Managing non-cancer pain

The most recent evidence on effective, safe strategies

Principal Consultant: Mohammed Issa, M.D.

Series Editors: Ellie Grossman, M.D., M.P.H., Chris Worsham, M.D., M.P.H. (co-principal editors), Jerry Avorn, M.D., Katsiaryna Bykov, PharmD, Sc.D., Jennifer Corapi, PharmD, Dawn Whitney, M.S.N./Ed., R.N., Ellen Dancel, PharmD, M.P.H.

Medical Editor: Alan Drabkin, M.D., F.A.A.F.P.

Alosa Health is a nonprofit organization which accepts no funding from any pharmaceutical company. None of the authors accepts any personal compensation from any pharmaceutical manufacturer.

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

Alosa Health

Managing non-cancer pain

Activity Start Date: February 17, 2023
Activity Termination Date: February 16, 2026

This activity offers CE credit for:

1. Medicine (AMA)
2. Nurses (ANCC)
3. Pharmacists (ACPE)
4. Other

All other attendees will receive a Certificate of Attendance

Activity Overview:

The primary goal of this educational program is to address the challenge of effectively managing patients with non-cancer pain. It focuses on setting functional goals, optimizing management with a combination of evidence-based options, both pharmacologic and non-pharmacologic, and understanding the latest recommendations regarding opioid prescribing and strategies to reduce specific risks, such as prescribing naloxone.

The educational program includes a written evidence report (print monograph) and several non-CME/CE components:

1. Summary document of top 4-5 key messages
2. “Academic detailing” educational sessions in clinicians’ offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
3. Reference cards for easy access to key materials
4. 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.

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 the risks outweigh the benefit of treatment.

Financial Support:

There is no commercial support associated with this activity.

Target Audience:

The educational program is designed for physicians, including general internal medicine doctors, family practice physicians, nurse practitioners, physician assistants, nurses, pharmacists and all other clinicians caring for patients who have pain.

Credit Information:

In support of improving patient care, this activity has been planned and implemented by CME Outfitters, LLC and Alosa Health. CME Outfitters, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians: CME Outfitters, LLC, designates this enduring activity for a maximum of 2.25 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Note to Osteopathic Physicians: The AOA automatically recognizes *AMA PRA Category 1 Credit* ™ as AOA Category 2 credit.

Note to Nurse Practitioners: Nurse practitioners can apply for *AMA PRA Category 1 Credit™* through the American Academy of Nurse Practitioners (AANP). AANP will accept *AMA PRA Category 1 Credit™* from Jointly Accredited Organizations. Nurse practitioners can also apply for credit through their state boards.

Nurses: This activity is designated for 2.25 nursing contact hours.

California Residents: This continuing nursing education activity was approved by the California Board of Registered Nursing. CME Outfitters LLC's provider number is CEP15510.

Pharmacists (ACPE): This knowledge-based activity is approved for 2.25 contact hours (0.225 CEUs) of continuing pharmacy credit (UAN JA0007185-9999-23-022-H08-P).

Disclosure Declaration

It is the policy of CME Outfitters, LLC, to ensure independence, balance, objectivity, and scientific rigor and integrity in all of their CME/CE activities. Faculty must disclose to the participants any relationships with commercial companies whose products or devices may be mentioned in faculty presentations, or with the commercial supporter of this CME/CE activity. CME Outfitters, LLC, has evaluated, identified, and attempted to resolve any potential conflicts of interest through a rigorous content validation procedure, use of evidence-based data/research, and a multidisciplinary peer review process. Relevant financial relationships exist between the following individuals and commercial interests: Dr. Worsham

consults with Analysis Group, Atheneum, Berkshire Hathaway, Chronius, FVC Health, GLG, Guidepoint, NuvoAir, Ogilvy, Philips, Simbo, and Tell Health.

Disclosures:

This material is provided by Alosa Health, a nonprofit organization which accepts no funding from any pharmaceutical company. No commercial support has been received for this activity. All individuals including planners, authors, reviewers, academic detailers, staff, etc., who are in a position to control the content of this educational activity have, on behalf of themselves and their spouse or partner, reported no financial relationships related to the content of this activity.

Faculty and Planners:

Mohammed Issa, M.D., is an Assistant Professor of Anesthesia at Harvard Medical School, the Program Director of the Pain Fellowship at Brigham and Women's Hospital and the Medical Director of the Pain Management Center at Brigham and Women's Faulkner Hospital. Dr. Issa has no relevant financial relationships to disclose.

Ellie Grossman, M.D., M.P.H., is an Instructor in Medicine at Harvard Medical School, the Medical Director of Primary Care/Behavioral Health Integration and an Attending Physician at the Cambridge Health Alliance. Dr. Grossman has no relevant financial relationships to disclose.

Christopher Worsham, M.D., M.P.H. is an Instructor in Medicine at Harvard Medical School, a Teaching Associate at the Harvard Medical School Department of Health Care Policy, and a pulmonologist and critical care physician at Massachusetts General Hospital. Dr. Worsham discloses no financial relationships relevant to the content of this document.

Jerry Avorn, M.D., is a Professor of Medicine at Harvard Medical School and Chief Emeritus of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. An internist, he has worked as a primary care physician and geriatrician and has been studying drug use and its outcomes for over 40 years. Dr. Avorn has no relevant financial relationships to disclose.

Katsiaryna Bykov, Pharm.D., Sc.D., is an Assistant Professor of Medicine at Harvard Medical School and an Associate Epidemiologist in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. Dr. Bykov has no relevant financial relationships to disclose.

Jennifer Corapi, Pharm.D., is a clinical pharmacist at Massachusetts General Hospital. Dr. Corapi has no relevant financial relationships to disclose.

Dawn Whitney, M.S.N./Ed., R.N. is a Clinical Educator at Alosa Health. She is a lecturer in the School of Nursing and Health Sciences at the University of Massachusetts - Boston and Bouvé College of Health Sciences at Northeastern University. Ms. Whitney has no relevant financial relationships to disclose.

Ellen Dancel, Pharm.D., M.P.H., is the Director of Clinical Materials Development at Alosa Health. Dr. Dancel has no relevant financial relationships to disclose.

Alan Drabkin, M.D., F.A.A.F.P., is a Clinical Associate Professor of Family Medicine at Tufts University School of Medicine. Dr. Drabkin has no relevant financial relationships to disclose.

Susan Yarbrough, CHCP is the Senior Director of Educational Excellence at CME Outfitters, LLC. Ms. Yarbrough has no relevant financial relationships to disclose.

Candice Gillett, M.P.H., at CME Outfitters, LLC, has no relevant financial relationships to disclose.

Reviewers

Gina Stenhouse, Pharm.D., B.C.P.P., D.P.L.A., is a Clinical Pharmacist Practitioner in Pain Management and the Pain Management, Opioid Safety Initiative, Prescription Drug Monitoring Program (PMOP) Coordinator at the Veteran Affairs (VA) in Boston. She manages patients with chronic pain in an ambulatory care clinic. She promotes quality pain management programming through multidisciplinary collaboration, ensuring Veterans are receiving safe and effective pain management to improve their quality of life and function. Gina trains pharmacy students, pharmacy practice residents, medical students, and medical residents. Dr. Stenhouse has no relevant financial relationships to disclose.

Scott Hershman, MD, FACEHP, CHCP, at CME Outfitters, LLC, has no relevant financial relationships to disclose.

Unlabeled Use Disclosure

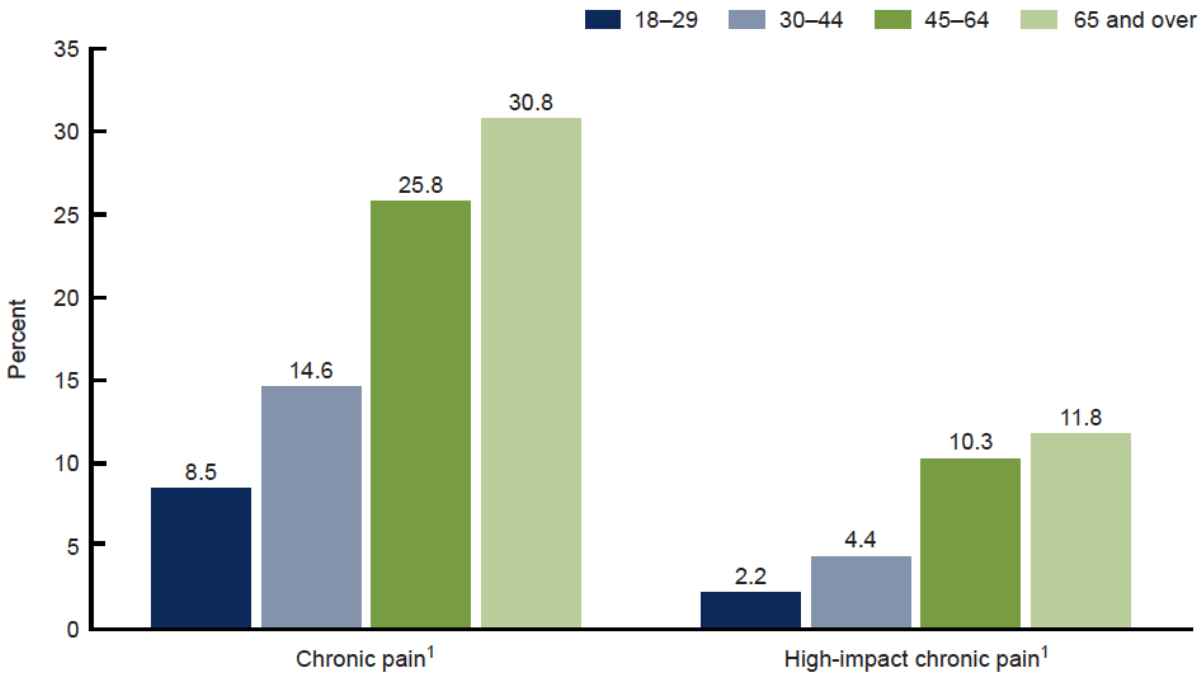
Faculty of this CME/CE activity may include discussions of products or devices that are not currently labeled for use by the FDA. The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices. CME Outfitters, LLC, the faculty, and Alosa Health, Inc. do not endorse the use of any product outside of the FDA labeled indications. Medical professionals should not utilize the procedures, products, or diagnosis techniques discussed during this activity without evaluation of their patient for contraindications or dangers of use.

Table of Contents

Introduction

Pain (acute and chronic) is a common medical symptom. In the 2019 National Health Interview Survey conducted by the National Center for Health Statistics at the Centers of Disease Control and Prevention (CDC), over 50 million people are estimated to report daily pain or pain on most days, accounting for over 20% of adults.[1] The prevalence of pain increases with age. It can become debilitating and associated with significant functional impairment, for example being unable to do household chores or go to work or school.[2]

Figure 1: Prevalence of chronic pain and high-impact chronic pain in the past 3 months[2]

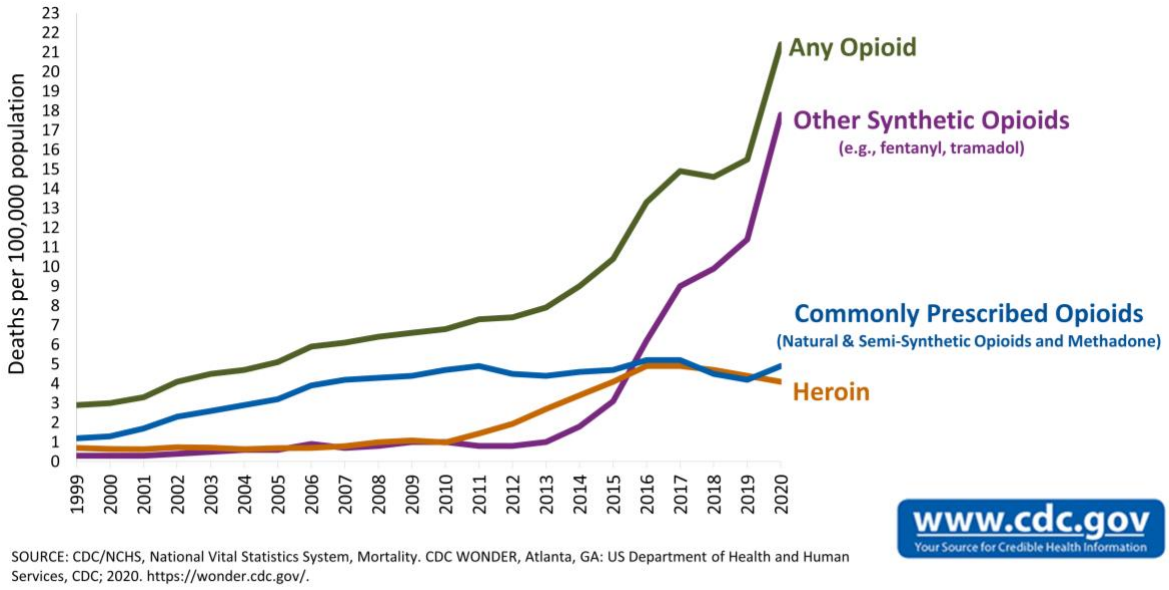


[1] Significant quadratic trend by age group ($p < 0.05$).
High-impact chronic pain is pain that limits work and life activities and occured on most or all days.
SOURCE: National Center for Health Statistics, National Health Interview Survey, 2019.

Clinicians 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 pain, however, can involve an additional level of complexity because one of the classes of pain medications—opioids—is at the center of an intense national debate regarding how best to curb the epidemic of opioid-related addiction, and overdose.[3]

The U.S. has seen three successive waves of overdose deaths related to both prescribed and non-prescribed opioid drugs.[4] The first began in the 1990s with steadily rising prescriptions for opioid analgesics. In the second wave, beginning in 2010, deaths from heroin overdose began to increase sharply.[5] The third wave began in 2013 with sharply rising overdose deaths attributed to synthetic opioids, particularly those involving illicitly-manufactured fentanyl. In 2020, opioid overdose deaths increased by 30%[6] and in 2021, the CDC estimated that over 108,000 people in the U.S. died from an opioid overdose (another 15% increase).[7]

Figure 2: Opioid-related overdose deaths by type in the U.S.[8]

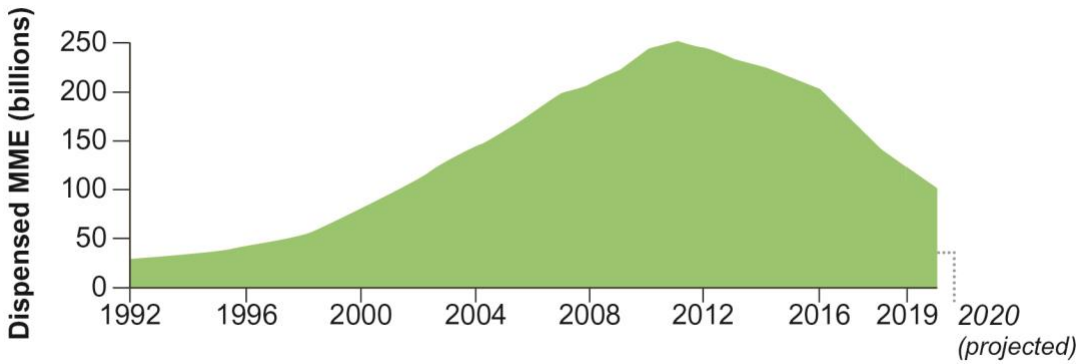


SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.

