológica. O risco de viés foi avaliado usando uma ferramenta desenvolvida para estudos epidemiológicos. A meta-análise foi realizada usando modelos de efeito aleatório para obter a prevalência combinada e seus intervalos de confiança de 95%. A qualidade geral da evidência foi avaliada usando a abordagem Grading of Recommendations Assessment, Development and Evaluation (GRADE). ***Resultados:*** Nove estudos (476.140 idosos) foram identificados. Seis estudos (66,6%) foram classificados como tendo baixo risco de viés. A prescrição de opioides entre idosos com dor crônica não oncológica foi de 35,6% (IC de 95%: 27,8% a 44,2%), enquanto a proporção de uso de opioides foi de 26,4% (IC de 95%: 16,6% a 39,3%). A qualidade geral da evidência de acordo com o GRADE foi moderada (rebaixada por inconsistência). ***Conclusão:*** Aproximadamente um terço dos idosos com dor crônica não oncológica usam ou recebem prescrição de opioides. Dados os benefícios limitados e o risco aumentado de danos associados ao uso de opioides, são necessárias estratégias para reduzir o uso excessivo de opioides entre idosos com dor crônica não oncológica.

Palavras-chave: Prevalência; Opioide; Prescrição; Idoso; Dor crônica.

ABSTRACT

Prevalence of opioid analgesic use and prescription for older people with chronic non-cancer pain: A systematic review with meta-analysis

Background: Chronic non-cancer pain is a common problem among older people. Opioids are among the treatment options for chronic non-cancer pain, this medication only provides limited benefits. This medication is also associated with a high risk of serious harms (e.g., overdoses) specially in older people. This review estimated the proportion of opioid use and prescription among older adults with chronic non-cancer pain. ***Methods:*** Searches were performed by identifying eligible studies included in two published systematic reviews, performing backward citations and updating the searches from October 2018 until June 2024. Observational studies investigating the proportion of opioid use and prescriptions in a representative sample of older adults (60 years or older) with chronic non-cancer pain were included. Risk of bias was assessed using a tool developed for epidemiological studies. Meta-analysis was performed using random effect models to obtain the pooled prevalence and their 95% confidence intervals. The overall quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. ***Results:*** Nine studies (476,140 older people) were included in this review. Six (66.6%) were classified as having a low risk of bias. The rate of opioid prescription among older people with chronic non-cancer pain was 35.6% (95% CI: 27.8% to 44.2%), while the proportion of opioid use was 26.4% (95% CI: 16.6% to 39.3%). The overall quality of evidence was moderate according to GRADE (downgraded for inconsistency). ***Conclusion:*** Approximately one-third of older people with chronic non-cancer pain are prescribed opioids and one-quarter reported their use. Given the limited benefits and increased risk of harm associated with opioid use, strategies to reduce the overuse of opioids among older people with chronic noncancer pain are needed.

Keywords: Prevalence; Opioid; Prescription; Aged; Chronic Pain.

LISTA DE SIGLAS

CI	– Confidence Interval
CNCP	– Chronic non-cancer pain
GRADE	– Grading of Recommendations Assessment, Development and Evaluation
PRISMA-P	– Preferred Reporting Items for Systematic review and Meta-Analysis Protocols

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SUMÁRIO

Prevalence of opioid analgesic use and prescription for older people with chronic non-cancer pain: A systematic review with meta-analysis

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Abstract

Chronic non-cancer pain is a common problem among older people. Opioids are among the treatment options for chronic non-cancer pain, this medication only provides limited benefits. This medication is also associated with a high risk of serious harms (e.g., overdoses) specially in older people. This review estimated the proportion of opioid use and prescription among older adults with chronic non-cancer pain. Searches were performed by identifying eligible studies included in two published systematic reviews, performing backward citations and updating the searches from October 2018 until June 2024. Observational studies investigating the proportion of opioid use and prescriptions in a representative sample of older adults (60 years or older) with chronic non-cancer pain were included. Risk of bias was assessed using a tool developed for epidemiological studies. Meta-analysis was performed using random effect models to obtain the pooled prevalence and their 95% confidence intervals. The overall quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Nine studies (476,140 older people) were included in this review. Six (66.6%) were classified as having a low risk of bias. The rate of opioid prescription among older people with chronic non-cancer pain was 35.6% (95% CI: 27.8% to 44.2%), while the proportion of opioid use was 26.4% (95% CI: 16.6% to 39.3%). The overall quality of evidence was moderate according to GRADE (downgraded for inconsistency). Approximately one-third of older people with chronic non-cancer pain are prescribed opioids and one-quarter reported their use. Given the limited benefits and increased risk of harm associated with opioid use, strategies to reduce the overuse of opioids among older people with chronic noncancer pain are needed.

Perspective: Around one third of older people with chronic pain are prescribed and one quarter reported their use. Strategies to reduce the use of this medication are needed as this population has a higher risk of serious harm as a result of the use of opioids.

Key words: Prevalence, Opioid, Prescription, Aged, Chronic Pain.

Introduction

Population aging is a growing worldwide phenomenon[1], which implies that we need to understand the health needs and conditions commonly experienced by this group, such as chronic non-cancer pain. Chronic non-cancer pain is defined as any painful condition (i.e., musculoskeletal pain or osteoarthritis) lasting for at least three months not attributed to cancer[2]. The 1-month prevalence of chronic non-cancer pain in older people is close to 50% and the most prevalent conditions include osteoarthritis, low back pain, and fibromyalgia[3-5]. This condition has an enormous economic impact on healthcare systems but also has several consequences for individuals, such as functional and social impairments, reduced mobility, and increased risk of falls[6-11].

One of the treatments options for chronic non- cancer pain is the opioids[12, 13]. However, evidence shows limited efficacy and a high risk of serious harm of opioids in this population, such as overdose and death[16, 17]. Specifically in older adults, a recent review showed they are three times more likely to experience an adverse event after taking opioids when compared to younger populations[17]. These adverse events can be potentiated by common metabolic changes (i.e., hepatic and renal; changes in body composition) in older people which may increase the risk of falls, fractures, cognitive impairment, delirium and opioid-induced respiratory depression[17-21]. Another concern is the high prevalence of polypharmacy in older people, which may increase the chances of serious drug interactions with benzodiazepines, for example, and lead to greater toxicity and misuse[17-21]. Despite the lack of benefits and high risk of harms[17], opioids have been a common treatment option for chronic non-cancer pain over time[15].

The "opioid epidemic" remains a major public health concern worldwide[13, 15, 22, 23]. Two reviews have investigated opioid use and prescription among adults with chronic non-cancer pain; however, they did not provide subgroup estimates for older people[13, 24]. These reviews found that nearly one third of people with chronic non-cancer pain reported opioid use (i.e., self-reported measure), or were prescribed opioids (i.e., dispensing data)[13, 24]. As evidence shows that the prevalence of chronic non-cancer pain increases with age[25], our hypothesis is that the use and prescription of opioids in older people would also be higher when compared to adults. Therefore, the objective of this systematic review was to estimate the proportion of opioid use and prescription among older people with chronic non-cancer pain

Methods

We followed the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) recommendations for reporting this review[26], which was prospectively registered in PROSPERO (CRD42024528791).

