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Review

How to treat chronic pain in rheumatic and musculoskeletal diseases (RMDs) – A pharmacological review

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ABSTRACT

Introduction: Chronic pain is a common symptom of rheumatic diseases that impacts patients' quality of life. While non-pharmacological approaches are often recommended as first-line treatments, pharmacological interventions are important for pain management. However, the effectiveness and safety of different pharmacological treatments for chronic pain in rheumatic diseases are unclear.
Methods: This review critically synthesizes the current evidence base to guide clinicians in selecting appropriate pharmacological treatments for their patients, considering the expected benefits and potential risks and side effects.
Results: For osteoarthritis, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, and antidepressants are commonly used, with NSAIDs being the most recommended. In addition, topical agents, such as topical NSAIDs, are recommended for localized pain relief. For fibromyalgia, amitriptyline, serotonin and noradrenaline reuptake inhibitors (SNRIs), and gabapentinoids are commonly used, with SNRIs being the most recommended. For back pain, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids are used only for acute of flare-up pain, whereas neuropathic pain drugs are only used for chronic radicular pain. For inflammatory rheumatic diseases, disease-modifying antirheumatic drugs (DMARDs) and biological agents are recommended to slow disease progression and manage symptoms.
Conclusion: While DMARDs and biological agents are recommended for inflammatory rheumatic diseases, pharmacological treatments for other rheumatic diseases only alleviate symptoms and do not provide a cure for the underlying condition. The use of pharmacological treatments should be based on the expected benefits and evaluation of side effects, with non-pharmacological modalities also being considered, especially for fibromyalgia.

1. Introduction

Pain is the main reason for consultation and a recurrent demand for treatment for both the symptoms and underlying causes of many musculoskeletal diseases. Traditional management involves the use of analgesics according to the World Health Organization levels: non-opioid analgesics to weak and strong opioid analgesics. However, the use of these drugs has been increasingly debated. First, when the underlying pathology is not an inflammatory disease, non-pharmacological treatments, including physical activity and physiotherapy, have been shown to be more effective than drugs or infiltrative treatments. In addition, opioid analgesics are directly responsible for many deaths related to the "opioid crisis." This crisis mainly affects the United States but is also responsible for deaths in other countries, such as Canada, England, and Australia. These deaths are linked to opioids prescribed by doctors and to illegally distributed synthetic opioids. Moreover, as reminded in this review, opioids have little efficacy in chronic pain and can lead to various side effects including secondary hyperalgesia. This highly publicized crisis has led to a lack of confidence from patients; most desire non-pharmacological treatment in addition to effective relief

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from their pain. Drug treatments with a different pharmacological action than opioids have also been proposed, such as antidepressant treatments that act on pain via noradrenaline inhibition. In addition, anti-epileptic treatments have long been used for neuropathic pain. These treatments, which are theoretically reserved for neuropathic pain, are increasingly used for chronic pain with the hope of relieving pain and having an opioid-sparing effect. However, the scientific evidence supporting the use of these drugs outside of neuropathic pain remains limited. The objective of this narrative review is to report on the efficacy and limitations of pharmacological treatments for musculoskeletal conditions. A search was conducted for pharmacological treatments evaluated in systematic reviews or cited in guidelines published in the last 10 years (between 2012 and 2022).

2. Back pain with or without radicular pain

Back pain is the most prevalent musculoskeletal condition, with a global point prevalence of 7.3% [1]. Many international guidelines are available, each with various conclusions about pharmacological treatments. Recommendations generally concern acute and chronic low back pain, with the use of the usual analgesics for acute low back pain, while for chronic pain, treatments are mainly non-drug and sometimes combined with neuropathic pain treatments. Paracetamol (acetaminophen), often used as a first-line painkiller, has "no clinical benefit" according to the Belgian guidelines, and the English, American, and Dutch guidelines do not recommend its use. French and Canadian guidelines allow its use only for symptomatic purposes. The advice not to use paracetamol has circulated since the publication of a large randomized controlled trial comparing 550 patients with low back pain and regular use, on-demand use, or placebo, with no difference in pain at 6 weeks [2]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the recommended first-line treatment in all guidelines, except the Danish guidelines, due to multiple meta-analyses identifying a positive effect in the immediate term (–9.2/100) and short term (–7.7/100), but also more side effects than placebo (relative risk 1.40 [1.02–1.93]) [3,4]. Only short-term use of NSAIDs is advised due to their side effects, especially renal and cardiovascular effects. Opioids are never recommended as a first-line treatment; however, they can be used as a second intention in most guidelines, except for the National Institute for Health and Care Excellence (NICE) guidelines, which advise never to use them. The overall efficacy of opioids is moderate, decreasing pain intensity to 10/100, with notable side effects [5]. Adverse effects are both short-term (constipation, nausea, drowsiness, respiratory depression) and long-term (dependence, misuse, overdose), especially when combined with benzodiazepines. A recent high-quality randomized control trial for oxycodone found no effect in acute back pain and could impact future back pain guidelines [6]. Tricyclic antidepressants and serotonin and noradrenaline reuptake inhibitors (SNRIs) are antidepressants that have an effect on pain; however, they are not recommended for acute back pain with or without radicular pain. For chronic back pain, opinions differ; they should not be used according to English and Belgian guidelines, whereas Canadian guidelines state that they can be used, and US guidelines state that duloxetine can be used. French guidelines recommend using antidepressants if there is concomitant depression or for chronic radicular pain.