The rise in opioid overdose deaths is related to dramatic increases in the number of persons misusing opioids (i.e., use of opioids other than as prescribed). In 2020, approximately 9.3 million Americans aged ≥12 years reported that they misused prescription opioids in the past year.[9] Among these, 2.7 million people met the criteria for opioid use disorder (OUD).

Increasing risk of overdose and addiction continues amid declining opioid prescribing. Since 2011, the volume of opioids dispensed, expressed in terms of morphine milligram equivalents (MME), declined 60%, approaching levels not seen since the early 2000s. The most significant drop in prescription opioid use occurred following the release of the 2016 CDC Opioid Prescribing Guideline.

Figure 3: Dispensed MME in billions of opioids*[10]



*excludes medications for the treatment of opioid use disorder

It is against the background of opioid-associated overdose risk that clinicians must make daily decisions about how best to treat their patients who have chronic pain. A failure to adequately treat chronic pain reduces patient quality of life. Patients with chronic pain report pain interfering in their professional life,

social life, relationships and family life, as well as in their physical function, sleep and mood. Reducing opioid prescribing removes an option in the toolkit of clinicians treating chronic pain. Clinicians are becoming increasingly familiar with the 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.[11,12] And unfortunately, many clinicians may 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 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-pharmacologic and non-opioid medication options. In addition, it reviews current evidence regarding opioid efficacy and harms, overdose prevention with naloxone, and planning an effective opioid dose tapering strategy.

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 (usually less than four weeks), improves over time, and in proportion to healing.[13]

Although pain is expected after injury or surgery, the patient's pain experience can vary markedly. Intensity of pain can be influenced by psychological distress (depression/anxiety), heightened concern or anxiety about an illness, and ineffective strategies to control pain and function despite it.[14] It may also be shaped by personality, culture, attitudes, and beliefs. For example, injured soldiers who had positive expectations of pain (e.g., evacuation and safe recuperation) requested less analgesic medication than civilians with comparable injuries who had more negative associations with pain (e.g., loss of wages and social hardship).[13]

In contrast, chronic pain is defined as lasting more than three months or past the time of normal tissue healing.[15] It can be the result of an underlying medical disease or condition, inflammation, injury, medical treatment, or an unknown cause. Similar to acute pain, the perception and experience of chronic pain is influenced by patient's psychological state, personality, culture, attitudes, beliefs, and support systems.

Pain mechanisms

Pain can also be classified based on its pathophysiology.

Nociceptive pain is caused by the activation of nociceptors (pain receptors), and is generally, though not always, short-lived, and is associated with the presence of an underlying medical condition.[16] This is "normal" pain: a physiological response to an injurious stimulus.

Neuropathic pain is an abnormal response to a stimulus caused by neuronal firing in the absence of active tissue damage. It results from nervous system injury or dysfunction. It may be continuous or episodic, and it varies widely in how it is perceived and how it affects daily life and functioning.

Neuropathic pain is complex and can be difficult to diagnose and to manage because available treatment options are limited.

Nociplastic pain arises from altered function of pain-related sensory pathways both in the peripheral and central nervous systems (as for example in fibromyalgia). It replaces previously ill-defined terms like 'dysfunctional pain' and 'medically unexplained somatic syndromes.' Nociplastic pain may occur in combination with other pain conditions.[17]

Related to all forms of 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).[16] 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 nociceptive, neuropathic and nociplastic components, which complicates assessment and treatment. **Differentiating between the types of pain is critical because different types of pain respond differently to different treatments.** Neuropathic pain, for example, responds poorly to both non-steroidal anti-inflammatory (NSAID) agents and most opioid analgesics.[19] Other classes of medications, such as anti-epileptics, antidepressants (e.g., serotonin norepinephrine re-uptake inhibitors), or local anesthetics, may provide more effective relief for neuropathic or nociplastic pain.[17,20]

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. Asking the patient *"how is pain affecting everyday life?"* can provide a foundation of understanding patient concerns regarding pain. A comprehensive pain assessment should also include evaluation of the pain quality, duration, location, aggravating or alleviating factors, and any previous treatments (both non-pharmacologic and pharmacologic) and their efficacy. Assessing the impact of pain on sleep and screening for mental health conditions potentially related to pain or treatment adherence (e.g., depression, anxiety, and memory issues) will 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 co-occurring depression and anxiety can be facilitated with the Patient Health Questionnaire (PHQ), either the two-item screen (PHQ-2) or longer 9-item form (PHQ-9), and the Generalized Anxiety Disorder (GAD) scale, either the two (GAD-2) or seven item (GAD-7) form. Additional resources for the screening, diagnosis, and treatment of depression are available at AlosaHealth.org/Depression.

Assessment tools

Multidimensional tools 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.

PEG scale

The PEG scale (Pain, Enjoyment, and General Activity) is a three-item tool based on the Brief Pain Inventory (BPI) and is used in the initial assessment and follow up of chronic pain in primary care and other ambulatory care clinics. Three 0-to-10 scales are used to assess pain intensity, interference with enjoyment of life, and interference of function. The PEG score is obtained averaging the three questions together. PEG can be self-administered or done by the clinician and is relatively brief.[22]

Figure 4: PEG scale[22]

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**

Brief pain inventory

The BPI is used frequently in randomized controlled trials to assess pain. The BPI more fully captures the impact of pain on patient function and quality of life than simple 0-10 scales.[23] The BPI includes a diagram allowing patients to map the location of their pain and track it through the course of management. Although developed specifically for chronic pain, it can also be useful for assessing acute pain.[24] While the BPI can be conveniently self-administered, it can be time consuming, taking between 5 to 10 minutes to complete, which may limit the role of the BPI in clinical practice.

Initial approaches to assessing pain severity used 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).[25] Unidimensional assessments of pain do not provide an understanding of how pain is affecting a patient's life and it is difficult to interpret from one patient to another.

Assessing pain in patients with cognitive impairment

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, clinicians need to observe pain-related behaviors, including facial expressions, verbal cues, body movements, changes in interpersonal interactions, activity patterns, and mental status. Caregiver observations and reports are critical for appropriate assessment and management of chronic pain in these patients.[26]

Overview of options for managing pain

Many pharmacologic and non-pharmacologic approaches to treating pain are available to primary care clinicians. 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.

Decisions regarding treatment goals and the options selected should be a collaboration between clinicians, providing evidence-based recommendations, and patients, based on identified needs, wishes, and goals.

(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-pharmacologic 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.[27-29]

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.[29]

Weight loss

Some pain syndromes, such as knee osteoarthritis, 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%.[30] Weight loss may occur with exercise, dietary changes, and/or pharmacologic options. Referral to a comprehensive clinical weight center may be appropriate for some patients, particularly those with a body mass index (BMI) > 35 kg/m^2.[31]

Passive physical options

Acupuncture involves the stimulation of specific points on the body, most often involving skin penetration with fine metallic needles manipulated by hand. It may also include electrical stimulation or low intensity laser therapy. Potential adverse events include minor bruising and bleeding at needle insertion sites.[32]

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.[33]

Transcutaneous electrical nerve stimulation (TENS) is a technique of applying mild electrical pulses generated by a small machine to the skin. The electrical stimulation 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.

Psychological approaches

Cognitive behavioral therapy (CBT) is a structured, time-limited (typically 3-10 weeks) intervention focused on how thoughts, beliefs, attitudes, and emotions influence pain. It teaches patients to use their minds to control and adapt to pain. This therapy includes setting concrete goals, often with recommendations to increase activity to reduce feelings of helplessness.[34]

Mindfulness meditation elicits the relaxation response and can promote pain relief. Programs typically include a time-limited (8 weeks; range 3-12 weeks) training with group classes and home meditation. The objective is to inculcate a long-term practice that helps patients refocus their thoughts on the present, increase awareness of self and surroundings, and reframe experiences.[35,36]

Self-management education program, originally developed for patients with chronic arthritis, has been expanded for application to other chronic diseases, and is generally referred to as the Stanford model.[37] 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.[38]

Pharmacologic approaches

Medications used to treat chronic pain include:

- acetaminophen
- non-steroidal anti-inflammatory drugs (NSAIDs)
  - oral
  - topical
- antidepressants
  - serotonin and norepinephrine reuptake inhibitors (SNRIs)
  - tricyclic antidepressants (TCAs)
- anticonvulsants/membrane stabilizers
- topical lidocaine or capsaicin
- cannabis/cannabinoids
- opioids

Acetaminophen

While its exact mechanism of action is unknown, acetaminophen provides analgesia by acting upon the central nervous system. It is available over the counter (OTC) in 325 mg, 500 mg, and 650 mg tablets. Patients should not exceed 1,000 mg in a single dose. The maximum recommended dose for healthy adults is 4,000 mg/day and 3,000 mg/day for elderly patients.[39] OTC product guidance for healthy adults suggests a dose of 3,000 mg/day and 2,000 mg/day elderly patients.[40]

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.[41] Patients should stay within recommended doses to help prevent side effects and should only take one acetaminophen-containing product at a time. Advise patients to read labels of all medications to determine if the product contains acetaminophen. Patients taking warfarin should be monitored when acetaminophen is started or stopped and with dose changes.

NSAIDs

NSAIDs reduce inflammation by inhibiting cyclooxygenase (COX), either selectively (COX-2 predominantly) or non-selectively (COX-1 and COX-2 effects).

Oral NSAIDs: 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.[42,43] NSAIDs should be avoided in patients with heart failure (due to fluid retention) or with a history of gastric bypass (due to increased ulcer risk). In addition to GI side effects, NSAIDs have been associated with an increased risk of renal and cardiac complications.

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.[44] 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 clinicians regarding celecoxib's safety.[45]

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.[46]

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 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). The risk of GI events was significantly lower with celecoxib than with naproxen (P=0.01) or ibuprofen (P=0.002). Notably, all patients in PRECISION received a proton pump inhibitor (PPI); a PPI is recommended regardless of the NSAID selected, especially for patients at increased risk for GI side effects.[46]

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.[47]

Serotonin norepinephrine reuptake inhibitors (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) are self-limiting, typically resolving in around two weeks. Monitoring is required for blood pressure (duloxetine and venlafaxine), heart rate (venlafaxine), and drug interactions (duloxetine and venlafaxine).

Tricyclic antidepressants (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. In older adults, side effects, such as anticholinergic effects (e.g., dry mouth, constipation, dizziness) and QTc prolongation, limit the use of TCAs. Secondary amines (i.e., nortriptyline) tend to be better tolerated than tertiary amines (i.e., amitriptyline). The majority of side effects are dose dependent. Doses used for pain are much lower than those used for depression.

Membrane stabilizers

Membrane stabilizers or anticonvulsants, such as gabapentin, pregabalin, topiramate, oxcarbazepine, and carbamazepine, are thought to exert their analgesic effect by inhibiting neuronal sodium or calcium channels. Potential side effects include sedation, dizziness, and peripheral edema. While many membrane stabilizers are used off-label for the treatment of pain, pregabalin is FDA approved for fibromyalgia, diabetic peripheral neuropathy, postherpetic neuralgia, and neuropathy associated with spinal cord injury. Gabapentin is FDA approved for postherpetic neuralgia. Oxcarbazepine and carbamazepine are rarely used for chronic pain management due to their side effect profile and drug interactions. Topiramate may be considered in patients who desire weight loss. It requires slow titration and close monitoring.

Gabapentinoid safety: In December 2019, the FDA issued a warning for gabapentinoids (i.e., gabapentin [Neurontin, Gralise, Horizant] and pregabalin [Lyrica, Lyrica CR]); they were reported to cause respiratory depression, particularly when co-administered with other central nervous system (CNS) depressants, such as opioids, in the setting of underlying respiratory impairment, or in the elderly.[48] A cohort study of patients who received perioperative gabapentinoids with opioids compared to those receiving opioids alone found an increased risk of overdose with the combination of a gabapentinoid and opioid vs. an opioid alone, though the rates were low (1.4 per 10,000 patients and 0.7 per 10,000 patients respectively).[49] Two case-control studies, nested with a cohort of patients receiving prescription opioids, identified an increased risk of opioid overdose death when pregabalin or gabapentin were co-prescribed with opioids.[50,51] In patients receiving any dose of pregabalin and also opioids, the risk of overdose death was significantly higher than in patients on opioid prescription alone (adjusted OR 1.68; 95% CI: 1.19-2.36).[50] Similar increase in overdose mortality was found in patients on opioids and gabapentin (adjusted OR 1.49; 95% CI: 1.18-1.88) vs. opioid prescription alone.[51] In both studies, the prescription of combination therapy to patients at higher risk of opioid misuse or abuse, cannot be excluded. Case reports in the literature as well as 49 cases reported to the FDA Adverse Event Reporting System (FAERS) database, of which 12 resulted in death, identify an increased risk of respiratory depression in patients who have underlying respiratory impairment or who are co-prescribed other CNS depressants, such as opioids or benzodiazepines.[48]

Changes in opioid prescribing led to an increase in gabapentin prescribing from 1.5 million episodes in 2006 to 8.1 million episodes in 2018.[52] An overlap in the proportion of opioid and gabapentin co-prescribing rose from 1.9% to 7.6% during the same period. The majority of these prescriptions were written by pain management specialists, to women, non-Hispanic white patients, for patients over age 65, in rural counties, and patients living in counties with the highest quartile of poverty.[52]

While concern for respiratory depression has been noted for gabapentinoids, increasing doses of opioids in order to stop use of gabapentinoids is not recommended. Evidence supporting the risk of serious breathing difficulties with gabapentinoids alone in otherwise healthy individuals is lacking.[48] For most patients, careful management can reduce the risk of respiratory depression, especially in those who are co-prescribed other CNS depressants, the elderly, those with renal dysfunction, and with underlying respiratory insufficiency. These management steps include:

- Start at the lowest dose and slowly titrate doses
- Monitor patients for symptoms of respiratory depression or sedation
- Adjust gabapentin and pregabalin doses for renal impairment
- Counsel patients about the risks of gabapentinoid respiratory suppression, especially when combined with opioids
- Prescribe naloxone in patients co-prescribed opioids

Pregabalin and gabapentin may have abuse potential in the general population, although the actual prevalence is poorly understood. According to one survey, nearly 20% of the U.S. population reported use of a gabapentinoid - with responses from 6.6% of the population suggesting misuse, abuse or non-prescription use.[53] Misuse and abuse were reported in as many as 1 in 3 gabapentinoid users. Those reporting misuse were younger, male, employed, had a higher income (>$100,000), but also reported prior incarceration, substance use disorder, and prior addiction treatment.[53] Because of the risk of misuse or addiction, pregabalin is currently classified as Schedule V by the DEA, and prescriptions for gabapentin 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.[54] The most common side effect is a mild-to-severe burning sensation at the application site.