Searches

The searches were conducted in three stages. First, we screened the included studies of two recent systematic reviews[13, 24] that investigated the proportion of opioid use and prescription in adults with chronic non-cancer pain for potentially eligible studies. In this phase, we identified potentially eligible studies providing estimates for older people. Second, we performed backward citation tracking in the included studies using the Web of Science database. In the third phase, we updated the searches performed in the previous reviews[13, 24], which were selected because they had a high methodological quality and were the most recent investigating this topic. Searches were conducted in the following electronic databases from October 2018 until the search date of June 2024: MEDLINE, EMBASE, Web of Science, and International Pharmaceutical Abstracts. The search strategy was performed considering the previous systematic review[13], which used a combination of search terms related to chronic non-cancer pain, opioids and observational studies (Appendix 1). Searches were not restricted to any specific language. When necessary, we used Google's translation tool or contacted native speakers to understand publications in other languages during study selection and data extraction.

Two authors (M.C.R.S.; R.V.C.V.) independently screened the titles and abstracts of records retrieved from the searches, and a third reviewer (C.B.O.) was available to resolve any disagreements. Two reviewers (M.C.R.S.; R.V.C.V.) then independently assessed the full texts of potentially eligible studies selected in the previous stage, and a third reviewer (C.B.O.) was available to resolve any disagreements.

Eligibility criteria

Observational studies investigating the proportion of opioid use and prescription in a representative sample (i.e., consecutive patients or random sample) of older people with

chronic non-cancer pain (in general or specific conditions; i.e., low back pain), both genders, aged 60 years or more[27] were included. Studies investigating the use of opioids after surgical procedures or anaesthesia, those recruiting a non-representative sample and those investigating opioid use for cancer-related-pain were excluded[13].

We included studies investigating opioid use, defined as self-reported consumption of any type, class and dose, for any duration, over any period of time, of opioid analgesic[24]. In addition, administrative data (not prescription data) was also considered eligible[24]. Prescription involves data from dispensing or prescription data (i.e., medical record reviews or data from insurance companies and databases)[13, 24].

Data extraction

Two independent reviewers (M.C.R.S.; R.V.C.V.) performed the data extraction using a standardized form containing the following information from the included studies: studies characteristics (i.e., author(s), year, country, continent, sampling year, study design use or prescription analysis, healthcare level [i.e., primary care, secondary care or tertiary care]); sample characteristics (i.e., number of participants, pain complaint/diagnoses) and outcome measures (i.e., prescription or use of opioids, opioids characteristics [i.e., type, class and dose]). In case of missing data, we contacted the authors and requested additional information.

The health care levels were categorized as: primary care (i.e., general practitioner, family physician); secondary care (i.e., medical specialists, multidisciplinary teams); and tertiary care (i.e., hospital, inpatient care). Opioid analgesics were classified using Anatomical Therapeutic Chemical classification (N02A) and categorised as 1) weak (codeine, tramadol, dihydrocodeine, dextropropoxyphene, and tilidine) or 2) strong (i.e., oxycodone, morphine, pethidine, fentanyl, hydromorphone, buprenorphine, tapentadol). The combination was categorised as a weak (i.e., codeine plus paracetamol) or strong combination opioid analgesic (i.e., oxycodone plus paracetamol)[28].

Risk of bias assessment

The risk of bias in included studies was evaluated using a specific tool for prevalence

studies developed by Hoy et al[29]. Two independent reviewers performed the risk of bias assessment and any case of disagreement was resolved by consulting a third reviewer. The tool consists of 10 items, which are scored as high or low risk of bias, with items 1 to 4 assessing the selection and non-response bias, items 5 to 9 assessing measurement bias, and item 10 assessing the bias related to the analysis[29]. If no information was provided, a high risk of bias was attributed to the specific item. The overall risk of bias was classified as high, moderate, or low risk of bias as follows: low risk of bias (if further research was very unlikely to change our confidence in the estimate); moderate risk of bias (if further research was likely to have an important impact on our confidence in the estimate and may change the estimate); and high risk of bias (if further research was very likely to have an important impact on our confidence in the estimate and was likely to change the estimate)[13, 24, 29].

Data analysis

Heterogeneity was reported using the I-square statistic, and an I-square value greater than 50% was considered as substantial heterogeneity. First, the estimates were calculated considering the proportion of opioid use and prescription in older people with chronic non-cancer pain. The proportion was calculated considering the number of older people with opioid use or prescription divided by the total number of older people with chronic non-cancer pain. The meta-analysis was calculated using random effect models to obtain the pooled prevalence and respective 95% confidence intervals. If needed, we converted the data using logit transformation to handle the variance. All analyses were performed in the RStudio program (version 1.2.5032) using the R program (version 4.3.2.).

Quality of evidence

The quality of the evidence was assessed using the Grading of Recommendations Assessment, Developing and Evaluation (GRADE) Approach[30, 31]. Our approach for each of the five domains was: risk of bias (i.e., downgraded one level if more than 15% of the studies in a meta-analysis were judged as having an overall high risk of bias), imprecision (i.e., downgraded one level if there are wide confidence intervals), inconsistency (i.e., downgraded one level if the substantial heterogeneity, that is, $I^2 > 50\%$), indirectness (i.e.,

downgraded one level if study population and outcome measures do not align with the purpose of the review), and publication bias (i.e., downgraded one level if evidence of publication bias is identified by an asymmetry of the funnel plot and Egger test with $P < 0.10$) [30, 31]. The overall quality of evidence was downgraded by one level, from high to very low, for each domain not met. The following interpretation was adopted for the different levels of evidence: high (further research is unlikely to change the confidence in the estimate), moderate (further research is likely to change the confidence in the estimate), low (further research is very likely to change the confidence in the estimate), or very low (the confidence in the estimate is uncertain) [30, 31].

Results

We identified 15,907 records through updating the searches in electronic databases and backward citation tracking of included studies in previous systematic reviews[13, 24]. After screening titles and abstracts, we assessed the full texts of the 159 potentially eligible studies. In total, 150 studies were excluded because they: did not investigate older people with chronic non-cancer pain (n = 92); did not provide separate data for older people (n = 22); did not provide a separate analysis for chronic cancer and non-cancer pain (n= 19); and, did not report the proportion of opioids (n= 17). Finally, nine studies were included in this review[22, 32-39]. Figure 1 details the review process.