Gabapentinoids are also controversial treatments; because these treatments are labelled for neuropathic pain, they are theoretically indicated for radicular pain but not for low back pain. However, a large randomized controlled trial including 209 patients with acute or chronic radicular pain found no efficacy of pregabalin, even for the subgroup with neuropathic pain, according to clinical examination [7]. A meta-analysis published before this trial reported that only a few studies evaluating the efficacy of gabapentinoids for back pain were available [8]. Gabapentin had no effectiveness in three trials including 185 participants, pregabalin had minimal efficacy (mean difference 0.42, confidence interval at 95% [0.20 to 0.64]), and both had significantly more side effects than placebo. Consequently, Belgian and English guidelines recommend against using gabapentinoids, Canadian guidelines do not draw any conclusions due to a lack of data, and French guidelines recommend them only if neuropathic pain is present.

Cannabis (cannabidiol [CBD] or tetrahydrocannabinol [THC]) treatment is sometimes used to reduce the prescription of opioid treatments; however, there is a lack of high-quality methodological evidence to recommend its use [9].

The combination of multiple drug treatments is a frequent situation in current practice, and it is linked to the partial effectiveness of analgesics and frequent side effects preventing the use of higher doses. The efficacy of this type of combination has been proven in the treatment of neuropathic pain, namely diabetic pain; however, to our knowledge, it has never been evaluated in low back pain [10].

3. Rheumatic inflammatory diseases

Pain is a leading symptom in rheumatic inflammatory diseases (RIDs), and its appropriate management is historically a high priority for patients. The treat-to-target approach is effective for reducing pain scores; however, as inflammation and tissue damage are predominant, they are not the only drivers of pain [11]. Multiple individual factors, such as illness beliefs, mood, or physical activity, influence pain experience. Due to alterations in central pain regulation mechanisms, a significant number of patients continue to experience moderate pain despite optimal control of inflammatory conditions [12,13]. Beyond their action on peripheral inflammation, overall data on biological disease-modifying anti-rheumatic drugs (bDMARDs) and Janus kinase inhibitors (JAKi) report an effect on pain, with a potential class effect that is more pronounced for JAKi [11]. Regarding other pharmacological treatments, non-specific analgesic drugs are recommended in RID management, with more extensive literature on rheumatoid arthritis (RA).

Paracetamol (acetaminophen) is generally indicated as a first-line treatment for mild pain [14]; however, there are no recent primary studies on paracetamol for the treatment of RID [15,16]. For safety in elderly patients, it may be the only alternative to treat ongoing pain despite optimal disease-modifying therapy. A French group demonstrated that there was no accumulation of the drug following multiples dosing in the elderly [17]. Paracetamol is frequently used in combination with opioids or NSAIDs. Combinations permit lower doses of each analgesic through the simultaneous targeting of different pain pathways.

Opioids are considered to be effective for acute pain but are associated with a number of limitations to their long-term use [14], and there is little data on the benefits and risks of chronic use. Weak opioids for 6 weeks or less can be used to support treatment of RA or spondylarthritis pain, and only if the expected benefits of both pain and function are anticipated to outweigh risks to the patients [18–20]. There is a higher rate of opioid use among RA patients than in the general population [21], yet, there is no evidence to support chronic opioid therapy in other RIDs. Opioids should be used only where other treatments have failed.