Cannabinoid preparations

As of October, 2022, 37 states and Washington DC permit the use of medical marijuana.[55] Cannabis contains more than 60 cannabinoids, with Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) 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. Some exogenous cannabinoids also function as an antiemetic and have anti-spasticity and sleep-promoting effects.[56] 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 most common presented in Table 1.

Table 1: Common cannabinoid-based preparations[57]

Preparation	Route	Potency
whole-plant cannabis *bud, leaf, weed*	• Smoked or vaporized • Orally if cooked into food or butters	>20% THC from dispensaries
cannabinoids (primarily THC and CBD)	• vaporized, sublingual tinctures, pills/capsules, and topical creams • oral FDA approved options: dronabinol, nabilone, Epidiolex,	often expressed as a ratio of THC:CBD
concentrates *wax, shatter, dab, butane honey oil*	• smoked	extremely high potency, THC often >90%
edibles (brownies, candies, mints, muffins, beverages)	• Oral ingestion	usually ≤10 mg of THC per 'serving'

Edibles require extra caution as they look like common food products and may be ingested by children and other adults. Patients need to understand the time to onset of effect is longer with edibles than other products. Ingesting another serving too soon may result in unintentionally consuming too much cannabinoid, potentially resulting in overdose.

A systematic review of both randomized trials (47) and observational studies (57) in patients with chronic non-cancer pain (across multiple pain conditions) published through July 2017 found moderate evidence that cannabinoids can relieve pain.[58] 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 (NNH) for all-cause adverse events was 6 (95% CI: 5-8). Another review found small but not statistically different pain relief across a variety of chronic pain conditions vs. placebo (37% vs. 31%; OR 1.41; 95% CI: 0.99-2.00). Side effects were three times more common in the cannabis group vs. placebo (OR 3.03; 95% CI: 2.42-3.80).[59] The substances studied were smoked cannabis and nabiximols, which are not available in the U.S. The role of cannabinoids in treatment may be best summarized by the National Academy of Medicine report:[60]

> *"while the use of cannabis for the treatment of pain is supported by well-controlled clinical trials, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States. Given the ubiquitous availability of cannabis products… more research is needed on the various forms, routes of administration, and combination of cannabinoids"*

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 cannabis 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.[56,60]

No FDA approved cannabinoid products are indicated for the treatment of acute or chronic pain.

These research findings do not apply to hemp-derived cannabis products, such as CBD oil, found at gas stations, convenience stores, and smoke or vape shops. These products may be available regardless of whether or not a state has legalized medical or recreational cannabis products. Few safeguards exist to ensure product quality, safety (e.g., prevention of the use of toxins or heavy metals in the synthesis process), or appropriate marketing. In many cases products are designed to attract youth, with no minimum age to buy these products, and they are sold alongside tobacco and alcohol.[61]

Opioids for 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:[62]

- 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 lower activity at mu-receptors, are less likely to cause respiratory depression due to a ceiling effect, and do not have a defined ceiling on analgesic effect.
- Antagonists (e.g., naloxone and naltrexone) block 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 a higher abuse potential than previously thought.[63]

Table 2: Opioids by schedule[62]

Schedule*	Description	Opioid (examples)
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 has been known for centuries, and opioids continue to be reliable—if potentially risky—agents for moderate-to-severe acute pain. The efficacy appears to wane by three months.[64] *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; disentangling the two, clinically, can be difficult.[65]

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.[11] 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).[11] In these studies, there were no significant differences in emotional functioning or role functioning.

The same meta-analysis compared opioids to non-opioid analgesics including NSAIDs, TCAs, membrane stabilizers, 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 membrane stabilizers, 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).[11]

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, membrane stabilizers) and followed them for one year.[12] The primary outcome was score for pain-related functioning using the 0-10 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."[12]

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.[66] 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.[67] According to the FDA, ER/LA opioids should only be used for patients who tolerate 60 morphine milligram equivalents (MME) per day for at least one week.[64,68]

Efforts to create formulations with lower risks of abuse have met with limited success. For example, Opana ER (oxymorphone) was removed from the market after reports of intravenous abuse of the oral formulation.[69] Abuse-deterrent or tamper-resistant formulations do not prevent users from becoming addicted or taking too much of an opioid by mouth (the most common route for abuse).[70,71] 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 November, 2022, four opioids FDA approved as abuse-deterrent formations are available: OxyContin (oxycodone), Hysingla ER (hydrocodone), Xtampza ER (oxycodone), and RoxyBond (oxycodone).[72]

Another attempt to improve opioid safety used benzhydrocodone, a pro-drug of hydrocodone that requires metabolism in the gut. Pharmaceutical company-funded studies suggested the need for gut metabolism would reduce the abuse potential via intravenous or inhaled routes.[73,74] The FDA rejected benzhydrocodone/acetaminophen (Apadaz) as an abuse deterrent formulation. It is currently approved for acute pain lasting less than 14 days.[75] Benzhydrocodone is Schedule II, with risks similar to other opioids.[76]

Opioid risks and side effects

To ensure clear communication regarding medical issues and avoid misunderstandings about the nature and risk of addiction, the CDC provides the following definitions:[77]

- **Tolerance** – The need for an increased dose of an opioid to achieve the same effect, which can occur even when taking a medication as prescribed

- **Physiologic dependence** - A state of physical adaptation that is manifested by a substance class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the substance, and/or administration of an antagonist.
- **Misuse** - Use of a medication other than as directed or as indicated, such as taking in greater amounts, more often, or for a longer duration, or using someone else's prescription.
- **Opioid use disorder or addiction** - 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.[78]

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.[79]

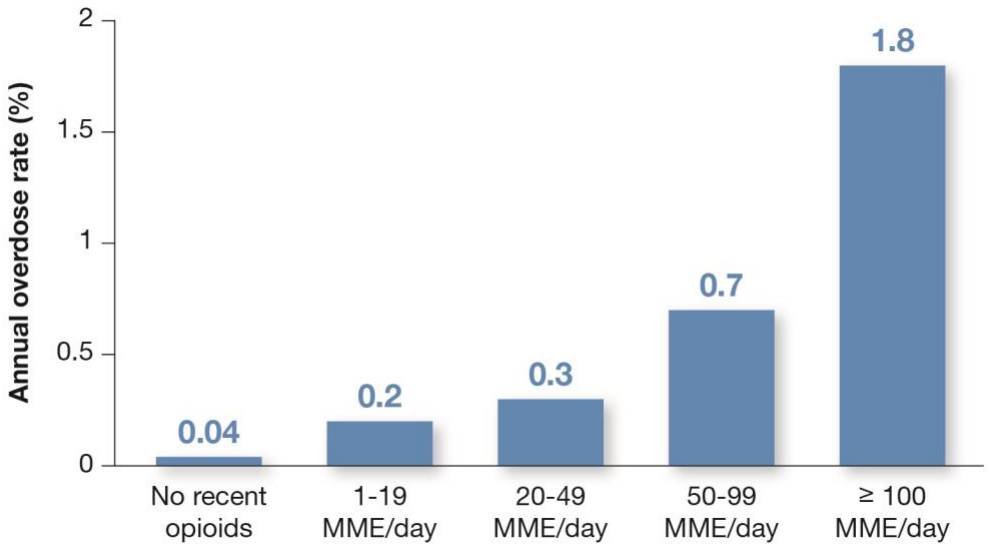
Table 3: Behaviors indicative of opioid misuse[79]

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%

A 2015 meta-analysis showed that the prevalence of opioid misuse among patients with chronic pain in primary care settings ranged from 0.6%-8%, and the prevalence of physiologic dependence ranged from 3%-26%.[80] In pain clinics, the prevalence of opioid misuse ranged from 8%-16%, and addiction ranged from 2%-14%.[80]

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 MME per day.[81]

Figure 5: Risk of overdose rises with MME dose per day[81]



Combining opioids with sedating substances such as benzodiazepines or alcohol increases the risk of respiratory depression and overdose death.[66] Benzodiazepines have been linked with overdose fatalities in 50-80% of heroin overdoses, and 40-80% of methadone-related deaths.[66,82] 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, a plan should be coordinated regarding continuing or tapering benzodiazepines in the setting of opioid co-prescribing. (Note: in its 2016 warning about the hazards of combining CNS depressants with opioids, the FDA included the benzodiazepine-like insomnia medications: eszopiclone, zaleplon, and zolpidem [so-called “z-drugs”], muscle relaxants and antipsychotics such as aripiprazole, olanzapine, and quetiapine.)[83]

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.[84]

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 use.[15] 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. Clinicians 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, polyethylene glycol (Miralax, generics), lactulose, or magnesium citrate.[85]

Medications for refractory, opioid-induced constipation include naloxone derivatives:

- naloxegol (Movantik) orally
- methylnaltrexone (Relistor) subcutaneous injection or oral tablet used daily
- naldemedine (Symproic) orally

Coverage of these naloxone derivatives varies between insurance carriers and may require a prior authorization in some cases.

Another option is a chloride channel activator, lubiprostone (Amitiza). An oral capsule (24 mcg) given twice daily, it increases secretion of fluid in the intestine to help stool pass through the gut.[86]

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

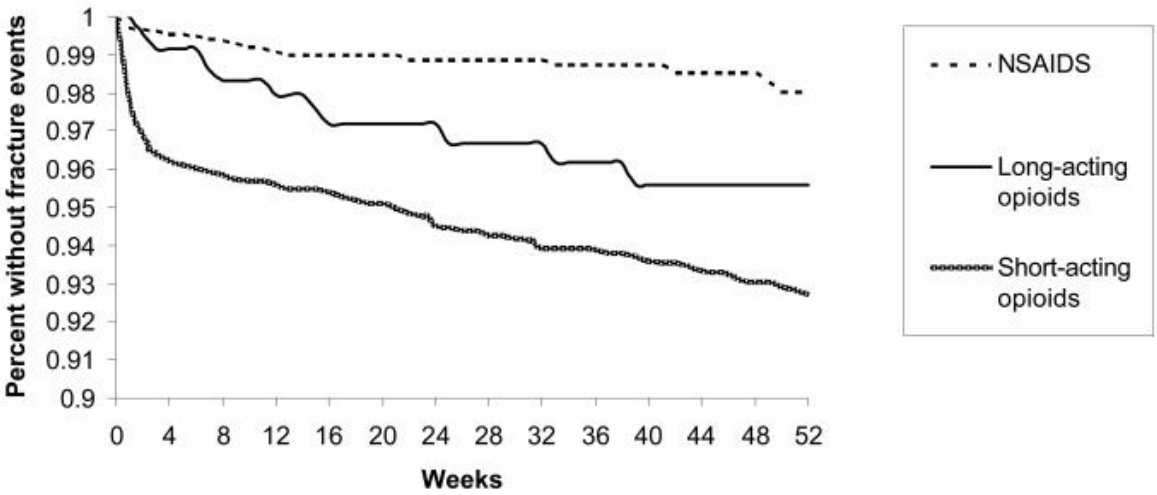
Sedation

If a patient or caregiver 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 facilitate reducing opioid dose, or add a stimulant in the morning. There is insufficient evidence to recommend opioid rotation as a possible means of reducing sedation.[66]

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 (hazard ratio [HR] 4.9; 95% CI: 3.5-6.9) in a dose-dependent fashion. The opioid formulation mattered (Figure 6), with much of the risk in the first month after initiation for short-acting opioids, though fracture increased for both long- and short-acting opioids over time.[87]

Figure 6: Fracture risk over time for NSAIDs, short-acting and long-acting opioids[87]



A systematic review and meta-analysis of 30 studies analyzed the risk of fall, fall injury and fracture with opioid use older adults and found a small but statistically significant increase in falls (standardized mean difference [SMD] 0.15; 95% CI: 0.02-0.27). Adults ages 65 and over were significantly more likely to have a fall related injury (SMD 0.40; 95% CI: 0.24-0.56) and fracture (SMD 0.71; 95% CI: 0.45-0.97).[88]

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% greater 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.[89]

Among a national cohort of 5,623 people with Alzheimer's disease (AD), use of opioid medications was associated with a 34% increase in the risk of hospital-treated pneumonia compared to not receiving opioids (95% CI: 1.14-1.57). Risk was greatest in the first two months of use (adjusted hazard ratio [aHR] 2.58; 95% CI: 1.87-3.55) and with more potent opioids (aHR 1.84; 95% CI: 1.15-2.97). Higher doses, such as ≥50 MME per day doubled the risk of hospitalization compared to opioid use <50 MME per day (aHR 2.03; 95% CI: 1.24-3.31).[90] Although not clearly understood, reasons for the increase in pneumonia have been attributed to direct immunosuppressive effects of specific opioids (e.g., fentanyl, morphine) and suppression of cough and respirations.[91]

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).[92]

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.[93]

Differentiating between opioids

Tramadol

Despite the categorization of tramadol as a non-opioid pain management strategy in the SPACE trial, tramadol is a mu-opioid receptor agonist and a reuptake inhibitor of the noradrenergic and serotonergic system. Its analgesic effects are similar to morphine, although it is only one-fifth to one-tenth as potent as morphine.[94] Patients taking tramadol should be monitored for nausea, vomiting, constipation, and drowsiness, all of which are similar to side effects with opioids.[95] There is potential risk of serotonin syndrome when combined with serotonergic drugs such as SSRIs and tricyclic antidepressants.[96] Tramadol may also lower the seizure threshold.