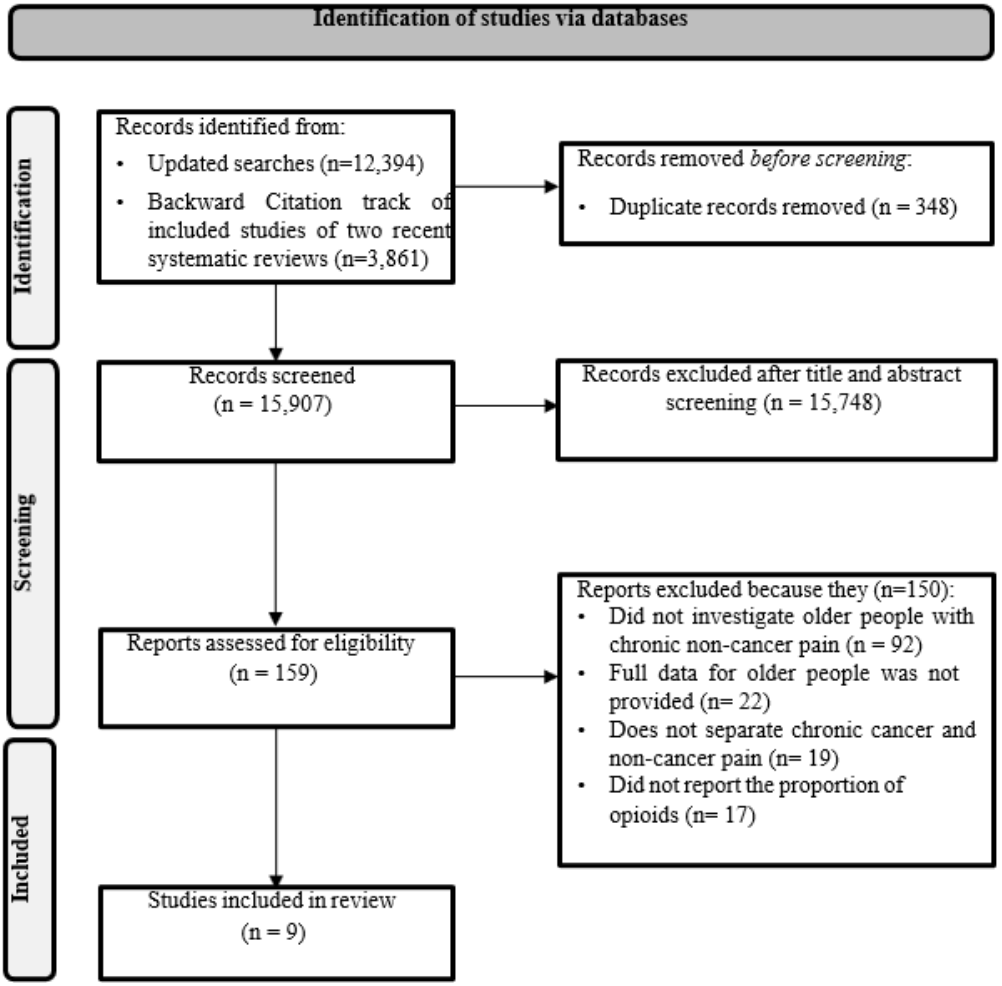

Figure 1. Study flow diagram.

The included studies were published between 2000 and 2024. The year samples of included studies ranged from 1993 to 2019. While five studies included exclusively older adults (55.5%)[32,35,38-40], four studies included a mixed sample but reported data separately for older adults (44.4%)[22, 33, 35, 36]. In total, the included studies analysed 476,140 older adults with chronic non-cancer pain. Most of the studies were conducted in the United States (66.6%)[22, 32, 33, 36, 37, 39], while the others were in Australia[38], Switzerland[34] and Norway[34] (11.1% each). Four studies (44.4%)[34,35,36,39] were cross-sectional and five were retrospective studies (55.5%)[22, 32, 33, 36, 37]. Regarding health settings, most studies included patients seeking primary care (77.7%)[22, 32, 36, 37, 39], and one study each included patients from secondary (pain specialist centre)[38] and tertiary (acute care, public teaching hospital)[34] levels (11.1% each). Studies included mainly older people with chronic non-cancer pain in general (66.6%)[22, 33-35, 38, 39] and the remaining studies specifically included older people with chronic musculoskeletal pain[37], arthritis[32], and chronic low back pain or arthritis[36] (11.1% each). Table 1 (Appendix 2) provides a detailed description of the included studies.

Risk of bias

Most studies were classified as having a low risk of bias (66.6%). The items that studies mostly failed to meet were related to providing acceptable case definition (55.5%) and a random selection/census undertaken (44.4%) and use of reliable and valid instruments (44.4% each). Table 2 demonstrates the risk of bias assessment of included studies.

Table 2. Risk of bias assessment using a tool for prevalence studies

Study	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	Overall risk of bias
Alenazi, 2023	−	+	−	+	+	+	+	+	+	+	Low
Edlund, 2014	+	+	+	+	+	−	+	+	+	+	Low
Goetschi, 2024	+	+	−	+	+	+	+	+	+	+	Low
Hansen, 2015	+	+	+	−	+	−	+	+	−	+	Moderate
Hayes, 2018a	+	−	+	+	+	−	−	+	+	+	Moderate
Hayes, 2018b	+	+	+	+	+	−	−	+	+	+	Low
Karmali, 2020	−	+	−	+	+	−	+	+	+	+	Moderate
Kung, 2000	−	+	+	+	+	+	−	+	+	+	Low
McDonald, 2022	+	+	−	+	+	+	−	+	+	+	Low

1. Was the study's target population a close representation of the national population in relation to relevant variables, i.e., age, sex, occupation?
2. Was the sampling frame a true or close representation of the target population?
3. Was some form of random selection used to select the sample, OR, was a census undertaken?
4. Was the likelihood of non-response bias minimal?
5. Were data collected directly from the subjects (as opposed to a proxy)?
6. Was an acceptable case definition used in the study?
7. Was the study instrument that measured the parameter of interest (i.e., prevalence of low back pain) shown to have reliability and validity (if necessary)?
8. Was the same mode of data collection used for all subjects?
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?

Proportion of opioid analgesic for older people with chronic non-cancer pain

Five studies[32-35, 37] reported the prescription of opioids for older adults with chronic non-cancer pain and the pooled proportion was 35.6% (95% CI: 27.8% to 44.2%) (Figure 2). Four studies[22, 36, 38, 39] assessed opioids use using self-reported questionnaires, and the pooled prevalence was 26.4% (95% CI: 16.6% to 39.3%) (Figure 2). The overall quality of evidence was moderate for the prescription and use of opioids (downgraded for inconsistency). Regarding the prescription/use by healthcare level, the proportion of the

prescription of opioids for older adults with chronic non-cancer pain ranged from 23.2% to 39.8% in primary care[32, 33, 35, 37], and 51.1% in tertiary care[34]. For the use of opioids, it ranged from 16.4 to 27.0% in primary care[39, 35, 36] and was 48.7% in secondary care[38].

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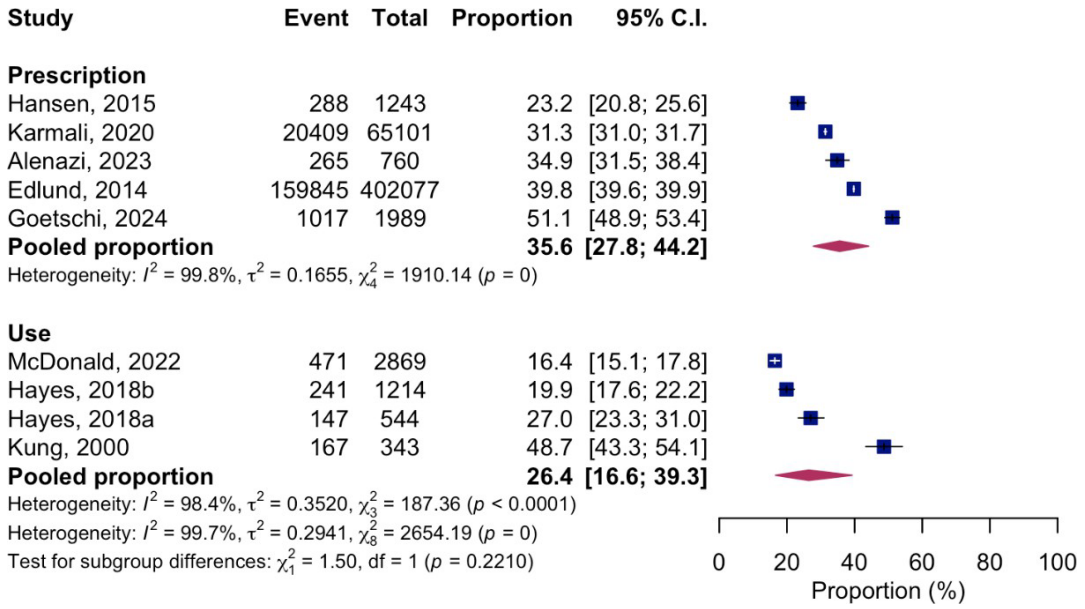

