



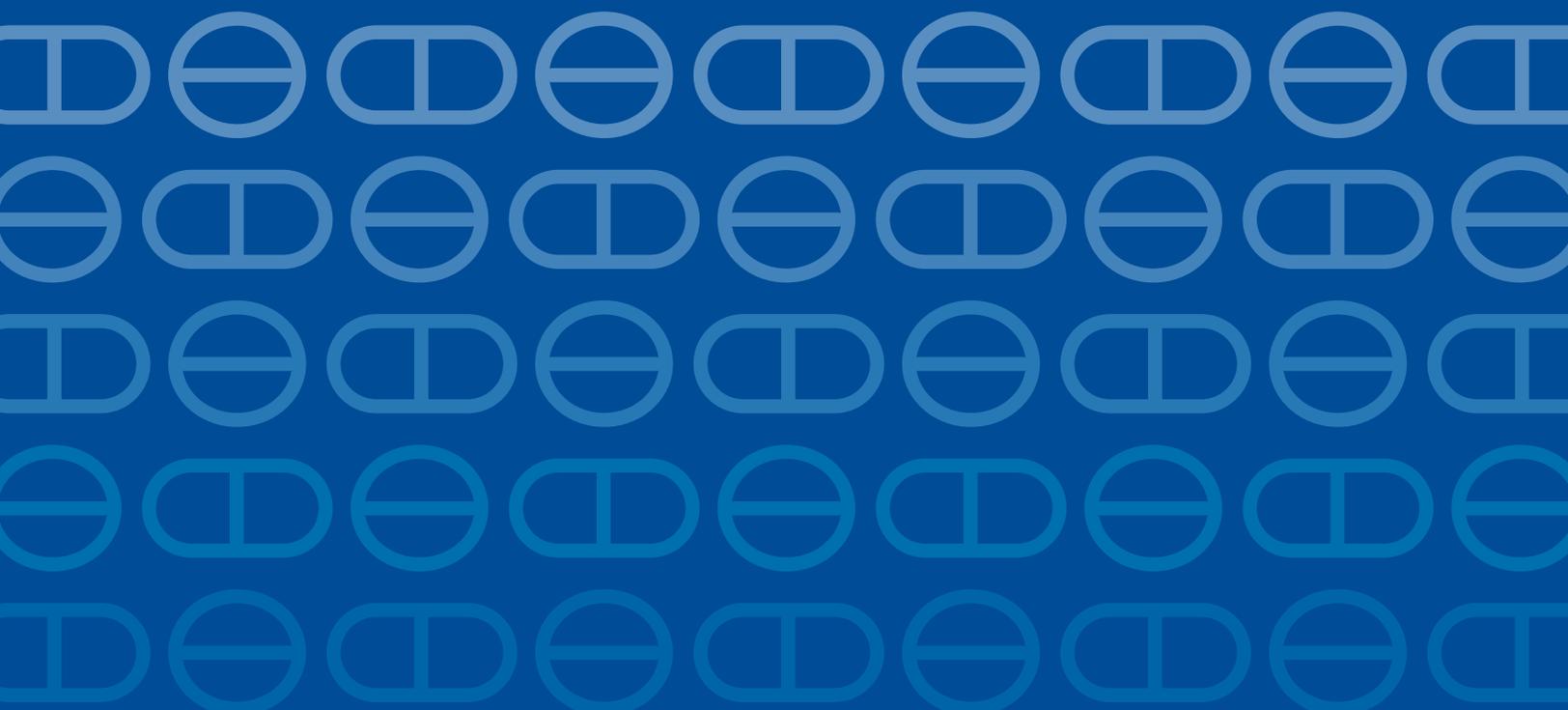
Pharmaceutical Assistance
Contract for the Elderly



Balanced information for better care

Managing chronic non-cancer pain

Evidence-based strategies to reduce opioid use



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Evidence-based strategies to reduce opioid use

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Managing chronic non-cancer pain

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Activity Overview:

The primary goal of this educational program is to address the challenge of effectively managing patients with chronic non-cancer pain. Achieving functional goals, while avoiding harms from side effects, addiction, or drug abuse, can be challenging in this patient population because of issues such as altered pharmacodynamics/pharmacokinetics with increasing age, polypharmacy, potential cognitive deficits, heightened risk of fractures from falls, and organ-specific vulnerabilities.

The education program has several components, which include:

1. The written evidence report (print monograph)
2. Summary document of top 4-5 key messages
3. “Academic detailing” educational sessions in physicians’ offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
4. Reference cards for easy access to key materials
5. Patient education information (brochure/tear off sheets)

This program synthesizes current clinical information on this topic into accessible, non-commercial, evidence-based educational material, which is taught interactively to providers by specially trained clinical educators.

Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family practice, and geriatrics, and other health care professionals who deliver primary care.

Learning Objectives:

After completing this activity, participants will be able to:

- Define clear functional goals and realistic expectations as part of a comprehensive pain management plan.
- Utilize multiple modalities, including non-pharmacologic and non-opioid pharmacologic options.

- When prescribing opioids, assess the risks and benefits of therapy, discontinue or taper opioids in the absence of meaningful benefit or significant harms.
- Recommend naloxone for patients with risk factors for possible overdose.
- Discuss tapering and discontinuing opioids whenever possible, particularly in patients who have severe side effects or exhibit problematic behaviors.

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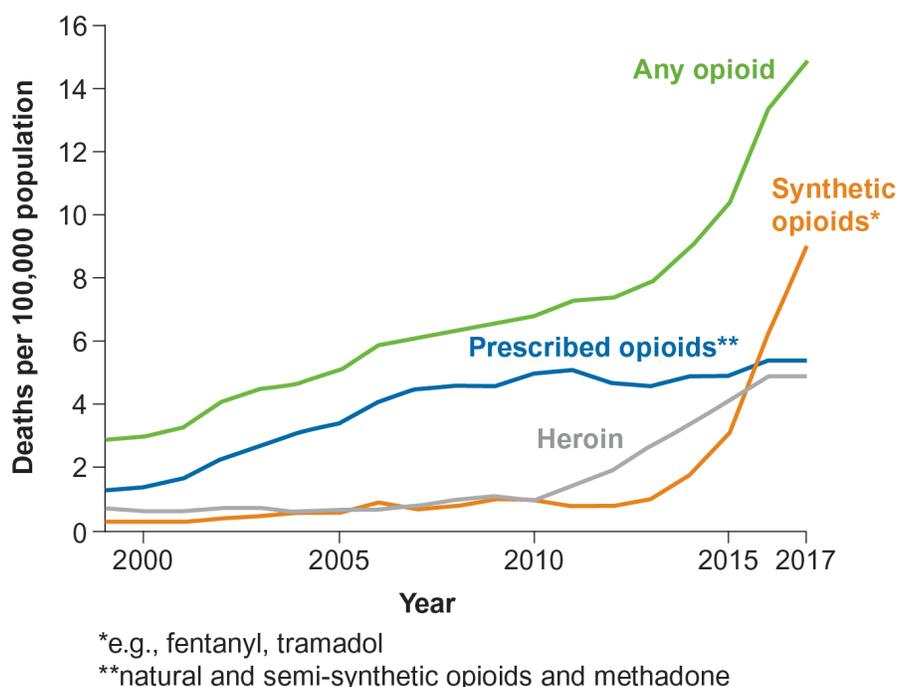
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Introduction

Physicians caring for patients with chronic pain face an unusually daunting set of challenges. As with many other chronic conditions, providers must carefully balance expected benefits of treatment with the potential for harm from such treatments. Treating chronic pain, however, can involve an additional level of complexity because one of the most commonly-used classes of pain medications—opioids—are at the center of a raging national debate about how best to stem the epidemic of opioid-related abuse, addiction, and overdose.¹

The United States has seen three successive waves of abuse and overdose deaths related to both legal and illegal opioid drugs.² The first began in the 1990s with steadily rising prescriptions for opioid analgesics. In 2010, deaths from heroin began to increase sharply.³ The third wave began in 2013 with sharply rising overdose deaths attributed to synthetic opioids, particularly those involving illicitly-manufactured fentanyl. By 2018 (the latest year for which data are available) an average of *130 people were dying every day* from opioid-related overdoses.⁴ Between 1999 and 2017, the CDC estimates that 399,230 people in the United States died from opioid-related overdose.⁵

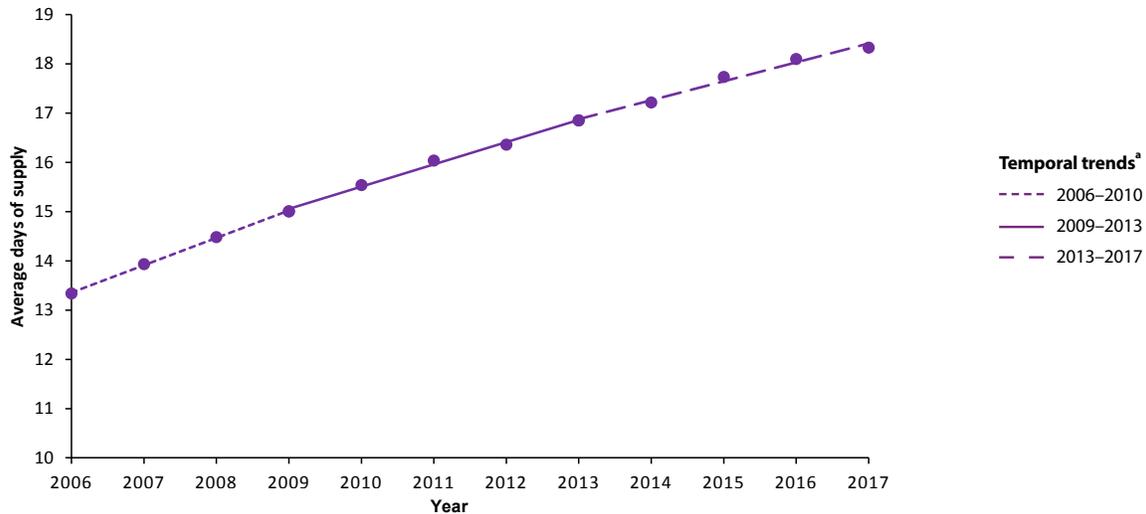
Figure 1: Opioid-related overdose deaths by type in the United States⁶



Coupled with rising rates of overdose death are equally dramatic increases in the number of people misusing or abusing opioids. As many as 1 in 4 patients on long-term opioid therapy in a primary care setting are estimated to be struggling with opioid addiction.⁷⁻⁹ In 2016 approximately 11.5 million Americans reported misusing prescription opioids in the previous year.¹⁰

Although the rates of opioid prescriptions have leveled off or declined slightly in recent years, the United States had the highest rate of opioid prescriptions among the 27 countries assessed in the most recent survey by the Organization for Economic Cooperation and Development.¹¹ In addition, in the U.S. the average days of supply per opioid prescription has continued to rise. Between 2006 and 2016, average days of supply per prescription increased from 13.3 days to 18.3 days, an overall relative increase of 37.6%.¹⁰

Figure 2: Average days of supply per opioid prescription in the U.S., 2006-2017¹⁰



The surge in opioid prescribing also occurred for older patients. Nearly one in three Medicare beneficiaries received a prescription for oxycodone sustained release (OxyContin), hydrocodone-acetaminophen, oxycodone-acetaminophen, or fentanyl in 2016.¹² Medicare spending under Part D for these opioid pain medications has grown substantially as well, exceeding \$4 billion in 2015.¹²

It is against this background that providers must make daily decisions about how best to treat their patients in chronic pain. Unfortunately, many providers are unfamiliar with the growing evidence base suggesting that opioids are not very effective for relieving chronic pain and, in fact, may be associated with *increased* pain and/or reduced functioning.^{13,14} Providers may also not be aware of the expanding range of both non-opioid medications and non-pharmacological therapies shown to be effective in reducing many common chronic pain conditions.

This document discusses the management of chronic pain, with a detailed look at four common pain syndromes accounting for most chronic pain in adults: osteoarthritis, chronic low back pain, diabetic neuropathy, and fibromyalgia. It reviews evidence for non-opioid therapies, including non-drug and non-opioid drug options, as well as current evidence regarding opioid efficacy, harms, and overdose prevention with naloxone, and how to slowly and safely taper opioid doses.

Describing Pain

Acute versus chronic pain

Acute pain typically has an abrupt onset due to an obvious cause, such as an injury or other process that is not ongoing (e.g., a recent surgical procedure). It has a generally short duration, and usually lasts less than four weeks, improving over time and in proportion to healing.¹⁵ In contrast, chronic pain is defined as lasting more than three months or past the time of normal tissue healing.¹⁶ It can be the result of an underlying medical disease or condition, injury, medical treatment, inflammation, or an unknown cause. (This evidence document is focused on chronic non-cancer pain because chronic pain associated with cancer or end-of-life pain have distinct patterns of treatment and a range of treatment considerations beyond the scope of this review.) These pain labels, however, provide little information about the biological nature of the pain itself, which is often critically important for optimal treatment.

Pain mechanisms

Pain can also be classified on the basis of its pathophysiology. Nociceptive pain is caused by the activation of nociceptors (pain receptors), and is generally, though not always, short-lived, and associated with the presence of an underlying medical condition.¹⁷ This is “normal” pain: a physiological response to an injurious stimulus. Neuropathic pain, on the other hand, results from nervous system injury or dysfunction. It is an abnormal response to a stimulus caused by abnormal neuronal firing in the absence of active tissue damage. It may be continuous or episodic and varies widely in how it is perceived. Neuropathic pain is complex and can be difficult to diagnose and to manage because available treatment options are limited.

Related to both nociceptive and neuropathic pain is the phenomenon of sensitization, which is a state of hyperexcitability in either peripheral nociceptors or neurons in the central nervous system. Sensitization may lead to either hyperalgesia (heightened pain from a stimulus that normally provokes pain) or allodynia (pain from a stimulus that is not normally painful).¹⁷ Sensitization may arise from intense, repeated, or prolonged stimulation of nociceptors, from the influence of compounds released by the body in response to tissue damage or inflammation, or—importantly—as an adaptation to prolonged exposure to opioid analgesics.¹⁸ Many patients—particularly those with chronic pain—experience pain that has both nociceptive and neuropathic components, which complicates assessment and treatment.

Differentiating between nociceptive and neuropathic pain is critical because the two respond differently to pain treatments. Neuropathic pain, for example, responds poorly to both opioid analgesics and non-steroidal anti-inflammatory (NSAID) agents.¹⁹ Other classes of medications, such as anti-epileptics, antidepressants, or local anesthetics, may provide more effective relief for neuropathic pain.²⁰

Assessing pain

Take a history

Assessing pain is critical to effective pain management interventions. Both patient and caregiver reports of pain should be the starting points. A comprehensive pain assessment should also include evaluation of the pain quality, duration, location, aggravating or alleviating factors, and any previous treatments and

their efficacy. Assessing the impact of pain on functional status and sleep and screening for mental health conditions potentially related to pain or treatment adherence (e.g., depression, anxiety, and memory issues) may provide useful information for pain management.²¹ Depression, for example, sometimes presents with somatic complaints of pain (particularly in older adults). Pain complaints may resolve when the underlying depression is treated. Screening for comorbid depression and anxiety can be facilitated with the Patient Health Questionnaire (PHQ) and the Generalized Anxiety Disorder 7-item (GAD-7) scale. Additional resources for the screening, diagnosis, and treatment of depression are available at AlosaHealth.org/Depression.

Assessment tools

Many tools have been developed to document and assess pain. Initial approaches to assessing pain severity use a visual analog scale (VAS) rating pain from 0 (no pain) to 10 (worst pain you can imagine) (some scales use a 0 to 100 scale). Such scales are often used in clinical trials of pain therapies, and the minimal clinically important difference using these scales is generally considered a 20%-30% change from baseline (i.e., 2-3 points on a 0-10 scale or 20-30 points on a 0-100 scale).²²

Multidimensional tools, such as those described below, include questions relating to quality of life and participation in daily activities. Such tools can provide a more comprehensive approach to assessing pain and response to treatment. The selection of a pain assessment tool must balance the comprehensiveness of the assessment obtained with the time and energy required to use the tool in a real-world practice setting.

Brief pain inventory

The Brief Pain Inventory (BPI) is used frequently in randomized controlled trials to assess pain. Specifically developed for patients with chronic pain, the BPI more fully captures the impact of pain on patient function and quality of life than simple 0-10 scales.²³ By including a pain map, the BPI allows tracking of the location of pain through the course of management. The BPI is self-administered but somewhat time-consuming, which may limit its role in clinical practice. See Appendix I for a sample of the BPI.

PEG scale

The PEG scale (Pain average, interference with Enjoyment of life, and interference with General activity) is a three-item tool based on the BPI. Zero-to-10 scales are used to assess pain, enjoyment of life, and general activity. PEG can be self-administered or done by the clinician and is relatively brief.²⁴

Figure 3: PEG scale²⁴

1. What number best describes your pain on average in the past week?

0 1 2 3 4 5 6 7 8 9 10

No pain

Pain as bad as
you can
imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0 1 2 3 4 5 6 7 8 9 10

Does not
interfere

Completely
interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0 1 2 3 4 5 6 7 8 9 10

Does not
interfere

Completely
interferes

Assessing pain in the cognitively impaired

Although patients with mild-to-moderate dementia can report their pain and its location, those with severe dementia are often unable to communicate their pain experience or request medication. In these patients, physicians need to observe pain behaviors, including facial expressions, verbal cues, body movements, changes in interpersonal interactions, activity patterns, and mental status. Caregiver observations and reports are critical to appropriate assessment and management of chronic pain conditions.²⁵

Overview of options for managing chronic non-cancer pain

Many pharmacologic and non-pharmacologic approaches to treating chronic pain are available to primary care physicians. These options should be employed using the following general principles:

- Identify and treat the source of the pain, if possible, although pain treatment can begin before the source of the pain is determined
- Select the simplest approach to pain management first. This generally means using non-pharmacologic approaches as much as possible and/or trying medications with the least severe potential side effects, and at the lowest effective doses
- Establish a function-based management plan if treatment is expected to be long-term

The following summaries are descriptive only—details about the evidence of effectiveness for the various forms of therapy will be provided in the condition-specific sections later in this document.