Historically used for the treatment of rheumatic diseases, NSAIDs offer analgesic and anti-inflammatory effects. The principal limitations of their prescription are their potential side effects, including gastrointestinal injury, cardiovascular risk, and premature mortality. Combinations of two or more NSAIDs should not be used [16]. Non-selective NSAIDs in combination with proton pump inhibitors (PPIs) or COX-2 selective inhibitors (alone or in

combination with a PPI) may be used at the lowest effective dose for the shortest possible duration in chronic pain, tailored to the individual patient's clinical condition and with close surveillance of adverse events [14]. For axial spondyloarthritis, NSAIDs are the first line treatment and should be use up to the maximum dose, with continuous use only if needed to control symptoms, considering risks of long-term use [18].

Corticosteroids have an analgesic role and are commonly prescribed for short-term pain relief or as a "bridge" while achieving the effects of disease-modifying therapy; however, their long-term side effects reduce their clinical utility in the long term [22]. For these reasons, patients with RIDs, especially RA, should only continue corticosteroids if all other treatments have been trialed and the complications of long-term corticosteroid treatment have been fully discussed. Guidelines recommend the lowest dose for the shortest possible time [23]. In the absence of signs and symptoms of inflammation, expert consensus does not recommend glucocorticoids for the management of pain [16].

Neuromodulators and tricyclic antidepressants alone are not recommended for pain management in RID but may be considered as useful adjuvants in analgesic strategies when pain is partly attributable to fibromyalgia (FM), neuropathy, or in individuals with difficulty sleeping [24,25]. Muscle relaxants, such as benzodiazepines and non-benzodiazepine antispasmodics, should not be used as analgesics in patients with RID as there is insufficient evidence for the treatment of pain and an association with adverse events [16,24].

Eventually, patients often resort to non-prescribed pharmacological alternatives, such as self-therapeutic cannabinoids [26]. Given the limited evidence and different compounds, doses, and routes of administration, there is no consensus on the use of cannabinoids for pain related to RID. Furthermore, there are concerns about potential interactions with drugs commonly used in rheumatology, such as painkillers and corticosteroids [27].

4. Osteoarthritis

International guidelines [28–30] recommend the use of oral NSAIDs, especially non-selective NSAIDs, preferably with an additional PPI or selective COX-2 inhibitor, depending on local guidelines, for patients with knee, hip, hand, and polyarticular OA. In a recent meta-analysis, diclofenac 150 mg/day and etoricoxib 60 mg/day were the most effective in improving chronic pain in patients with knee or hip OA [31]. However, NSAIDs may interact with other medicinal products. Special caution regarding the patient's risk profile and close monitoring is recommended, especially for elderly patients and patients with gastrointestinal, cardiovascular, or renal comorbidities [30,32,33]. These drugs should be taken at the lowest possible dose and for the shortest possible treatment duration. Also, choice of molecule should be considered. Recent analysis showed an increased cardiovascular risk associated with non-selective NSAIDs and diclofenac initiation higher than for other COX-2 inhibitors [34,35].

Paracetamol is commonly used as a first choice for OA pain management, but its efficacy remains unclear. The most recent Osteoarthritis Research Society International (OARSI) guidelines do not recommend paracetamol for any OA phenotype or comorbidity subgroup [30] due to little or no efficacy, especially when used as a long-term single-agent therapy [31]. European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) provides a weak recommendation that paracetamol should not be a long-term, regular treatment [28], and EULAR notes that paracetamol can still be administered for a condensed duration [33].

Tramadol was not recommended by OARSI due to a lack of evidence. Tramadol alone and in combination had no significant benefit in reducing mean pain compared to placebo in patients with OA, and moderate-quality evidence reported a greater risk of developing adverse events [36]. The American College of Rheumatology (ACR) conditionally recommends tramadol as an alternative for patients with contraindications to other medications or lack of therapeutic options [29]. Careful monitoring is warranted in chronic pain management strategy, especially for older adults, due to severe safety events, including falls and fractures [37,38]. Extended release should be preferred in geriatric patients [39].

Oral or transdermal opioids are not recommended due to chemical dependency and the strong evidence for limited or no relevant benefit of opioids for OA symptoms. In pain-related function over 12 months, opioids were not superior to treatment with nonopioid medications [40]. Furthermore, chronic use is associated with increased risk of fractures, cardiovascular events, opioid dependence, and mortality [41], and higher doses increase the risk of harm [31]. Opioid use in the elderly requires close supervision, preferably at reduced doses.