Figure 2. Meta-analysis of the proportion of prescription and use of opioids among older adults with chronic non-cancer pain

There was a lack of information in the included studies regarding the characteristics of opioids prescription or use. Five described the doses (stratified by Milligrams Morphine Equivalent- MME)[22, 33, 35-37], but only one[37] reported data separately for older people with chronic pain. This study[37] showed that 38.3% had prescribed high daily dose ≥ 50 MME and 18.9% had prescribed high daily dose ≥ 90 MME. One study found that 28.6% of opioids prescriptions were for strong opioids and 22.6% for weak opioids (According to the classification proposed by the World Health Organization in 1996)[34]. Another study detailed the proportion of opioids use for each medication: codeine (16.9%), dextropropoxyphene (6.1%), and morphine (3.4%)[38]. The remaining studies[32, 39] did not report any data regarding the type, class or dose of opioids.

Discussion

Our review reporting data of 476,140 older people with chronic pain found that the

proportion of prescription or use of opioids among this population is approximately 36% and 26%, respectively. Based on data from one study, more than half of the opioids prescription for older adults are for strong opioids, which contradicts guideline recommendations on providing weak opioids if other treatments failed. Considering the moderate quality of evidence, additional studies on this topic may change our estimates.

Our estimates closely align with recent reviews investigating the use and prescription of opioids in adults with chronic pain. The previous reviews found that the prescription and use of opioids were 30.7% (95% CI: 28.7% to 32.7%)[13] and 26.8% (95% CI: 23.1% to 30.8%)[24], respectively. Despite the overlap of confidence intervals of prescription and use of opioids among younger and older adults, some reasons can explain the lack of differences. The previous reviews provided combined estimates for both young and older adults, meaning that estimates for younger adults only are unknown. Another explanation is the small number of studies in our review which led to wider confidence intervals when compared to the previous reviews. Additional studies focusing on the prescription and use of opioids in older people may result in more precise estimates and change our findings.

This review was the first to examine the proportion of opioids prescribed and used by older adults with chronic noncancer pain. We conducted an extensive literature search associated with backward citation tracking to identify all the potentially eligible studies. However, we could not exclude the possibility of missing studies, although this is a limitation of any systematic review. Another limitation is that we could not perform a subgroup analysis, mainly due to the lack of sufficient details in the included studies, such as age subgroups and type of opioids.

We suggest that future research should conduct specific analyses of substance use in older adults, especially in low-income countries, since the studies contained in this review involved high-income countries. It is also interesting to consider which health systems (i.e., public, private, mixed) are available in these countries and how these factors may influence the distribution of medications in these populations. We also propose that future research also include the age subgroup and types of medications used, as this information will enable us to investigate any specific prescription patterns of opioids among older people with chronic non-cancer pain. Furthermore, future studies should avoid common methodological flaws detected in the included studies of this review, such as providing information if the recruited sample was a random selection/census undertaken and

providing an acceptable case definition.

Conclusions

The proportion of prescription or use of opioids among older adults with chronic non-cancer pain was 35.6% and 26.4%, respectively. Based on the findings of one study, half of the opioids prescriptions among older people with chronic non-cancer pain are for strong opioids. Future studies should be conducted investigating the use and prescription of opioids in older adults with chronic pain in low-middle income countries and providing more details about the type of opioids.

Acknowledgements/ Funding information

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Conflict of interest

The authors don’t have any conflict of interests to declare.

References

1. Brazilian Institute of Geography and Statistics (IBGE). Population projection. Accessed on: 05/03/2024. https://www.ibge.gov.br/estatisticas/sociais/populacao/9109-projecao-da-populacao.html; 2024.
2. Treede RD, Rief W, Barke A, et al. Chronic non-cancer pain as a symptom or a disease: the IASP Classification of Chronic non-cancer pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1):19-27. DOI: 10.1097/j.pain.0000000000001384.
3. Schwan J, Sclafani J, Tawfik VL. Chronic non-cancer pain management in the elderly. Anesthesiology Clin. 2019;37(3):547-60. DOI: 10.1016/j.anclin.2019.04.012.
4. Patel KV, Guralnik JM, Dansie EJ, Turk DC. Prevalence and impact of pain among older adults in the United States: findings from the 2011 National Health and Aging Trends Study. Pain. 2013;154(12):2649-57. DOI: 10.1016/j.pain.2013.07.029.
5. Santiago BV, Araujo JG, Oliveira RS, Vasconcelos GC, Reis FJ. Prevalence of chronic non-cancer pain in Brazil: A systematic review and meta-analysis. Clinics. 2023;78:100209. DOI: 10.1016/j.clinsp.2023.100209.
6. Langford S, Hunter E. Interventions to reduce opioid use for pain management in the older adult population: A systematic review. J Appl Gerontol. 2021;40(11):1637-48. DOI: 10.1177/0733464820975550.
7. Galicia-Castillo M. Opioids for persistent pain in older adults. Cleve Clin J Med. 2016;83(6):443-51. DOI: 10.3949/ccjm.83a.15023.
8. Chang YP. Factors associated with prescription opioid misuse in adults aged 50 or older. Nurs Outlook. 2018;66(2):112-20. DOI: 10.1016/j.outlook.2017.10.007.
9. West NA adults. Pharmacoepidemiol Drug Saf. 2016;25(5):539-44. DOI: 10.1002/pds.3934.
10. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. BMJ. 2015;350:h694. DOI: 10.1136/bmj.g6380.
11. Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195

countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1211-59. DOI: 10.1016/S0140-6736(17)32154-2.

12. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A brief history of the opioid epidemic and strategies for pain medicine. Pain Ther. 2018;7:13-21. DOI: 10.1007/s40122-018-0097-6.

13. Mathieson S, Wertheimer G, Maher CG, et al. What proportion of patients with chronic noncancer pain are prescribed an opioid medicine? Systematic review and meta-regression of observational studies. J Intern Med. 2020;287(5):458-74. DOI: 10.1111/joim.13026.

14. Reid MC, Eccleston C, Pillemer K. Management of chronic non-cancer pain in older adults. BMJ. 2015;350:h532. DOI: 10.1136/bmj.h532.

15. Shipton EA, Shipton EE, Shipton AJ. A review of the opioid epidemic: what do we do about it? Pain Ther. 2018;7:23-36. DOI: 10.1007/s40122-018-0096-7.

16. Shaheed CA, Maher CG, Williams KA, McLachlan AJ, Reid MC. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis. JAMA Intern Med. 2016;176(7):958-68. DOI: 10.1001/jamainternmed.2016.1251.

17. Megale RZ, Ferreira ML, Ferreira PH, et al. Efficacy and safety of oral and transdermal opioid analgesics for musculoskeletal pain in older adults: a systematic review of randomized, placebo-controlled trials. J Pain. 2018;19(5):475-83. DOI: 10.1016/j.jpain.2017.12.001.

18. Gazelka HM, Leal JC, Lapid MI, Rummans TA. Opioids in older adults: indications, prescribing, complications, and alternative therapies for primary care. Mayo Clin Proc. 2020;95(9):2051-65. DOI: 10.1016/j.mayocp.2020.02.002.

