Nonopioid Pharmacologic Management of Chronic Noncancer Pain

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Chronic pain (ie, present for at least 3 months) is highly prevalent, affecting 1 in 5 US adults, and can be debilitating. Treatment includes a comprehensive, patient-centered biopsychosocial approach that identifies pain type, focuses on improving function and quality of life, sets reasonable expectations around pain control, promotes self-management strategies, addresses mental health comorbidities, and includes pharmacotherapy and nonpharmacotherapy options. For osteoarthritis, topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs) provide significant pain relief; limited evidence suggests benefit from serotonin-norepinephrine reuptake inhibitors (SNRIs) and gabapentinoids. For chronic low back pain, no pharmacotherapy offers significant pain or functional benefit; evidence is limited to short-term outcomes. Oral and topical NSAIDs and SNRIs appear to improve pain slightly in the short term. For neuropathic pain, duloxetine, gabapentin, pregabalin, and high-concentration (8%) topical capsaicin provide moderate pain benefit. For fibromyalgia, pregabalin has the best evidence for moderate pain benefit, followed by the SNRIs duloxetine and milnacipran. Opioids should be considered only after other strategies have been tried and after risk-benefit assessment.

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Chronic pain is a highly prevalent condition that is experienced by 1 in 5 US adults.[1] In addition to being the leading cause of disability, chronic pain is associated with reduced life expectancy.[2,3] Unlike acute pain, which signals tissue injury that is transient, chronic pain is a complex phenomenon that persists for 3 months or longer, after injured tissue has healed, and is influenced by biologic, psychological, and social factors.[4,5]

PAIN MANAGEMENT PRINCIPLES

An individualized, patient-centered approach using shared decision-making is recommended for managing chronic pain. Some general principles include the following[6]:

- Assessing and documenting the source(s) and type(s) of pain
- Focusing on functional goals and quality of life
- Setting reasonable expectations around pain control
- Promoting self-management strategies (including patient education about the condition)
- Taking a multimodal approach that addresses mental health comorbidities and offers nonpharmacologic and nonopioid pharmacologic options

When initiating pharmacotherapy, physicians should titrate to the lowest effective dose that improves pain and function, monitor for adverse effects, and consider alternative drugs when minimal benefit occurs after a therapeutic dose is reached or the adverse effects become intolerable.[7-9] More resources are available in the American Academy of Family Physicians Chronic Pain Management Toolkit.[6]

Evidence supporting nonopioid pharmacologic management of chronic pain has significant limitations. In general, most studies last only a few months and most compare drugs with placebo rather than direct comparisons. Evidence can be limited to specific sources or types of chronic pain. Systematic reviews and meta-analyses are hampered by heterogeneity in patient populations, study procedures, and outcomes measures.

CONDITION MANAGEMENT

Osteoarthritis

For osteoarthritis (OA), the bulk of evidence comes from studies of hip and knee OA, although evidence for topical drugs for hip OA is limited due to concerns about inability of topical drugs to reach the deep joint. The statements presented here generally follow the 2019 American College of Rheumatology/Arthritis Foundation guidelines, with explanations for differences.[10]

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TABLE 1

Drugs for Managing Chronic Neuropathic Pain and Fibromyalgia

Drugs	Typical dosage	Major adverse effects	Select prescribing information	Evidence rating*
Tricyclic antidepressants				
Amitriptyline	Starting: 10-25 mg/day Usual: 25-125 mg/day Maximum: 150 mg/day	Blurred vision, constipation, disorientation, dizziness, drowsiness, dry mouth, headache, orthostatic hypotension, tremors, urinary retention, weight gain	Use with caution in older patients, those with kidney or liver impairment, with a history of cardiovascular disease (eg, prior myocardial infarction, stroke, tachycardia, conduction abnormalities), and those taking other serotonergic or anticholinergic drugs Avoid abrupt discontinuation Monitor for worsening of depression symptoms and suicide risk at beginning of treatment Secondary amines (eg, nortriptyline) may be better tolerated than tertiary amines (eg, amitriptyline)	C
Nortriptyline	Starting: 10-25 mg/day Usual: 25-100 mg/day Maximum: 150 mg/day			
Serotonin-norepinephrine reuptake inhibitors				
Duloxetine	Starting: 30 mg/day Usual: 60 mg/day (once daily or divided in 2 doses/day) Maximum: 120 mg/day	Constipation, dizziness, drowsiness or fatigue, dry mouth, headache, increased blood pressure, insomnia, nausea	Avoid use in those with chronic liver disease, if creatinine clearance < 30 mL/min/1.73 m2 (0.5 mL/s/m2), and with other serotonergic drugs Avoid abrupt discontinuation Monitor for worsening of depression symptoms and suicide risk at beginning of treatment	A
Milnacipran (Savella)	Starting: 12.5 mg/day Usual: 50 mg, 2 times/day Maximum: 100 mg, 2 times/day	Constipation, dizziness, dry mouth, headache, hyperhidrosis, increased blood pressure, increased heart rate, insomnia, nausea, palpitations, vomiting	Dose adjustment for kidney impairment Use caution with other serotonergic drugs Avoid abrupt discontinuation Monitor for worsening of depression symptoms and suicide risk at beginning of treatment	A
Venlafaxine	Starting: 37.5 mg/day Usual: 150-225 mg/day Maximum: 225 mg/day	Anorexia, constipation, dry mouth, erectile dysfunction, increased blood pressure, nausea, somnolence, sweating	Dose adjustments for kidney and liver impairment Use caution with other serotonergic drugs Avoid abrupt discontinuation Monitor for worsening of depression symptoms and suicide risk at beginning of treatment	C