Duloxetine is a potent SNRI that modulates pain in the central nervous system. It may be used for knee OA patients with widespread pain and/or depression due to its specific effect on depressive symptoms, and it may be an option for managing neuropathic pain related to chronic musculoskeletal pain due to OA [42–44]. OARSI guidelines do not recommend duloxetine for patients with hip or polyarticular OA due to a lack of evidence [30]; in contrast, ACR recommend duloxetine for patients with knee, hip, and hand OA in belief of a similar effect on depressive symptoms and neuropathic like pain features [29].

Topical agents, especially topical NSAIDs, are recommended in the first line, with similar pain relief as oral NSAIDs, especially when few or small joints are affected [29,31,33]. Diclofenac has the greatest effect on pain and physical function, regardless of the dose [31]. Because of its deep location, no guidelines have considered topical NSAIDs for hip OA. There are no data available on the long-term effects of topical NSAID use [45]. Capsaicin can occasionally be used as a topical analgesic, and it is conditionally recommended for knee OA by the ACR; however, the OARSI and EULAR do not recommend capsaicin due to concerns about poor efficacy and local adverse effects [29,30,33]. Cannabinoids were associated with a greater improvement in osteoarthritis pain compared with other rheumatic diseases in an exploratory cross-sectional study [46]; however, this conclusion was found to be inconsistent [27]. Currently, there is no indication for cannabinoid use in OA.

5. Fibromyalgia

FM is a chronic disorder combining diffuse pain, fatigue, cognitive impairment, and psychological disorders. Recently, FM was classified as chronic primary pain in the 11th International Classification of Diseases (ICD-11) [47]. FM is one of the most common causes of chronic pain, with prevalence ranging from 2% to 8% [48,49] depending on the chosen criteria and sample. There is a predominance of women with FM, with a sex ratio (men/women) of 1/3 depending on the cohorts [50,51]. The most recent diagnostic criteria were revised in 2016 [52], and FM can be diagnosed in adults meeting all the following criteria:

- generalized pain, defined as pain in at least four of five regions;
- symptoms have been present at a similar level for at least 3 months;
- Widespread Pain Index (WPI) $\geq$ 7 and Symptom Severity Scale (SSS) score $\geq$ 5 OR WPI 4–6 and SSS score $\geq$ 9;

- a diagnosis of FM is valid irrespective of other diagnoses. A diagnosis of FM does not exclude the presence of other clinically important illnesses.

The authors note that these criteria cannot be used to self-report clinical diagnosis in individual patients [52].

The most recent international recommendations for the management of FM are the revised EULAR recommendations from 2017 [48]. Based on evidence gathered from systematic reviews and meta-analyses investigating the pharmacological/non-pharmacological management of FM, the multidisciplinary international working group concluded that there was a modest effect size for most treatments [48].

5.1. Amitriptyline

The recommendation for amitriptyline in the EULAR review is "weak for" [48]. The working group describes two reviews in which amitriptyline showed efficacy regarding pain, sleep, and fatigue improvement at a dose of 25 mg/day. Since this review, other reviews [53–56], including a Cochrane review, concluded that there was low-quality evidence for the use of amitriptyline to treat pain, with a number needed to treat of 4.1 (2.9–6.7) for 50% pain relief calculated in the Cochrane review by Moore et al. [54]. The effective dose of amitriptyline is low, between 10 to 75 mg/day [55].

Two recent network meta-analyses [57,58] compared the efficacy of amitriptyline to other US Food and Drug Administration (FDA)-approved drugs for FM. In Alberti et al.'s study, amitriptyline 25 mg/day was superior to duloxetine and pregabalin for the outcome of 50% pain relief [58]. According to Farag et al., amitriptyline was more effective than duloxetine, milnacipran, and pregabalin for improving sleep, fatigue, and quality of life.

5.2. Serotonin and noradrenaline reuptake inhibitors

In the EULAR recommendations, the SNRIs duloxetine and milnacipran have a "weak for" recommendation for use [48]. Since the publication of these recommendations, several reviews and meta-analyses were published confirming the findings of the EULAR review.