19. Herzig SJ, LaSalvia MT, Gagne JJ, et al. Relative risks of adverse events among older adults receiving opioids versus NSAIDs after hospital discharge: a nationwide cohort study. PloS Med. 2021;18(9):e1003804. DOI: 10.1371/journal.pmed.1003804.

20. Salkar M, Udoji MA, Kaye AM, et al. Do formulation and dose of long-term opioid therapy contribute to risk of adverse events among older adults? J Gen Intern Med. 2021;36(11):3380-7. DOI: 10.1007/s11606-021-06792-8.

21. Baruth JM, Gassler JP, Meehan S. Polypharmacy in older adults: the role of the multidisciplinary team. Hosp Pract (1995). 2020;48(Suppl 1):56-62. DOI: 10.1080/21548331.2019.1706995.

22. Hayes CJ, Krebs EE, Hudson TJ, Martin BC. Health-related quality of life among chronic opioid users, nonchronic opioid users, and nonopioid users with chronic noncancer pain. Health Serv Res. 2018;53(5). DOI: 10.1111/1475- 6773.12836.

23. United Nations Office on Drugs and Crime (UNODC). *World Drug Report 2024 – Statistical Annex* [Internet]. Vienna: United Nations; 2024 [cited 2025 Apr 23]. Available from: https://www.unodc.org/documents/data-and-analysis/WDR_2024/WDR_2024_SPI.pdf

24. Wertheimer G, Ziegeler C, Mathieson S, et al. The prevalence of opioid analgesic use in people with chronic noncancer pain: systematic review and meta-analysis of observational studies. Pain Med. 2021;22(2):506-17. DOI: 10.1093/pm/pnaa322.

25. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic non-cancer pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open. 2016;6(6):e010364. DOI: 10.1136/bmjopen-2015-010364.

26. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. DOI: 10.1136/bmj.n71.

27. World Health Organization. Active ageing: A policy framework. Geneva: WHO; 2002.

28. World Health Organization. Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Oslo: WHO; 2013.

29. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65(9):934-9. DOI: 10.1016/j.jclinepi.2011.11.014.

30. Huguet A, Hayden JA, Stinson J. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Syst Rev. 2013;2:71. DOI: 10.1186/2046-4053-2-71.

31. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidenceJ Clin Epidemiol. 2011 Apr;64(4):401-6. doi: 10.1016/j.jclinepi.2010.07.015.

32. Alenazi AM, Alswat K, Hammad LF, et al. Generalized and localized osteoarthritis and risk of fall among older adults: the role of chronic diseases and medications using real world data from a single center. Eur Rev Med Pharmacol Sci. 2023;27(9):3721-35. DOI: 10.26355/eurrev_202305_32302.

33. Edlund MJ, Austen MA, Sullivan MD, et al. Patterns of opioid use for chronic

noncancer pain in the Veterans Health Administration from 2009 to 2011. Pain. 2014;155(11):2337-43. DOI: 10.1016/j.pain.2014.08.033.

34. Goetschi AN, Lüthi F, Naegeli B, et al. Prescribing pattern insights from a longitudinal study of older adult inpatients with polypharmacy and chronic non-cancer pain. Eur J Pain. 2024;28(1):76-89. DOI: 10.1002/ejp.2298.

35. Hansen AB, Laursen MB, Jarbæk N, et al. Consumption of and satisfaction with health care among opioid users with chronic non-malignant pain. Acta Anaesthesiol Scand. 2015;59(10):1355-66. DOI: 10.1111/aas.12568.

36. Hayes CJ, Payakachat N, Li C. Evaluation of opioid use among patients with back disorders and arthritis. Qual Life Res. 2018;27:3021-35. DOI: 10.1007/s11136-018-1941-1.

37. Karmali RN, Skinner AC, Weinberger M, et al. The association between the supply of nonpharmacologic providers, use of nonpharmacologic pain treatments, and high-risk opioid prescription patterns among Medicare beneficiaries with persistent musculoskeletal pain. Med Care. 2020;58(5):433-44. DOI: 10.1097/MLR.0000000000001299.

38. Kung F, Gibson SJ, Helme RD. Factors associated with analgesic and psychotropic medication use by community-dwelling older people with chronic pain. Aust N Z J Public Health. 1999;23(5):471-4. DOI: 10.1111/j.1467-842x.1999.tb01301.x.

39. McDonald DD, Walsh SJ. Predictors of older adults' chronic pain in the context of opioid adverse drug events. J Am Assoc Nurse Pract. 2022;34(8):968-77. DOI: 10.1097/JXX.0000000000000734.

40. NICE Guideline NG193. Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. Methods. 2021;10.

41. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016;315(15):1624-45. DOI: 10.1001/jama.2016.1464.

42. Goodyear K, Haass-Koffler CL, Chavanne D. Opioid use and stigma: The role of gender, language and precipitating events. Drug Alcohol Depend. 2018;185:339-46. DOI: 10.1016/j.drugalcdep.2017.12.037.

43. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. JAMA. 2018;320(23):2448-60. DOI: 10.1001/jama.2018.18472.

Appendix 1. Search strategy performed in Medline (via OVID)

I. **Chronic non-cancer pain**

1. ((chronic pain) or (chronic non-cancer pain) or (chronic non cancer pain) or (chronic noncancer pain) or (chronic non-malignant pain) or (chronic non malignant pain) or (chronic nonmalignant pain) or (pain adj (long-term) or (long term) or (longterm) or persistent)) or human).mp

II. **Opioids**

2. (NO2A* or (opioid* adj3 analges*) or opioid* or (opioid* adj3 med*) or (opioid* adj3 drug*) or narcotic* or (narcotic* adj3 drug*) or (narcotic* adj3 analges*) or morphine or (morphine adj3 sul*) or ordine or hydromorphone or dilaudid or oxy* or oxycodone or endone or targin or oxymorphone or OPANA* or codeine or dihydrocodeine or (opi* adj3 alkaloid*) or ketobemidone or (phenylpiperidine adj3 deriv*) or pethidine or fentanyl or durogesic or diphenylpropylamine or dextromoramide or piritramide or dextropropoxyphene or di-gesic or capodex or bezitramide or methadone or physeptone or (benzomorphan adj3 deriv*) or pentazocine or phenazocine or (oripavine adj3 deriv*) or buprenorphine or norspan or suboxone or subutex or etorphine or (morphinan adj3 deriv*) or tilidine or trama* or tramadol or dezocine or tapendatol or meptazinol or nicomorphine or butorphanol or nalbuphine).mp

III. **Observational studies**

3. ((epidemiologic studies) or (cohort studies) or (cross sectional studies) or (epidemiologic adj (study or studies)) or (follow up adj (study or studies)) or retrospective* or prospective* or (observ* adj (study or studies)) or community) and (prevalence or occurrence or burden).mp

IV. 1 and 2 and 3

Appendix 2. Detailed description of the included studies

Table 1. Description of included studies

Study	Country/ Continent	Sampling Year	Study Desing	Health care level	Pain Complaint/ Diagnoses	Nº of older people with CNCP	Nº of older people with CNCP using opioids
Alenazi, 2023	United States/ North America	2011-2017	Retrospective cohort	Primary care	Arthritis	760	265
Edlund, 2014	United States/ North America	2009-2011	Retrospective cohort	Primary care	CNCP	402077	159845
Goetschi, 2024	Switzerland/ Europe	2015-2018	Cross-sectional	Tertiary care	CNCP	1989	1017
Hansen, 2015	Norway/ Europe	2006-2008	Cross-sectional	Primary care	CNCP	1243	288
Hayes, 2018a	United States/ North America	2010-2014	Retrospective cohort	Primary care	CNCP or arthritis	544	147
Hayes, 2018b	United States/ North America	2010-2013	Retrospective cohort	Primary care	CNCP	1214	241
Karmali, 2020	United States/ North America	2007-2014	Retrospective cohort	Primary care	Persistent musculoskeletal pain and CNCP	65101	20409
Kung, 2000	Australia/ Oceania	1993-1996	Cross-sectional	Secondary care	CNCP	343	167
McDonald, 2022	United States/ North America	2019	Cross-sectional	Primary care	CNCP	2869	471

Legend: CNCP (Chronic non-cancer pain).