Non-drug approaches

Movement-based options

Movement therapies that may be helpful in patients with chronic pain include muscle-strengthening, stretching, and aerobic exercise (e.g., walking, aquatics). Recommended exercise programs typically occur one to three times a week for a total of 60-180 minutes per week, but any regimen must be carefully tailored to a patient's existing level of physical conditioning, comorbidities, and cognitive status.²⁶⁻²⁸

Additional movement-based options include:

- **Physical therapy** supervised by a licensed physical therapist, which can include resistance, aerobic, balance, and flexibility exercises as well as elements of massage, manipulation, or transcutaneous electrical nerve stimulation.
- **Tai chi**, a mind-body practice that combines controlled movements, meditation, and deep breathing. “Chair tai chi” can be an option for patients with limited mobility.
- **Yoga**, exercises or a series of postures designed to align muscle and bones, and increase strength and flexibility. It can also relax mind and body through breathing exercises and meditation. Gentler forms of yoga that may be more appropriate for older patients include Iyengar, Hatha, or Viniyoga.

Although these interventions may cause muscle soreness, increased back pain, or falls, movement-based options are generally considered safe.²⁸

Weight loss

Some pain syndromes, such as knee OA, are worsened by obesity. For some patients, pain due to this condition is improved by reducing body weight because of reduced loads and physical stresses on the affected joints. The goal of body weight reduction is a baseline weight loss of 7%-10% by calorie reduction using a balanced diet with less than 30% of calories from fat, 15%-20% from protein, and 45%-60% from carbohydrates.²⁹

Passive options

Acupuncture involves the stimulation of specific points on the body, most often involving skin penetration with fine metallic needles manipulated by hand but sometimes also including electrical stimulation or low intensity laser therapy. Potential adverse events include minor bruising and bleeding at needle insertion sites.³⁰

Massage is the manual manipulation of the body to promote relaxation, reduce stress and improve well-being. Handheld devices may also provide relief for some patients. Some patients may report muscle soreness.³¹

Transcutaneous electrical nerve stimulation (TENS) is a machine that generates mild electrical pulses which are applied cutaneously. The electrical stimulation from TENS may block or disrupt pain signals to

the brain, reducing pain perception. TENS machines can be used at home or in conjunction with other interventions like physical therapy.

Cognitive and behavioral options

Cognitive behavioral therapy (CBT) is a structured, time-limited (typically 3-10 weeks) intervention focused on how thoughts, beliefs, attitudes, and emotions influence pain and can help patients use their minds to control and adapt to pain. This therapy includes setting goals, often with recommendations to increase activity to reduce feelings of helplessness.³²

Mindfulness meditation

Mindfulness meditation programs typically include a time-limited (8 weeks; range 3-12 weeks) trainings with group classes and home meditation. The objective is to inculcate a long-term practice that helps patients refocus their minds on the present, increase awareness of self and surroundings, and reframe experiences.^{33,34}

Self-management education programs

Lorig and colleagues developed a self-management training program for patients with chronic arthritis, which was later expanded to other chronic diseases, and is generally referred to as the Stanford model.³⁵ The elements of Stanford model programs include group meetings, trained leaders (health professionals or lay people), disease management education, goal setting and action plans, and feedback.³⁶

Drug approaches

Medications used to treat chronic pain include:

- acetaminophen
- NSAIDs
 - oral
 - topical
- antidepressants
 - serotonin and norepinephrine reuptake inhibitors (SNRIs)
 - tricyclic antidepressants (TCAs)
 - selective serotonin reuptake inhibitors (SSRIs)
- anticonvulsants
- topical lidocaine or capsaicin
- cannabinoid-based therapies
- opioids

Acetaminophen

Acetaminophen is available over the counter (OTC) in 325 mg, 500 mg, and 650 mg tablets. Patients should not exceed 650 mg in a single dose. The maximum recommended dose for healthy adults is 4000 mg/day and 3000 mg/day for elderly patients.³⁷

The most severe potential side effect of acetaminophen is liver toxicity. Acetaminophen is the most common cause of acute liver failure, accounting for 46% of all cases.³⁸ Patients should stay within

recommended doses to help prevent side effects and should only be prescribed one acetaminophen-containing product at a time. Advise patients to read labels of all medications to determine if the product contains acetaminophen.

NSAIDs

NSAIDs reduce inflammation by inhibiting cyclooxygenase (COX), either selectively (COX-2 predominantly) or non-selectively (COX-1 and COX-2 effects). Chronic use of NSAIDs may be limited by gastrointestinal (GI) toxicity, including GI bleeding, upper GI symptoms, ulcers, and related complications. For high-risk patients, including the elderly, patients on warfarin or aspirin, and those with coagulopathies, adding a proton pump inhibitor (PPI) may help reduce the risk.^{39,40} In addition to GI side effects, NSAIDs have been associated with an increased risk of renal and cardiac complications.

Topical NSAIDs: Side effects with NSAIDs are typically lower with topical formulations. The effects on coagulation and renal function are unknown, but likely not clinically significant given limited systemic absorption.⁴¹

Evidence regarding the comparative safety of celecoxib:

Some early trials suggested that COX-2 inhibitors, as a class, were associated with higher risks for myocardial infarction and stroke compared to other NSAIDs, and the COX-2 inhibitor rofecoxib (Vioxx) was removed from the market in 2004 because of such concerns.⁴² More recent trials and meta-analyses, however, provide strong evidence that the risks of CV events with celecoxib are no greater than those of other NSAIDs, and in 2018 two Food and Drug Administration (FDA) advisory panels recommended that the FDA change its advice to physicians regarding celecoxib's safety.⁴³

The advisory panel's decision was based largely on the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (**PRECISION**) study, a prospective non-inferiority trial of 24,081 patients comparing celecoxib (100-200 mg twice daily, n=8,072) vs. ibuprofen (600-800 mg three times daily, n=8,040) or naproxen (375-500 mg twice daily, n=7969) in patients with osteoarthritis or rheumatoid arthritis with established cardiovascular disease or risk factors for cardiovascular disease.⁴⁴

After a mean follow-up of 20 months, a primary outcome event (composite of CV death, nonfatal myocardial infarction, or nonfatal stroke) occurred in 188 patients in the celecoxib group (2.3%), 201 patients in the naproxen group (2.5%), and 218 patients in the ibuprofen group (2.7%) (P<0.001 for noninferiority for both comparisons). The risk of GI events was significantly lower with celecoxib than with naproxen (P=0.01) or ibuprofen (P=0.002). The risk of renal events was significantly lower with celecoxib than with ibuprofen (P=0.004) but was not significantly lower with celecoxib compared with naproxen (P=0.19).⁴⁵

SNRIs

SNRIs such as duloxetine, venlafaxine, and milnacipran are characterized by a mixed action on norepinephrine and serotonin, though their exact mechanism of action for pain reduction is unknown. Side effects (e.g., nausea, dizziness, and somnolence) may limit treatment. Monitoring is required for blood pressure (duloxetine and venlafaxine), heart rate (venlafaxine), and drug interactions (duloxetine).

TCAs

TCAs inhibit reuptake of norepinephrine and serotonin, but their mechanism of action for pain relief is unknown. Examples of TCAs studied for the management of chronic pain include amitriptyline,

desipramine, and nortriptyline. Side effects, such as anticholinergic effects (e.g., dry mouth, constipation, dizziness) and QTc prolongation limit the use of TCAs in elderly patients. The majority of side effects occur at the typically higher doses used to treat depression.

SSRIs

SSRIs, such as citalopram, fluoxetine, and paroxetine, block the reuptake of serotonin in the brain, making more serotonin available in the synapse. The mechanism of SSRIs for pain remains unknown. Potential side effects include weight gain, sexual dysfunction, and QTc prolongation, especially with citalopram.

Anticonvulsants

Anticonvulsants, such as gabapentin, pregabalin, oxcarbazepine, and carbamazepine, are often prescribed for neuropathic pain and are thought to exert their analgesic effect by inhibiting neuronal calcium channels. Potential side effects include sedation, dizziness, and peripheral edema. Pregabalin and gabapentin have abuse potential in the general population, are currently classified as Schedule V by the DEA, and prescriptions for these drugs are tracked by some state Prescription Drug Monitoring Programs (PDMPs).

Topical lidocaine and capsaicin

Topical lidocaine inhibits ionic fluxes required for initiation and conduction of nerve impulses. Irritation at the application site is the most common side effect. The most common products for chronic pain management are lidocaine 5% patches, available by prescription, and lidocaine 4% patches available over-the-counter (OTC). Capsaicin is an active component of chili peppers and has moderate analgesic properties at 8% concentrations for musculoskeletal and neuropathic pain.⁴⁶ The most common side effect is a mild-to-severe burning sensation at the application site.

Cannabinoid preparations

As of April, 2019, 33 states and Washington DC have enacted medical marijuana laws.⁴⁷ Medical marijuana contains more than 60 cannabinoids, with Δ^9 -tetrahydrocannabinol (THC) and cannabidiol being the two of primary interest to patients and clinicians. Exogenous cannabinoids act on cannabinoid receptors located throughout the body, primarily in the brain and spinal cord, to inhibit release of multiple neurotransmitters (e.g., acetylcholine, dopamine, and glutamate) with indirect effects on opioid, serotonin, and other receptors. Activation of cannabinoid receptors can reduce pain, and some exogenous cannabinoids also function as an antiemetic and have anti-spasticity and sleep-promoting effects.⁴⁸ Cannabinoids may also cause side effects of euphoria, psychosis, cognitive impairment, reduced locomotor function, and increased appetite.

A variety of doses and routes of administration are available, with the three most common presented in Table 1 (next page).

Table 1: Cannabis preparations⁴⁸

Preparation	Description	Route
Marijuana	Dried plant product consisting of leaves, stems, and flowers	Smoked or vaporized
Tincture	Cannabinoid liquid extracted from plant	Sublingual
Infusion	Plant material mixed with nonvolatile solvents such as butter or cooking oil	Oral

A systematic review of both randomized trials (47) and observational studies (57) in patients with chronic non-cancer pain published through July 2017 found moderate evidence that cannabinoids can exert analgesia.⁴⁹ Across RCTs, the overall number needed to treat to obtain a 30% reduction in pain was relatively high (NNT 24; 95% CI: 15-61), while the number needed to harm (for all-cause adverse events) was 6 (95% CI: 5-8).

Cannabis preparations may pose both short-term and long-term risks. Short-term effects include impaired memory, motor coordination, and judgment. Paranoid ideation and psychotic symptoms, while rare, may occur with high doses of THC. Possible long-term effects include impaired brain development in young adults, potential for habituation, and increased risk of anxiety or depression. Abrupt cessation of marijuana in long-term users may cause withdrawal symptoms such as anxiety, irritability, craving, dysphoria, and insomnia. There is an increased risk of chronic bronchitis, respiratory infections, and pneumonia with inhaled products.⁴⁸

The use of cannabis may have an opioid-sparing effect at a population level. The use of medical cannabis has been associated with a 25% reduction in opioid overdose mortality in states that legalized medical use (for information about cannabis-related laws in the states that are the focus of this educational program, visit AlosaHealth.org/Opioids).⁵⁰

FDA-approved cannabinoids include dronabinol (Marinol), indicated for second-line treatment of chemotherapy-induced nausea and vomiting, and anorexia-associated weight loss in patients with HIV. Nabilone (Cesamet) is indicated for chemotherapy-induced nausea and vomiting. Common side effects include dizziness/vertigo and euphoria. Dronabinol may cause nausea/vomiting, abdominal pain, and abnormal thinking. Nabilone may cause ataxia and dry mouth.^{48,51,52}

Opioids for chronic pain

Mechanism of Action

Opioids exert their analgesic effects by acting on the mu, kappa, and delta opioid receptors. Individual agents may be classified as agonists, partial agonists, or antagonists of those receptors:⁵³

- Agonists (e.g., morphine, codeine, hydromorphone, hydrocodone) stimulate at least one of the opioid receptors and provide continued analgesia with increasing doses.
- Partial agonists (e.g., buprenorphine) have high affinity but low efficacy at mu-receptors, have a ceiling for analgesic effect, and are less likely to cause respiratory depression.

- Antagonists (e.g., naloxone and naltrexone), block, rather than activate, opioid receptors and do not have an analgesic effect. Use of an opioid antagonist in patients taking chronic opioids will precipitate an acute withdrawal syndrome.

Opioids are classified by the Drug Enforcement Agency (DEA) according to their presumed abuse and addiction potential, although the evidence base for making these differentiations continues to evolve. Tramadol, for example, is now known to have as much potential for abuse as opioids in more restrictive classes.⁵⁴

Table 2: Opioids by schedule⁵³

Schedule*	Description	Opioid
Schedule I	No medical use, lack of accepted safety, and a high potential for abuse	Heroin
Schedule II	High potential for abuse, which may lead to physical or psychological dependence	Hydrocodone Oxycodone Morphine Hydromorphone Tapentadol Methadone Fentanyl
Schedule III	Less potential for abuse than schedules I and II, low to moderate physical dependence and high psychological dependence	Buprenorphine Codeine + acetaminophen
Schedule IV	Lower potential for abuse than schedule III medications	Tramadol
*Note: DEA schedules may not accurately reflect the actual abuse or dependence potential for these medications.		

Relative effectiveness

The analgesic efficacy of opioids for treating acute pain have been known for centuries and they continue to be reliable—if potentially risky—agents for moderate-to-severe acute pain. *But the evidence for opioid efficacy for acute pain cannot be extended to chronic pain.* Neuronal and physiologic adaptations to long-term opioid use can result in reduced analgesic effectiveness, or even, paradoxically, increased pain or sensitivity to pain.¹⁸ Opioid-induced hyperalgesia is different pharmacologically from the phenomenon of opioid tolerance, although both can lead to an increased need for opioids and disentangling the two, clinically, can be difficult.⁵⁵

For chronic pain, the evidence that opioids reduce pain and improve function more than placebo is surprisingly weak. A 2018 systematic review and meta-analysis of 96 trials comparing various opioids vs. placebo or non-opioid analgesics in 26,169 patients with chronic non-cancer pain found that opioids may slightly reduce pain and increase physical functioning compared to placebo, but not compared to non-opioids.¹³ In 76 trials comparing opioids vs. placebo with median follow-up of 60 days (range 30-84 days), the reduction in pain scores with opioids (on a 10-point scale) was only 0.69 points, which is below the generally-accepted minimum clinically important difference for pain. Physical function scores (on a 100-point scale) improved with opioids by 2.04 points, which, again, may not be clinically important. The risk of vomiting with opioids, however, was more than four times higher than with placebo (RR 4.12; 95% CI: 3.34-5.07).¹³ There were no significant differences in emotional functioning or role functioning.

The same meta-analysis compared opioids to non-opioid analgesics including NSAIDs, TCAs, anticonvulsants, and synthetic cannabinoids. No significant differences were found in physical functioning scores for any of the comparisons, and no significant differences were found in pain scores for comparisons with NSAIDs (9 trials), TCAs (3 trials), or cannabinoids (1 trial). As compared to anticonvulsants, opioids were associated with slightly lower pain scores, although the confidence interval includes differences that may not be clinically significant (weighted mean difference -0.9 points; 95% CI: -1.65 points to -0.14 points).¹³

The Strategies for Prescribing Analgesics Comparative Effectiveness (**SPACE**) trial randomized 240 patients with moderate to severe chronic low back pain or knee or hip osteoarthritis to regimens of morphine, oxycodone, or hydrocodone or non-opioid analgesics (e.g., acetaminophen, NSAIDs, antidepressants, anti-epileptics) and followed them for one year.¹⁴ The primary outcome was score for pain-related functioning using the 0-10 Brief Pain Inventory (BPI) scale (lower score indicates better function). At 3, 6, 9, and 12 months there were no significant differences in BPI scores (overall P=0.58). At one year, pain intensity was significantly better in the non-opioid group (P=0.03). No differences in treatment response were seen in analyses by pain condition. The authors concluded that their results “do not support initiation of opioid therapy for moderate-to-severe chronic back pain or hip or knee osteoarthritis pain.”¹⁴

Opioid formulations

Prescription opioids are available in immediate-release and extended-release/long-acting (ER/LA) formulations. Immediate-release agents are recommended in opioid-naïve patients and for all acute pain conditions, with ER/LA agents reserved for patients or conditions in which the longer duration of action (and, hence, less frequent dosing) are preferred.⁵⁶ A trial comparing immediate release to an ER/LA opioid did not find evidence that the continuous, time-scheduled use of ER/LA opioids was more effective or safer than intermittent use of the immediate-release opioid.⁵⁷ According to the FDA, ER/LA opioids should only be used for patients who tolerate 60 morphine milligram equivalents per day (MMED) for at least one week.⁵⁸

Efforts to create formulations with lower risks of abuse have met with limited success. For example, Opana ER was removed from the market after reports of intravenous abuse of the oral formulation.⁵⁹ Abuse-deterrent or tamper-resistant formulations do not prevent users from becoming addicted or taking too much of an opioid by mouth, which is the most common route for abuse.^{60,61} No prospective randomized clinical trials or rigorous observational studies have measured the impact of abuse-deterrent opioids on the risk of abuse or misuse. As of August, 2018, eight opioids with abuse-deterrent properties have been approved by the FDA: OxyContin, Targiniq ER, Embeda, Hysingla ER, MorphaBond ER, Xtampza ER, Arymo ER, and RoxyBond.⁶²

Atypical opioids: tramadol and tapentadol

Tramadol and tapentadol are mu receptor agonists and norepinephrine reuptake inhibitors. Their exact mechanisms of action are unknown, but their analgesic effects are similar to morphine. Patients taking tramadol should be monitored for nausea, vomiting, constipation, and drowsiness, all of which are similar to side effects with opioids.⁶³ There is potential risk of serotonin syndrome when combined with SSRIs and tricyclic antidepressants.⁶⁴

As noted above, tramadol is classified as Schedule IV, which has led some to view it as less potent or safer than other opioids. The 2016 National Survey on Drug Use and Health, however, found that 1.7

million people in the U.S. aged >12 years reported misusing tramadol products (e.g., Ultram, Ultram ER, Ultracet) in the previous year.⁵⁴ In addition, a 2019 cohort study of 88,902 patients with osteoarthritis (mean age 70 years) showed increased risks of death at one year compared to NSAIDs naproxen (HR 1.7; 95% CI: 1.4-2.1), diclofenac (HR 1.9; 95% CI: 1.5-2.6), and celecoxib (HR 1.7; 95% CI: 1.3-2.2).⁶⁵ In that study, the hazard ratio for death at one year was not significantly different between tramadol and codeine (HR 0.94; 95% CI: 0.83-1.1).