continues ➤

*—A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

†—Used only for neuropathic pain.

TABLE 1 (continued)

Drugs for Managing Chronic Neuropathic Pain and Fibromyalgia

Drugs	Typical dosage	Major adverse effects	Select prescribing information	Evidence rating*
Antiepileptic drugs				
Gabapentin	Starting: 100-300 mg/day Usual: 900-3,600 mg/day in 3-4 divided doses Maximum: 3,600 mg/day	Ataxia, dizziness, edema, somnolence, weight gain	Dose adjustment for kidney impairment Can increase risk of respiratory depression in combination with opioids Risk of misuse Monitor for worsening of depression symptoms and suicide risk	B
Pregabalin	Starting: 75-150 mg in 2-3 divided doses Usual: 300-450 mg/day in 2-3 divided doses Maximum: 600 mg/day	Blurred vision, dizziness, dry mouth, edema, somnolence, weight gain	Dose adjustment for kidney impairment Can increase risk of respiratory depression in combination with opioids Risk of misuse Monitor for worsening of depression symptoms and suicide risk Patients who do not experience adequate benefit with gabapentin may benefit from switch to pregabalin, given different pharmacokinetic profile Gabapentin to pregabalin conversion is approximately 6:1	A
Topical drugs				
Capsaicin				
Cream†	Usual: apply film to affected area 3-4 times/day	Application-site reaction (erythema, itching, pain)	Wash hands thoroughly after applying Derived from chili peppers, so may cause burning or stinging sensation at application site	C
8% patch†	Usual: apply up to 4 patches for 30-60 minutes (depending on indication) every 3 months	Application-site reaction (erythema, itching, pain), increased blood pressure	Must be applied by health care professional in a well-ventilated area (inpatient or outpatient setting) Requires administration per protocol	B
Lidocaine				
Cream or ointment	Based on product, usually applied 2-4 times/day	Application-site reaction (burning, irritation, itching, redness)	Available in multiple strengths	C
4% or 5% patch	Usual: 1-3 patches; used once for up to 12 hours in 24-hour period Maximum: 3 patches/day	Application-site reaction (burning, irritation, itching, redness)	Patches may be cut into smaller sizes	C

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†—Used only for neuropathic pain.