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Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify compliance, your article may be checked by Crossref Similarity Check and other originality or duplicate checking software.

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Inclusion, diversity, equity, antiracism, and accessibility

The *Journal of Pain* is committed to addressing pain inequities across the pain scientific community. Please read the editorial from the Antiracism CoaliTION in Pain Research (ACTION-PR) here and plans for implementation at The *Journal of Pain*. As part of ACTION-PR's efforts, they have developed the Inclusion, Diversity, Equity, Antiracism, and Accessibility (IDEAA) guidelines. These guidelines were informed by state-of-the-science recommendations from health equity scholars (i.e., Boyd et al., 2020, Health Affairs; Flanagin et al., 2021, JAMA) and insights from stakeholders, including people with lived experience of pain and pain researchers across the translational spectrum. The *Journal of Pain* will be the first journal to adopt these guidelines which provide a checklist of items to guide authors, reviewers, and editors in promoting equity and transparency in their reporting. Editors from multiple pain journals have banded together to promote equity, inclusion and diversity in pain science, please review the general principles for

authors, reviewers, and editors here. Societal oppression occurs globally and can include racism, colorism, sexism, ageism, classism, ableism, biases related to a person's LGBTQ2S+ identity, and limited proficiency in a society's dominant language. These forms of oppression - and their intersections - are detrimental to individuals' well-being, lead to health inequities, and must be addressed through active change. The IDEAA guidelines are designed to help authors submit articles that center the experiences of people living with pain who have additional burdens on physiological processes, well-being, and adequate pain care due to societal oppression. Authors are encouraged to think deeply about how their work can advance equity in the pain field and act beyond strict compliance to the IDEAA guidelines. The full version of the IDEAA guidelines is forthcoming. In the interim, authors are asked to address the following items in their manuscript submissions to The *Journal of Pain*:

1. **Inclusive language**. Use language that minimizes bias and holds oppressive systems accountable. Authors should consult available style guides (eg, the APA Style and Grammar Guidelines for Bias-Free Language available here and the AMA Style Manual: Inclusive Language for best practices.
2. **Accurate interpretation of race, ethnicity, sex, and gender**. Describe and interpret racialized identity and ethnicity as social and cultural constructs. Describe and interpret sex assigned at birth and gender identity as separate constructs.
3. **Inclusion and representativeness of study samples (human and animal)**. Describe efforts (i.e., recruitment strategies, people with lived experience of pain in the research team) to promote diversity and inclusion in the study sample, including inclusion of people who experience racism and/or societal oppression in the country of interest and that improve accessibility (i.e., for a range of abilities/disabilities, language fluency, etc.) in human participants studies, and equal representation of female and male animals in preclinical studies.
4. **Comprehensively report sample characteristics**. Provide a comprehensive description of the sample's characteristics i.e., reporting of racialized or gender identities (including human participants, human in vitro, non-human animals, and systematic review/meta-analysis studies). Describe how the sample's inclusivity advances or limits progress toward pain equity in the population of interest and the specific steps that will be taken in future work.
5. **Describe the level of patient and public involvement in the research**. Provide a description in the Methods section of how patients or the public were involved in the study's conceptualization, design and conduct (i.e., choice of outcome measures, recruitment), and/or dissemination of the study results. We fully appreciate that this is a movement in evolution and not all researchers will have involved patients and the public in their studies. We also recognize that for some papers co-production may not be appropriate. For this reason, we continue to consider research papers where there has been no patient or public involvement but we ask that authors state this in the methods section. Please also consider using the GRIPP2 reporting checklist for best reporting of patient and public involvement. When patient/public contributions have been substantial and meet authorship criteria, they should be invited to coauthor the manuscript. See examples of statements of patient and public involvement.

Reporting sex- and gender-based analyses

Reporting guidance

For research involving or pertaining to humans, animals or eukaryotic cells, investigators should integrate sex and gender-based analyses (SGBA) into their research design according to funder/sponsor requirements and best practices within a field. Authors should address the sex and/or gender dimensions of their research in their article. In cases where they cannot, they should

discuss this as a limitation to their research's generalizability. Importantly, authors should explicitly state what definitions of sex and/or gender they are applying to enhance the precision, rigor and reproducibility of their research and to avoid ambiguity or conflation of terms and the constructs to which they refer (see Definitions section below). Authors can refer to the Sex and Gender Equity in Research (SAGER) guidelines and the SAGER guidelines checklist. These offer systematic approaches to the use and editorial review of sex and gender information in study design, data analysis, outcome reporting and research interpretation - however, please note there is no single, universally agreed-upon set of guidelines for defining sex and gender.

Definitions

Sex generally refers to a set of biological attributes that are associated with physical and physiological features (i.e., chromosomal genotype, hormonal levels, internal and external anatomy). A binary sex categorization (male/female) is usually designated at birth ("sex assigned at birth"), most often based solely on the visible external anatomy of a newborn. Gender generally refers to socially constructed roles, behaviors, and identities of women, men and gender-diverse people that occur in a historical and cultural context and may vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact and how power is distributed in society. Sex and gender are often incorrectly portrayed as binary (female/male or woman/man) and unchanging whereas these constructs actually exist along a spectrum and include additional sex categorizations and gender identities such as people who are intersex/have differences of sex development (DSD) or identify as non-binary. Moreover, the terms "sex" and "gender" can be ambiguous--thus it is important for authors to define the manner in which they are used. In addition to this definition guidance and the SAGER guidelines, the resources on this page offer further insight around sex and gender in research studies.

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Language services

Text should be presented in English (American or British usage is accepted, but not a mixture of these). Authors who submit to international journals but are not native speakers of English sometimes receive negative feedback regarding language usage. We strongly encourage such authors to have submissions pre-reviewed by colleagues with English fluency, or to be considered by a professional editing service such as https://webshop.elsevier.com/language-editing/.

Open and Transparent Science

The Journal of Pain encourages open and transparent science and will support authors to completely report their research and share their data openly, which includes raw datasets, code, videos, software, models, algorithms and any other methodological material. Below are a number of ways in which we can support you

Checklists and Reporting Guidelines

The Journal of Pain requires the use of an appropriate reporting guideline when writing any manuscript. You must submit a completed checklist for the relevant guideline (and flow diagram if applicable) alongside your manuscript, indicating the manuscript page on which each checklist item is found. Checklists are not simply an administrative hurdle. We ask you to complete a checklist because this helps you to ensure transparent and complete reporting in your paper, an essential element for editors and reviewers to evaluate quality and rigor of the study.