Abrupt cessation of tramadol is associated with flu-like symptoms, restlessness, and drug cravings (similar to those associated with other opioids) as well as hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and numbness/tingling in extremities (which are less typical of other opioids).⁶⁶

Tapentadol, an opioid with potency and side effect profiles similar to other common opioids such as oxycodone, is FDA-approved for treating neuropathic pain, although it is also used for musculoskeletal pain. A 2015 Cochrane review of four randomized trials with 4,094 patients with osteoarthritis or back pain found modest reductions in pain with tapentadol vs. placebo (mean difference -0.56 points on 11-point scale; 95% CI: -0.92 to -0.2 points), although the CI includes differences that may not be clinically important.⁶⁷

Opioid risks and side effects

To ensure clear communication regarding medical issues and avoid misunderstandings about the nature and risk of addiction, the American Society of Addiction Medicine recommends the following definitions:

- **Abuse** - Any use of an illegal drug, or the intentional self-administration of a medication, for a non-medical purpose, such as altering one's state of consciousness (e.g., getting high).
- **Misuse** - Use of a medication other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.
- **Dependence** - A state of physical adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
- **Opioid use disorder** - Problematic opioid use leading to clinically significant impairment or distress, with at least two additional criteria, such as taking more opioids or for longer than prescribed, persistent desire or unsuccessful efforts to cut down or control opioid use, and craving or a strong desire or urge to use opioids, occurring within a 12-month period.

Problematic opioid use

Although evidence for the long-term effectiveness of opioids for chronic pain is weak, evidence for opioid-related harms is abundant and strong.

In a 2007 study assessing behaviors indicative of opioid misuse, many patients in primary care practices reported having engaged in aberrant behaviors one or more times.⁹

Table 3: Behaviors indicative of opioid misuse⁹

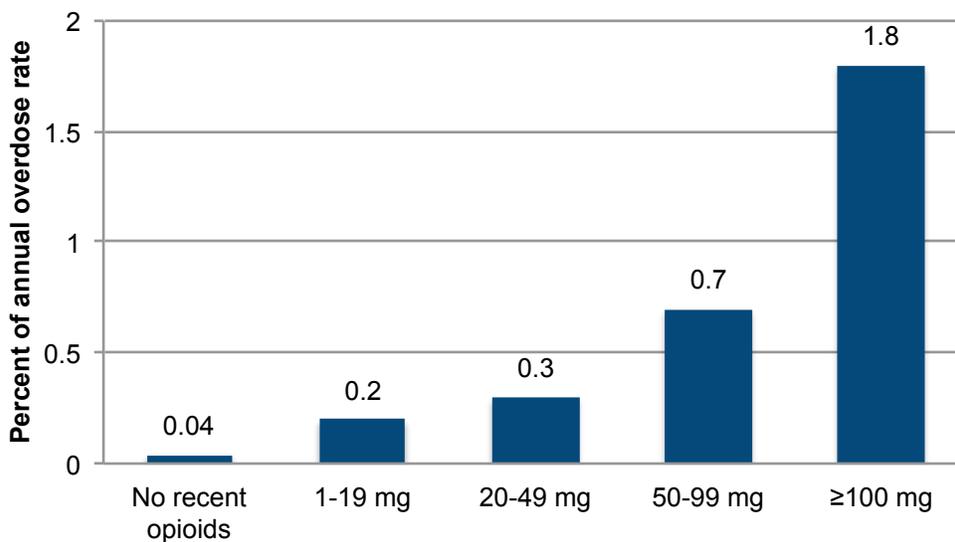
Behavior	Frequency in patients with opioid misuse
Requested early refills	47%
Increased dose on own	39%
Felt intoxicated from pain medication	35%
Purposely over sedated oneself	26%
Used opioids for purpose other than pain	18%

Among adults without a prescription, 41% obtained prescription opioids from friends or relatives for their most recent episodes of misuse.⁶⁸

A 2015 meta-analysis showed that the prevalence of opioid abuse among chronic pain patients in primary care settings ranged from 0.6%-8%, and the prevalence of dependence ranged from 3%-26%.⁶⁹ In pain clinics, the prevalence of opioid abuse ranged from 8%-16%, and addiction ranged from 2%-14%.⁶⁹ In eastern Pennsylvania, the lifetime prevalence of opioid use dependence among chronic opioid users was estimated at 35%.⁸

For prescription opioids, long-term therapy is associated with an increased risk in accidental overdose and death. A retrospective study including 9,940 patients who received three or more opioid prescriptions within 90 days for chronic pain between 1997 and 2005 found that annual overdose rates rose significantly as doses exceeded 50 MMED.⁷⁰

Figure 4: Risk of overdose rises with daily milligram morphine-equivalent dose.⁷⁰



Combining opioids with sedating drugs such as benzodiazepines or alcohol increases the risk of respiratory depression and overdose death.⁷¹ Benzodiazepines have been linked with overdose fatalities

in 50-80% of heroin overdoses, and 40-80% in methadone-related deaths.^{71,72} Patients on benzodiazepines who are being initiated on opioids should have their benzodiazepine tapered and discontinued whenever possible. For patients being co-managed by mental health professionals, coordinate a plan regarding continuing or tapering benzodiazepines in the setting of opioid co-prescribing. (Note: the FDA included the benzodiazepine-like insomnia drugs eszopiclone, zaleplon, and zolpidem [so-called “z-drugs”], muscle relaxants and antipsychotics, like aripiprazole, olanzapine, and quetiapine, in its 2016 warning about the hazards of combining CNS depressants with opioids.)⁷³

Other adverse events

In addition to risks of misuse, addiction, respiratory depression, and overdose death, there are many well-known side effects associated with chronic opioid use that can significantly compromise quality of life, including constipation, nausea or vomiting, sedation, pruritus, erectile dysfunction, fracture, immunosuppression, hallucinations, and hyperalgesia.

Gastrointestinal side effects

Constipation is one of the most common opioid-related adverse events, affecting most patients to at least some degree, and which usually does not resolve with continued exposure.¹⁶ To mitigate this side effect, patients should use a mild stimulant laxative such as senna or bisacodyl and increase the dosage in 48 hours if no bowel movement occurs. Physicians should perform a rectal examination if no bowel movement occurs in 72 hours. If there is no impaction, consider other therapies such as an enema, suppository, or magnesium citrate.⁷⁴ Medications for refractory, opioid-induced constipation include naloxone derivatives: naloxegol (Movantik), methylnaltrexone (Relistor), or naldemedine (Symproic). Naloxegol is an oral tablet that is used daily while methylnaltrexone is a subcutaneous injection or oral tablet used daily. Naldemedine is taken by mouth daily (0.2 mg) and may cause side effects such as abdominal pain or discomfort, diarrhea, and nausea.⁷⁰ In the **COMPOSE-1** trial, patients on naldemedine had significantly more spontaneous bowel movements (defined as ≥ 3 per week) than those on placebo (47.6% vs. 34.6%, $P=0.002$).⁷⁵

For **nausea or vomiting**, physicians should consider a prophylactic antiemetic, add or increase non-opioid pain control agents (e.g., acetaminophen), and decrease opioid dose by 25% if analgesic is satisfactory.

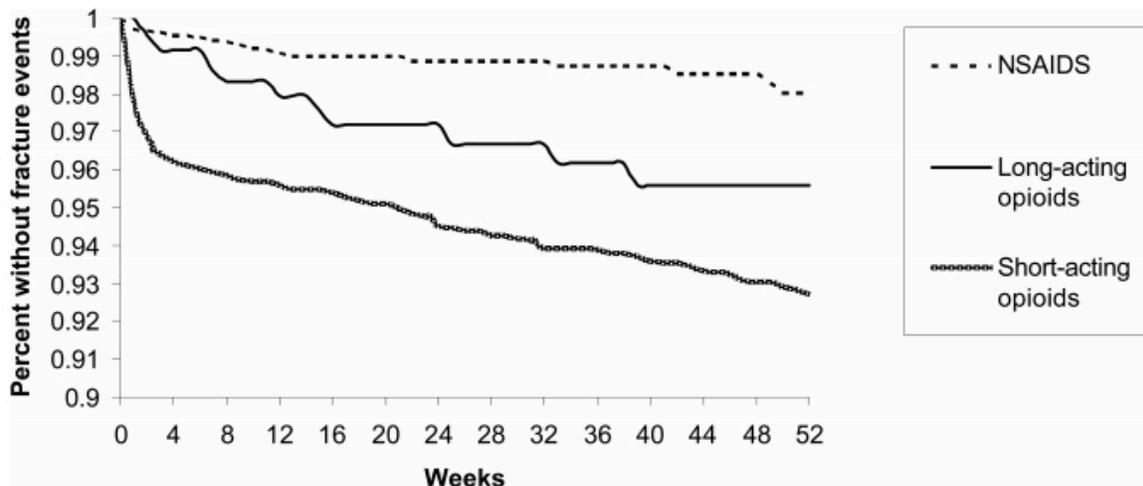
Sedation

If patient complains of sedation, determine whether sedation is related to the opioid, eliminate nonessential depressants (such as benzodiazepines or alcohol), reduce dose by 10%-15% if analgesia is satisfactory, add or increase non-opioid or non-sedating adjuvant for additional pain to reduce opioid dose, or add a stimulant in the morning. There is insufficient evidence to recommend opioid rotation as a possible means of reducing sedation.⁵⁶

Fracture

A retrospective cohort study over seven years compared the risk of fracture associated with starting opioids vs. NSAIDs (2,436 patients initiated on opioids and 4,874 initiated on NSAIDs; mean age 81, 85% female). Opioids significantly increased the risk of fracture (HR 4.9; 95% CI: 3.5-6.9) in a dose-dependent fashion. The opioid formulation mattered (Figure 5), with much of the risk in the first month after drug initiation for short-acting opioids, though fracture increased for both long- and short-acting opioids over time.⁷⁶

Figure 5: Fracture risk over time for NSAIDs, short-acting and long-acting opioids⁷⁶



Infection

Opioids may increase risk of infection in older adults. A case-control study of 3,061 older community dwelling adults ages 64-95 years evaluated the association between pneumonia and opioid use. Current prescription opioid users had a 38% increased risk of pneumonia (OR 1.38; 95% CI: 1.08-1.76) compared with nonusers. The risk was highest for opioid users categorized as being immunosuppressed, such as those with cancer, recent cancer treatment, or chronic kidney disease, or those receiving immunosuppressive medications or medications for HIV.⁷⁷

Myocardial Infarction (MI)

A case-control study assessed the risk of MI among adults on opioids for chronic pain in the UK General Practice Research Database (11,693 cases with up to four matched controls). Current opioid use was associated with a 28% increased risk of MI compared to non-use (HR 1.28; 95% CI: 1.19-1.37).⁷⁸

Erectile Dysfunction (ED)

In a cross-sectional analysis of 11,327 men with back pain, 909 (8%) received ED medications or testosterone. Long-term opioid use was associated with greater use of medications for ED or testosterone replacement compared to patients with no opioid use (OR 1.45; 95% CI: 1.12-1.87). Men prescribed daily doses of 120 mg morphine or more had a 1.58-fold increase in medication for ED or testosterone compared to patients without opioid use, suggesting that dose and duration of opioid use were associated with ED.⁷⁹

Creating a chronic pain management plan

Managing chronic pain requires balancing analgesic effectiveness with safety. A treatment or management plan is a written roadmap for setting functional goals (e.g., walking certain distances, engaging in previously enjoyed activities, or returning to work), monitoring progress toward those goals, and adjusting therapies as needed. The goal, whether the patient is opioid naïve or already on an opioid, is to maximize function while minimizing risks and adverse events.

For all patients with chronic pain, management begins by establishing treatment goals, exploring non-opioid treatment options, and addressing comorbid depression and anxiety, if present. Pain management goals may include both pain and functional targets, with the understanding that being 100% pain free is neither realistic nor desirable. Functional goals should focus on activities that are meaningful to the patient and attainable based on the severity of the painful condition. Multi-modal approaches that include non-drug and drug interventions are recommended.¹⁶

Be aware that comorbid conditions such as depression and anxiety can impact pain management. (In a study of 250 patients with chronic pain and moderate depression, using antidepressant therapy reduced pain levels before analgesic interventions were added.⁸⁰)

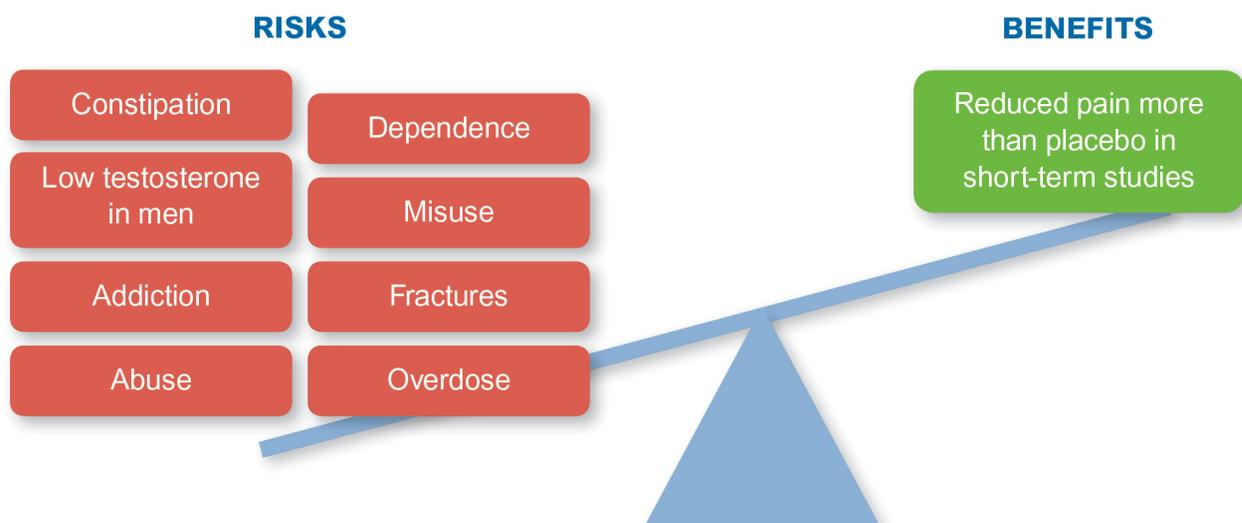
Although the evidence for long-term effectiveness of opioids is lacking, for patients with intractable, moderate-to-severe non-cancer nociceptive pain unresponsive to non-opioid treatment options, an opioid may be indicated guided by the following principles (each detailed below):

- Discuss risks and benefits of opioid use.
- Establish a written treatment agreement.
- Check or monitor opioid use.
- Use caution with dose escalation.
- Prescribe naloxone.
- Screen for opioid misuse or abuse.
- Taper or discontinue opioids when possible.

Discuss opioid risks and benefits

Educate patients about the risks and benefits of opioid use prior to initiating opioids and discuss them at each subsequent visit. For most patients, the risks of opioid therapy, as shown in Figure 6, outweigh the benefits. However, for some patients with nociceptive chronic pain, intermittent use of low-dose opioids on an as-needed basis may be a reasonable approach.

Figure 6: Balancing the risks and benefits of opioid therapy



Screen for opioid abuse

The Screening, Brief Intervention, and Referral to Treatment (SBIRT) algorithm can help primary care providers identify patients with problematic opioid use or potential opioid use disorder (OUD). SBIRT assesses the severity of opioid use, is brief (typically 5-10 minutes), and targets behaviors specific to substance use. Visit [AlosaHealth.org/OUD](https://www.AlosaHealth.org/OUD) for more information on SBIRT.

Establish a written treatment agreement

Prepare a written agreement/treatment plan when opioids are initiated to clarify how opioids will be prescribed, goals of therapy, possible risks and side effects, monitoring requirements, and a discontinuation or tapering plan.⁷¹ A signed informed consent document detailing the potential risks and benefits may be either incorporated into the larger agreement or added as a separate form. Agreements may specify that prescriptions be obtained from a single pharmacy or a single provider. Patients should be informed that opioid prescriptions are tracked and will be monitored. Additional monitoring may include pill counts or urine drug screens. Visit [AlosaHealth.org/Opioids](https://www.AlosaHealth.org/Opioids) for a link to a sample treatment agreement from the National Institute of Drug Abuse (NIDA) and other useful resources.

Initiating therapy

When initiating opioids, start with immediate-release formulations because their shorter half-life reduces the risk of inadvertent overdose. Prescribe low doses on an intermittent, as-needed basis and emphasize to patients that they should avoid daily use, which will typically lead to tolerance/physical dependence within 5-7 days.⁸¹ For elderly patients who have comorbidities, consider starting at an even lower dose and intensify monitoring for adverse effects.⁵⁶

Long-term opioid use often begins with treatment for acute pain, and research shows that opioids are often over-prescribed for acute pain. For example, a study of 1,416 patients in a 6-month period found that surgeons prescribed a mean of 24 pills (standardized to 5 mg oxycodone) but patients reported using a mean of only 8.1 pills (utilization rate 34%).⁸² For acute pain, only enough opioids should be prescribed to address the expected duration and severity of pain from an injury or procedure (or to cover pain relief until a follow-up appointment). Several guidelines about opioid prescribing for acute pain from emergency departments^{83,84} and other settings^{85,86} have recommended prescribing ≤ 3 days of opioids in most cases, whereas others have recommended ≤ 7 days,⁸⁷ or ≤ 14 days.⁸⁸ CDC guidelines suggest that for most painful conditions (barring major surgery or trauma) a 3-day supply should be enough, although many factors must be taken into account (for example, some patients might live so far away from a health care facility or pharmacy that somewhat larger supplies might be justified).⁵⁶

Monitoring opioid use

Follow-up appointments should occur one to four weeks after initiation of opioids or with dose changes; maintenance therapy visits should occur at least every three months. Each visit should include an assessment using a pain and function tool, questions about side effects, evaluation of overdose risk, and discussions about how the medication is being used.⁷¹

Many strategies to assess opioid use and ensure patient safety have been recommended. However, simply asking patients how they are using the medication, how often they take it, how many pills they take at one time, and what triggers them to take the medication, can identify patients who may be misusing

opioids or need changes to their pain management plan. Other ways to objectively monitor opioid use are checking prescription drug monitoring programs, completing urine drug screens, or random pill counts.