TABLE 2

Drugs for Managing Nonneuropathic Pain

Drugs	Typical dosage	Key indications	Major adverse effects
Serotonin-norepinephrine reuptake inhibitors			
Duloxetine	Starting: 30 mg/day Usual: 60 mg/day (once daily or divided 2 times/day) Maximum: 120 mg/day	Osteoarthritis Low back pain	Constipation, dizziness, dry mouth, fatigue, headache, increased blood pressure, insomnia, nausea
Milnacipran (Savella)	Starting: 12.5 mg/day Usual: 50 mg 2 times/day Maximum: 100 mg, 2 times/day	Musculoskeletal pain	Constipation, dizziness, dry mouth, headache, hyperhidrosis, increased blood pressure, increased heart rate, insomnia, nausea, palpitations, vomiting
Venlafaxine	Starting: 37.5 mg/day Usual: 150-225 mg/day Maximum: 225 mg/day	Musculoskeletal pain	Anorexia, constipation, dry mouth, erectile dysfunction, increased blood pressure, nausea, somnolence, sweating
Topical drugs			
Capsaicin cream	Usual: apply film to affected area 3-4 times/day	Low back pain	Application-site reaction (erythema, itching, pain)
Diclofenac 1% gel (topical)	Usual: 2 or 4 g (depending on location), 4 times/day Maximum: 32 g/day	Osteoarthritis Low back pain	Application-site reaction (erythema, itching, pain; less severe than capsaicin)
Lidocaine			
Cream or ointment	Based on product, usually applied 2-4 times/day	Osteoarthritis Low back pain	Application-site reaction (burning, irritation, itching, redness)
4% or 5% patch	Usual: 1-3 patches; applied once for up to 12 hours in 24-hour period Maximum: 3 patches/day	Osteoarthritis Low back pain	Application-site reaction (burning, irritation, itching, redness)
Menthol/methyl salicylate	Usual: apply to affected area 3-4 times/day	Osteoarthritis Low back pain	Application-site reaction (burning, irritation, itching, redness, and dryness)

CNS = central nervous system; NSAID = nonsteroidal anti-inflammatory drug.

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Select prescribing information	Evidence rating*
Avoid use in those with chronic liver disease and if creatinine clearance < 30 mL/min/1.73 m^2 (0.5 mL/s/m^2) Use caution with other serotonergic drugs Avoid abrupt discontinuation Monitor for worsening of depression symptoms and suicide risk at beginning of treatment	A
Dose adjustments for kidney impairment Use caution with other serotonergic drugs Avoid abrupt discontinuation Monitor for worsening of depression symptoms and suicide risk at beginning of treatment	A
Dose adjustments for kidney and liver impairment Use caution with other serotonergic drugs Avoid abrupt discontinuation Monitor for worsening of depression symptoms and suicide risk at beginning of treatment	C
Wash hands thoroughly after applying Derived from chili peppers, so may cause burning or stinging sensation at application site	C
Dosing depends on extremity being applied to Less systemic absorption compared with oral NSAIDs (up to 6% of the systemic levels of a single oral dose) Prescribing information lists same risks as with oral NSAIDs; however, may be better tolerated given less systemic absorption Use dosing card to measure dose	A
Available in multiple strengths	C
Patches may be cut into smaller sizes	C
Available in multiple forms (eg, balm, cream, patch)	C

continues ➤

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have high-quality evidence of benefit for knee OA, are safe, and are well tolerated.[11,12] A Cochrane review comprising information mostly about knee OA, with some inclusion of hand OA, showed topical diclofenac has a number needed to treat (NNT) of 10 and topical ketoprofen (available in the United States through compounding pharmacies) has an NNT of 7 to achieve at least 50% reduction in pain.[13]

Oral NSAIDs are also beneficial for OA, with a network meta-analysis showing improvements in pain and physical function in hip and knee OA.[14]

Fewer safety concerns occurred with topical NSAIDs than with oral NSAIDs.[14] Topical NSAIDs have similar adverse event rates to placebo. Although adverse event rates are relatively low for all oral NSAIDs, they are consistently higher than placebo. With similar effectiveness for improvement in pain but a better side effect profile, topical NSAIDs are first-line pharmacotherapy for knee and hand OA, followed by oral NSAIDs for knee, hip, or hand OA.[10,14]

Serotonin-norepinephrine reuptake inhibitors appear to be beneficial for OA based primarily on studies of duloxetine. Although these studies demonstrate a clinically insignificant mean improvement in pain scores and physical function for knee and hip OA, more patients treated with duloxetine had at least 50% improvement in pain (NNT = 6) compared with placebo. This suggests that a subpopulation of patients will have notable benefit from duloxetine as OA treatment.[15]

There is limited evidence that gabapentinoids may offer a small improvement in pain levels compared with placebo.[16]

Numerous drugs have no benefit and should be avoided to prevent inappropriate use and wasted resources. Cochrane reviews document lack of benefit with acetaminophen, chondroitin, or glucosamine in treatment of OA.[17-19] Although the 2019 American College of Rheumatology/Arthritis Foundation guidelines conditionally recommend topical capsaicin for knee OA, a Cochrane review found low-quality evidence to support it and relatively high rates of adverse events.[10,20]

Low Back Pain

In the treatment of chronic low back pain, no drug provides significant improvement in pain

or function, and no studies report on long-term (greater than 12 month) outcomes.