Tramadol is classified as Schedule IV (which is lower than most opioids), but it still can be misused. The 2020 National Survey on Drug Use and Health found that 1.5 million people in the U.S. aged >12 years reported misusing tramadol products (e.g., Ultram, Ultram ER, Ultracet) in the previous year.[97] In addition, a 2019 cohort study of 88,902 patients with osteoarthritis (mean age 70 years) showed increased risks of

death with tramadol use at one year compared to the 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), although it is possible that patients receiving tramadol were at higher risk of death due to underlying comorbidities.[98] In that study, the hazard ratio for death at one year was not significantly different between tramadol and codeine (HR 0.94; 95% CI: 0.83-1.10). Compared to other opioids, the risk of overdose is lower at FDA approved doses. Maximum daily dose is 400 mg per day,[99] while a median dose of 2,500 mg was ingested when respiratory depression occurred due to tramadol alone.[100]

Abrupt cessation of tramadol is associated with withdrawal symptoms similar to those associated with other opioids (such as flu-like symptoms, restlessness, and substance cravings) as well as symptoms which are less typical of other opioids that are likely related to its noradrenergic and serotonergic activity (such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and numbness/tingling in extremities).[101]

Tapentadol

Tapentadol (Nucynta) is an opioid with a mechanism of action similar to tramadol, and it has potency and side effect profiles similar to other common opioids such as oxycodone. It is FDA approved for treating neuropathic pain and should be limited to situations when a potent mu opioid is required.

Buprenorphine

An atypical opioid with unique pharmacology, buprenorphine has advantages over full agonist opioids, such as oxycodone. It is a partial agonist with high binding affinity at the mu receptor, which provides analgesia while having a ceiling effect on respiratory depression.[102,103] Buprenorphine also has higher potency and exhibits a slow dissociation rate compared to full agonist opioids, allowing for effective and long-lasting analgesia.[103] An antagonist at the kappa opioid receptors, buprenorphine may also improve mood and reduce tolerance.[104]

Buprenorphine formulations prescribed differ by indication. FDA approved formulations for pain severe enough to require daily, around-the-clock, long-term opioid treatment include buccal film (Belbuca) and transdermal system (Butrans). Transdermal and buccal delivery provide analgesia for patients who may not have optimal absorption orally, such as in patients with gastric bypass. Both the buccal and transdermal products are dosed in micrograms, which differs from buprenorphine's higher strength sublingual formulations (which are dosed in milligrams). See Table 4 (next page). Buprenorphine's sublingual formulations (e.g. Subutex, Suboxone, Zubsolv, generics) are FDA approved for treatment of opioid use disorder, but may be used off-label for treatment of chronic pain.[105] Sublingual buprenorphine is available both as the monoproduct (Subutex, generics) and in a co-formulation with naloxone (Suboxone, Zubsolv, generics). To learn more about the treatment of OUD, visit AlosaHealth.org/OUD.

Table 4: Initial dosing and titration of buprenorphine for pain[106,107]

	Transdermal buprenorphine (Butrans)	Buccal film (Belbuca)
initial dosing	5 mcg/hour patch	75 mcg film once daily or every 12 hours, as tolerated
titration frequency	no sooner than every 72 hours	no sooner than every 4 days
titration dose	based on analgesic response and side effects	from 75 mcg every 12 hours, increase to 150 mcg every 12 hours from 150 mcg every 12 hours, increase by 150 mcg increments every 12 hours
maximum dose	20 mcg/hour	900 mcg every 12 hours

Safety concerns for buprenorphine at initiation are similar to other opioids. Common complaints are nausea, vomiting, constipation, dizziness, and headache. One review suggests buccal buprenorphine is less likely to have these adverse effects than full agonist opioids.[108] Buprenorphine may also be used in opioid-experienced patients. In these patients, the transition from full agonist opioid to buprenorphine causes risk of precipitated withdrawal. Precipitated withdrawal occurs due to buprenorphine's high affinity for mu receptors that displaces full agonist opioids, causing withdrawal. (Switching from a full agonist opioid to buprenorphine is discussed on page 35.) The two formulations FDA approved for pain, buprenorphine transdermal patch and buccal film, are less likely to cause precipitated withdrawal than the formulations used for OUD.

Buprenorphine may be more favorable for the management of chronic pain as compared to a full agonist opioid in selected patients for the following reasons:[105]

- ease of ordering by clinicians
  - option for refills
  - clinician's ability to call in prescriptions
- favorable therapeutic index and safety profile when used as directed
- ceiling effect on respiratory depression
- can be used to treat chronic pain in patients both with and without OUD

Who may benefit from buprenorphine?[105]

- patient characteristics that increase the risk of life-threatening opioid-related adverse events:
  - high BMI
  - obstructive sleep apnea
  - co-occurring psychiatric diagnosis
  - pulmonary disease
  - concomitant use of substances known to increase risk (e.g., benzodiazepines, gabapentin, pregabalin, muscle relaxants, alcohol)
  - taking high MME per day

- patients who are CYP2D6 poor or rapid metabolizers and are unable to take medications such as tramadol or codeine due to increased risk of increased toxicity or lack of effectiveness
- patients with chronic pain and history of substance/opioid use disorder or at increased risk of overdose

Note: when used for the treatment of OUD or in patients with overlapping OUD and chronic pain, high dose buprenorphine (i.e., sublingual OUD treatment formulations) should be used in divided doses.

Developing a pain management strategy

A central tenet of pain management, whether acute or chronic, is that the goal of treatment is not necessarily to eliminate pain, but rather make it tolerable to permit maximum physical and emotional functioning with the lowest risk of side effects, progression to chronic pain, or misuse or addiction.[109] This requires an adroit balancing of patient-related factors (e.g., comorbidities, medical history, risk of addiction) and medication-related factors (e.g., potency, mechanism of action, expected side effects). A commonly-recommended way to achieve this balance is with **multimodal analgesia**, in which several therapeutic approaches are used, each acting at different sites of the pain pathway, which can reduce dependence on a single medication and may reduce or eliminate the need for opioids and associated risks/side effects.[110]

Setting functional goals

Tracking treatment requires the establishment of a goal. For patients with pain, these goals should be life activities of importance to the individual patient. These goals can vary for each patient based on their current limitations, what can be expected after treatment for their given pain condition, and what is important to them in life. Example goals could be walking from bed to the living room, gardening, or going out to dinner with friends. These goals create a guide for when changes to the pain management strategy are needed.

Managing patient expectations

Patients in pain are understandably worried that the pain will persist or get worse with time. Clinicians can reduce such fears and set realistic expectations for treatment effectiveness and healing with clear, compassionate communication couched in terms that patients can easily understand. It can be helpful, for example, to tell patients that most forms of acute nociceptive pain (e.g., nonspecific low back pain) are self-limited, subside within weeks, and do not require invasive interventions. (In a systematic review of 15 prospective cohort studies, 82% of people who stopped work due to acute low back pain returned to work within one month.[111]). An example of appropriate expectation-setting language is: “Some pain is normal. You should be able to walk and do light activity but may be sore for a few days. This will gradually get better.”[112]

A systematic review of 14 controlled trials of patient education interventions for acute low back pain showed that compared with usual care/control education, structured messaging by providers can reassure patients with acute pain in both the short and long term.[113] Messaging was significantly more reassuring to patients when delivered by physicians than other primary care practitioners, and such communication reduced the frequency of primary care visits.

Examples of effective messaging specific to patients with low back pain include:

- “Based on the history and exam, you have a good prognosis.”
- “The acute pain you are experiencing is not the result of serious injury and is likely to resolve without need for x-rays or invasive treatments.”
- “Avoid bed-rest…daily exercise is helpful.”

For patients who have chronic pain, education about the condition increases understanding of what various treatment strategies can or cannot accomplish.

Addressing mental health

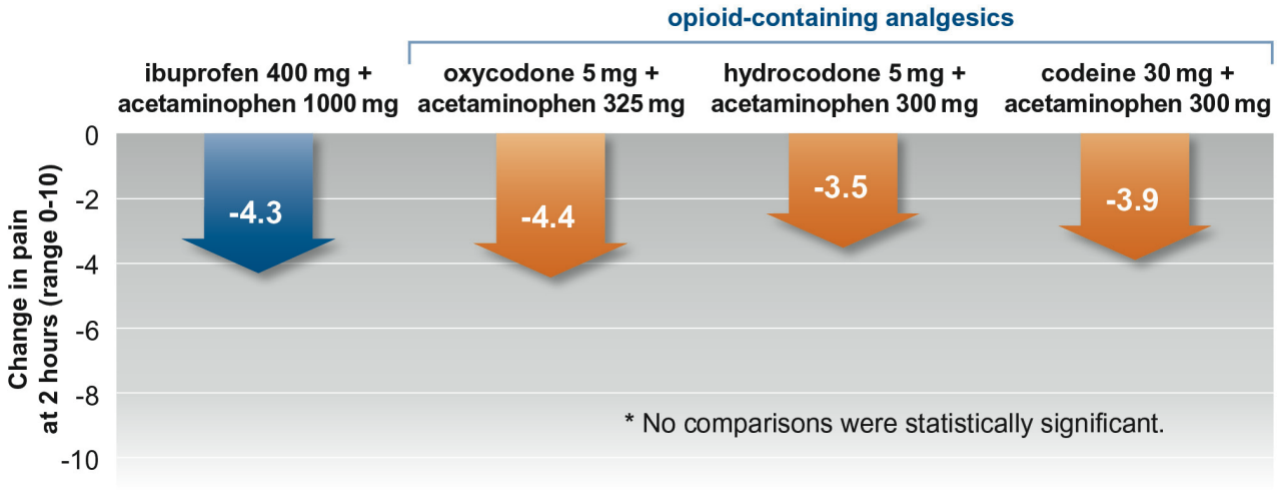
Comorbid conditions such as depression and anxiety can impact pain management. Clinicians and teams should ensure that patients have been screened for depression and anxiety when initiating treatment. In a study of 250 patients with chronic pain and moderate depression, using antidepressant therapy reduced pain levels before analgesic interventions were added.[114] Selecting a medication with antidepressant and analgesic effects can help address both conditions and may become part of the multimodal strategy. For more on the management of depression, visit AlosaHealth.org/depression.

Selecting a multimodal management strategy

Once patients have identified the treatment goal, discussion transitions to how to achieve it. Multimodal analgesia, using medications from two or more classes, or a medication plus a non-pharmacologic treatment can produce synergistic effects, reduce side effects, or both. One example of multimodal analgesia is the use of both a NSAID and acetaminophen, plus physical approaches (e.g., cold, compression, or elevation) to manage acute postoperative pain. Demonstrated benefits of multimodal analgesia include earlier ambulation, earlier oral intake, and earlier hospital discharge for postoperative patients, as well as higher levels of participation in activities necessary for recovery (e.g., physical therapy).[110]

Combining ibuprofen plus acetaminophen is as effective as opioids for acute, severe, musculoskeletal pain. In a randomized controlled trial, 416 patients with acute extremity pain were randomized to receive either ibuprofen+acetaminophen, oxycodone+acetaminophen, hydrocodone+acetaminophen, or codeine+acetaminophen.[115] The mean pain scores at two hours after ingestion decreased by 4.3 points (95% CI: 3.6-4.9) with ibuprofen and acetaminophen; by 4.4 points (95% CI: 3.7 to 5.0) with oxycodone and acetaminophen; by 3.5 points (95% CI: 2.9-4.2) with hydrocodone and acetaminophen; and by 3.9 points (95% CI: 3.2-4.5) with codeine and acetaminophen (Figure 7). None of the differences between analgesics were statistically significant.[115]

Figure 7: Effectiveness of ibuprofen and acetaminophen compared with three opioid-containing regimens in patients with severe musculoskeletal pain[115]



In a patient with chronic pain, putting together various strategies, including movement-based, psychological, and other interventional options, combined with medication options and interventions, creates a menu of modalities that together can meaningfully reduce pain and improve function.

Figure 8: Management approaches for chronic pain[116]

Assessing treatment

Determining the success of treatment relies on the unique functional goals identified for each patient. The use of a consistent tool to monitor change (e.g., VAS for acute pain or P.E.G. for chronic pain) can help track change over time. Discussions about tolerability of each intervention (e.g., side effects of medications or challenges with completing selected movement-based options) determine what adjustments to the pain management plan are needed. Some medications require titration to reach optimal doses and need an adequate duration to determine optimum benefit. See Appendix II for initial dosing, titration, and dose information. A sufficient trial should be attempted before labeling the option as unsuccessful.

Strategies for patients requiring opioids

Although the evidence for long-term effectiveness of opioids is lacking, an opioid may be indicated for patients with intractable, moderate-to-severe non-cancer nociceptive pain unresponsive to non-opioid treatment options. However, patients are not required to fail multiple treatment strategies before utilizing opioids. Patients with contraindications to other medications, fragility, or hepatic or renal dysfunction may not be able to utilize other analgesic strategies. In cases where opioids are needed, additional steps to reduce risk to patients and household members are required.[64]

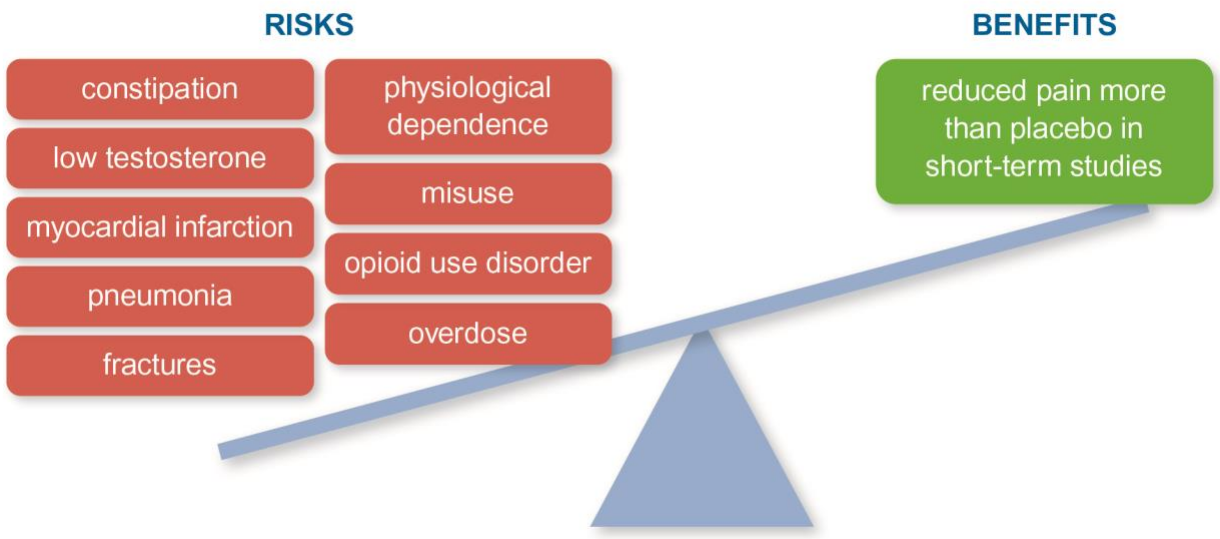
Prescription should be guided by the following principles (each detailed below):

- 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 addiction.
- Taper or discontinue opioids when risk outweighs the benefit.