In a network meta-analysis, duloxetine, with dose ranging from 60 to 120 mg/day, was associated with the highest pain reduction (SMD, −0.33; 95% CI, −0.36 to −0.30) compared with other FDA-approved pharmacological treatments for FM [57]. In addition, duloxetine was significantly more effective than placebo for the outcome of 30% pain relief [58]. Lee et al. confirmed the superiority of both duloxetine and milnacipran over placebo for achieving pain relief of 30% or more [59]. Finally, a Cochrane review in 2018 for both SNRIs [60] and one in 2015 for milnacipran [61] found no clinically relevant benefit over placebo for 50% pain relief and found clinically relevant benefit for 30% pain relief.

5.3. Gabapentinoids

Regarding anticonvulsants, EULAR conclusions range from "weak" for pregabalin to "research only" for gabapentin [48]. Since the publication of the EULAR systematic review, few reviews and meta-analyses have been published with the same conclusions regarding pregabalin. Pregabalin (dose 450 mg/day) is significantly more effective than placebo for the 30% pain relief outcome [58] and is associated with (in addition to duloxetine) the highest probability of effectiveness in treating FM [57].

Gabapentin is far less studied than pregabalin, and since the publication of the EULAR systematic review, there has only been one extensive review on its effectiveness. In their Cochrane review, Cooper et al. concluded that evidence for both efficacy and harm were very low, and it was thus impossible to support or refute the suggestion that gabapentin reduces pain in FM [62].

5.4. Other molecules

5.4.1. Tramadol

In the EULAR recommendations, tramadol has a "weak for" evaluation. Since the EULAR publication, two systematic reviews regarding tramadol use for FM have been published that yielded different conclusions. The review by MacLean and Schwartz reported "fair evidence" for the use of tramadol as a second-line therapy [63]. In contrast, in their review, da Rocha et al. suggested that there is not enough available evidence to support or refute the use of tramadol in FM [64].

5.4.2. Cyclobenzaprine

EULAR issued a "weak for" recommendation for cyclobenzaprine [48]. Since the EULAR systematic review, only one review has been published. Calandre et al. retrieved nine studies evaluating cyclobenzaprine in FM and reported conflicting results regarding its efficacy on pain relief [56]. Cyclobenzaprine improves global functioning and moderately improves sleep quality [56]. Its lack of efficacy on pain was highlighted in the EULAR recommendations [48].

5.4.3. Mirtazapine

A Cochrane systematic review concluded, based on low- to very low-quality evidence, that there was no evidence for the effect of mirtazapine on the 50% pain relief outcome but clinically significant benefit on the 30% pain relief outcome; however, these improvements might be overshadowed by potential harms [65].

5.4.4. Ketamine

In three reviews regarding the use of ketamine in FM, none of the authors reported a long-term lasting effect of ketamine on pain [66–68].

5.4.5. Cannabinoids

A Cochrane systematic review on cannabinoids for FM was published in 2016 [69]. Only two studies were included in this review, and the authors concluded that there was a lack of evidence to support the use of cannabinoids in FM [69]. More recent reviews suggest the efficacy of cannabinoids in FM; however, these reviews are associated with serious methodological limitations [70,71].

Therefore, only a small proportion of FM patients will achieve substantial pain relief. As highlighted in the EULAR recommendations, management of FM should focus primarily on non-pharmacological modalities [48].

6. Conclusion

Overall, the available pharmacological treatments for rheumatic diseases (Table 1) highlight the challenge of managing these conditions with medication alone. While treatments, such as NSAIDs, acetaminophen, opioids, and antidepressants, can provide symptom relief, they do not modify the underlying course of the disease. As a result, the use of pharmacological treatments should be guided by assessment of the potential benefits and risks.

Inflammatory rheumatic diseases, such as RA, require aggressive treatment with DMARDs to slow or stop disease progression. However, for most other rheumatic conditions, pharmacological treatments provide only symptomatic relief. This highlights the importance of a comprehensive approach to disease management that includes non-pharmacological therapies, such as exercise, physical therapy, and behavioral interventions.

Table 1
Pharmacological treatments for chronic pain in rheumatic musculoskeletal diseases.