Oral NSAIDs have low-quality evidence of benefit for chronic low back pain with 3 to 12 months of use. Oral NSAIDs are associated with small improvements in pain and disability, without an increase in reported adverse events.[21] Topical NSAIDs are recommended in the treatment of chronic low back pain and are as effective as oral NSAIDs, with greater

TABLE 2 (continued)

Drugs for Managing Nonneuropathic Pain

Drugs	Typical dosage	Key indications	Major adverse effects
Muscle relaxants			
Baclofen	Starting: 5 mg, 3 times/day Usual: 5-10 mg, 3 times/day Maximum: 80 mg/day	Low back pain	Dizziness, drowsiness, weakness
Carisoprodol	Usual: 250-350 mg, 3 times/day and at bedtime Maximum: 1,400 mg/day	Low back pain	Dizziness, drowsiness, headache
Cyclobenzaprine	Starting: 5-10 mg/day Usual: 5-10 mg, 3 times/day Maximum: 40 mg/day	Low back pain	Drowsiness, dry mouth, fatigue, headache
Methocarbamol	Starting: 1,500 mg 3-4 times/day for 2-3 days then decrease Usual: 750 mg, 4 times/day Maximum: 8,000 mg/day	Low back pain	Confusion, dizziness, drowsiness
Tizanidine	Usual: 2-4 mg every 8-12 hours Maximum: 36 mg/day	Low back pain	Constipation, dizziness, dry mouth, dyskinesia, elevated liver function test results, hypotension, nervousness, rhinitis, somnolence, vomiting
Other			
Acetaminophen	Usual: 325-1,000 mg every 4-8 hours, depending on product Maximum: 4,000 mg/day	Osteoarthritis Low back pain	Nausea, vomiting, headache, insomnia
NSAIDs (oral)	Depends on the specific drug	Osteoarthritis Low back pain	Abdominal pain, constipation, diarrhea, dizziness, dyspepsia, edema, elevated liver enzymes, flatulence, headaches, heartburn, nausea, vomiting

CNS = central nervous system; NSAID = nonsteroidal anti-inflammatory drug.

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safety.[22] Acetaminophen has not been studied in chronic low back pain.

There is low-quality and limited evidence for the benefit of benzodiazepine and muscle relaxant use in low back pain, but most trials assessed benefit for less than 3 weeks.[23-26] Long-term use has not been studied and is not recommended, based on the risk of adverse events with both drug classes.

There is moderate-quality evidence that serotonin-norepinephrine reuptake inhibitors have a small effect on pain intensity and a trivial effect on disability.[27] There is low-quality evidence that selective serotonin reuptake inhibitors have little to no effect on pain intensity or disability.[27] There is moderate-quality evidence that tricyclic antidepressants have little to no effect on pain intensity and a small effect on disability and are associated with frequent adverse events, with a number needed to harm of 12.[27] The National Institute for Health and Care Excellence guidelines recommend against routine use of serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants for chronic low back pain.[28]

There is no evidence of benefit, but there is evidence of harms, with antiepileptics, including gabapentinoids.[4,28] The National Institute for Health and Care Excellence guidelines recommend against gabapentinoid and antiepileptic use in low back pain due to adverse effects, including dizziness, somnolence, fatigue, headache, weight gain, and peripheral edema.[28]

Select prescribing information	Evidence rating*
Recommended for short-term use only Use with caution with other CNS depressants due to sedation risk Avoid abrupt discontinuation if using chronically Use with caution in kidney impairment	C
Recommended for short-term use only Use with caution with other CNS depressants due to sedation risk Risk of misuse	C
Recommended for short-term use only Use with caution with other CNS depressants due to sedation risk Avoid use in those with liver impairment	C
Recommended for short-term use only Use with caution with other CNS depressants due to sedation risk	C
Recommended for short-term use only Avoid use with other alpha$_2$ agonists due to risk of hypotension and in those with severe kidney impairment and liver impairment Use with caution with other CNS depressants due to sedation risk	C
Dose adjustment in liver impairment Be aware of total dose of acetaminophen being taken from all sources (including combination products)	C
Avoid use in those with kidney and liver impairment and in those taking anticoagulant drugs due to increased risk of bleeding Use with caution in patients with a history of cardiovascular disease or history of gastrointestinal bleeding or peptic ulcer disease; consider coprescribing proton pump inhibitor Selective cyclooxygenase-2 inhibitors are associated with a lower risk of gastrointestinal complications	A

Neuropathic Pain

Evidence for neuropathic pain treatment comes primarily from studies of postherpetic neuralgia and painful diabetic neuropathy.