Prescription drug monitoring programs (PDMPs)

As of April, 2019, all U.S. states (except Missouri) and the District of Columbia have operational PDMPs.^{89,90} Information available through PDMPs varies based on reporting requirements and restrictions, but may include DEA schedules reported, timeliness of pharmacy dispensing information, access, and required reviews. Recommendations for PDMP use include:

- Check the PDMP before starting anyone on opioid therapy.
- Review the PDMP periodically throughout opioid therapy (at least every three months).
- Look for prescriptions for other controlled substances, like benzodiazepines, that can increase risk of overdose death.
- Review the total MMED.

Some states have specific requirements for PDMP use, such as requiring review prior to initial prescription or any time a specific prescription is written, such as for hydrocodone ER (Zohydro), therefore clinicians should remain updated about the specific requirements of their state PDMPs.

Drug testing

All patients on long-term opioid therapy should be periodically tested for drug use.⁹¹ Testing frequency and intensity can be tailored based on perceived risk of abuse, or all patients can be tested in an identical manner (universal testing), which may help de-stigmatize testing and remove any perceived bias related to who is tested. Every effort should be made to frame drug testing as a therapeutic, rather than punitive, component of treatment.⁹² Rather than setting up an “us vs. them” mentality, drug testing can actually improve the therapeutic alliance by transferring the role of detector from the provider to the test.⁹²

Although urine drug testing (UDT) remains the most common matrix for drug testing, technology using saliva, sweat, exhaled breath, and hair is becoming increasingly sophisticated, albeit with a currently-limited evidence base.⁹² Advantages of non-urine testing include their relative simplicity, ease of administration, and reduction in the possibilities of sample tampering.

The two main types of UDT are immunoassay (“presumptive” testing) and chromatography/mass spectrometry (“definitive” testing) (see Table 4 for details). Providers using UDTs should be familiar with the metabolites and expected positive results based on the opioid prescribed. For example, a patient taking oxycodone may test positive for both oxycodone and oxymorphone (a metabolite).⁷¹

Table 4: Comparison of two major types of UDT⁹¹

Immunoassay	Gas chromatography/mass spectrometry
Less expensive, fast, easy to use	More expensive, labor intensive
Most frequently used test in all settings	Requires advanced laboratory
Commonly used for screening	Used mostly to confirm positive immunoassay result
Engineered antibodies bind to drug metabolites	Directly measures drugs and drug metabolites
Qualitative testing: positive or negative results only	Quantitative test with precise results
Does not differentiate between various natural opioids	Differentiates all opioids
Typically misses semi-synthetic and synthetic opioids	More accurate for semi-synthetic and synthetic opioids (e.g., fentanyl, hydrocodone, buprenorphine)
Often has high cut-off levels giving false negative results	Very sensitive to low drug levels, minimizing false negatives
May show false positives from poppy seeds, quinolone antibiotics, or over-the-counter medications	Very specific, less cross-reactivity, low rates of false positives

Prior to any type of drug testing, discuss the following points with the patient:⁹¹

- Purposes/goals of testing
- Framing of testing as a normal part of standard safety measures that does not imply a lack of trust on the part of the provider
- What drugs the test covers
- Timing and dose of more recently consumed opioids
- Potential costs if testing is not covered by insurance
- Possibility of random testing, depending on treatment agreement and monitoring approach
- What might happen based on test results

When results of a drug test come back, clinicians can:⁹¹

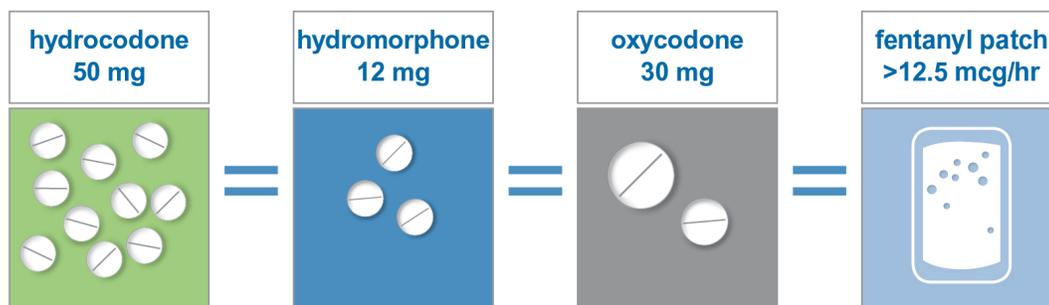
- Inform the patient of the results.
- Discuss with the patient any unexpected results or findings of drug use (note: it can be helpful to ask patients beforehand what they expect the drug test will show).
- Review the treatment agreement and reiterate concerns about the patient's safety.
- Determine if frequency and intensity of monitoring should be increased.

Decision tools and help with interpreting UDT results are available at mytopcare.org/udt-calculator/interpret-opiates-test-result.

Caution with dose escalation

When escalating opioid doses, be aware of two critical daily thresholds—50 and 90 MMED.⁷¹ According to the CDC, doses >50 MMED are associated with more than double the risk of overdose compared to patients on <50 MMED.⁵⁶ For patients on >90 MMED, a 9-fold increase in mortality risk was observed compared with the lowest opioid doses. Ninety MMED, or the equivalent of 60 mg of oxycodone, is considered by several guidelines as a “red flag” dose beyond which careful assessment, more frequent monitoring, and documentation of expected benefits are required. The total MMED for all prescribed opioids should be used (MMED is automatically calculated on many state PDMP reports).

Figure 7: Morphine equivalents of commonly prescribed opioids for 50 MMED



Role of ER/LA opioids and methadone

ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, oxymorphone, hydrocodone, and morphine. A 2015 study found a higher risk for overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with immediate-release opioids.⁹³ As noted above, continuous, time-scheduled use of ER/LA opioids is not more effective or safer than intermittent use of immediate-release opioids, it will quickly lead to tolerance/physical dependence, and may increase risks for opioid misuse or addiction.⁵⁶

ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received immediate-release opioids daily for at least 1 week.⁵⁶ Additional caution is required when prescribing ER/LA opioids in older adults or patients with renal or hepatic dysfunction because decreased clearance of drugs among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations.

When an ER/LA opioid is prescribed, using one with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk (i.e., the unusual characteristics of methadone and transdermal fentanyl make safe prescribing of these medications for pain especially challenging).⁵⁶

The use of methadone for chronic pain in primary care should generally be avoided because of higher methadone-related risks for QTc prolongation and fatal arrhythmias.⁵⁶ Equianalgesic dose ratios are highly variable with methadone, making conversion from other opioids difficult, with attendant increased risk of overdose. While methadone-related death rates decreased 9% from 2014 to 2015 overall, the rate increased in people ≥65 years of age.⁹⁴ If methadone is considered, refer patients to pain management specialists with expertise in using this medication.

Prescribe naloxone

Naloxone (e.g., Narcan) is an opioid antagonist that quickly reverses the effects of opioid overdose. Naloxone is increasingly available to first responders, patients, and friends and family members of those prescribed opioids, and a generic formulation of nasal-spray naloxone was approved by the FDA in April, 2019.⁹⁵ Primary care providers should prescribe naloxone to patients at risk of overdose, including those:

- taking opioid doses >50 MMED
- with renal or hepatic dysfunction
- co-prescribed benzodiazepines or other sedating medications
- who smoke, have COPD, asthma, or sleep apnea
- with a history of overdose or diagnosis of OUD

In many states, including Illinois, Maine, Ohio, Pennsylvania, and West Virginia, a standing order or protocol allows patients, family members, caregivers, and/or friends to request naloxone from their local pharmacist. In 2017, two states implemented mandatory co-prescription of naloxone for patients receiving opioids at doses of >90 MMED (Vermont) or >120 MMED (Virginia).⁹⁶ Rates of naloxone co-prescription have been rising nationwide in recent years but remain very low in absolute terms (the nationwide rate rose from 1.5 per 1000 patients in 2016 to 4.6 per 1000 in 2017).⁹⁶ Naloxone co-prescribing rates vary widely in states without legal mandates, from 0.7 per 1000 in Nebraska to 16.9 per 1000 in Maryland (the rates in Virginia and Vermont are both approximately 33 per 1000).⁹⁶

Anyone receiving naloxone should be taught how to use the device and about the common signs of overdose (slow or shallow breathing, gasping for air, unusual snoring, pale or bluish skin, not waking up or responding, pinpoint pupils, slow heart rate). A variety of naloxone products are available (Table 5). The intranasal device with atomizer and intramuscular (IM) shots require the most manipulation in order to administer. Intranasal naloxone and the auto-IM injector are easier to use, but vary greatly in terms of price and insurance coverage.

Table 5: Dosage forms available for naloxone

	Intranasal (w/atomizer)	Intranasal	Intramuscular (IM)	Auto-IM
				
Brand name		Narcan		Evzio
Strength	1 mg/1 mL	4 mg/ 0.1 mL	0.4 mg/1 mL	0.4 mg/1 mL
Sig for suspected overdose	Spray 1 mL into each nostril.	Spray full dose into one nostril.	Inject 1 mL into shoulder or thigh.	Use as directed by voice-prompt. Press firmly on outer thigh.
Second dose	Repeat after 2-3 min if no or minimal response.	Repeat into other nostril after 2-3 min if no or minimal response.	Repeat after 2-3 min if no or minimal response.	Repeat after 2-3 min if no or minimal response.
How supplied	Vial + mucosal atomizer	2 sprays	2 syringes	2 injectors
Cost	\$40	\$136	\$20	\$3,845

Depending on the opioid involved in the overdose, more than one dose may be required. All patients who receive naloxone reversal should be taken to an emergency room in case additional doses of naloxone or other medical support is needed.

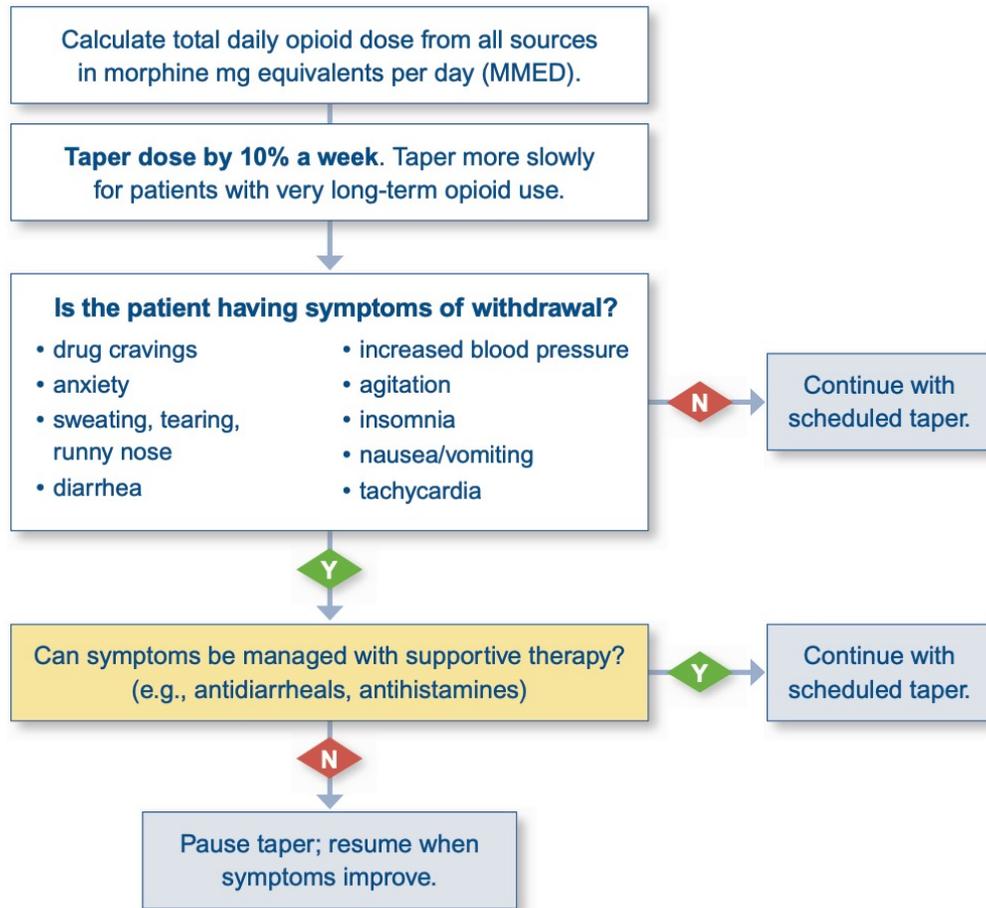
Tapering and discontinuing opioids

Patients who do not achieve functional goals on stable or increasing opioid doses or those with unacceptable side effects, should have the opioid tapered or discontinued. Patients sometimes resist tapering or discontinuation, fearing increased pain. However, a 2017 systematic review found that dose reduction or discontinuation resulted in *reduced* pain (eight studies), improved function (five studies) and improved quality of life (three studies).⁹⁷ A 2018 retrospective study of 551 veterans with chronic pain (mostly musculoskeletal) assessed pain one year before, and one year after discontinuation of long-term opioids (MMED 75.8 mg).⁹⁸ Pain was assessed on a 0-10 scale with higher score indicating worse pain. The mean overall pain score at the time of discontinuation was 4.9, and pain scores dropped during discontinuation by a mean of 0.2 points/month. Patients with moderate pain experienced the greatest reduction in pain after discontinuation.

Recommendations for tapering schedules vary. A 10% decrease weekly is recommended, based on years of opioid use (i.e., 10% decrease monthly for patients using opioids ≥ 4 years). For patients on high-dose opioids (i.e. ≥ 90 MMED), taper 10% until patient is taking 30% of the total initial dose, then recalculate 10% taper based on the new total opioid dose to slow taper.^{97,99} The rate of opioid taper

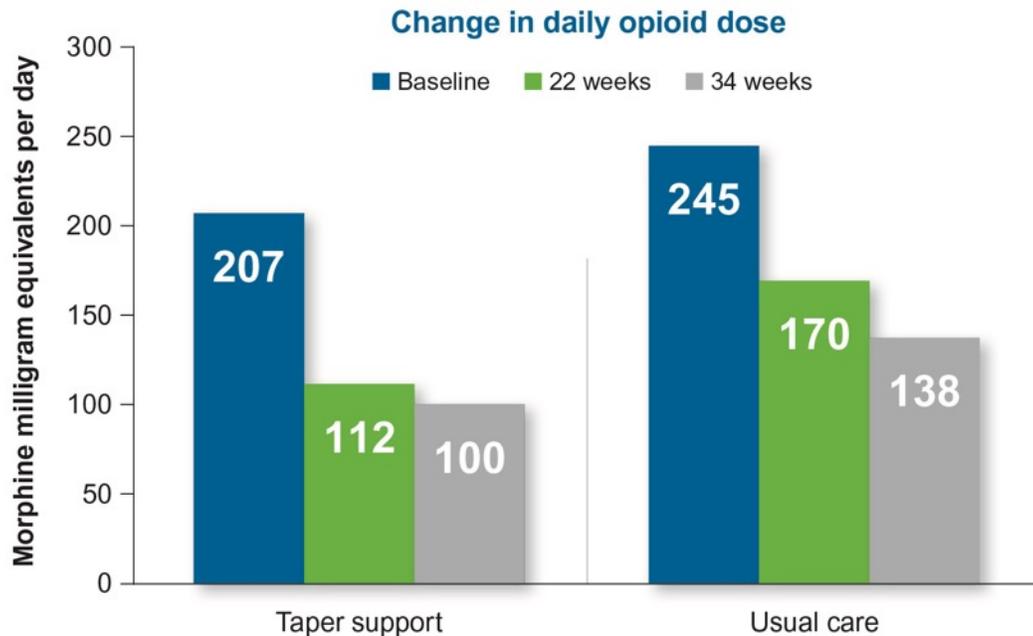
should be adjusted based on patient-specific factors such as the severity of withdrawal symptoms. One approach to managing an opioid taper is presented in Figure 8.

Figure 8: Tapering algorithm



A structured support program for opioid tapering may improve outcomes. A small trial of 35 patients with long-term opioid use compared a structured intervention including weekly individual counseling sessions vs. standard care and found reduced opioid doses in the intervention group at 34 weeks (mean 100 MMED vs. 138 MMED) although the difference was not statistically significant at 34 weeks (Figure 9 next page).¹⁰⁰ Pain scores decreased in both groups by about one point on a 10-point scale (not significant).

Figure 9: Change in daily opioid dose¹⁰⁰



In 2019 the FDA, recognizing the risks associated with abrupt discontinuation of opioid analgesics, required new labeling for opioid analgesics to guide prescribers about safe tapering practices.¹⁰¹ The key elements include:¹⁰¹

- Do not abruptly discontinue opioid analgesics in patients physically dependent on opioids. Counsel patients not to discontinue their opioids without first discussing the need for a gradual tapering regimen.
- Abrupt or inappropriately rapid discontinuation of opioids is associated with serious withdrawal symptoms, uncontrolled pain, and suicide.
- Ensure ongoing care of the patient and mutually agree on an appropriate tapering schedule and follow-up plan.
- In general, taper by an increment of no more than 10-20% every 2-4 weeks.
- Pause taper if the patient experiences significantly increased pain or serious withdrawal symptoms.
- Use a multimodal approach to pain management, including mental health support (if needed).
- Reassess the patient regularly to manage pain and withdrawal symptoms that emerge and assess for suicidality or mood changes.
- Refer patients with complex comorbidities or substance use disorders to a specialist.