Some common study types and the appropriate guidelines are listed below. We strongly encourage authors to visit the Equator Network for a comprehensive overview of reporting guidelines, and visit www.goodreports.org to assist in identifying the appropriate reporting guideline.

-Systematic review or meta-analysis of the existing literature. Use the **PRISMA** guideline for systematic reviews or meta-analyses, and the PRISMA-ScR for scoping reviews.

- Qualitative study or focus group. Use the COREQ checklist.

- Animal research. Use the **ARRIVE** guideline for research on animals in a lab.

- Research into diagnosis. Use the **STARD** guideline if you compared the accuracy of a diagnostic test with an established reference standard test.

- Multivariable prognostic research. Use the **TRIPOD** for prognostic model research.

Reporting clinical trials. We encourage authors to enhance the quality of their intervention reporting by using the TIDieR guideline. Specific reporting checklists based on clinical trial design is described below.

Reporting research into an intervention, treatment, exposure, or protective factor on people.

Use the **CONSORT** guideline or one of its extensions: If you selected your participants before they received the intervention/exposure/etc. under study, AND You controlled which intervention/exposure/etc. they each received, AND You used a random allocation method to decide which intervention/exposure/etc. they each received. ie: a randomized controlled trial.

Randomized controlled trials should be presented according to the CONSORT guidelines. You can use CONSORT checklist extensions (i.e., cluster trials) for different designs and types of trials. At manuscript submission, authors must provide the CONSORT checklist accompanied by a flow diagram that illustrates the progress of patients through the trial, including recruitment,

enrollment, randomization, withdrawal and completion, and a detailed description of the randomization procedure.

Use the **STROBE** guideline or one of its extensions: If you selected your participants after they received the intervention/exposure/etc. under study, OR You selected your participants before they received the intervention/exposure/etc. under study AND you did not control which intervention/exposure/etc. they received (they decided/their doctor decided/life just happened) ie: an observational study.

Use the **TREND** guideline: If you selected your participants before they received the intervention/exposure/etc. under study, AND You used a non-random way to decide which intervention/exposure/etc. your participants received, such as which hospital they went to or what their clinical symptoms were. ie: a non-randomised trial

Study registration

The Journal of Pain strongly encourages registration of all empirical studies through mechanisms such as the Open Science Framework (www.osf.io), or publication of a protocol. Any pre-registration should be timestamped and available to access at the time of submission. These protocols should include the aims of the research, independent and dependent variables, and measures/methodology used to assess the independent and dependent variables. A full methodology including analysis plan is preferable.

Clinical trials. The Journal will only consider for publication randomized clinical trials that were registered with an appropriate registration agency (such as clinicaltrials.gov) before the first subject was recruited. Registration information must be included at the end of the Abstract.

Systematic reviews. The Journal will only consider for publication systematic reviews and meta-analyses that were registered with an appropriate registration agency such as PROSPERO, an international database of prospectively registered systematic reviews (www.crd.york.ac.uk/PROSPERO/). Please note that registration should take place prospectively -- before the article search was initiated and if this is not the case, please be transparent about when registration took place and reasons for this. Please include registration information at the end of the Abstract.

Scoping reviews. Although pre-registration of protocols for these reviews is not required, authors are encouraged to pre-register their protocols at Open Science Framework (www.osf.io) and are required to communicate whether the study was pre-registered in the manuscript.

Research Data, Code and Materials

This journal encourages and enables you to share data openly that supports your research publication where appropriate, and enables you to interlink the data with your published articles. Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, we encourage use of the FAIR (findable, accessible, interoperable, and reusable) data principles.

This checklist may be helpful for authors to facilitate use of FAIR data principles:

- Digitally-shareable and publicly available on an open repository
- Persistent identifier
- In a format that is time-stamped, immutable and permanent (i.e., university repository, registered on Open Science Framework, or an independent repository)
- Are the raw data available?
- If not, derived data must include descriptions of how the data were constructed or, even better, provide the code used to construct the data
- Is a data dictionary (i.e., a codebook or meta-data describing the data) included with sufficient description for an independent researcher to reproduce the reported analyses and results?
- Does the data have an open license allowing others to copy, distribute and make use of the

data while allowing the license to retain credit and copyright as applicable? i.e., Creative commons copyright licenses - CC0, CC-BY etc.)

- Are all the collected data available?
- If not, and only a subset of the data is available, is it the data used to conduct the reported analyses? It must include descriptions of how the data were reduced from the complete dataset or, even better, provide the code to reduce the dataset.
- Is the data protected access? If so, the repository must publicly describe the steps necessary to obtain the data and detailed data documentation (i.e., variable names and allowed values) must be made available publicly.

This journal also encourages you to share your software, code, models, algorithms, protocols, methods and other useful study materials related to the project.

Below are a number of ways in which you can associate data with your article and make a statement about the availability of your data when submitting your manuscript. If you are sharing data in one of these ways, you are encouraged to cite the data in your manuscript and reference list. Please refer to the "References" section for more information about data citation. For more information on depositing, sharing and using research data and other relevant research materials, visit the research data page.

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (i.e., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

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References

There are no strict requirements on reference formatting upon initial submission. References can be in any style or format as long as the style is consistent; however, requirements for reference

formatting are more stringent if authors are asked to revise (see REVISED SUBMISISONS section below.). Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is highly encouraged.

The International Committee of Medical Journal Editors (ICJME) state that authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. We require authors to adhere to this recommendation during manuscript preparation. Authors should identify retractions during study screening and immediately prior to publication. This can be achieved automatically through certain versions of reference management software EndNote, Zotero or Papers which notifies the user when referenced articles are retracted and listed in the Retraction Watch Database. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by searching PubMed for "Retracted publication [pt]", where the term "pt" in square brackets stands for publication type, or by going directly to PubMed's list of retracted publications. Due to a potential delay in the time taken for publishers to transmit retraction metadata to PubMed, it is recommended to supplement this search through the Retraction Watch Database (http://retractiondatabase.org/RetractionSearch.aspx)

Reference style

Indicate references in the text by using superscript Arabic numerals in the order in which they appear in the text. The numerals are to be used outside periods and commas, inside colons and semicolons. For further detail and examples, you are referred to the *Manual of Style, A Guide for Authors and editors,* 11th Edition.

In the reference list, number the references in the order in which they appear in the text.

Abbreviate journal names according to the List of Title Word Abbreviations (LTWA).

Examples:

Reference to a journal publication:

1. Van der Geer J, Handgraaf T, Lupton RA. The art of writing a scientific article. J Sci Commun. 2020;163:51–59. https://doi.org/10.1016/j.sc.2020.00372

Reference to a journal publication with an article number:

2. Van der Geer J, Handgraaf T, Lupton RA. The art of writing a scientific article. Heliyon. 2022;19:e00205. https://doi.org/10.1016/j.heliyon.2022.e00205

Reference to a book:

3. Strunk W Jr, White EB. The Elements of Style. 4th ed. New York, NY: Longman; 2000.

Reference to a chapter in a book:

4. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, eds. Introduction to the Electronic Age. New York, NY: E-Publishing Inc; 2020:281–

304.

Reference to a website:

5. Cancer Research UK. Cancer statistics reports for the UK. Accessed 13 March 2023. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2023.

Reference to a dataset:

6. Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions [dataset], Mendeley Data, v1; 2015. https://doi.org/10.17632/xwj98nb39r.1.