Moderate-quality evidence supports duloxetine 60 mg/day, resulting in at least 50% reduction in pain (NNT = 5) compared with placebo for neuropathic pain, based primarily on studies of diabetic peripheral neuropathy.[29] Common adverse effects of duloxetine include nausea, dry mouth, dizziness, and drowsiness or fatigue; serious adverse effects are uncommon.[29] A 2015 Cochrane review and a 2017 meta-analysis found little evidence to support the use of venlafaxine for neuropathic pain due to strong placebo effects and considerable risk of bias from small, short-duration studies.[30,31] Evidence for milnacipran (Savella) in neuropathic pain is limited.[32] Tricyclic antidepressants, including amitriptyline and nortriptyline, are commonly used to treat neuropathic pain; however, large, high-quality studies are lacking.[33,34]

Gabapentin and pregabalin have moderate-quality evidence for at least moderate pain relief.[35,36] Gabapentin at dosages of

1,200 mg/day or greater leads to at least moderate benefit in neuropathic pain compared with placebo, with an NNT ranging from 5 to 7 based on dose and indication. Similarly, pregabalin at dosages of 300 mg/day or greater leads to at least moderate benefit compared with placebo, with an NNT between 4 and 22 based on dose and indication. Patients discontinue gabapentin with a number needed to harm of 30 compared with placebo, whereas the number needed to harm for pregabalin varies from 7 at 600 mg/day to 35 at 300 mg/day. Dizziness and somnolence are the most common adverse events.

Other antiepileptic drugs are less beneficial. Carbamazepine and valproic acid have little evidence for pain benefit. Other anticonvulsants, including lacosamide, lamotrigine, levetiracetam, oxcarbazepine, and topiramate, have no benefit.[37,38]

High-concentration (8%) topical capsaicin has very low- to moderate-quality evidence for moderate pain relief in postherpetic neuralgia, HIV neuropathy, and diabetic neuropathy.[39] There is insufficient data to draw conclusions about low-concentration (less than 1%) topical capsaicin for the treatment of neuropathic pain.[40] Local adverse events are reported by up to two-thirds of patients with low- and high-concentration capsacin.[39-41] The high-concentration capsaicin patch requires administration by a clinician in a well-ventilated area and possibly topical anesthetic before application to reduce discomfort.

Although several studies demonstrate superior effectiveness of two-drug combinations in neuropathic pain, not enough evidence is available to recommend one combination over another.[42]

Fibromyalgia

High-quality evidence demonstrates that pregabalin reduces pain intensity by between 30% and 50% in patients with moderate to severe fibromyalgia pain, with an NNT between 7 and 14.[43] Adverse events are similar to those seen in the neuropathic pain studies.[43] For pain relief of 50% or greater, pregabalin has an NNT of 11 compared with placebo, which was judged too high to be clinically relevant by a Cochrane review.[44,45] Evidence for gabapentin in fibromyalgia is limited to a few small studies.[46]

Based on very low- to low-quality evidence, the serotonin-norepinephrine reuptake inhibitors duloxetine and milnacipran reduce pain by 30% or greater with an NNT of 10 compared with placebo.[44,45] Although evidence is lacking for venlafaxine, small studies of desvenlafaxine (Pristiq) demonstrate no improvement over placebo for fibromyalgia.[44]

In limited studies with significant bias, selective serotonin reuptake inhibitors do not appear to be effective.[47] Despite this evidence, the European Alliance of Associations for Rheumatology recommends antidepressants, including amitriptyline, duloxetine, fluoxetine, and milnacipran, for the treatment of fibromyalgia to reduce pain and improve function.[48]

The European Alliance of Associations for Rheumatology also recommends consideration of pramipexole and pregabalin for pain reduction.[48] The evidence for pramipexole, which is off-label without an indication for fibromyalgia, is based on one small, randomized controlled trial.[48]

Generalized Chronic Pain

High-quality evidence supports that the serotonin-norepinephrine reuptake inhibitor duloxetine at 60 mg/day and milnacipran at 100 mg/day slightly improve pain in multiple chronic pain conditions, including fibromyalgia, neuropathic pain, and musculoskeletal pain.[22,29,49]

High-quality evidence also supports that low-concentration topical capsaicin cream provides small benefits in chronic neuropathic and musculoskeletal pain, with an NNT of 6 to 8 for a 50% reduction in pain compared with placebo.[41] However, one-third of patients report local adverse events, with the most common one being intense burning sensation after application.[41]