Opioid use disorder

More than 2 million Americans have OUD, and the number is growing.⁵⁴ OUD can be effectively managed with medication-based treatment, but only an estimated 20% of adults with OUD currently receive such treatment.¹⁰²

OUD is defined as problematic opioid use leading to significant impairment or distress. It is marked by at least two of the following in the past 12 months:¹⁰³

- use of opioids at higher doses or longer than prescribed
- unsuccessful attempts to control or reduce use
- significant time lost obtaining, consuming, or recovering from opioids
- craving for opioids
- failure to fulfill obligations (i.e., work, home, or school) because of opioid use
- persistent social or interpersonal problems due to opioids
- opioid use displaces social, work, or recreational activities
- recurrent opioid use creates a hazardous situation (e.g., while driving)
- continued use despite a physical or psychological problem caused or worsened by opioid use
- tolerance or withdrawal in patients taking opioids other than as prescribed

Medication options include:

- methadone
- buprenorphine (as buprenorphine/naloxone tablets or sublingual film (e.g., Suboxone, Bunavail) or buprenorphine-only monthly injection (e.g., Sublocade) or 6-month implant (e.g., Probuphine)
- naltrexone extended-release injection (Vivitrol) or generic tablets.

Buprenorphine and methadone are both effective for helping patients avoid relapse and regain function, but they have different characteristics (Table 6). (Note that buprenorphine can also be prescribed for pain, and these formulations include a patch [Butrans], sublingual film [Belbuca], and injection [Buprenex].)

Table 6: Comparison of buprenorphine and methadone

	Buprenorphine	Methadone
Who can provide treatment	anyone with a DEA “X-waiver”	certified opioid treatment program
Treatment delivery	no daily clinic visits are required	generally requires daily visits to a clinic for supervised administration
Patient characteristics	preferred as first line treatment for most patients	helpful for patients who have had multiple unsuccessful treatment attempts, and/or need daily support
OUD severity	moderate to severe	moderate to severe
Initiating treatment	home or in office	certified opioid treatment program locations
When to start	patient must have mild to moderate withdrawal symptoms	any time

Injectable naltrexone (Vivitrol) may be an option for patients who have successfully completed a detoxification protocol (7-10 days of abstinence from opioid use). Guidelines suggest that naltrexone MAT is most effective in patients who are highly motivated and/or in patients whose adherence to taking the medication can be closely monitored.¹⁰⁴ Clinicians should be vigilant for signs of suicidality because suicidal thoughts, attempted suicide, and depression have been reported with naltrexone use.¹⁰⁴

For more information about identifying and managing patients with OUD, see AlosaHealth.org/OUD.

Naloxone vs. Naltrexone

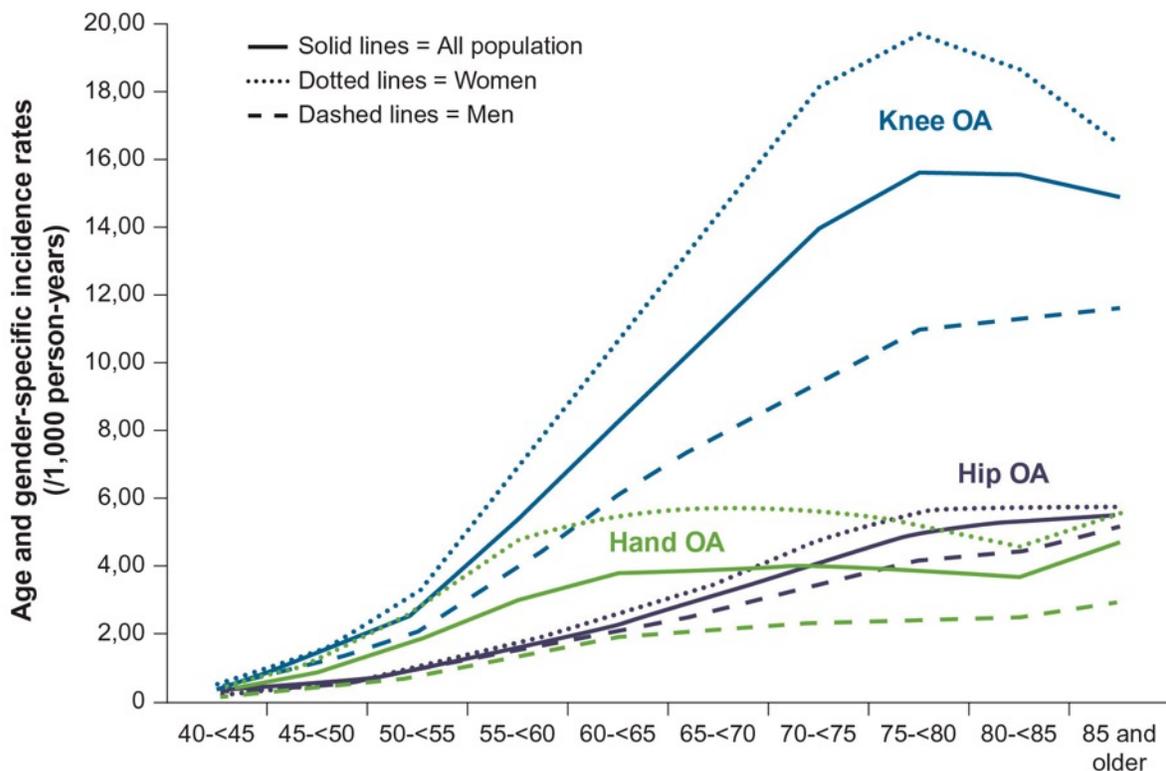
Naloxone (Narcan) is an opioid antagonist given by injection or nasal spray to reverse overdoses. It acts within minutes and lasts for only about an hour due to rapid metabolism.

Naltrexone is also an opioid antagonist, but has very different effects. It must be given by injection, and can precipitate acute withdrawal in a patient who is still taking opioids. Once successfully initiated, it can block opioid cravings for about a month.

Osteoarthritis

Osteoarthritis (OA) is a common source of pain and disability that affects nearly 70% of those over 65 years of age.¹⁰⁵ The joints involved tend to be the hand, hip, and knee, with knee being most common. As shown in Figure 10, more women than men suffer with OA.¹⁰⁶

Figure 10: Incidence rates of OA by involved joints¹⁰⁷



Non-drug options

Exercise and physical activity

Evidence demonstrates that exercise and physical activity can modestly reduce pain and improve function in patients with OA.

Table 7: Effects of exercise on pain and function for knee and hip OA^{26,108}

		Effect on pain		Effect on function	
Condition	# of RCTs	SMD	Relative Change	SMD	Relative change
OA of knee	44	-0.49	27% (21-32%)	-0.52	26% (20-32%)
OA of hip	9	-0.38	28% (14-38%)	-0.38	24% (3-42%)

SMD = standardized mean difference

In addition, A 2018 Cochrane review of 21 randomized trials including 2,372 patients with hip, knee, or hip and knee OA found that exercise-based interventions reduced pain scores (on a 0-20 scale) by a mean of 1.2 points after about 45 weeks (6% absolute reduction compared to non-exercise treatments; 95% CI: -9% to -4%).¹⁰⁹ Physical functioning improved by 5.6 points on a 0-100 scale but the result was not significant (5.6% absolute reduction; 95% CI: -7.6% to 2%). Exercise interventions were diverse and included tai chi, physical therapy, strength training, and aerobic exercise (e.g., walking, cycling).

The importance of clear patient education about the potential benefits of exercise for patients with OA was suggested by results from a review of 12 qualitative studies, conducted as part of the same Cochrane review. The authors noted that patients are often worried that they might hurt themselves by exercising, or that the exercise might worsen their symptoms. Patients wanted providers to give better information about the safety and value of exercise as well as exercise recommendations tailored to individual patient needs and abilities.¹⁰⁹

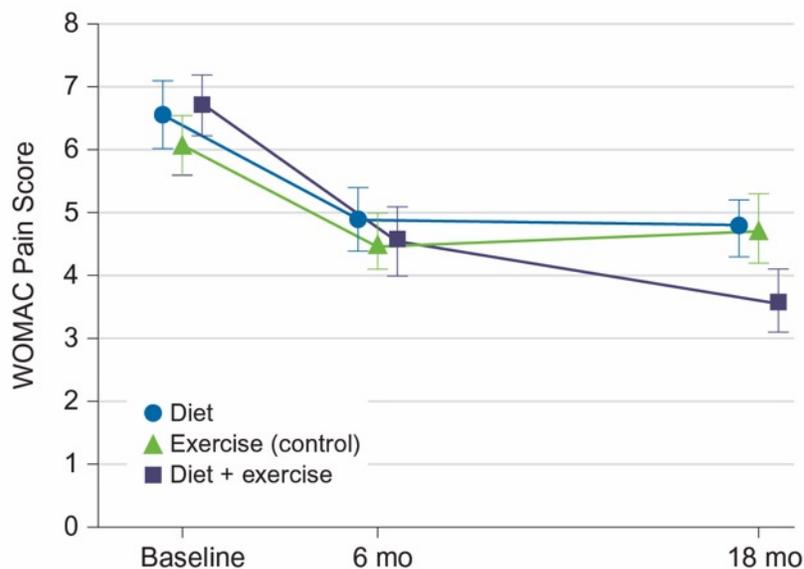
A recent trial randomized 171 adults aged ≥ 60 years with knee OA to a 12-week home-based exercise intervention plus health education vs. health education only.¹¹⁰ The exercise intervention involved group training sessions plus at-home strength and flexibility exercises to be done 30-40 minutes/day, three days per week. At 12-week follow-up, mean pain scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) dropped 3.06 points in the intervention group vs. 1.46 points in the control group ($P=0.007$), and stiffness level decreased one level vs. no change ($P=0.008$).

Weight loss

Weight loss interventions studied for OA typically focus on joint stress or injury rather than pain. However, in the Intensive Diet and Exercise for Arthritis (IDEA) randomized trial, the investigators assessed pain as a secondary outcome.²⁹ The study included 545 older adults with knee OA and overweight who were randomized to one of three approaches: diet plus exercise, diet alone, or exercise alone. Diet focused on calorie restriction to achieve at least a 10% reduction in body weight. The recommended exercise program called for one hour of aerobic and strength training activities three times a week. Pain was measured with the WOMAC pain subscale at baseline, 6 months (end of intervention), and 18 months (Figure 11). At 18 months the diet plus exercise intervention was associated with greater pain reduction

than the diet or exercise alone groups. In the diet plus exercise group 38% of patients reported little or no pain compared with 20% and 22% of patients with diet or exercise alone, respectively (P=0.002 for both comparisons).²⁹

Figure 11: WOMAC pain scores across 18 months²⁹



WOMAC function scores improved significantly in the diet plus exercise group compared to the diet group (mean difference 4.29 points; P<0.001) and the exercise alone group (mean difference 3.3 points; P=0.003).²⁹

Tai chi

A meta-analysis of 15 randomized trials in patients with musculoskeletal pain (80% OA) found tai chi to be moderately effective in improving both pain (SMD -0.66; 95% CI: -0.85 to -0.48) and disability (SMD -0.66; 95% CI: -0.85 to -0.46) at up to 3 months compared to no intervention.¹¹¹ No statistically significant differences were observed at 3 months to 1 year, or >1 year.

A randomized trial with 204 adults with symptomatic knee OA compared 12 weeks of twice-weekly tai chi vs. standard physical therapy and followed patients for 52 weeks. Both study arms showed significant improvements from baseline pain scores at 52 weeks, but there was no statistically significant difference between groups in terms of pain or function.¹¹²

Yoga

A review of 12 studies (including four RCTs) involving 589 patients with OA symptoms comparing a variety of yoga regimens to usual care found suggestions that pain, stiffness, and swelling were reduced (no meta-analyses were conducted due to clinical heterogeneity). No effect on physical function was observed.¹¹³

A randomized trial of 131 patients (mean age 75) with lower extremity OA compared twice-weekly sessions of chair yoga vs. a health education program.¹¹⁴ At 3-month follow-up, participants in the yoga group showed greater reductions in pain interferences (P=0.01) compared to control. During the

intervention, patients in the yoga group had reduced pain on the WOMAC scale ($P=0.048$), and improved gait speed ($P=0.024$) compared to the control group, but the differences were not sustained at 3-month follow-up.¹¹⁴

Acupuncture

A Cochrane review of six randomized trials evaluating acupuncture in 413 patients with hip OA (mean age range 61 to 67 years) found conflicting evidence on its effects on pain and function.¹¹⁵ In analysis of two trials with 105 patients comparing acupuncture to sham acupuncture there were no significant differences after 5-9 weeks in pain (absolute mean difference in pain score 2.1%; 95% CI: -7.9% to 3.6%) or function (absolute reduction 2.1%; 95% CI: -7.3% to 3%). One trial, however, that compared 13 weeks of acupuncture plus routine primary care vs. routine primary care alone in 137 patients found reduced pain (mean score at follow-up on 0-100 scale 26.3 points vs. 49.2 points; $P<0.0001$) and improved function (mean score 30.2 points vs. 49.2 points; $P<0.001$). Two trials reported minor side effects with acupuncture, mostly bruising, bleeding, or pain at needle insertion site.

An unblinded trial randomized 221 adults with hip or knee OA to acupuncture, sham acupuncture, or mock electrical stimulation.¹¹⁶ After five weeks of treatment no significant differences in mean improvements on a 0-100 pain scale were found for any comparisons.

Acupuncture trials can be particularly susceptible to placebo effects, as illustrated in a study comparing needle or laser acupuncture to no acupuncture or sham laser treatment in 282 patients with chronic knee pain (mean age 63). After 12 weeks of treatments, needle and laser acupuncture reduced self-reported knee pain more than no acupuncture (control) but not more than sham acupuncture, suggesting strong placebo effects. The benefits were not sustained at one year follow up.³⁰

Massage

A review of seven randomized trials with 352 participants suggests that massage may be better than no treatment for reducing OA pain.¹¹⁷ The trials were diverse with respect to outcomes, massage techniques, and patient populations. Clinical effect sizes for pain were moderate with about a 20-point reduction in WOMAC scores from a baseline of 50-60 points. The functional benefits were less clear; some trials showed no benefit while others showed improvements in the 50-foot walk test.^{31,117}

Self-management education programs

Small effects were noted in three meta-analyses of studies evaluating self-management education programs, though the benefits were not considered clinically important (Table 8).¹¹⁸⁻¹²⁰ Arthritis-specific programs included techniques to deal with problems associated with arthritis, appropriate exercises and medications, nutrition, and effective communication with healthcare providers and family.

Table 8: Self-management education programs¹¹⁸⁻¹²⁰

Meta-analysis	Number of RCTs	Setting	Effect sizes vs. controls (lower scores indicate improvements)
Chodosh, et al. 2005	14 (pain) 12 (function)	OA	-0.05 (pain) -0.06 (function)
Warsi, et al. 2003	17	OA and RA	-0.12 (pain) -0.07 (function)
Foster, et al. 2008	11 (pain) 8 (function)	OA and low back pain	-0.10 (pain) -0.15 (function)

Other non-drug interventions

TENS has been used for pain relief for decades, but studies evaluating effectiveness have shown mixed results. Data from four trials, including two RCTs, showed no statistical improvement in pain over placebo.¹²¹

CBT interventions typically address comorbid conditions, such as insomnia and depression. A systematic review, without meta-analysis, of four trials involving CBT or CBT-like pain coping skills trainings found inconsistent evidence for reduced pain at 12-month follow-up.¹²²

A meta-analysis of 30 randomized trials evaluating mindfulness meditation for chronic pain (5 trials in patients with OA or RA) found a moderate improvement in pain (standardized mean difference 0.32, result limited by significant heterogeneity) compared to standard care, passive controls, or education/support groups.³⁴

Non-drug summary for OA

Evidence supporting the effectiveness of non-drug interventions for OA is limited, but these interventions are generally safe and therefore may be considered as first-line or adjunctive treatments. For a complete summary of the non-drug interventions presented, see Appendix II.