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 9, outweigh the benefits. However, for some patients with nociceptive chronic pain, the use of low-dose opioids may be a reasonable approach for short-term use. For these patients, also discuss the duration for which opioid use is anticipated and set a clear end date as part of the decision for opioid use.

Figure 9: Balancing the risks and benefits of opioid therapy



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.[66] 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 toxicology screens. While the use of a written agreement / treatment plan has been recommended by experts, but no trials assess the benefit of such agreements.[64] Visit 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 scheduled, around-the-clock use, which will typically lead to tolerance/physical dependence within 5-7 days.[117] For elderly patients who have comorbidities, consider starting at an even lower dose and intensify monitoring for adverse effects.[66]

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%).[118] 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[119,120] and other settings[121,122] have recommended prescribing ≤3 days of opioids in most cases, whereas others have recommended ≤7 days,[123] or ≤14 days.[124]

Check or monitor opioid use

Follow-up appointments should occur one to four weeks after initiation of opioids or with dose changes, and 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.[66] At every visit, there should be an active clinical decision as to whether or not to continue the opioid - based on whether the benefits exceed the risks.

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 toxicology screens, or random pill counts.

Utilize prescription drug monitoring programs (PDMPs)

All 50 U.S. states and the District of Columbia have operational PDMPs. Information available through PDMPs varies based on reporting requirements and restrictions. Differences between PDMPs may include DEA schedules reported, timeliness of pharmacy dispensing information, access, and required reviews.

Some states have specific requirements for PDMP use, such as requiring review prior to initial prescription or any time a specific prescription is written (for example hydrocodone ER [Zohydro]). Clinicians should remain updated about the specific requirements of their state PDMPs. The 2022 CDC updated pain management guidelines recommend the PDMP is checked upon initial opioid prescribing and then periodically during opioid therapy.[64]

Minimum recommendations for PDMP use include:

- Check the PDMP before starting any patient 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 MME per day.

Toxicology testing

All patients on long-term opioid therapy should be periodically (at least annually) tested for substance use.[64] Universal testing (testing all patients in an identical manner) may help de-stigmatize testing and remove any perceived bias related to who is tested. Effort should be made to ensure toxicology testing is not financially burdensome or treatment limiting to patients. Toxicology testing should be framed as a therapeutic, rather than a punitive, component of treatment.[125] Rather than setting up an “us vs. them” mentality, toxicology testing can actually improve the therapeutic alliance by transferring the role of detector from the clinician to the test.[125] The 2022 CDC guidelines recommend that toxicology screening should be used in the context of clinical information in order to inform and improve patient care, and should not be used in a punitive manner.[64]

Although urine remains the most common matrix for toxicology testing, technology using saliva, sweat, exhaled breath, and hair has becoming increasingly sophisticated, albeit with a currently-limited evidence base.[125] 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 urine toxicology testing are immunoassay ("presumptive" testing) and chromatography/mass spectrometry ("definitive" testing) (see Table 5 for details). Providers using urine toxicology tests 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).[66]

Table 5: Comparison of two major types of urine toxicology testing

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 metabolites	directly measures substance and its 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 (e.g., fentanyl, oxycodone, buprenorphine)	more accurate for semi-synthetic and synthetic opioids
often has high cut-off levels giving false negative results	very sensitive to low levels of a substance, 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 toxicology testing, discuss the following points with the patient:[126]

- 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 substances the test covers
- timing and dose of opioids and other substances consumed recently
- 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 toxicology test come back, clinicians should:[126]

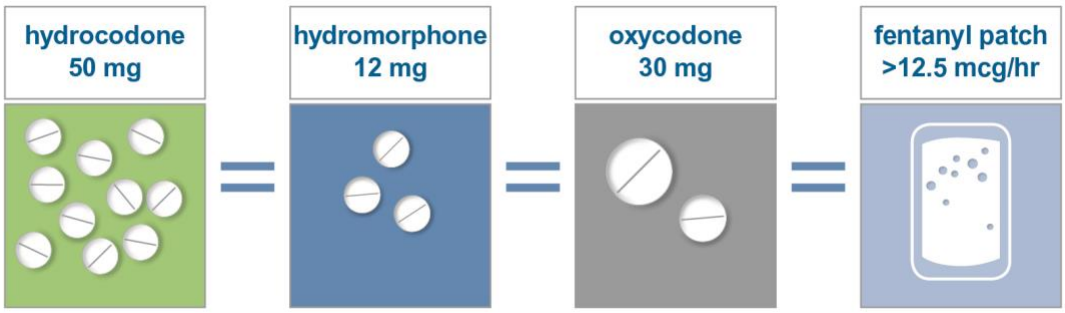
- inform the patient of the results
- discuss with the patient any unexpected results or findings of substance use (note: it can be helpful to ask patients beforehand what they expect the toxicology test will show)
- review the treatment agreement and reiterate concerns about the patient's safety
- determine if frequency and intensity of monitoring should be increased

Decision tools and help with interpreting urine toxicology results are available at mytopcare.org.

Caution with dose escalation

When escalating opioid doses, be aware of the 50 MME/day dosing threshold.[66] According to the CDC, doses >50 MME/day are associated with more than double the risk of overdose compared to patients on <50 MME/day.[66] The effect on pain is minimal, and doses higher than 50 MME/day are not associated with functional improvement.[64] The total MME/day for all prescribed opioids should be noted and monitored. MME/day is automatically calculated on many state PDMP reports but should be confirmed by asking patients how prescribed opioids are being taken.

Figure 10: Morphine equivalents of commonly prescribed opioids for 50 MME/day



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.[127] 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.[66] When starting opioids, begin with immediate release options for both acute and chronic pain.[64]

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 one week.[66] Additional caution is required when prescribing ER/LA opioids in older adults or patients with renal or hepatic dysfunction because decreased clearance of medications among these patients can lead to accumulation of medications 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. The unusual characteristics of methadone and transdermal fentanyl make safe prescribing of these medications for pain especially challenging.[66]

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.[66] 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.[128] If methadone is considered, refer patients to pain management specialists with expertise in using this medication. Also, clinicians should not be using methadone as a treatment for opioid use disorder outside of an Opioid Treatment Program setting.

Prescribe naloxone

Naloxone (e.g., Narcan, Kloxxado, Zimhi, generics) is an opioid antagonist that quickly reverses the effects of opioid overdose. Naloxone is available to first responders, patients, and friends, family, and household members of those prescribed opioids. Primary care providers should prescribe naloxone to all patients at risk of overdose. Indications include

- opioid dose >50 MMED
- renal or hepatic dysfunction
- co-prescription of benzodiazepines or other sedating medications
- patients who smoke, have COPD, asthma, or sleep apnea
- history of overdose or diagnosis of OUD or other substance use disorder

All 50 states have in place a standing order or protocol that allows patients, family members, caregivers, and/or friends to request naloxone from their local pharmacist.[129] Twenty states have some form of co-prescribing requirement with 12 requiring naloxone co-prescribing in certain cases such as high MME/day dose, concurrent benzodiazepine use, or prior history of overdose. Rates of naloxone co-prescription have been rising nationwide in recent years but remain very low in absolute terms. Naloxone dispensing increased from 0.55 per 100,000 population in 2012 to 292.3 per 100,000 population in 2019.[130] The highest rate of naloxone dispensing occurred in states with a co-prescribing requirement. By the end of 2020, naloxone prescribing in the Medicare population dropped significantly.[131,132] This drop did correspond to a decrease in chronic opioid prescriptions.[132]

Anyone receiving naloxone should be taught how to use the particular 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 6, next page). The intramuscular (IM) vials require the most manipulation in order to administer. Intranasal naloxone and the IM/SQ injector are easier to use but vary greatly in terms of price and insurance coverage.

Table 6: Dosage forms available for naloxone

	Intranasal		IM/subcutaneous (SQ)	Intramuscular (IM)
				
Brand name	Narcan	Kloxxado	Zimhi	—
Strength	4 mg/0.1 mL	8 mg/0.1 mL	5 mg/0.5 mL	0.4 mg/1 mL
Sig for suspected overdose	Spray full dose into one nostril.	Spray full dose into one nostril.	Follow steps on device.	Inject 1 mL into shoulder or thigh.
Second dose	Repeat into other nostril 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	2 sprays	2 sprays	1 injector	2 syringes
Cost	$136 (Narcan) $73 (generic)	$150	$156	$35

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.

Screen for opioid use disorder

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 for more information on SBIRT.

Patients reporting significant impairment or distress as a result of their opioid use may have OUD. More than 2.7 million Americans have OUD, and the number is growing.[133] OUD can be effectively managed with medications, but only an estimated 1 in 10 of adults with OUD currently receive such treatment.[9]

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:[78]

- 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, Zubsolv, generics) or buprenorphine-only monthly injection (e.g., Sublocade)
- naltrexone extended-release injection (Vivitrol)

Buprenorphine and methadone are both effective for helping patients avoid relapse and regain function, and they both have proven mortality benefit in treatment of OUD.[134] However, they are different chemically and also in how they can be prescribed/used (Table 7). (Note that buprenorphine can also be prescribed for pain, and formulations include a patch [Butrans], sublingual film [Belbuca], and injection [Buprenex].)

Table 7: Comparison of buprenorphine and methadone

	Buprenorphine	Methadone
Who can provide treatment	any prescriber with a DEA license that has Schedule III authority	certified opioid treatment program
Treatment delivery	no daily clinic visits are required	Supervised daily administration or limited take-home treatment
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

Naltrexone, as an injectable (Vivitrol), may be an option for patients who have successfully completed a detoxification protocol (7-10 days of abstinence from opioid use).[135] Clinicians should be vigilant for signs of suicidality because suicidal thoughts, attempted suicide, and depression have been reported with naltrexone use.[135]

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 can be given orally or 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 with the injectable formulation.

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

Taper opioids

While the goal is to provide flexible, individualized, patient centered care, for some patients the best decision may be to reduce or stop opioids for pain management when the risks outweigh the benefits.[136] Forced or rapid tapers for patients who are physiologically dependent on opioids is not recommended.[64] Patients who are not taking prescribed opioids (e.g., patients who are diverting all opioids they obtain) do not require tapers.[64] These recommendations do not apply to pregnant patients, who should be managed by someone experienced in identifying and managing opioid withdrawal in a pregnant patient and the fetus.[64]

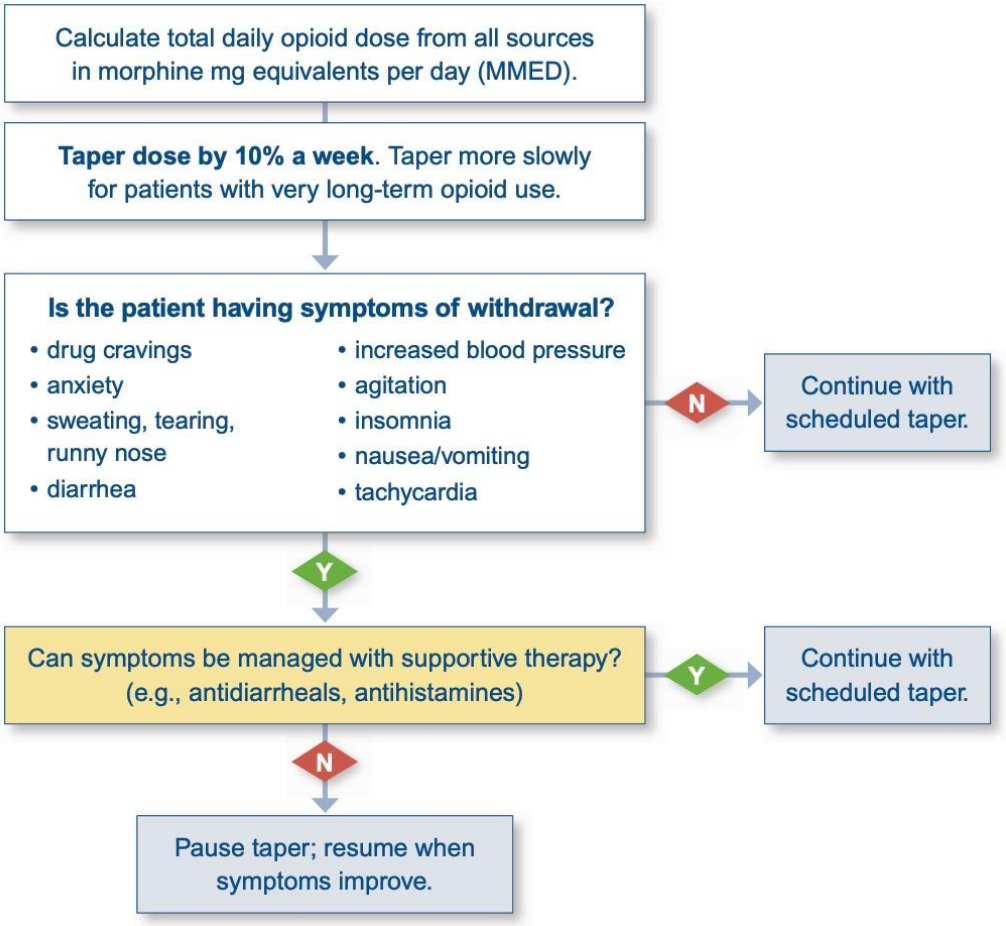
Patients who do not achieve functional goals on stable or increasing opioid doses, have diminished quality of life, have unacceptable side effects (such as an overdose, hospitalization or injury), or have had healing of the injury (for acute pain) should be engaged in a plan to taper or discontinue opioids.[137] Patients sometimes resist tapering or discontinuation, fearing increased pain. However, a 2020 systematic review found that dose reduction or discontinuation resulted in a decrease in pain severity (9 studies), improvement in pain-related function (7 studies), increase in quality of life (4 studies), and improvement in anxiety and depression symptoms (4 studies).[138] 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 (MME/day 75.8 mg).[139] 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 and should always be individualized. The rate of opioid taper should be adjusted based on patient-specific factors such as the severity of withdrawal symptoms One way to recommend a taper is based on duration of opioid use:[64]

- ≤ 3 days of scheduled use or as needed: no taper required
- > 3 days but < 7 days of scheduled use: 50% reduction over two days
- ≥ 7days but ≤ 1 month: 20% reduction every 2 days
- ≥ 1 month but ≤ 1 year: 10% reduction every week
- ≥ 1 year: 10% reduction each month

Another approach to managing an opioid taper is presented in Figure 11. Note, that this is an example opioid taper plan; each taper should be individualized based on patient specific factors including length of time on opioid therapy and patient response to taper.