Topical lidocaine lacks clear, high-quality evidence supporting its effectiveness for chronic pain. Most studies demonstrate only low-quality evidence due to limitations in study design and small sample sizes; further research is needed to definitively assess its effectiveness and safety.[50]

Tables 1 and 2 summarize common drugs used to treat chronic noncancer pain, including those with evidence of

TABLE 3

Key Principles of Opioid Therapy for Chronic Pain Management

Opioids should not be considered as first-line drugs for any chronic noncancer pain
Only after a full risk-benefit assessment, consider opioids for patients with intractable, moderate to severe, noncancer pain who have not benefited from a variety of nonpharmacotherapy approaches and the nonopioid drugs discussed in this article
If opioids are prescribed, patients should be monitored carefully and reassessed at regular intervals, with no expectation that these drugs will be continued long term
If opioids are prescribed, expert opinion recommends prescribing buprenorphine (a partial opioid agonist) over full opioid agonists, given its similar analgesic effectiveness, better safety profile (with a ceiling effect on respiratory depression and hence low risk for overdose), slower onset of tolerance, and less misuse potential than full agonist opioids
If full agonist opioids are prescribed, immediate-release formulations are preferred for their safety profile; these should be prescribed at the lowest effective dose with a goal of < 50 morphine milliequivalents per day

Note: More information about safe prescribing of opioids can be found in the Centers for Disease Control and Prevention's updated guidelines.

Information from references 51 and 52.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
For knee or hand osteoarthritis, consider topical nonsteroidal anti-inflammatory drugs as a first-line treatment because of effectiveness and minimal adverse effects, followed by oral nonsteroidal anti-inflammatory drugs (due to similar effectiveness with more adverse effects) and duloxetine; recommendations for hip osteoarthritis are similar, with a lack of evidence for topical drugs.[13-15]	A	Systematic reviews showing significant reduction in pain scores
For chronic low back pain, preferentially use topical nonsteroidal anti-inflammatory drugs and oral nonsteroidal anti-inflammatory drugs and serotonin norepinephrine reuptake inhibitors.[4,22,27]	B	Systematic reviews showing small to moderate pain benefit over short periods
For chronic low back pain, avoid using antiepileptics, including gabapentinoids, due to no benefit and associated harms.[4,28]	B	Expert opinion and consensus guidelines from mostly small studies
For neuropathic pain, use gabapentin, pregabalin, or duloxetine based on evidence for treatment of postherpetic neuralgia and diabetic neuropathy.[29,35-37]	A	Systematic reviews showing moderate pain benefit
For fibromyalgia pain, consider pregabalin if tolerated at a dose that provides therapeutic benefit or consider duloxetine and milnaciprine.[43-45]	B	Systematic reviews demonstrating moderate pain benefit in variable quality studies
Prescribe serotonin-norepinephrine reuptake inhibitors, such as duloxetine and milnacipran, for the treatment of fibromyalgia, neuropathic pain, and musculoskeletal pain and topical nonsteroidal anti-inflammatory drugs for chronic musculoskeletal pain.[22,49]	A	Systematic reviews showing small pain benefit

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benefit for certain chronic pain conditions and those lacking an evidence base but are commonly used in practice.

OPIOIDS IN MANAGING CHRONIC PAIN

Opioids should be considered for chronic pain only if nonopioid pharmacologic and nonpharmacologic treatments do not improve pain and function.[51] A thorough discussion of the use of opioids for chronic pain management is beyond the scope of this article; however, Table 3 provides an overview for opioid use in the context of chronic pain management.[51,52] More detailed information can be found in a 2025 *AFP* article on long-term opioid therapy for nonterminal pain.[53]

Data Sources: We searched PubMed using the search terms chronic, non-cancer pain; chronic pain; osteoarthritis; low back pain; neuropathic pain; and fibromyalgia. We included only studies that were systematic reviews, meta-analyses, and randomized controlled trials. Additionally, we searched other evidence-based resources that focus on patient-oriented evidence, including Essential Evidence Plus and its associated POEMs, Cochrane reviews, NICE guidelines, and guidelines of related professional societies using the same search terms. We also searched for previous *AFP* articles on this topic as a starting point from which to build and expand, using new and updated evidence and approaches. Search dates: August 4, 2024; September 5, 2024; November 1, 2024; and May 18, 2025.

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