RMD/Molecule	Back pain with or without radicular pain	Rheumatic inflammatory diseases	Osteoarthritis	Fibromyalgia
Paracetamol (acetaminophen)	First line	First line	In short-term use	No sufficient data to conclude
Opioids	Second line after evaluation of benefits and risks	Second line after evaluation of benefits and risks	Controversial	Controversial
NSAIDs	At the lowest effective dose and shortest duration	At the lowest effective dose and shortest duration	At the lowest effective dose and shortest duration	No sufficient data to conclude
Corticosteroids	Not recommended	At lowest effective dose and shortest duration in case of active inflammation	Not recommended	Not recommended
SNRIs or tricyclic antidepressants	Only if associated with chronic radicular pain	If associated with fibromyalgia, neuropathy, or difficulty sleeping	In case of widespread pain and/or associated depression	At the lowest effective dose (SNRI or amitriptyline)
Gabapentinoids	Only if associated with chronic radicular pain	Not recommended	Not recommended	Pregabalin recommended (insufficient evidence for gabapentin)
Cannabinoids	No sufficient data to conclude	No sufficient data to conclude	Controversial	Controversial
High-concentration capsaicin	Not recommended	Not recommended	For knee osteoarthritis	Not recommended
Topical NSAIDs	Not recommended	Symptomatic use for small joints	Recommended	Not recommended

RMD: rheumatic and musculoskeletal diseases; NSAIDs: non-steroidal anti-inflammatory drugs; SNRIs: serotonin and noradrenaline reuptake inhibitors.

When considering pharmacological treatments, it is essential to evaluate the expected benefits and potential side effects. While NSAIDs are widely used for pain relief in many rheumatic conditions, their use can be associated with gastrointestinal, cardiovascular, and renal side effects, especially in elderly patients and in patients with comorbidities. Similarly, opioids are associated with a risk of dependence and increased morbidity and mortality, especially with long-term use.

Therefore, healthcare providers must carefully balance the benefits and risks of pharmacological treatments and tailor treatment plans to individual patients. While medications can provide temporary relief of symptoms, non-pharmacological interventions should be considered as part of a comprehensive treatment approach. Ultimately, the goal of treatment for rheumatic diseases should be to improve the patient's quality of life and function while minimizing the risks associated with pharmacological therapies.

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The authors declare that they have no competing interests.

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References

[1] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789–858.
[2] Williams CM, Maher CG, Latimer J, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. Lancet 2014;384:1586–96.
[3] Machado GC, Maher CG, Ferreira PH, et al. Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis. Ann Rheum Dis 2017;76:1269–78.
[4] van der Gaag WH, Roelofs PD, Enthoven WT, et al. Non-steroidal anti-inflammatory drugs for acute low back pain. Cochrane Database Syst Rev 2020;4:CD013581.
[5] Abdel Shaheed C, Maher CG, Williams KA, et al. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis. JAMA Intern Med 2016;176:958–68.
[6] Jones CMP, Day RO, Koes BW, et al. Opioid analgesia for acute low back pain and neck pain (the OPAL trial): a randomised placebo-controlled trial. Lancet 2023;402:304–12 [S0140-6736(23)00404-X].
[7] Mathieson S, Maher CG, McLachlan AJ, et al. Trial of pregabalin for acute and chronic sciatica. N Eng J Med 2017;376:1111–20.
[8] Shanthanna H, Gilron I, Rajarathinam M, et al. Benefits and safety of gabapentinoids in chronic low back pain: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2017;14:e1002369.
[9] Takakuwa KM, Hergenrather JY, Shofer FS, et al. The impact of medical cannabis on intermittent and chronic opioid users with back pain: how cannabis diminished prescription opioid usage. Cannabis Cannabinoid Res 2020;5:263–70.
[10] Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. Lancet 2022;400:680–90.
[11] Alciati A, Di Carlo M, Siragusano C, et al. Effect of biological DMARDs and JAK inhibitors in pain of chronic inflammatory arthritis. Expert Opin Biol Ther 2022;22:1311–22.
[12] Vergne-Salle P, Pouplin S, Trouvin AP, et al. The burden of pain in rheumatoid arthritis: impact of disease activity and psychological factors. Eur J Pain 2020;24:1979–89.
[13] Monforte Gasque MP, Lázaro Gallardo EM, Lázaro Castellano AM, et al. [Assessment of pain in patients with rheumatic disease under biological therapy treatment]. An Sist Sanit Navar 2022;45:e1020.
[14] Geenen R, Overman CL, Christensen R, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. Ann Rheum Dis 2018;77:797–807.
[15] National Guideline Centre (UK). Analgesics: rheumatoid arthritis in adults: diagnosis and management: evidence review G. London: National Institute for Health and Care Excellence (NICE); 2018.
[16] Whittle SL, Colebatch AN, Buchbinder R, et al. Multinational evidence-based recommendations for pain management by pharmacotherapy in inflammatory arthritis: integrating systematic literature research and expert opinion of a broad panel of rheumatologists in the 3e Initiative. Rheumatology (Oxford) 2012;51:1416–25.
[17] Bannwarth B, Pehourcq F, Lagrange F, et al. Single and multiple dose pharmacokinetics of acetaminophen (paracetamol) in polymedicated very old patients with rheumatic pain. J Rheumatol 2001;28:182–4.
[18] Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 2023;82:19–34.
[19] Whittle SL, Richards BL, Husni E, et al. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev 2011;11:CD003113.
[20] Whittle SL, Richards BL, Buchbinder R. Opioid analgesics for rheumatoid arthritis pain. JAMA 2013;309:485–6.
[21] Anastasiou C, Yazdany J. Review of publications evaluating opioid use in patients with inflammatory rheumatic disease. Curr Opin Rheumatol 2022;34:95–102.
[22] Oray M, Abu Samra K, Ebrahimiadib N, et al. Long-term side effects of glucocorticoids. Expert Opin Drug Saf 2016;15:457–65.
[23] Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–99.
[24] Sánchez-Flórez JC, Seija-Butnaru D, Valero EG, et al. Pain management strategies in rheumatoid arthritis: a narrative review. J Pain Palliat Care Pharmacother 2021;35:291–9.