Drug options

NSAIDs

Given the inflammatory mechanism of OA, NSAIDs are the first-line pharmacologic option for managing OA-related chronic pain. In a network meta-analysis of 76 randomized trials evaluating oral celecoxib, ibuprofen, or naproxen vs. placebo in 58,451 patients with knee or hip OA, NSAIDs were associated with small-to-moderate effect sizes for improvements in pain (SMD range: 0.32-0.57) and function (SMD range: 0.31-0.51), although results were not significant for naproxen at daily dose of 750 mg, or ibuprofen at daily dose of 1200 mg.¹²³

A 2017 Cochrane review of trials comparing topical NSAIDs vs. placebo in patients with hand or knee OA found moderate evidence for analgesia, with greater pain relief seen in trials of shorter durations (Table 9).¹²⁴

Table 9: NNTs to obtain 50% reduction in pain with topical NSAIDs¹²⁴

NSAID	Trial duration	# of studies	# of patients	Number needed to treat (NNT)
diclofenac	<6 weeks	5	732	5
diclofenac	6-12 weeks	4	2343	10
ketoprofen	6-12 weeks	4	2573	7

Topical vs. Oral NSAIDs

Topical NSAIDs may be as effective as oral NSAIDs for OA pain. A randomized trial of 282 older patients with chronic knee pain comparing oral vs. topical ibuprofen found equivalent changes in the WOMAC OA index (mean difference on 0-100 point scale was 2 points; 95% CI: -2 to 6 points).¹²⁵ While side effects in the study did not vary between oral and topical NSAIDs, a small, statistically significant increase in serum creatinine was observed for oral NSAIDs. Generally, topical NSAIDs are considered safer due to a lack of systemic absorption. Topical NSAIDs may be recommended over oral NSAIDs for localized, single joint pain (e.g., knee OA).⁴¹

Acetaminophen

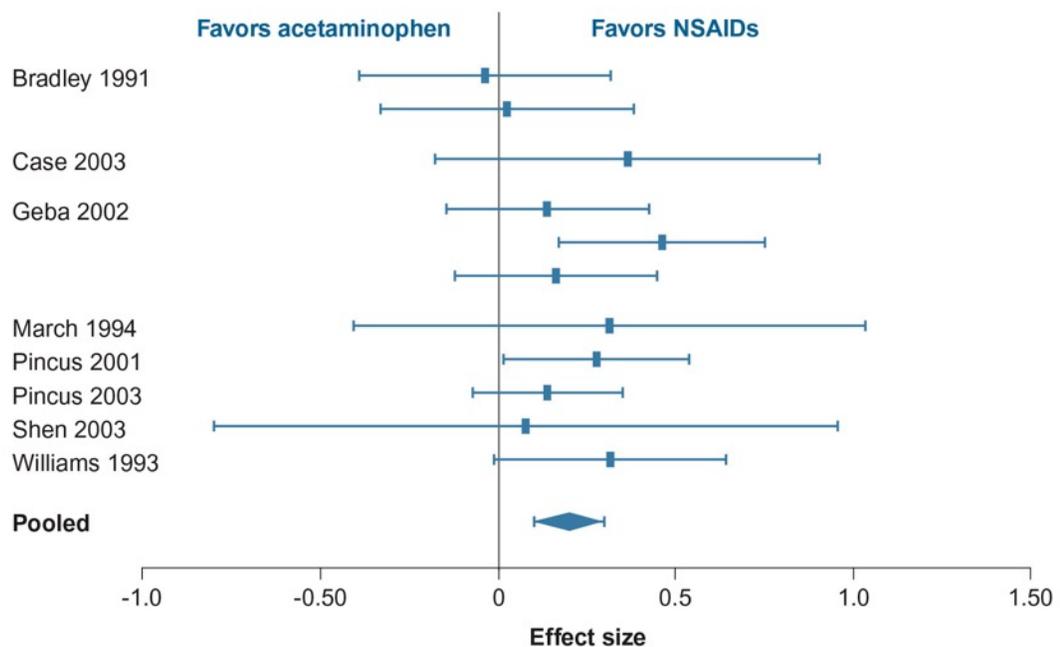
A 2019 Cochrane review of 10 randomized trials comparing acetaminophen vs. placebo in 3,541 patients with knee or hip OA found small, but not clinically important, reductions in pain and improvements in function with acetaminophen (mean daily doses ranged from 1950 mg to 4000 mg) when used from between 3 weeks and 3 months.¹²⁶ Mean change in pain scores (scale 0-100) were 26 points for acetaminophen vs. 23 points for placebo (absolute reduction 3%; 95% CI: 1%-5%, minimum clinically important difference 9%). Mean change in physical functioning scores (scale 0-100) were 2.9 points better for acetaminophen compared to placebo (absolute improvement 3%; 95% CI: 0.95%-4.89%; minimum clinically important difference 10%). These results should be interpreted cautiously, however, because daily acetaminophen doses of ~2,000 mg may not be effective over longer time frames (i.e., 3 months). The incidence of adverse events was similar between groups (risk ratio 1.01; 95% CI: 0.92-1.11).¹²⁶

Generally, scheduled dosing is better than as-needed dosing for relief of chronic pain. The recommended starting dose of acetaminophen for elderly patients is 325 mg every 4 hours, with a maximum daily dose of 3000 mg.^{41,127}

Acetaminophen vs. NSAIDs

A meta-analysis of six OA trials comparing acetaminophen and NSAIDs found a small, but statistically significant, treatment effect favoring NSAIDs (effect size 0.2; 95% CI: 0.1-0.3; P<0.05), as shown in Figure 12. NSAIDs, therefore, are preferred over acetaminophen unless patients have high risk for gastrointestinal, renal, or cardiovascular adverse effects.¹²⁷

Figure 12: Effect size of pain reduction from baseline¹²⁷



SNRIs

A meta-analysis of three trials of duloxetine for knee OA showed patients on duloxetine (60 or 120 mg daily) were 49% more likely to have a moderate pain response ($\geq 30\%$ reduction in pain intensity).¹²⁸ Overall the mean difference in pain score with duloxetine compared to placebo on a 0-10 scale was -0.88 points (95% CI: -1.11 to -0.65 points). Physical function (assessed by the WOMAC subscale, range 0-68) improved by a mean difference of -4.25 points ($P < 0.001$). A small pilot study suggests a possible role for venlafaxine XR, but further study is needed.¹²⁹ No SNRIs are FDA approved to treat OA.

Anticonvulsants

A small randomized controlled trial (RCT) of 89 patients with knee OA suggests pregabalin may reduce pain and improve function compared to the NSAID meloxicam, but the combination of meloxicam with pregabalin was better than either alone.¹³⁰ The study lasted four weeks, and longer-term RCT data are still needed. Pregabalin is not FDA approved for OA.

Topical lidocaine

A 12-week RCT of 143 patients with knee OA found that a lidocaine 5% patch had similar effects on OA pain and function as celecoxib 200 mg daily using WOMAC pain and function subscales.¹³¹ However, lidocaine patches are not FDA approved for the treatment of OA, and more data are needed to support their use.

Opioids

A Cochrane Review of 22 trials of 8,275 patients using opioids for knee or hip OA found small reductions in pain (SMD -0.28; 95% CI: -0.35 to -0.20) and improvements in function (SMD -0.26; 95% CI: -0.35 to -

0.17) compared to placebo at follow-up periods <16 weeks.¹³² Intermittent, as-needed use is preferred because time-scheduled use can be associated with greater total average daily opioid dosage. As noted earlier, however the **SPACE trial**, which included 240 patients with moderate to severe chronic low back pain or knee or hip osteoarthritis, found no significant differences in pain-related functioning comparing regimens of morphine, oxycodone, or hydrocodone to non-opioid analgesics (e.g., acetaminophen, NSAIDs, antidepressants, anti-epileptics) at any time points up to 1 year.¹⁴

Other treatment options

Glucosamine and chondroitin, either alone or in combination, do not provide long-term benefit in OA. A small number of clinical trials demonstrated that maximum effects were achieved at 3-6 months.¹³³ Topical capsaicin gel reduced pain 53% from baseline compared to a 27% reduction with placebo in one 12-week study. In a review of 2 studies, redness and burning sensation was reported by 44% and 46% of patients, respectively, randomized to capsaicin.¹³⁴

A 2018 network meta-analysis of 28 trials, however found that topical capsaicin 0.025% four times daily and topical NSAIDs were equally effective for relieving pain in patients with knee or hand OA (the effect size of topical NSAID vs. placebo was 0.32 [95% CI: 0.24-0.39] in direct comparison of 13 trials, and the effect size of capsaicin vs. placebo was 0.41 [95% CI: 0.17-0.64] in direct comparison of 4 trials).¹³⁵

Intra-articular injections

A number of injectable intra-articular agents are available to treat knee OA, with the two most-recently-approved being the synthetic corticosteroid triamcinolone acetonide extended release injection (Zilretta) and single-injection hyaluronic acid gel (Durolane). The evidence base for these treatments, however, is very weak, with effects frequently time-limited and study outcomes focused on cartilage and joint structure rather than pain and function.¹³³ A meta-analysis of 14 double-blind, sham-controlled trials with at least 60 patients in each trial found no clinically relevant differences between hyaluronic acid and sham injections.¹³⁶ Two randomized trials comparing single injection hyaluronic acid gel (Durolane) vs. placebo in a total of 564 patients with knee OA found no significant differences in pain, function, or joint stiffness at 6 weeks or 26 weeks.^{137,138}

OA is a common reason for joint replacement surgery. For older patients with functionally disabling chronic pain unresponsive to other therapies, surgery may provide relief.

Drug summary for OA

NSAIDs remain the most effective pharmacologic therapy for managing OA, with duloxetine, acetaminophen, and pregabalin as second-line options. Opioids should be reserved for patients with moderate-to-severe pain for whom all other options have been ineffective. No evidence supports intra-articular injections for knee OA. For a complete summary of the drug interventions presented, see Appendix II.

Low back pain

Low back pain (LBP) is one of the most common reasons for physician visits in the U.S., and about 25% of U.S. adults reported having LBP lasting at least a day in the past three months.¹³⁹ Imaging is of limited utility in diagnosing the cause of LBP because most patients have nonspecific findings, and asymptomatic patients often have abnormal findings. Magnetic resonance imaging (MRI) is recommended for red flag symptoms (for example, incontinence or saddle anesthesia), radicular symptoms, or risks for pathologic fracture.¹⁴⁰

Current guidelines recommend trying nonpharmacological options such as exercise, multidisciplinary rehabilitation, acupuncture, or yoga as first-line treatments for chronic low back pain, followed by pharmacologic treatment with an NSAID.¹³⁹ If the patient has an inadequate response, second-line options are a tricyclic antidepressant or duloxetine. Opioids, including tramadol, should be reserved for patients with pain unresponsive to all other treatments, with all of the caveats and cautions described previously¹⁴¹, although some experts in pain medicine assert that opioids should never be used to treat nonstructural low back pain.¹⁴²

Non-drug options

Exercise

In a review of 19 RCTs, exercise provided small reductions in pain with a weighted mean difference (WMD) of 10 points on a 0-100 scale (95% CI: 1.3-19.1 points) as compared to no exercise. Small, but not statistically significant, improvements in function were also observed (WMD 3 points; 95% CI: -0.53 to 6.48 points).¹⁴³ Types and duration of exercise from RCTs included in the meta-analysis were not specified. Although physical therapy has a role in the management of acute low back pain, no RCTs of physical therapy were identified for chronic low back pain.

Weight loss

Only small, uncontrolled pilot studies suggest possible benefit from weight loss for patients with chronic low back pain.^{144,145} After bariatric surgery, there was a 44% reduction in pain and a 26% improvement in function from a BMI reduction of 3 kg/m² (n=58).¹⁴⁴ Calorie restriction among obese patients suggests a reduction in pain and a significant improvement in function (n=46).¹⁴⁵ RCTs are needed to provide more conclusive evidence of benefit.

Tai Chi

Two trials (n=160 and n=320) found that tai chi reduced pain versus wait list or no tai chi on a 0- to 10-point scale (mean difference [MD] 1.3 points; P<0.001 and MD 0.9 points; P<0.05 respectively) although these differences may not be clinically important.^{146,147} The first trial randomized 160 adults with persistent non-specific low back pain to tai chi (18 sessions, 40 minutes each, over a 10-week period) vs. usual care. In addition to reducing pain, tai chi reduced “bothersome” back symptoms by 1.7 points, and improved self-report disability by 2.6 points on the 0-24 Roland-Morris Disability Questionnaire scale (RMDQ).¹⁴⁶

Yoga

Several relatively high-quality RCTs suggest that yoga can modestly reduce chronic pain. A recent study, for example, found that people with chronic LBP who took weekly yoga classes for 12 weeks had less pain and greater physical function compared to those who just got information about how to deal with back pain.¹⁴⁸ The yoga in the study emphasized strengthening back and core muscles. In addition to reducing pain, those in the yoga group were more likely to have stopped taking pain relievers at one-year follow-up. A 2012 systematic review comparing yoga to standard care found moderate effect sizes for reductions in pain-related disability, with evidence that even short-term interventions might be effective.¹⁴⁹

A 2017 Cochrane review of 9 RCTs involving 810 participants with chronic low back pain found small to moderate improvements in pain and function associated with yoga compared to no-exercise controls (see Table 10). For pain, a clinically meaningful reduction in pain score based on the RMDQ of 15 points was not achieved.¹⁵⁰ (A 2017 systematic review of 14 RCTs by the American College of Physicians came to similar conclusions.)¹⁴³

Table 10: Yoga: improvement in pain and function

	3-4 months effect size (95% CI)	6 months effect size (95% CI)	12 months effect size (95% CI)
Pain (weighted difference)	-4.55 (-7.04 to - 2.06)	-7.81 (-13.37 to - 2.25)	-5.40 (-14.5 to -3.7)
Function (standard mean difference)	-0.40 (-0.66 to - 0.14)	-0.44 (-0.66 to - 0.22)	-0.26 (-0.46 to - 0.05)

Mindfulness meditation

Mindfulness meditation is a secular form of Buddhist meditation used in some pain clinics because it elicits the relaxation response and can promote pain relief. A randomized trial of 342 adults with LBP found that participating in 8 weekly training sessions in mindfulness meditation was associated with significantly higher levels of function and reduced pain compared to usual care (61% vs. 44%, $p=0.04$).¹⁵¹ The neural correlates of the analgesic effects of mindfulness meditation were explored in a trial at Wake Forest University in which 76 healthy volunteers were taught mindfulness meditation and then monitored by MRI while a pain-inducing heat device was applied to their leg for six minutes.¹⁵² Meditation reduced pain unpleasantness by more than half (57%) and pain intensity by 40%. The study also showed that mindfulness meditation was associated with deactivation of the “default mode network,” a system of brain structures including the primary somatosensory cortex, the anterior cingulate cortex, the anterior insula, and the orbitofrontal cortex.¹⁵²

Acupuncture

A 2017 systematic review of four trials evaluating acupuncture vs. sham acupuncture in patients with chronic LBP found modest improvements in pain (WMDs -16.7 points on a 0-100 scale; 95% CI: -33.3 to -0.19 points), but no improvements in function.¹⁴³ A meta-analysis of 4 trials comparing acupuncture to no acupuncture found larger effect sizes, but the quality of the evidence is lower due to the large placebo effects known to manifest in acupuncture studies without a sham comparison.¹⁴³

Massage

A 2015 Cochrane review of 25 RCTs compared massage vs. inactive (e.g., sham treatment or waitlist) or active (e.g., TENS, acupuncture, traction, physical therapy) controls in 3,096 adults with LBP.¹⁵³ Massage compared to sham massage or no treatment showed moderate reductions in pain (SMD -0.75; 95% CI: -0.9 to -0.6) and disability (SMD -0.72; 95% CI: -1.05 to -0.39) in the short term (<6 months), but not in the long-term. In studies comparing massage to active therapies, massage resulted in greater pain reduction both in the short term (SMD -0.37; 95% CI: -0.62 to -0.13), and in the long term (SMD -0.40; 95% CI: -0.80 to -0.01), but no difference in disability reduction was observed.¹⁵³

TENS

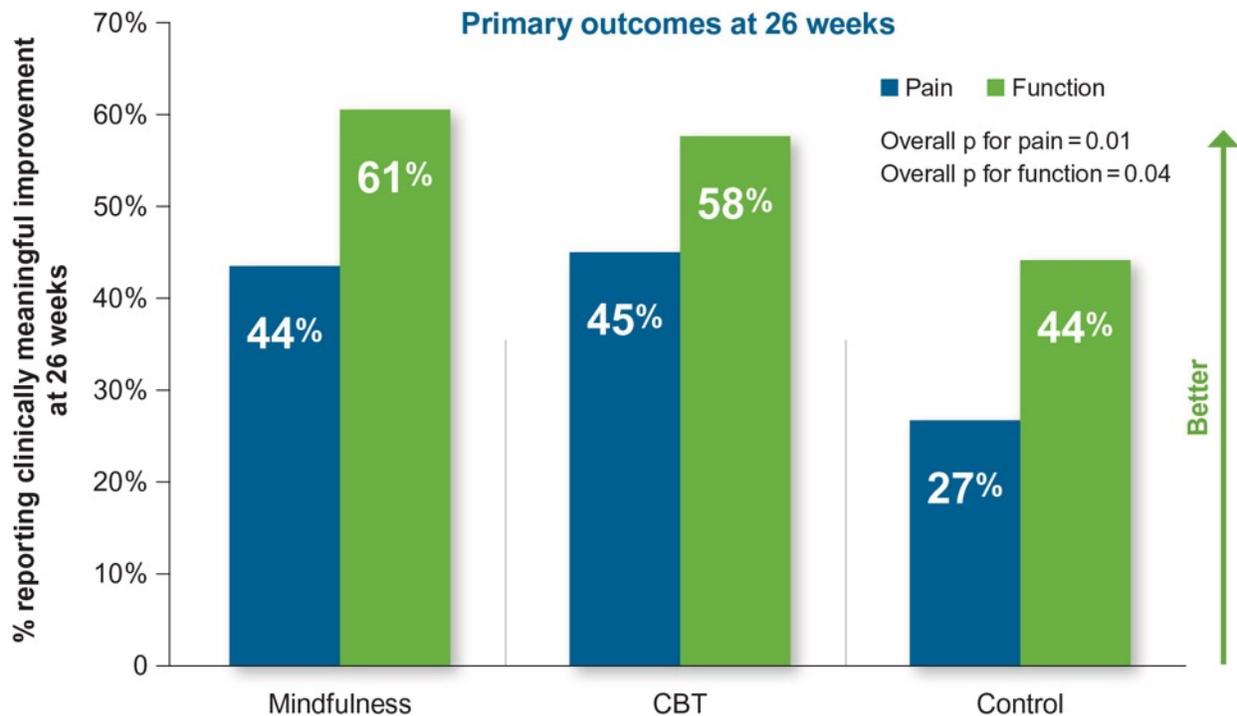
Existing clinical studies indicate that TENS has no beneficial effect on pain or function versus sham or placebo.^{139,153,154}

Cognitive and behavioral/mindfulness therapies

A meta-analysis of five RCTs evaluating CBT found no difference in function but a moderate reduction in pain intensity compared to waitlist controls (SMD -0.6; 95% CI: -0.97 to -0.22).¹⁴³

A more recent trial randomized 342 patients with chronic LBP to CBT, mindfulness-based stress reduction, or usual care. Both the CBT and mindfulness intervention consisted of eight weekly two-hour classes. Both mindfulness and CBT were associated with greater improvements in pain and function compared to usual care at 26 weeks (with benefit persisting at 52 week follow-up vs. usual care) with no statistically significant differences between CBT and mindfulness groups.¹⁵¹

Figure 13: Primary outcomes at 26 weeks¹⁵¹



Self-management

Self-management programs showed small effects on pain and function. Based on a meta-analysis of 11 studies, a small reduction in pain was observed (SMD -0.10; 95% CI: -0.17 to -0.04) while eight RCTs demonstrated a small improvement in disability (SMD -0.15; 95% CI: -0.25 to -0.05).¹⁵⁵

Non-drug summary for chronic low back pain

Tai chi, acupuncture, massage, and cognitive behavioral therapy can modestly reduce pain and improve function in patients with chronic, nonspecific LBP. Other interventions such as exercise, mindfulness meditation, and self-management have smaller or mixed effects, but all of these interventions are generally considered safe. Guidelines recommend initiating non-drug therapies for managing chronic LBP as the first step in treatment.¹³⁹ For a complete summary of the non-drug interventions presented, see Appendix II.