Figure 11: Tapering algorithm



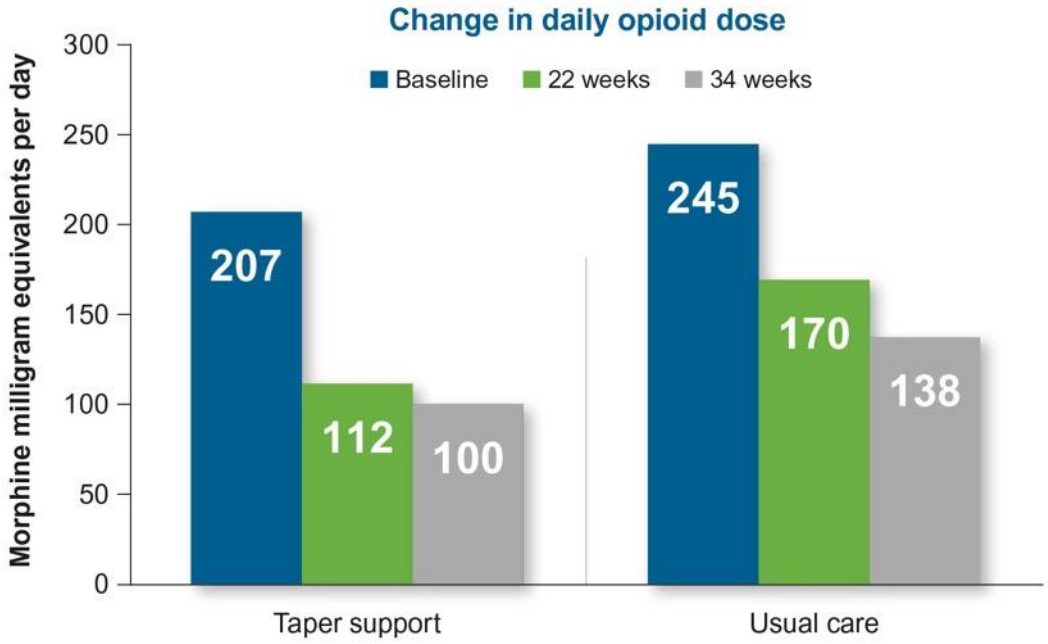
When symptoms of opioid withdrawal appear during a taper, the first approach should be to pause or slow the rate of the taper. Short term use of medications to help address symptoms of opioid withdrawal may be needed to help with specific symptoms. Examples include:

- central-acting alpha agonists (such as clonidine or lofexidine [Lucemyra]) for autonomic symptoms such as sweating or tachycardia
- loperamide for diarrhea
- ondansetron for nausea
- trazodone for insomnia
- dicyclomine for stomach cramping
- hydroxyzine for anxiety, dysphoria, lacrimation, rhinorrhea
- acetaminophen or NSAIDs for myalgias

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 MME/day vs. 138 MME/day) although the difference was not statistically significant at 34 weeks (Figure 12).[140] Pain scores decreased in both groups by about one point on a 10-point scale (not significant).

Figure 12: Change in daily opioid dose[140]



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.[141] The key elements include:[141]

- 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 when needed.

While the intent of opioid dose reduction and discontinuation is to decrease harms associated with opioid use, recent observational studies have identified potential *increase* in harms such as withdrawal symptoms, increase in the development of substance use disorders, opioid overdose, and suicide. A

2020 systematic review found very low to low quality evidence in observational studies that abrupt discontinuation and/or tapering of opioids led to OUD/overdose (4 studies) and suicidal ideation or suicidal self-directed violence (2 studies).[138] An additional observational review found that among patients who have their long-term opioid therapy discontinued or tapered, there is an increased risk of illicit opioid use, increase in opioid-related hospital and ED visits, increased incidence in mental health crises or overdose events, and increased risk of death from suicide.[142] While these risks have not been seen in patient level data, when factors affecting opioid prescribing are available (such as in randomized controlled trials) these flags are nonetheless concerning. Ensuring access to naloxone, assessing for mental health concerns or inadequate treatment of conditions like anxiety and depression, and engaging additional support for patients with mental health concerns can help with pain management and can reduce risks of unintended adverse effects from tapering.

Converting to buprenorphine

A question often arises - can buprenorphine provide adequate pain control for those already on full agonist opioids? How can a patient successfully transition from a full agonist opioid to a partial agonist such as buprenorphine? A 2021 systematic review analyzed 22 studies that included patients transitioning from various full agonist opioids for reasons including inadequate analgesia, intolerable adverse effects, risky opioid regimens, and aberrant opioid use. Very low-quality evidence suggested that rotation to transdermal or buccal buprenorphine was associated with maintained or improved analgesia with a low risk of precipitating opioid withdrawal when transitioned appropriately.[143]

Prior to transitioning from a full agonist opioid to a partial agonist such as buprenorphine, a period of mild-to-moderate opioid withdrawal is required. Novel approaches, including using small doses of buprenorphine in conjunction with full agonist opioids (micro-dosing) have been studied in patients with opioid use disorder to avoid this period of mild-moderate opioid withdrawal and decrease the risk of precipitated withdrawal on starting buprenorphine. A 2022 systematic review reviewed these novel induction approaches in patients with OUD, with chronic pain, or both. Overall, there was no significant difference in successful rotation to sublingual buprenorphine between patients in the traditional initiation group (95.6%) and patients in the micro-dosing group (96%).[144]

Why convert from a full opioid receptor agonist to buprenorphine?[105]

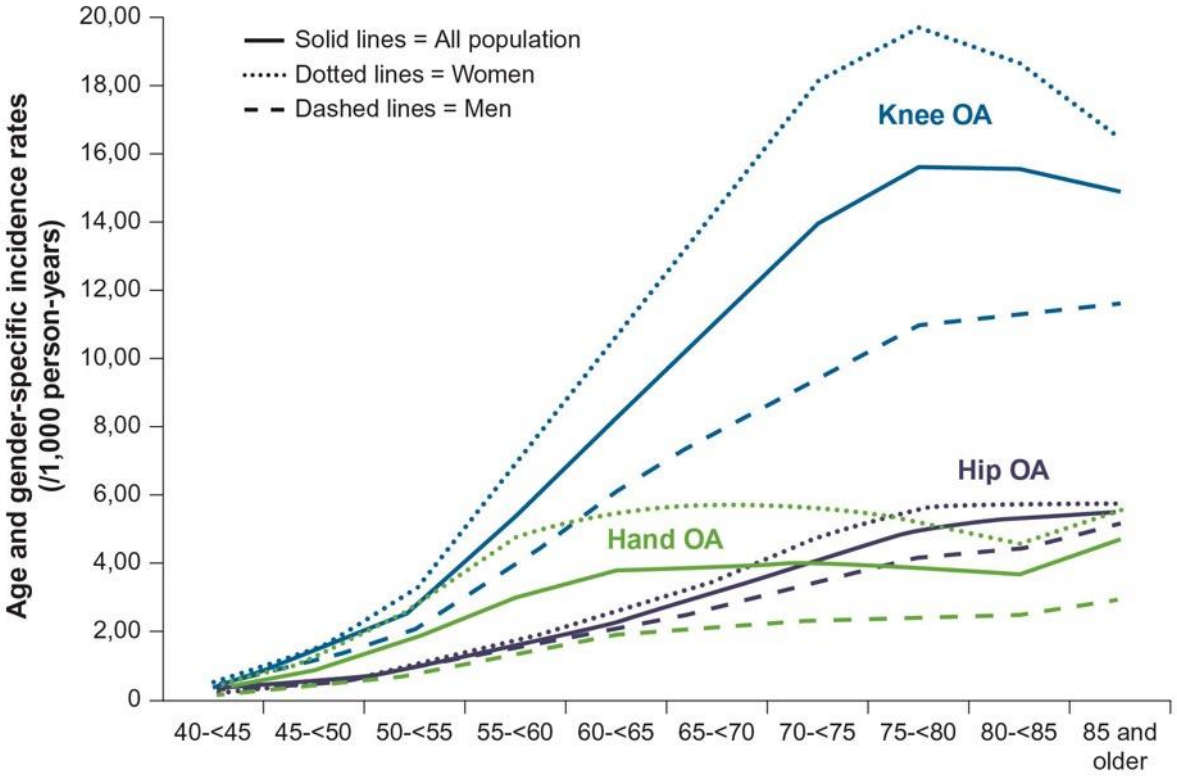
- lack of efficacy (including tolerance or hyperalgesia)
- risk of adverse effects from using a full mu-agonist opioid
- risk of addiction, misuse, and/or overdose
- limited ability to utilize oral formulations in patients with altered gastrointestinal motility/function

Some organizations provide suggestions for how to transition from one full agonist opioid to buprenorphine (qrco.de/VA_bup_chronicpain).

Osteoarthritis

Osteoarthritis (OA) is a common source of pain and disability that affects nearly 70% of those over 65 years of age.[145] The joints involved tend to be the hand, hip, and knee, with knee being most common. As shown in Figure 13, more women than men suffer with OA.[146]

Figure 13: Incidence rates of OA by involved joints[147]



Non-pharmacologic options

Exercise and physical activity

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

Table 8: Effects of exercise on pain and function for knee and hip OA[27,148]

		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					

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%).[149] Physical functioning improved by 5.6 points on a 0-100 scale but the result was not significant (absolute difference -5.6%; 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.[149]

Exercise programs delivered via internet or smart phone can also be effective. At 6 weeks, an app- based exercise program reduced pain scores vs. usual care by 1.5 points (95% CI: 0.8-2.2) on a scale from 0-10 and improved function 3.4 points (95% CI: 0.7-6.2) using the 68 point Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) .[150] A web-based intervention with text message support found longer term benefit vs. a control website with a reduction in knee pain (mean difference 1.6; 95% CI: 0.9-2.2) on a scale from 0-10 and improvement in function (mean difference 5.2; 95% CI: 1.9-8.5) on the WOMAC index at 24 weeks.[151] The program is available for free at mykneeexercise.org.au/my-knee-strength/.

Tai chi

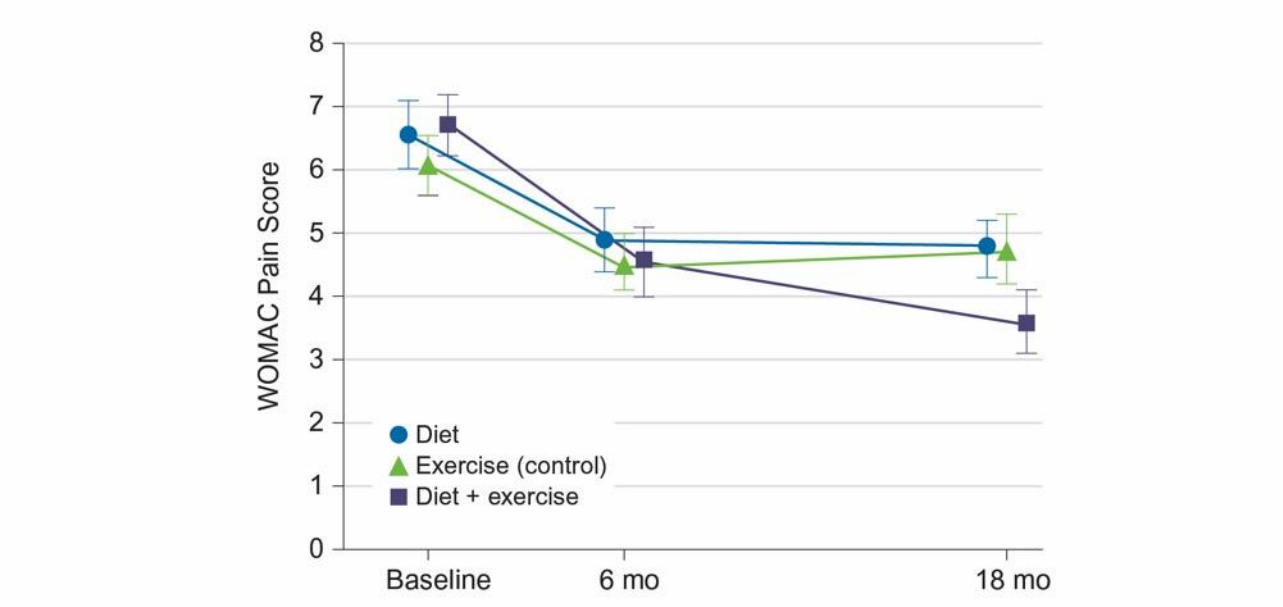
A meta-analysis of 15 randomized trials in patients with musculoskeletal pain (due to OA in 80%) found tai chi to be moderately effective compared to no intervention in improving both pain (SMD -0.66; 95% CI: -0.85 to -0.48) and disability (SMD -0.66; 95% CI: -0.85 to -0.46) at up to 3 months.[152] No 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.[153]

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.[30] 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 14). 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).[30]

Figure 14: WOMAC pain scores across 18 months[30]



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).[30] Secondary analysis of IDEA trial also showed that there were significant dose responses to weight loss for pain (P=0.01), function (P<0.01), physical (P<0.01) and mental (P=0.03) health-related quality of life in overweight and obese adults with knee OA. 18-month weight loss of 10-20% of baseline body weight had substantial clinical benefits, including less pain, compared with less weight loss.[154] Five year follow up of 94 patients from IDEA suggests improvement in pain compared to baseline was maintained and weight remained lower, though it rose from the end of the original trial period.[155] Given the significant drop-out, the long term impact on weight reduction is unclear.