[25] Katz WA. Use of nonopioid analgesics and adjunctive agents in the management of pain in rheumatic diseases. Curr Opin Rheumatol 2002;14:63–71.
[26] Rampakakis E, Thorne C, Cesta A, et al. Medical cannabis use by rheumatology patients in routine clinical care: results from The Ontario Best Practices Research Initiative. Clin Exp Rheumatol 2023;41:118–25.
[27] Jain N, Moorthy A. Cannabinoids in rheumatology: friend, foe or a bystander? Musculoskeletal Care 2022;20:416–28.
[28] Bruyère O, Honvo G, Veronese N, et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum 2019;49:337–50.
[29] Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2020;72:149–62.
[30] Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019;27:1578–89.
[31] da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ 2021;375:n2321.
[32] Pelletier J-P, Martel-Pelletier J, Rannou F, et al. Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: evidence from real-life setting trials and surveys. Semin Arthritis Rheum 2016;45:S22–7.
[33] Kloppenburg M, Kroon FP, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Ann Rheum Dis 2019;78:16–24.
[34] Schmidt M, Sørensen HT, Pedersen L. Cardiovascular risks of diclofenac versus other older cox-2 inhibitors (meloxicam and etodolac) and newer cox-2 inhibitors (celecoxib and etoricoxib): a series of nationwide emulated trials. Drug Saf 2022;45:983–94.
[35] Pontes C, Marsal JR, Elorza JM, et al. Analgesic use and risk for acute coronary events in patients with osteoarthritis: a population-based, nested case-control study. Clin Ther 2018;40:270–83.
[36] Toupin April K, Bisaillon J, Welch V, et al. Tramadol for osteoarthritis. Cochrane Database Syst Rev 2019;5:CD005522.
[37] Li L, Marozoff S, Lu N, et al. Association of tramadol with all-cause mortality, cardiovascular diseases, venous thromboembolism, and hip fractures among patients with osteoarthritis: a population-based study. Arthritis Res Ther 2022;24:85.
[38] Musich S, Wang SS, Schaeffer JA, et al. Safety events associated with tramadol use among older adults with osteoarthritis. Popul Health Manag 2021;24:122–32.
[39] Vorsanger G, Xiang J, Jordan D, et al. Post hoc analysis of a randomized, double-blind, placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. Clin Ther 2007;29:2520–35.
[40] Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. JAMA 2018;319:872–82.
[41] Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med 2010;170:1968–76.
[42] Pergolizzi JV, Raffa RB, Taylor R, et al. A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. Pain Pract 2013;13:239–52.
[43] Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. Age Ageing 2012;41:646–52.
[44] Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain 2009;146:253–60.
[45] Zeng C, Wei J, Persson MSM, et al. Relative efficacy and safety of topical non-steroidal anti-inflammatory drugs for osteoarthritis: a systematic review and network meta-analysis of randomised controlled trials and observational studies. Br J Sports Med 2018;52:642–50.
[46] Frane N, Stapleton E, Iturriaga C, et al. Cannabidiol as a treatment for arthritis and joint pain: an exploratory cross-sectional study. J Cannabis Res 2022;4:47.
[47] Treede R-D, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the International Classification of Diseases (ICD-11). Pain 2019;160:19–27.
[48] Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017;76:318–28.