Drug options

Acetaminophen

Two small trials have evaluated acetaminophen in patients with chronic LBP. A trial conducted in the early 1980s randomized 30 patients to 1000 mg acetaminophen four times daily vs. the NSAID diflunisal 500 mg twice daily for 4 weeks.¹⁵⁶ Another trial randomized 45 patients with either acute or chronic LBP to 500 mg acetaminophen vs. amitriptyline 37.5 mg four times daily.¹⁵⁷ No significant differences were found between acetaminophen and diflunisal in pain relief or reduced disability, and acetaminophen was less effective than amitriptyline for reducing pain.¹⁵⁸

No trials have compared acetaminophen vs. placebo for chronic pain, however a 2016 Cochrane review of three trials with 1,825 patients with acute LBP found high-quality evidence that acetaminophen was no more effective than placebo for pain, disability, function, and quality of life.¹⁵⁹

NSAIDs

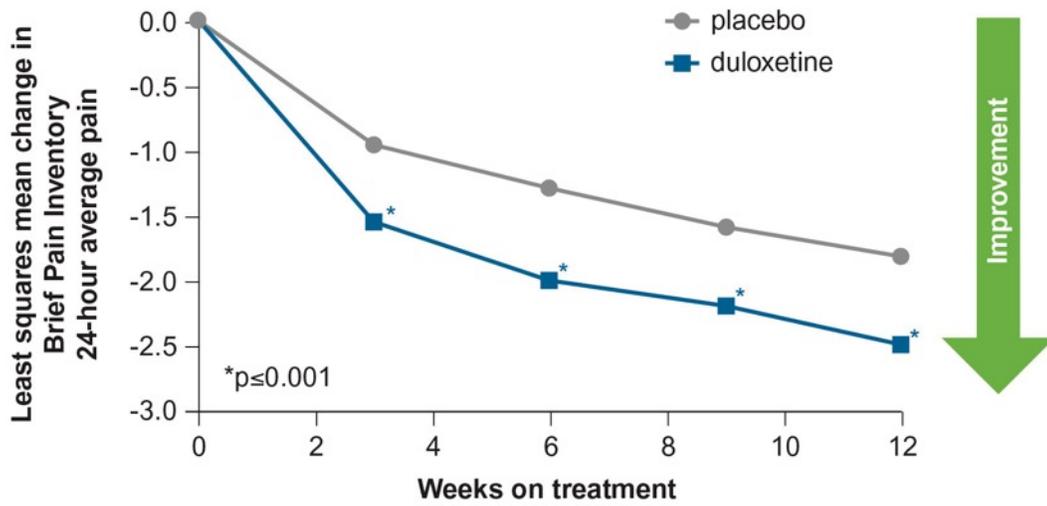
A review of six RCTs for the American College of Physicians showed that oral NSAIDs are more effective than placebo regarding pain intensity, with a small reduction in pain at 12 weeks (WMD -12.4 points on a 0-100 scale; 95% CI: -15.53 to -9.26).¹⁶⁰ No differences in efficacy between different NSAIDs, including non-selective NSAIDs vs. selective COX2 inhibitors, were identified. No trials were identified evaluating the efficacy of topical NSAIDs on chronic LBP.

Antidepressants

Duloxetine

An analysis of three moderate-quality RCTs found small improvements in pain and function with duloxetine vs. placebo at 12 to 13 weeks.¹⁶¹ One of the studies involved 401 patients randomized to duloxetine 60 mg daily or placebo. Compared with placebo, duloxetine-treated patients reported a significantly greater reduction ($P \leq 0.001$) in pain on the Brief Pain Inventory (BPI) (Figure 14).¹⁶²

Figure 14: Change in BPI score duloxetine vs. placebo¹⁶²



A 2017 systematic review found that SSRIs and TCAs were not significantly better than placebo for reducing pain or improving function in patients with chronic LBP.¹⁶¹

Opioids

The risks associated with using opioids for chronic LBP are likely to outweigh potential benefits. A systematic review of RCTs published through November 2016 found that as compared to placebo, opioids provided small short-term pain relief for chronic low-back pain and small improvement in function, but had a higher risk of nausea, vomiting, dizziness, somnolence, constipation, and dry mouth.¹⁶¹ No difference in pain response was observed between immediate release or ER/LA opioid products. None of the reviewed trials evaluated the long-term effect (>1 year) of opioids on either pain or function.¹⁶¹

In addition, as noted earlier, the **SPACE trial**, which included patients with moderate to severe chronic low back pain, found no significant differences in pain-related functioning comparing regimens of morphine, oxycodone, or hydrocodone to non-opioid analgesics (e.g., acetaminophen, NSAIDs, antidepressants, anti-epileptics) at any time points up to one year.¹⁴

Other therapies

Other drug options such as gabapentin, pregabalin, topical lidocaine, and muscle relaxants have little or no data for use in managing chronic low back pain. For the anticonvulsants pregabalin and gabapentin, a small number of low-quality RCTs failed to show a reduction in pain or improvement in function compared to placebo.¹⁶³ No data exist to support the use of topical lidocaine for low back pain without a neuropathic component. While widely prescribed, use of skeletal muscle relaxants for chronic LBP is not supported by evidence.¹⁶¹

Additional interventions

Epidural steroid injections

Lumbar epidural steroid injections under fluoroscopic guidance are commonly used to treat low back and lower extremity radicular pain,¹⁶⁴ although evidence for their efficacy is weak. A 2008 Cochrane review of 18 trials (1,179 patients) with subacute or chronic LBP (without meta-analyses due to clinical heterogeneity) found insufficient evidence to support the use of injection therapies.¹⁶⁵

Spinal fusion

An RCT of 349 patients with chronic low back pain comparing spinal fusion surgery against intensive rehabilitation showed small functional benefits in favor of surgery (mean difference in Oswestry disability index (0-100 scale) -4.1 (95% CI: -8.1 to -0.1; p=0.045). The minimum clinically important difference on the Oswestry scale is estimated to be between 4 and 17. Those assigned to surgery had more complications (dural tears, excessive bleeding, repeat surgery).¹⁶⁶

Drug summary for chronic low back pain

NSAIDs are the first-line pharmacologic option if non-drug options are inadequate. Acetaminophen may be tried for chronic LBP. Duloxetine can be considered a second-line treatment. For a complete summary of the drug interventions presented, see Appendix II.

Diabetic neuropathy

Neuropathy has a lifetime prevalence of 30%-50% in patients with diabetes and most commonly affects the distal extremities in a symmetric fashion causing numbness, tingling, pain, loss of vibratory sensation, and altered proprioception. Improved glucose control may reduce the risk of acquiring diabetic neuropathy and slow its progression,¹⁶⁷ and in those who have neuropathy, pain management may improve quality of life.¹⁶⁸

Current American Diabetes Association guidelines suggest initial management with pregabalin, duloxetine, or gabapentin.¹⁶⁷ Second-line options include TCAs (use cautiously in older adults), venlafaxine, or carbamazepine. Opioids, and particularly tapentadol, are not recommended to treat neuropathy due to their high risk for addiction and limited evidence for efficacy.¹⁶⁷ Tapentadol is FDA-approved to treat diabetic neuropathy, but the approval was based on two trials that used a design enriched for patients who responded to tapentadol, therefore the results are not generalizable.¹⁶⁷ Because tapentadol incurs similar risks of addiction and safety compared to typical opioids, its use is generally not recommended as first- or second-line therapy for neuropathic pain.¹⁶⁷

Non-drug options

Movement-based options

A small RCT of 39 Korean patients with type 2 diabetes and neuropathy found tai chi improved quality of life on five domains, including pain, physical functioning, social functioning, vitality and a mental

component score, compared with usual care, but there was no significant difference in neuropathy scores.¹⁶⁹

Acupuncture and massage

Small studies suggest a possible effect of acupuncture and massage on pain and function. A pilot study of 46 patients found overall symptom improvement from baseline with acupuncture in 77% of patients with 67% discontinuing medication. However, the study didn't have a control group nor did it specifically identify pain as an endpoint.¹⁷⁰ A 4-week trial involving 46 patients who received aromatherapy and massage had reduced pain and improved quality of life compared to usual care.¹⁷¹ A 2014 trial randomized 45 patients to acupuncture vs. sham acupuncture for 10 weeks and found no significant differences in pain outcomes (SMD -0.43; 95% CI: -1.02 to 0.16).¹⁷² Further studies are required to provide a more clear understanding of the role of acupuncture and massage in managing pain in diabetic neuropathy.

TENS

A meta-analysis of three trials comparing TENS vs. placebo in 78 patients with diabetic neuropathy found reduced pain severity at four weeks (SMD -5.37 points; 95% CI: -6.97 to -3.77 points) and six weeks (SMD -1.01 points; 95% CI: -2.01 to -0.01 points) but not at 12 weeks.¹⁷³

An analysis by the Agency for Healthcare Research and Quality (AHRQ), however, did not find significant or compelling evidence to suggest TENS was more effective than placebo for diabetic neuropathy.¹⁷⁴

Cognitive and behavioral interventions

Little data support cognitive and behavioral interventions for patients with diabetic neuropathy. A small trial of 20 patients receiving CBT showed a greater decrease in pain scores at 4-month follow-up, compared with usual care.¹⁷⁵ A small study of 20 patients found no difference with mindfulness meditation versus placebo on pain or quality of life.¹⁷⁶

Non-drug summary for diabetic neuropathy

Few non-drug options have been studied or shown to be effective for diabetic neuropathy. For a complete summary of the non-drug interventions presented, see Appendix II.

Drug options

Pregabalin, duloxetine, and tapentadol are FDA-approved for the treatment of neuropathic pain in diabetes. Other medications, such as gabapentin, oxcarbazepine, TCAs, topical lidocaine or capsaicin have been used off-label with varying degrees of success.

Acetaminophen and NSAIDs

No published trials have evaluated the use of acetaminophen alone or NSAIDs, either oral or topical, for diabetic neuropathy.

SNRIs

Both duloxetine and venlafaxine have been shown to reduce pain related to diabetic neuropathy compared to placebo. A network meta-analysis found relatively large effect sizes for pain reduction for duloxetine vs. placebo (SMD -1.33; 95% CI: -1.82 to -0.86 in four trials), and venlafaxine vs. placebo (SMD -1.53; 95% CI: -2.41 to -0.65 in three trials).¹⁷⁷ A 12-week study randomized 457 patients with painful diabetic neuropathy to three duloxetine groups (20 mg/day, 60 mg/day, and 120 mg/day) or placebo.¹⁷⁸ At follow-up, the mean daily pain severity score in the placebo group had dropped 1.91 points (on a 0-10 scale), with greater reductions in the three duloxetine groups: 2.36 points in the 20 mg group (not significant vs. placebo), 2.89 points in the 60 mg group ($P < 0.001$ vs. placebo), and 3.24 points in the 120 mg group ($P < 0.001$ vs. placebo).¹⁷⁸

TCAs

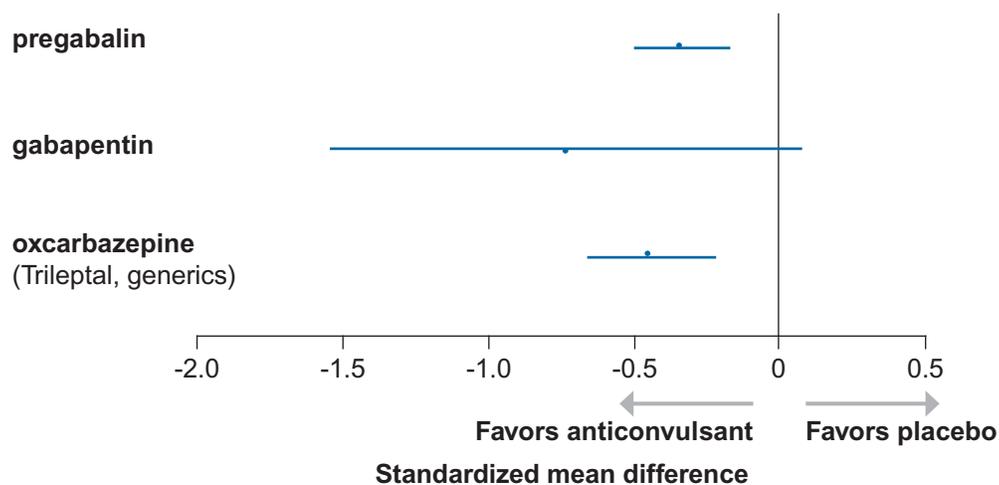
TCAs studied for diabetic neuropathy include amitriptyline, imipramine, and desipramine. A meta-analysis of five RCTs found a modest effect size for pain reduction for amitriptyline (SMD -0.72; 95% CI: -1.35 to -0.08).¹⁷⁷ Adverse effects with TCAs included somnolence and dizziness, which may be particularly important in older patients.

Anticonvulsants

In a meta-analysis of 16 RCTs with 4,017 patients, pregabalin was effective at reducing pain compared with placebo (SMD -0.34; 95% CI: -0.50 to -0.18).¹⁷⁹ Similarly, oxcarbazepine modestly reduced pain compared to placebo (SMD -0.45; 95% CI: -0.68 to -0.21) in an analysis of 3 trials with 634 patients.¹⁷⁹

Gabapentin is a commonly prescribed off-label to treat diabetic neuropathy. Based on a review of five RCTs with 766 patients, gabapentin had a large overall effect on pain severity, however, the result was not statistically significant (SMD -0.73; 95% CI: -1.54 to 0.09). These effect sizes are summarized in Figure 15.

Figure 15: Effect size of anticonvulsants for diabetic neuropathy compared to placebo¹⁷⁹



A 2019 Cochrane review of 20 randomized trials compared pregabalin 75-600 mg/day for 4-15 weeks vs. placebo in 5,943 patients with painful diabetic neuropathy.¹⁸⁰ The review found that pregabalin 300 mg/day modestly increased the likelihood that patients would have:

- >30% reduction in pain intensity (RR 1.1; 95% CI: 1.01-1.2)
- >50% reduction in pain intensity (RR 1.3; 95% CI: 1.2-1.5)
- “much” or “very much” improvement on Patient Global Impression of Change score (RR 1.8; 95% CI: 1.5-2)

Doubling the pregabalin dose to 600 mg/day did not result in substantially different levels of pain reduction. Rates of somnolence and dizziness were significantly higher with pregabalin vs. placebo.

The American Diabetes Association recommends using pregabalin or gabapentin, noting that gabapentin may be less expensive than pregabalin, although it is not FDA-approved for the indication of neuropathic pain.¹⁶⁷ Other anticonvulsants (e.g., carbamazepine, topiramate, valproic acid, lacosamide, lamotrigine) lack clear evidence of benefit but have documented harms.¹⁸¹

Topical lidocaine

Although lidocaine patches are FDA approved for post-herpetic neuralgia, no RCTs of patches have been conducted in diabetic neuropathy. One open-label, 4-week trial of 300 patients with painful diabetic polyneuropathy or post-herpetic neuralgia evaluated 5% lidocaine medicated plaster vs. pregabalin. In post-herpetic neuralgia more patients responded to 5% lidocaine medicated plaster treatment than to pregabalin (62.2% vs. 46.5% [no P value reported]), while response was comparable for patients with painful diabetic polyneuropathy (in the per-protocol set): 66.7% vs. 69.1% (no P value reported).¹⁸²

Cannabinoids for diabetic neuropathy

Weak evidence suggests that medical marijuana and cannabinoids may reduce pain related to diabetic neuropathy.

A Cochrane review of 16 randomized trials published through November 2017 comparing cannabis-based treatments to placebo in 1,750 adults with chronic neuropathic pain found slight reductions in pain intensity (SMD 0.35; 95% CI: 0.09-0.6) and increased numbers of patients achieving 50% or greater reductions in pain (21% vs. 17%; risk difference 0.05; 95% CI: 0-0.09).¹⁸³ The results, however, are limited by poor trial quality (only 2 trials were judged high-quality) and heterogeneity in treatments (10 trials evaluated an oromucosal spray containing THC or CBD, 2 trials evaluated a synthetic THC, 2 trials evaluated plant-derived THC, and 2 trials evaluate inhaled herbal cannabis). There were no significant differences in the rates of serious adverse events, but more people reported sleepiness, dizziness, or confusion in the cannabis groups.

A study of high and low potency cannabis cigarettes (7% or 3.5% THC) in 44 patients with neuropathic pain showed reduced pain scores in both cannabis cigarette groups vs. placebo cigarettes ($P < 0.01$) with no significant differences between the two doses of cannabis.¹⁸⁴ A 2012 study evaluated the oral cannabinoid nabilone (Cesamet) used as adjuvant to regular pain medications in 37 patients with diabetic neuropathy.¹⁸⁵ At 4 weeks, 70% of patients had at least a 30% reduction in pain. An open-label 5-week extension treatment period found a THC dose of 3 mg (range 1-4 mg) effective for continued pain reduction.¹⁸⁵

A small randomized cross-over trial in 16 patients with diabetic peripheral neuropathy compared the analgesic effects of three doses of inhaled cannabis (1% THC, 4% THC, or 7% THC) vs. placebo with pain sensitivity assessed after 4 hours.¹⁸⁶ Mean spontaneous pain scores (using 10-point scale) were modestly lower with all THC doses vs. placebo (-0.44 points with low dose, -0.42 points with medium dose, and -1.2 points with high dose, $P < 0.05$ for all comparisons). Mean pain scores with evoked pain were only significant with high-dose THC ($P < 0.001$). The percentage of patients with 30% or greater reductions in spontaneous pain were higher in the medium and high dose groups, but the differences with placebo did not reach statistical significance.

Another trial randomized 30 patients with chronic painful diabetic neuropathy to a sublingual spray containing 27 mg/mL THC and 25 mg/mL CBD (Sativex) vs. placebo spray, both administered four times daily for 12 weeks.¹⁸⁷ No significant differences were reported for change in pain scores from baseline for superficial, deep, or muscular pain, or in the percentages of patients reporting 30% or greater reductions in pain.