Obesity impacts recovery after total knee replacement. A trial of 82 obese patients who were waiting to receive a total knee replacement were randomized to either undergo bariatric surgery prior to joint surgery or treatment as usual prior to knee replacement.[156] Patients who had bariatric surgery had significantly fewer post-operative complications compared to those with treatment as usual (difference 22%; 95% CI: 3.7-40.3%; p=0.02). Secondary outcomes suggested no difference in pain or function. Incidentally, after bariatric surgery, 12 patients (29.3%) declined knee surgery while 2 patients (4.9%) declined knee replacement in the treatment as usual group.

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 some evidence that pain, stiffness, and swelling were reduced, although no meta-analyses were conducted due to clinical heterogeneity. No effect on physical function was observed.[157]

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.[158] 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.[158]

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.[159] 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.[160] After five weeks of treatment no significant differences in mean improvements on a 0-100 pain scale were found for any comparisons.

Massage

An RCT of Swedish massage vs. light touch in 222 adults with osteoarthritis found significant improvement in pain and function compared to light touch and usual care at eight weeks. The short-term improvement in pain and function attenuated over time with no difference in either outcome between light touch and Swedish massage at 52 weeks.[161]

A review of seven randomized trials with 352 participants suggests that massage may be better than no treatment for reducing OA pain.[162] 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.[33,162]

Cognitive behavioral therapy (CBT)

Benefit to pain and function with CBT for patients with OA is lacking. A randomized trial of 111 patients randomized to group CBT or control found no difference in pain or function at three and 12 months.[163] Similarly, an RCT of 180 non-Hispanic white and 180 non-Hispanic African American patients with OA comparing a positive psychological skills program with a neutral program (control) found no benefit in pain or function between the two treatment groups at 1, 3, or 6 months.[164]

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 9, next page).[165-167] 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 9: Self-management education programs[165-167]

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-pharmacologic interventions

Transcutaneous nerve electrostimulation (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.[168]

Mindfulness meditation for chronic pain was evaluated in a meta-analysis of 30 randomized trials (5 trials of questionable quality in patients with OA or RA) and suggest 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.[36]

Non-pharmacologic summary for OA

Exercise should be encouraged based on patient ability. Evidence supporting the effectiveness of non-pharmacologic 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-pharmacologic interventions presented, see Appendix I.

Pharmacologic options

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.[169] 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).[169]

Generally, scheduled dosing of acetaminophen 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 3,000 mg.[47,170]

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 (standard mean difference [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 1,200 mg.[171]

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 10).[172]

Table 10: NNTs to obtain 50% reduction in pain with topical NSAIDs[172]

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

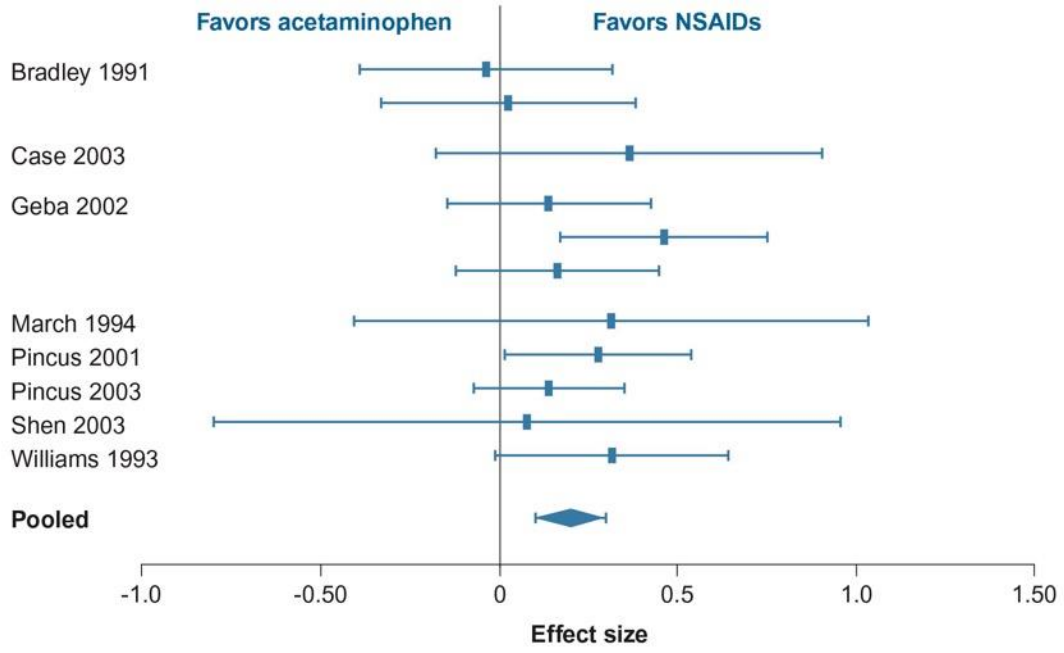
Topical vs. oral NSAIDs

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).[173] 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 minimal systemic absorption. Topical NSAIDs may be recommended over oral NSAIDs for localized, single joint pain (e.g., knee OA).[47]

Acetaminophen vs. NSAIDs

A meta-analysis of six trials comparing acetaminophen and NSAIDs in patients with OA 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 15 (next page). NSAIDs, therefore, are preferred over acetaminophen unless patients have high risk for gastrointestinal, renal, or cardiovascular adverse effects.[170]

Figure 15: Effect size of pain reduction from baseline[170]



Serotonin-norepinephrine reuptake inhibitors (SNRIs)

A meta-analysis of three trials of duloxetine for patients with knee OA showed patients on duloxetine (60 or 120 mg daily) were 49% more likely to have a moderate pain response (≥30% reduction in pain intensity).[174] 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 sustained-release, but further study is needed.[175] No SNRIs are FDA approved to treat OA.

Membrane stabilizers

A small 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.[176] 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.[177] However, lidocaine patches are not FDA approved for the treatment of OA, and more data are needed to support their use.

Tramadol

A Cochrane review of eight RCTs of 3,972 patients using tramadol for 1 week to 3 months for OA found small improvements in pain (SMD -0.25; 95% CI: -0.32 to -0.18) with 50% more patients reporting a 20% improvement in pain with tramadol compared to placebo. Small improvements in function were found (SMD -0.2; 95% CI: -0.29 to -0.12). For both pain and function the number of patients needed to treat for one patient to benefit (NNT) is 13.[178]

Opioids

A Cochrane review of 22 trials of 8,275 patients using opioids, including buprenorphine, 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.[179] 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, membrane stabilizers) at any time points up to one year.[12]

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.[180]

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, who were randomized to capsaicin.[181] 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).[182]

Intra-articular injections

A number of injectable intra-articular agents are available to manage knee OA pain, 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 surrogate (non-clinical) outcomes (such as cartilage and joint structure) rather than clinical ones (such as pain and function).[180] 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.[183] 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.[184,185]

Surgery

OA is a common reason for joint replacement surgery. For older patients with functionally disabling chronic pain unresponsive to other therapies for about six months or who have significant reduction in quality of life due to end-stage OA, surgery may provide relief.[186]

Pharmacologic 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 or intolerable. No evidence supports intra-articular hyaluronic acid injections for knee OA. Intra-articular injections of steroids may provide short term relief. For a complete summary of the pharmacologic interventions presented, see Appendix I.

Low back pain

Low back pain (LBP) is one of the most common reasons for primary care 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.[187] 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.[188]

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.[187] If the patient has an inadequate response, second-line options are duloxetine or tramadol. Other opioids should be reserved for patients with pain unresponsive to all other treatments, with all of the caveats and cautions described previously[189], although some experts in pain medicine assert that opioids should never be used to treat nonstructural low back pain.[190]

Non-pharmacologic 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).[191] Types and duration of exercise from RCTs included in the meta-analysis were not specified.

Early physical therapy for low back pain, particularly with sciatica, can have lasting effects. A trial of acute low back pain randomized 220 patients to usual care or early physical therapy which entailed 6 to 8 sessions over a 4-week timeframe. Oswestry Disability index scores (range 0-100) improved 8.2 points (95% CI: 4.3-12.1) at 4 weeks, a clinically important difference. Sustained, if attenuated, improvements continued at 6 months (5.4; 95% CI: 1.3-9.4) and 1 year (4.8; 95% CI: 0.7-8.9). Small improvements in

back pain (score range 0-10) were noted as well with reductions of 1.4 points at 4 weeks, 0.7 points at 6 months, and 1 point at 1 year.[192]

Tai chi

Two trials (n=160 and n=320) found that compared to wait list or no tai chi, tai chi reduced pain 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.[193,194] 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).[193]

Weight loss

Only small, uncontrolled pilot studies suggest possible benefit from weight loss for patients with chronic low back pain.[195,196] After bariatric surgery, there was a 44% reduction in pain and a 26% improvement in function from a BMI reduction of 3 kg/m^2 (n=58).[195] Calorie restriction among obese patients suggests a reduction in pain and a significant improvement in function (n=46).[196] A meta-analysis of weight-loss interventions identified two low to moderate quality RCTs for low back pain with no benefit to pain, improvement in disability, weight loss, or changes in mental health status.[197]

Yoga

Several relatively high-quality RCTs suggest that yoga can modestly reduce chronic low back pain. A 2017 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.[198] 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.[199]

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 11). For pain, a clinically meaningful reduction in pain score based on the RMDQ of 15 points was not achieved.[200]

Table 11: Yoga: improvement in pain and function[200]

	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)

A 2020 meta-analysis of 18 studies found similar benefit to pain and function over time. However at one year the benefit to pain attenuated, becoming no different from placebo at 12 months, while function maintained improvement at 12 months (SMD -0.33; 95% CI: -0.54 to -0.12).[201]

Acupuncture

A 2017 systematic review of four trials evaluating acupuncture vs. sham acupuncture in patients with chronic LBP found modest improvements in pain (WMD -16.7 points on a 0-100 scale; 95% CI: -33.3 to -0.19 points), but no improvements in function.[191] 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.[191] A 2020 Cochrane review of 33 RCTs for non-specific low back pain found acupuncture improved pain (mean difference -12.30; 95% CI: -15.28 to -9.32) and function (SMD -0.44; 95% CI: -0.55 to -0.33) based on intermediate term follow-up vs. usual care. No long-term trials (i.e., 12 months or longer) were identified.[202]

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.[203] 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.[203]

TENS

Several clinical studies indicate that compared to sham or placebo, TENS has no beneficial effect on pain or function.[187,203-205]

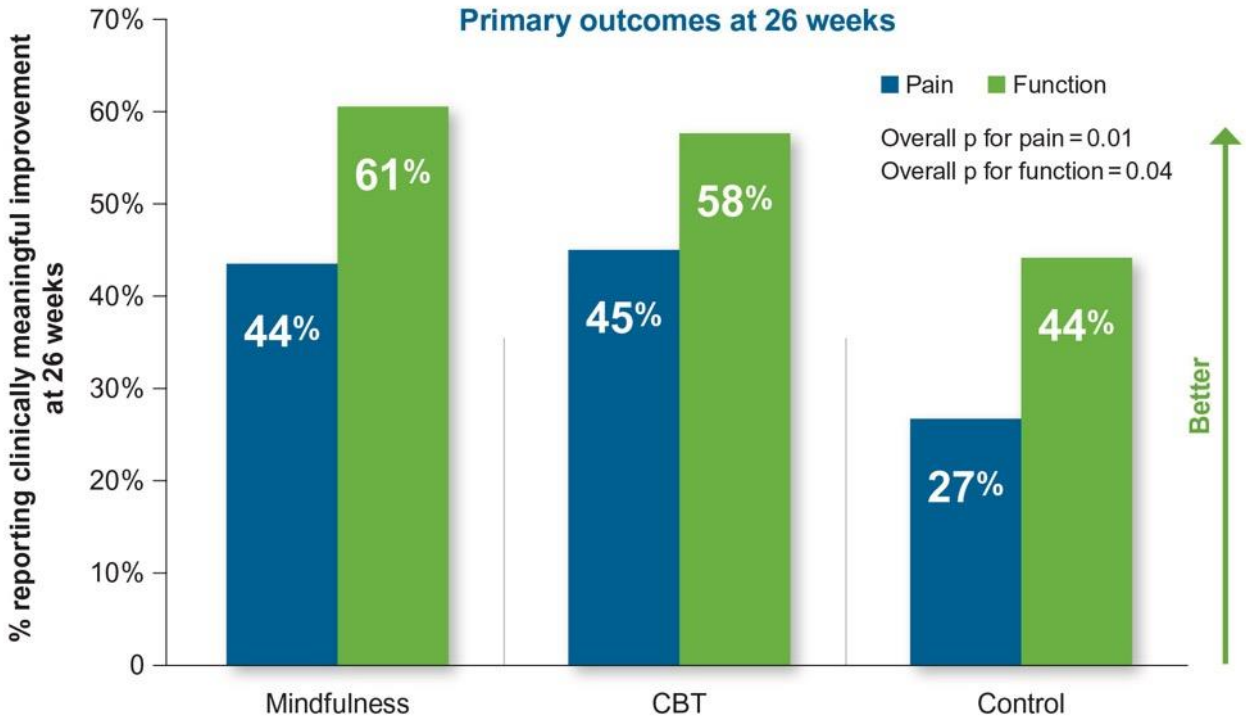
Cognitive and behavioral/mindfulness therapies

A systematic review evaluating CBT found large improvements in disability scores (SMD -0.88; 95% CI: -1.50 to -0.26) but a moderate reduction in pain intensity compared to controls (SMD -0.73; 95% CI: -1.20 to -0.26).[206] One randomized trial of CBT of 701 adults with subacute and chronic low back pain found moderate improvement in RMDQ at 3 months (the end of the intervention), with sustained benefit in function and improvement in pain at 12 months when compared with usual care.[207] Mindfulness had small improvements in pain (SMD -0.30; 95% CI: -0.47 to -0.13) but no improvement in disability.[206]

An RCT of 521 patients with chronic LBP randomized patients to CBT, mindfulness, behavioral therapy or usual care. By the end of the 8-week intervention, pain improved significantly in the intervention groups compared to usual care. This benefit persisted at 6-month follow-up. Functional benefits were not seen during the intervention but appeared during 6 month follow-up, suggesting persistence of benefit beyond the intervention timeframe.[208]

Another 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 (Figure 16).[209]

Figure 16: Primary outcomes at 26 weeks[209]



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).[209] 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.[210] Meditation reduced pain unpleasantness by more than half (57%) and pain intensity by 40%.