Reference to software:

7. Coon E, Berndt M, Jan A, Svyatsky D, Atchley A, Kikinzon E, Harp D, Manzini G, Shelef E, Lipnikov K, Garimella R, Xu C, Moulton D, Karra S, Painter S, Jafarov E, Molins S. Advanced Terrestrial Simulator (ATS) v0.88 (Version 0.88) [computer software]. Zenodo; 2020, March 25. https://doi.org/10.5281/zenodo.3727209.

Formatting requirements

There are no strict formatting requirements but all manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions.

If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes.

Divide the article into clearly defined sections.

Please ensure the text of your paper is double-spaced and includes page numbers - this is an essential peer review requirement.

Figures and tables

Please ensure the figures and the tables included in the single file are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file. The corresponding caption should be placed directly below the figure or table.

Peer review

This journal operates a single anonymized review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. Editors are not involved in decisions about papers which they have written themselves or have been written by family members or colleagues or which relate to products or services in which the editor has an interest. Any such submission is subject to all of the journal's usual procedures, with peer review handled independently of the relevant editor and their research groups. More information on types of peer review.

Revised submissions

Revisions that do not meet journal requirements will be returned to authors and will not be processed. This could cause delays. Please use this checklist to be sure your revision is correctly prepared.

Use of word processing software

Regardless of the file format of the original submission, at revision you must provide us with an

editable file of the entire article. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

This section describes the article structure for this journal.

Pages must be numbered consecutively, beginning with the title page. Manuscripts without numbered pages will be returned to authors for correction. Materials should be presented in this order:

- Cover letter
- Manuscript (as a single file that contains the following): title page (include all authors' names and affiliations), abstract, perspective, key words, text, disclosures, acknowledgments (optional), references, figure legends
- Figures
- Tables
- Reporting Checklists

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List funding sources in this standard way to facilitate compliance to funder's requirements:

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If no funding has been provided for the research, it is recommended to include the following sentence:

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The title should be a concise and informative description of the study and should indicate animal species if the research was conducted on nonhuman animal subjects. Within the title, use nonproprietary names for drugs, and descriptions for devices. Brand name may be mentioned only once within the text (upon first reference), unless essential to the study. The title page should include the authors' names, department(s), institution where the work was done, and institutional affiliations of authors. The corresponding author must be clearly identified and phone/fax/e-mail information must be provided. The corresponding author noted on the manuscript's title page must

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Data Statement should also be included in all manuscripts, outlining availability of the data to readers of the article (if applicable). The Journal of Pain encourages open data at submission.

Study pre-registration statement should also be included in all manuscripts, outlining the registration status of the article and a link to the registration (if applicable). The Journal of Pain encourages pre-registration of all study types.

Open materials statement should also be included in all manuscripts stating if the components of the research methodology needed to reproduce the reported procedure(s) and analyses are publicly available.

Abstract (page 2)

An abstract of 250 words or less should describe concisely the purpose of the study, the main findings, and conclusions, all in one paragraph without subheadings. Abstracts should be specific, clear, unbiased, precise, and balanced. Results of primary and secondary objectives should be included with actual data (i.e., 95% confidence intervals, effect sizes, odds ratios, etc). References may not be included in the abstract.

Perspective

This item, limited to 50 words, should appear at the end of the abstract. The perspective presents a synopsis of the work to facilitate understanding of its significance. Authors of basic science reports should highlight the potential clinical relevance of their results for the benefit of clinical readers. Authors of clinical science reports should highlight the underlying mechanisms for the results, for the benefit of clinical scientists and basic scientists. Example: "Perspective: This article presents the psychometric properties of a new measure of spouse responses to patient chronic pain and well behavior. This measure could potentially help clinicians who seek to assess how spouse responses may contribute to patient pain and disability." References should not be included in the Perspective.

Key words

Five key words should be provided following the Perspective.

Text

Text headings should be as follows:

Introduction: State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results. Limit the introduction to 600 words.

Methods: Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference; only relevant modifcations should be described. Include a statement of patient and public involvement.

Results: Results should be clear and concise.

Discussion: This should explore the significance of the results of the work, not repeat them. Avoid extensive citations and discussion of published literature. Limit the discussion to 1500 words.

Subheadings in the *Methods, Results,* and *Discussion* sections should be used as necessary to aid

organization and presentation, but subheadings and sections should not be numbered. All sections should be written concisely. Note that section labels may not apply to some article types, including Focus Articles and Review Articles.

Essential title page information

- ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
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Highlights are optional yet highly encouraged for this journal, as they increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the example Highlights.

Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

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Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 x 1328 pixels (h x w) or proportionally more. The image should be readable at a size of 5 x 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view Example Graphical Abstracts on our information site.

Acknowledgments

Collate acknowledgments in a separate section at the end of the article before the references; do not include them on the title page, as a footnote to the title, or otherwise. List here those individuals who provided help during the research (e.g, serving on community advisory boards, providing language help, data collection assistance, writing assistance, or proofreading the article). The Acknowledgments section is optional.

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors build footnotes into the text, and this feature may be used. Should this not be the

case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article.

Artwork

This section describes the artwork for this journal.

Artwork

All figures must be cited in the text; figures must be cited in consecutive order (this also applies to individual panels within figures). Within figures, patients' eyes must be masked unless authors receive patient permission. For a consent form, contact the Editorial Office at jpain@jpain.us. TIFF and EPS are the preferred formats for artwork. All type fonts used in studio-created artwork must be either "embedded" in the file or supplied separately. All graphic files supplied as bitmap format (not vector format) in TIFF, JPEG, or GIF must be submitted in sufficiently high resolution (240-300 dpi for grayscale or color images and 600-1000 dpi for line art) to allow for printing. See Elseviers website for guidelines for preparing electronic artwork: https://www.elsevier.com/about/policies-and-standards/author/artwork-and-media- instructions.

Electronic artwork

General points

- Make sure you use uniform lettering and sizing of your original artwork.
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- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Indicate per figure if it is a single, 1.5 or 2-column fitting image.
- For Word submissions only, you may still provide figures and their captions, and tables within a single file at the revision stage.
- Please note that individual figure files larger than 10 MB must be provided in separate source files.

A detailed guide on electronic artwork is available.

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Palermo TM, Riley CA, Mitchell BA. Daily functioning and quality of life in children with sickle cell disease pain: relationship with family and neighborhood socioeconomic distress. *J Pain* 2008;9(9):833-840. doi: 10.1016/j.jpain.2008.04.002

Books

Moseley G, Butler D. Explain Pain Supercharged: The Clinician‘s Manual. Noigroup Publications; 2017

Chapter/article in book Vetter TR. The epidemiology of pediatric chronic pain. In: McClain B, Suresh S, eds. *Handbook of Pediatric Chronic Pain.* Springer; 2011:1-14

Software

Gamer M, Lemon J, Fellows I, Singh P. *Kendall's W: Various coefficients of interrater reliability and agreement.* R package version 0.84.1. Murray Hill, New Jersey: Bell Laboratories; 2019.

Supplement

Buchbinder R, Underwood M, Hartvigsen J, Maher CG. The Lancet Series call to action to reduce low value care for low back pain: An update. *Pain*. 2020; 161(1) (Suppl 1): S57-S64.

Preprint/Epub Ahead of Print Wiech K, Eippert F, Vandekerckhove J, et al. Cortico-Brainstem Mechanisms of Biased Perceptual Decision-Making in the Context of Pain. *J Pain*. Preprint. Posted online Nov 29, 2021. doi:10.1016/j.jpain.2021.11.006.

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