An un-published clinical trial that randomized 297 patients with diabetic neuropathy to Sativex oromucosal spray (maximum daily dose of 65 mg THC and 60 mg CBD) vs. placebo for 14 weeks found no significant differences in pain intensity between groups.¹⁸⁸

None of the reviewed studies evaluated long-term efficacy and safety of cannabinoid exposure.

Opioids

Opioid analgesics are ineffective for treating pain in diabetic neuropathy based on pooled data from four RCTs (SMD -0.58; 95% CI: -1.53 to 0.36) compared to control. This analysis excluded tramadol and tapentadol.¹⁷⁹ Due to their effect on serotonin and norepinephrine receptors, tramadol and tapentadol are thought to be slightly more effective than other opioids at reducing pain in diabetic neuropathy. An analysis of 5 placebo-controlled RCTs (3 of tapentadol and 2 of tramadol) showed that these opioids were more effective at reducing pain at up to 12-weeks (SMD -0.68; 95% CI: -0.80 to -0.56 vs. placebo).¹⁷⁹ Both medications, as noted earlier, are associated with all of the risks and adverse events common to typical opioids.

Other drug options

Evidence for the SSRIs paroxetine and citalopram is inconsistent and insufficient to recommend their use in managing pain in diabetic neuropathy. However, these drugs may be effective if patients have coexisting pain and depression.¹⁸⁹ Earlier studies showed that treatment with topical capsaicin was beneficial for relieving pain in patients with diabetic neuropathy.^{190,191} However, a 2017 meta-analysis of 5 randomized trials found that 0.075% capsaicin cream was no more effective than placebo (SMD -0.46; 95% CI: -0.95 to 0.03).¹⁷⁹

Drug summary for diabetic neuropathy

The American Diabetes Association recommends either pregabalin, duloxetine, or gabapentin as first-line pharmacologic treatments for diabetic neuropathic pain (gabapentin may be less expensive than pregabalin). TCAs are effective but should be used with caution because of the higher risk of serious side effects, especially in the elderly. Opioids are not recommended as first- or second-line options, considering their lack of efficacy and risks of addiction and other harms.¹⁹² Although based on efficacy, tramadol or tapentadol may be considered as third-line treatment options in some patients, they share all

the risks associated with other opioid analgesics. For a complete summary of the drug interventions presented, see Appendix II.

Additional interventions

Spinal cord stimulation has been studied for pain relief in diabetic neuropathy but has insufficient evidence for any recommendation and most studies were single-arm with fewer than 10 patients.^{193,194} RCTs are needed to determine efficacy.

Fibromyalgia

Fibromyalgia should be suspected in patients having multifocal pain not fully explained by injury or inflammation. Chronic headaches, sore throats, visceral pain, and sensory hyper-responsiveness are very common. Checking 18 tender points (9 pair) on the body may aid in diagnosing fibromyalgia. These tender points are sometimes confused with trigger points, which are associated with chronic myofascial pain. The primary difference between tender points and trigger points is that trigger points can produce referred pain. Guidelines suggest that people with fibromyalgia have pain in at least 11 of these tender points when a doctor applies pressure.¹⁹⁵

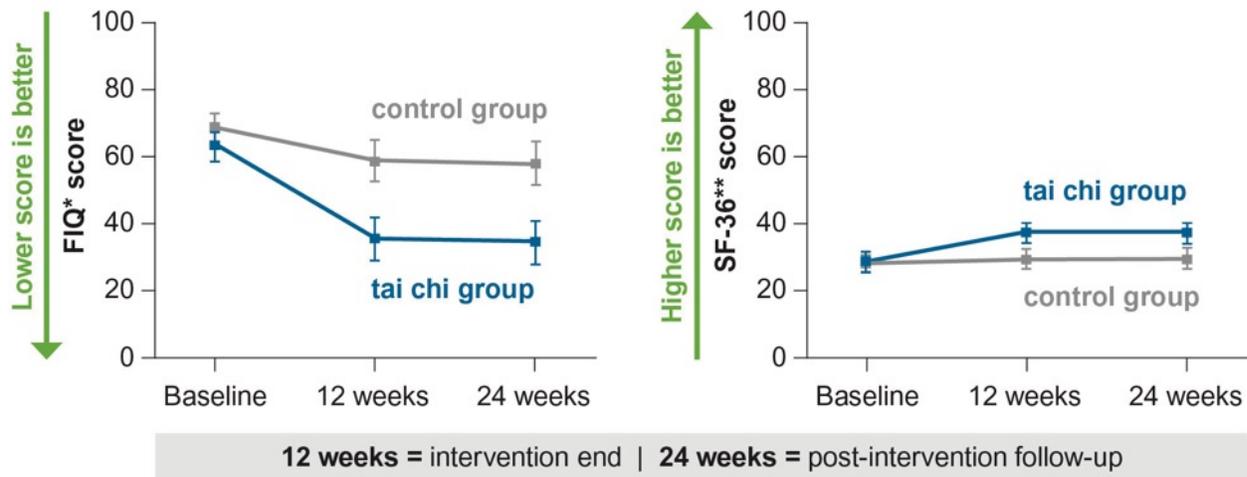
Non-drug options

Movement-based options

Exercise training is often recommended for patients with fibromyalgia,¹⁹⁶ not only for potential pain reductions, but for the other known physiologic benefits associated with exercise. The effects of exercise in fibromyalgia have been assessed in more than 30 trials, with the overall quality rated as moderate.¹⁹⁷ Some reviews have concluded that the strongest evidence was in support of aerobic exercise,¹⁹⁸ which is the current recommendation by the American College of Rheumatology. However, resistance training can be of benefit as well.¹⁹⁹ A 2017 Cochrane review of eight RCTs (n=456) comparing aerobic exercise training vs. no exercise or another type of intervention found small improvements (relative to comparators) in pain intensity (relative improvement 18%), stiffness (11.4%) and physical function (22%).²⁰⁰ A separate Cochrane review of 5 studies with 219 women with fibromyalgia found that moderate-to-high intensity resistance training improves function and reduces pain and tenderness vs. control, and that eight weeks of aerobic exercise was superior to moderate-intensity resistance exercise for reducing pain, although the quality of the evidence was rated as low.²⁰¹

Tai chi may help reduce pain and other symptoms related to fibromyalgia. One trial randomized 66 patients with fibromyalgia to tai chi twice weekly for 12 weeks vs. wellness education and stretching exercises. Tai chi improved scores on the Fibromyalgia Impact Questionnaire (FIQ) that assessed pain, physical functioning, fatigue, morning stiffness, and on the Medical Outcomes Study 36 Item Short Form Health Survey (SF-36) both at the end of the intervention (12 weeks) and at 24-week follow-up (Figure 16). At 12 weeks, mean between group difference was -18.4 FIQ points (P<0.001).²⁰²

Figure 16: Mean changes in FIQ and SF-36 scores at 12 and 24 weeks²⁰²



*Fibromyalgia Impact Questionnaire **Medical Outcomes Study 36-Item Short-Form Health Survey

Acupuncture, massage, and TENS

One in five patients with fibromyalgia try **acupuncture** within two years of diagnosis,²⁰³ and low-quality evidence suggests that acupuncture may be associated with reduced fibromyalgia-related pain. A 2013 Cochrane review of 9 RCTs with 395 adults with fibromyalgia found reduced pain and stiffness at 1 month with electro-acupuncture compared to either placebo or sham acupuncture, but there were no significant differences in pain, fatigue, or sleep comparing manual acupuncture to placebo or sham acupuncture (4 trials, 182 adults).²⁰³

Based on two small trials, myofascial **massage** may improve pain over placebo.²⁰⁴ Although data recommending other forms of massage for reducing pain are limited, most styles of massage therapy consistently improved quality of life for patients with fibromyalgia.

Six RCTs failed to show that **TENS** reduced pain in fibromyalgia.²⁰⁵

Cognitive and behavioral interventions

A Cochrane Review of 18 RCTs showed a small benefit from traditional CBT programs on pain (SMD - 0.30; 95% CI: -0.44 to -0.15) and function (SMD -0.31; 95% CI: -0.45 to -0.18).²⁰⁶ Controls included waitlist controls, active controls, or treatment as usual, and the overall quality of evidence was rated as low.

In seven RCTs of mindfulness medication, no reduction in pain was observed. Methods were varied and incorporated different components of mindfulness-based stress relief, CBT, and yoga.³⁴ In two RCT, self-management education did not improve pain or disability, as compared to controls.³⁴

Non-drug summary for fibromyalgia

Exercise has the most favorable benefit/risk profile for fibromyalgia with Tai chi, massage, and CBT as possibly helpful adjunctive options. For a complete summary of the non-drug interventions presented, see Appendix II.

Drug options

The FDA has approved three drugs for the treatment of fibromyalgia: duloxetine, milnacipran and pregabalin. Other options used off-label include gabapentin, amitriptyline, and SSRIs.

Acetaminophen and NSAIDs

No data support the efficacy of acetaminophen or NSAIDs for treating pain in patients with fibromyalgia,²⁰⁷ although they may be useful to treat pain triggers of fibromyalgia.¹⁹⁶

SNRIs

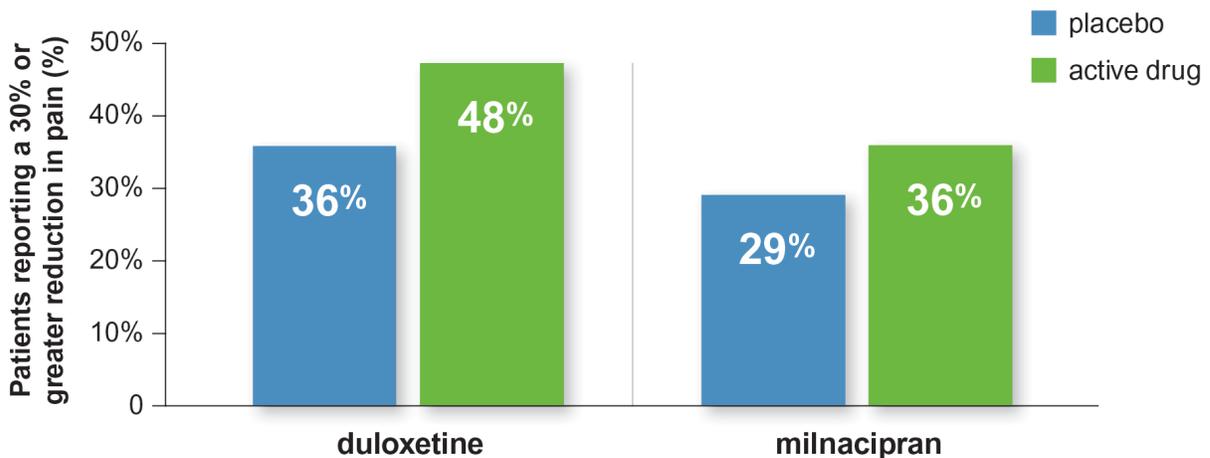
Duloxetine

A 2014 Cochrane review included six RCTs randomizing 2249 adults with fibromyalgia to duloxetine vs. placebo with 12-week to 6-month follow-up.²⁰⁸ At 12 weeks, duloxetine was superior to placebo for pain reduction (RR for $\geq 50\%$ reduction 1.57; 95% CI: 1.2-2.06), with superiority also shown at 28 weeks (RR 1.58; 95% CI: 1.1-2.27).

Milnacipran

In a Cochrane meta-analysis of three RCTs evaluating milnacipran 100 mg daily vs. placebo in 1,925 patients with fibromyalgia, milnacipran was more effective for inducing at least 30% reduction in pain (RR 1.38; 95% CI: 1.22-1.57).²⁰⁹ A similar effect on pain relief was noted with milnacipran 200 mg daily.

Figure 17: Percentage of patients reporting pain reduction $\geq 30\%$ with milnacipran and duloxetine vs. placebo^{208,209}



An updated (data through August 2017) Cochrane review identified additional 7 trials of duloxetine and 9 of milnacipran.²¹⁰ The updated analysis did not change findings from previous reviews: both drugs were better than placebo in reducing pain by at least 30%. Both drugs were also found to improve health-related quality of life, although more SNRI patients dropped out of trials due to adverse events as compared to placebo.

Antidepressants

A meta-analysis of nine trials of the TCA amitriptyline found a small improvement in pain (SMD -0.43; 95% CI: -0.75 to -0.11).²¹¹ A Cochrane review of seven RCTs found a small difference in patients who reported a 30% pain reduction between SSRIs (33%) and placebo (23%). SSRIs included in the review included citalopram, fluoxetine, and paroxetine.²¹² These data are insufficient to recommend SSRIs for the treatment of pain alone in patients with fibromyalgia.

Anticonvulsants

Pregabalin

A meta-analysis of five RCTs found pregabalin, overall, had a small effect on pain (SMD -0.28; 95% CI: -0.35 to -0.20). Low doses (150 mg per day) were no different than placebo, but doses of 300 mg daily or greater were more likely to result in a 50% reduction in pain than placebo (RR 1.45; 95% CI: 1.03-2.05).²¹³

A crossover randomized trial with 41 patients with fibromyalgia found that combining pregabalin with duloxetine more effectively reduced pain (68% reporting at least moderate global pain relief) vs. either pregabalin (39%) or duloxetine (42%) alone ($P < 0.05$ for both comparisons with combination).²¹⁴

Gabapentin

Evidence supporting the use of gabapentin for fibromyalgia is limited. A Cochrane review of RCTs lasting 8 weeks or longer (searched through May 2016) identified two trials, one of which was only a conference abstract. The other trial randomized 150 patients with fibromyalgia to gabapentin 1200-2400 mg/day vs. placebo for 12 weeks.²¹⁵ Gabapentin was associated with a small reduction in pain (mean difference between groups at 12 weeks: -0.92 points on 0-10 point BPI scale; 95% CI: -1.75 to -0.71 points) but this difference may not be clinically important.

Other options

Opioids

A Cochrane review found no RCTs of opioid therapy in patients with fibromyalgia lasting more than eight weeks.²¹⁶ An observational study followed a cohort of fibromyalgia patients initiating either opioids or non-opioid treatments for 12 months and found no difference in pain severity between the groups, with less reduction in BPI interference scores in the opioids group.²¹⁷ One RCT suggests that tramadol plus acetaminophen may reduce pain compared to placebo, but the trial duration was limited to 91 days, and long-term evidence is not available.²¹⁸ The American Academy of Neurology does not currently recommend opioids for treating fibromyalgia due to the lack of evidence for efficacy and the known risks of harms.²¹⁹

Cannabinoids

Two small trials have evaluated the oral cannabinoid nabilone (a synthetic form of THC) in patients with fibromyalgia. One trial randomized 46 patients to nabilone 0.5 mg to 1 mg twice daily for 4 weeks vs. placebo and found significant reductions in pain and improvements in anxiety on the Fibromyalgia Impact Questionnaire ($P < 0.05$ for both outcomes).²²⁰ Another trial randomized 31 patients with fibromyalgia and chronic insomnia to nabilone 0.5 mg to 1 mg at bedtime vs. amitriptyline 10-20 mg at bedtime for 4

weeks.²²¹ Although nabilone was associated with improved sleep quality, no significant effects were reported for pain, mood, or quality of life.

Drug summary for fibromyalgia

The European League Against Rheumatism (EULAR) guidelines for managing fibromyalgia-related pain recommend beginning with non-drug approaches (exercise, CBT, acupuncture, yoga, tai chi, and mindfulness) and then advancing to pharmacologic options (low dose amitriptyline, duloxetine or milnacipran, pregabalin). Most recommendations were considered weak, with the exception of exercise.¹⁹⁷ In the elderly, duloxetine or milnacipran and pregabalin or gabapentin may be the more favorable pharmacologic options. For a complete summary of the drug interventions presented, see Appendix II.

Putting it all together

Managing chronic pain is always challenging, and more so in those with comorbidities, polypharmacy, or physical or cognitive impairments. Physicians and caregivers need to develop individualized pain treatment plans identifying realistic functional goals and the level of pain management needed to reach those goals using a shared decision-making approach. As detailed in this evidence document, pain syndromes respond differently to available pharmacologic and non-pharmacologic treatments, but, in general, non-drug options (which can be as effective as drug options) should be tried first. When drug options are considered, it is important to maximize non-opioid options before prescribing opioids. Opioids are rarely indicated for the treatment of chronic pain conditions. When prescribed, the risk of long-term opioid treatment should be minimized through patient education, screening of high-risk patients for OUD, continuous monitoring, use of alternative non-opioid options, and careful tapering.

STUDY ID #: _____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Date: ____/____/____ Time: _____
Name: _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No Complete
Relief Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

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Appendix II: Strength of evidence for non-drug and drug approaches to managing chronic pain

INTERVENTION	Osteoarthritis	Low back pain	Diabetic neuropathy	Fibromyalgia	
NON-DRUG OPTIONS	exercise	●	●	⊘	●
	physical therapy	●	⊘	⊘	⊘
	tai chi	●	●	○	●
	weight loss	○	○	⊘	●
	yoga	●	●	⊘	○
	acupuncture	●	●	○	○
	massage	●	●	○	●
	TENS*	○	○	○	○
	cognitive behavioral therapy	⊘	●	○	●
	mindfulness meditation	○	●	○	○
self-management	●	●	⊘	○	
DRUG OPTIONS	acetaminophen	●	○	⊘	⊘
	NSAIDs—oral	●	●	⊘	⊘
	NSAIDs—topical	●	⊘	⊘	⊘
	duloxetine (Cymbalta, generics)	●	●	●	●
	tricyclic antidepressants (TCAs)	⊘	●	●	○
	pregabalin (Lyrica, Lyrica CR)	●	○	●	●
	gabapentin (Neurontin, generics)	⊘	○	○	●
	topical lidocaine (Lidoderm, generics)	○	⊘	●	⊘
	medical marijuana	⊘	⊘	●	○
	opioids	○	○	●	●

Risk/benefit: ● = favorable; ● = potentially favorable; ● = unfavorable; ○ = neutral; ⊘ = not studied

* TENS: transcutaneous electrical nerve stimulation

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About this publication

These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.



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