[49] Sarzi-Puttini P, Salaffi F, Di Franco M, et al. Pain in rheumatoid arthritis: a critical review. Reumatismo 2014;66:18–27.
[50] Sarzi-Puttini P, Giorgi V, Atzeni F, et al. Fibromyalgia position paper. Clin Exp Rheumatol 2021;39:186–93.
[51] Wolfe F, Walitt B, Perrot S, et al. Fibromyalgia diagnosis and biased assessment: sex, prevalence and bias. PLoS One 2018;13:e0203755.
[52] Wolfe F, Clauw DJ, Fitzcharles M-A, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46:319–29.
[53] de Farias ÁD, Eberle L, Amador TA, et al. Comparing the efficacy and safety of duloxetine and amitriptyline in the treatment of fibromyalgia: overview of systematic reviews. Adv Rheumatol 2020;60:35.
[54] Moore RA, Derry S, Aldington D, et al. Amitriptyline for fibromyalgia in adults. Cochrane Database Syst Rev 2019;5:CD011824.
[55] Rico-Villademoros F, Slim M, Calandre EP. Amitriptyline for the treatment of fibromyalgia: a comprehensive review. Expert Rev Neurother 2015;15:1123–50.
[56] Calandre EP, Rico-Villademoros F, Slim M. An update on pharmacotherapy for the treatment of fibromyalgia. Expert Opin Pharmacother 2015;16:1347–68.
[57] Farag HM, Yunusa I, Goswami H, et al. Comparison of amitriptyline and us food and drug administration–approved treatments for fibromyalgia: a systematic review and network meta-analysis. JAMA Netw Open 2022;5:e2212939.
[58] Alberti FF, Becker MW, Blatt CR, et al. Comparative efficacy of amitriptyline, duloxetine and pregabalin for treating fibromyalgia in adults: an overview with network meta-analysis. Clin Rheumatol 2022;41:1965–78.
[59] Lee YH, Song GG. Comparative efficacy and tolerability of duloxetine, pregabalin, and milnacipran for the treatment of fibromyalgia: a Bayesian network meta-analysis of randomized controlled trials. Rheumatol Int 2016;36:663–72.
[60] Welsch P, Üçeyler N, Klose P, et al. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. Cochrane Database Syst Rev 2018;2:CD010292.
[61] Cording M, Derry S, Phillips T, et al. Milnacipran for pain in fibromyalgia in adults. Cochrane Database Syst Rev 2015;2015:CD008244.
[62] Cooper TE, Derry S, Wiffen PJ, et al. Gabapentin for fibromyalgia pain in adults. Cochrane Database Syst Rev 2017;1:CD012188.
[63] MacLean AJB, Schwartz TL. Tramadol for the treatment of fibromyalgia. Expert Rev Neurother 2015;15:469–75.
[64] da Rocha AP, Mizzaci CC, Nunes Pinto ACP, et al. Tramadol for management of fibromyalgia pain and symptoms: systematic review. Int J Clin Pract 2020;74:e13455.
[65] Welsch P, Bernardy K, Derry S, et al. Mirtazapine for fibromyalgia in adults. Cochrane Database Syst Rev 2018;8:CD012708.
[66] Littlejohn G, Guymer E. Modulation of NMDA receptor activity in fibromyalgia. Biomedicines 2017;5:15.
[67] Israel JE, St Pierre S, Ellis E, et al. Ketamine for the treatment of chronic pain: a comprehensive review. Health Psychol Res 2021;9:25535.
[68] Pastrak M, Abd-Elsayed A, Ma F, et al. Systematic review of the use of intravenous ketamine for fibromyalgia. Ochsner J 2021;21:387–94.
[69] Walitt B, Klose P, Fitzcharles M-A, et al. Cannabinoids for fibromyalgia. Cochrane Database Syst Rev 2016;7:CD011694.
[70] Fitzcharles M-A, Petzke F, Tölle TR, et al. Cannabis-based medicines and medical cannabis in the treatment of nociplastic pain. Drugs 2021;81:2103–16.
[71] Cameron EC, Hemingway SL. Cannabinoids for fibromyalgia pain: a critical review of recent studies (2015–2019). J Cannabis Res 2020;2:19.