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).[211]

Spinal manipulation

Chiropractic care typically involves manual therapy, including spinal manipulation, which may be augmented with exercises, massage, electrical or laser stimulation, nutritional counseling, or other approaches. Manual treatment techniques used by chiropractors may involve stretching, pressure, or joint manipulations (typically on the spine, but sometimes on other joints).

Evidence from a 2019 meta-analysis of 47 randomized trials involving 9,211 patients with chronic back pain found that spinal manipulation had similar effects to other recommended therapies for short term pain relief (e.g., exercise or pharmacologic treatments), and was slightly better than no treatment or non-

recommended treatments.[212] A review of professional guidelines for the use of spinal manipulation for low back pain suggests that it be considered a second-line or adjuvant treatment option after exercise or cognitive behavioral therapy.[213] A 2020 updated evidence review by the Agency for Healthcare Research and Quality found that spinal manipulation improved function and/or pain for lower back injury and tension headaches, but not for fibromyalgia, hip or knee osteoarthritis, or neck pain.[214]

Non-pharmacologic summary for chronic low back pain

Tai chi, yoga, acupuncture, cognitive behavioral therapy and mindfulness can modestly reduce pain and improve function in patients with chronic, nonspecific LBP. Other interventions such as exercise and self-management have smaller or mixed effects, but all of these interventions are generally considered safe. Guidelines recommend initiating non-pharmacologic therapies for managing chronic LBP as the first step in treatment.[187] For a complete summary of the non-pharmacologic interventions presented, see Appendix I.

Pharmacologic 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.[215] Another trial randomized 45 patients with either acute or chronic LBP to 500 mg acetaminophen vs. amitriptyline 37.5 mg four times daily.[216] 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.[217]

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.[218]

NSAIDs

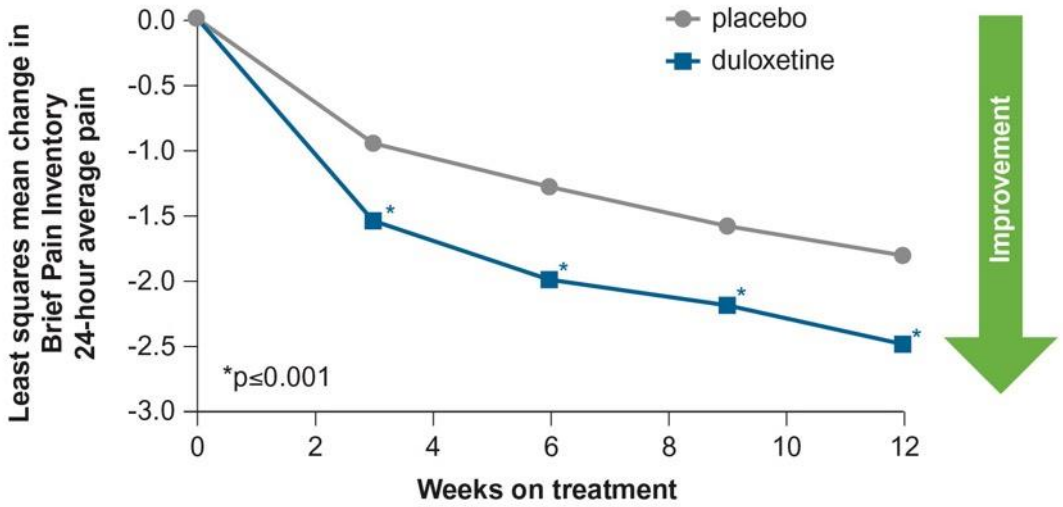
A review of six RCTs for the American College of Physicians showed that oral NSAIDs are more effective than placebo regarding pain intensity, with a small reduction in pain at 12 weeks (WMD -12.4 points on a 0-100 scale; 95% CI: -15.53 to -9.26).[219] No differences in efficacy between different NSAIDs, including non-selective NSAIDs vs. selective COX-2 inhibitors, were identified. An additional PEER systemic review of randomized controlled trials for the management of chronic low back pain in primary care identified four RCTs with 1,637 patients on oral NSAIDs who were followed for 4 to 16 weeks.[220] 55% of patients receiving oral NSAIDs and 37% receiving placebo attained meaningful pain relief (RR 1.44; 95% CI: 1.17-1.78; NNT=6). Individual adverse events reported and trial withdrawals were simliar between groups. One RCT compared topical NSAID flurbiprofen vs. placebo in 127 individuals with chronic low back pain.[221] No statistical difference in cumulative pain intensity was found (p=0.30).

Antidepressants

An analysis of three moderate-quality RCTs found small improvements in pain and function with duloxetine vs. placebo at 12 to 13 weeks.[222] 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≤0.001) in pain on the BPI (Figure 17).[223] The other two trials found similar results, although one did not maintain significance at 13 weeks.[224,225]

Figure 17: Change in BPI score duloxetine vs. placebo[223]



A 2021 meta-analysis supports this finding, adding one additional study from the prior analysis.[226] Disability improved between 3 to 13 weeks on duloxetine vs. placebo (mean difference -3.55; 95% CI: -5.22 to -1.88). While statistically significant, the pain benefit is unlikely to be clinically important and those in duloxetine arms had greater adverse effects.

The same 2021 review did not identify any reduction in pain or improvement in function with TCAs, SSRIs trazodone or bupropion.[226]

Membrane stabilizers

A systematic review identified nine trials comparing topiramate, gabapentin, or pregabalin to placebo in 859 individuals. Fourteen of 15 comparisons found membrane stabilizers ineffective in reducing pain or disability in chronic LBP. Gabapentin was accompanied by an increased risk for adverse events.[227]

Topical lidocaine

Evidence supporting the use of lidocaine in chronic LBP is mixed. Five open-label studies reported statistically significant reductions on pain severity and improvements in quality of life, however, two RCTs failed to find a difference vs. placebo.[228]

Tramadol

In the short term, tramadol reduced pain moderately more than placebo (SMD -0.55; 95% CI: -0.66 to -0.44) with small improvements in function (SMD -0.18; 95% CI: -0.29 to -0.07).[222]

Buprenorphine

Transdermal and buccal buprenorphine have reduced pain in patients with chronic LBP compared to placebo, but functional improvements are less clear.[222] A recent systematic review and network meta-

analysis suggests buprenorphine is more than two times more likely to achieve a 30% reduction in pain than placebo (OR 2.29; 95% CI: 1.05-5.07). Pain response was similar with buprenorphine as other full agonist opioids.[229]

Other 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.[222] 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.[222]

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, membrane stabilizers) at any time points up to one year.[12]

Muscle relaxants

While widely prescribed, use of skeletal muscle relaxants for chronic LBP is not supported by evidence.[222] A 2021 systematic review analyzed 31 trials of 6,505 patients comparing muscle relaxants vs. placebo in non-specific LBP.[230] Most trials evaluated muscle relaxants in acute low back pain. Those that looked at chronic LBP did not find evidence of improvement for pain or disability.

Additional interventions

Epidural steroid injections

Lumbar epidural steroid injections under fluoroscopic guidance are commonly used to treat low back and lower extremity radicular pain,[231] 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.[232]

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).[233]

Pharmacologic summary for chronic low back pain

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

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,[234] and in those who have neuropathy, pain management may improve quality of life.[235]

Current American Diabetes Association guidelines suggest initial management with pregabalin, duloxetine, or gabapentin.[236] Second-line options include TCAs (use cautiously in older adults), venlafaxine, carbamazepine or topical capsaicin. Opioids, and particularly tapentadol, are not recommended to treat neuropathy due to their high risk for addiction and limited evidence for efficacy.[236] Tapentadol is FDA approved for treatment of diabetic neuropathy, but the approval was based on two trials that used a design enriched for patients who responded to tapentadol and the results are therefore not generalizable. 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.

Non-pharmacologic 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.[237]

Acupuncture and massage

The evidence for effectiveness of acupuncture and massage on symptoms of diabetic neuropathy is limited to several small studies. 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 did not have a control group nor did it specifically identify pain as an endpoint.[238] A 4-week trial with 46 patients showed that, compared to usual care, aromatherapy and massage reduced pain and improved quality of life.[239] 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).[240] 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 Cochrane review of 15 trials of TENS for peripheral neuropathic pain identified five trials comparing TENS to sham TENS in 204 patients. Using a visual analog scale, TENS significantly reduced pain (mean difference -1.58; 95% CI: -2.09 to -1.09) although the evidence was found to be very low quality. Heterogeneity in the 10 trials of TENS vs. usual care precluded meta-analysis.[241] Another meta-analysis of three small 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.[242]

An analysis by the Agency for Healthcare Research and Quality, however, did not find significant or compelling evidence to suggest TENS was more effective than placebo for diabetic neuropathy.[243]

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.[244] A small study of 20 patients found no difference with mindfulness meditation vs. placebo on pain or quality of life.[245]

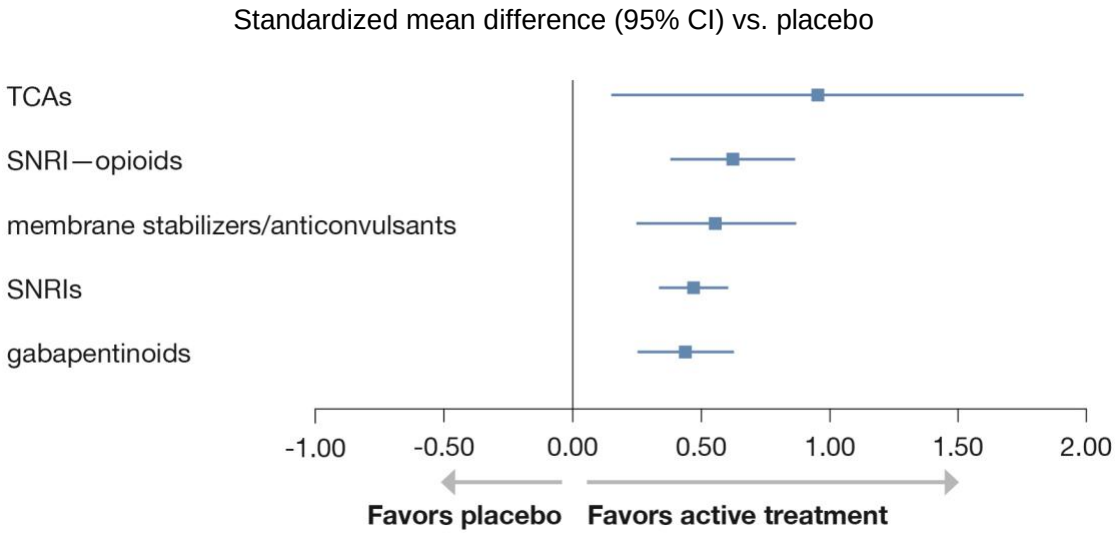
Non-pharmacologic summary for diabetic neuropathy

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

Pharmacologic 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. A meta-analysis of evidence, conducted by American Academy of Neurology (AAN) guidelines subcommittee, showed that gabapentinoids, SNRIs (e.g., duloxetine), sodium channel blockers (e.g., lidocaine, carbamazepine), and SNRI/opioid dual mechanism agents (e.g., tramadol) all have comparable effects on pain (Figure 18).[246] Decisions about which medication may be best depends on overlapping comorbidities and patient factors. Unless significant side effects manifest, trials of 12 weeks at optimal doses determine treatment efficacy.[246]

Figure 18: Similar efficacy among common medications to treat pain from diabetic neuropathy[246]



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).[247] 457 patients with painful diabetic neuropathy were randomized to one of three duloxetine dosage groups (20 mg/day, 60 mg/day, and 120 mg/day) or placebo for 12 weeks.[248] 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).[248]

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).[247] The AAN 2022 analysis of evidence has also shown that amitriptyline is more likely than placebo to improve pain (no Class I or II studies were found for other TCAs); however, there was less confidence in the effect size, and additional analyses revealed that amitriptyline was no more likely to improve pain than gabapentin.[246] Adverse effects with TCAs included somnolence and dizziness, which may be particularly important in older patients.

Membrane stabilizers

Gabapentinoids

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).[249] 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.[249]

Gabapentin is 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).[249] The AAN analysis showed that gabapentin was more likely than placebo to improve pain (SMD 0.53; 95% CI: 0.22 to 0.84; values > 0 indicating intervention is clinically better than placebo); the conclusion was based on one study that was deemed of acceptable quality to be included in the analysis.[246]

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.[250] 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, duloxetine, or gabapentin as the initial treatment.[236]

Other membrane stabilizers

Carbamazepine, topiramate, valproic acid, lacosamide, oxcarbazepine, and lamotrigine can be as effective as gabapentinoids and SNRIs for neuropathic pain, though their use is off-label and associated with side effects.[246]

Topical lidocaine

Although lidocaine patches are FDA approved for post-herpetic neuralgia, no RCTs of patches have been conducted in patients with 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).[251]

Cannabinoids

Weak evidence suggests that medical 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: 0.09-0.60) and increased numbers of patients achieving 50% or greater reductions in pain (21% vs. 17%; risk difference 0.05; 95% CI: 0-0.09).[252] 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 evaluated inhaled herbal cannabis). Similarly, a 2018 systematic review found a small signal that cannabinoids likely improved pain by 30% or greater. This benefit was limited to short term use, less than five weeks.[253] There were no significant differences in the rates of serious adverse events, but more people reported sleepiness, dizziness, or confusion in the cannabis groups.

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

Tramadol

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 five placebo-controlled RCTs (three of tapentadol and two 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).[249] Both medications, as noted earlier, are associated with all of the risks and adverse events common to typical opioids, though tramadol is theoretically preferred over tapentadol in regard to serious opioid-related adverse events, given its weaker opioid agonist effect. No studies have evaluated long-term efficacy or safety of these agents in patients with diabetic neuropathy.

Buprenorphine

A meta-analysis of opioid trials found substantial benefit on neuropathic pain between 4 and 12 weeks.[254] A 12-week trial of transdermal buprenorphine for diabetic neuropathy found patients were no more or less likely to have a 30% pain reduction compared to placebo.[255] Nearly 2 in 5 patients dropped out of the study in the buprenorphine arm due to side effects, primarily nausea and vomiting.

Other opioids

Opioid analgesics are ineffective for treating pain in diabetic neuropathy based on an analysis of pooled data from four RCTs (SMD -0.58; 95% CI: -1.53 to 0.36) comparing opioids to control. This analysis excluded tramadol and tapentadol.[249]

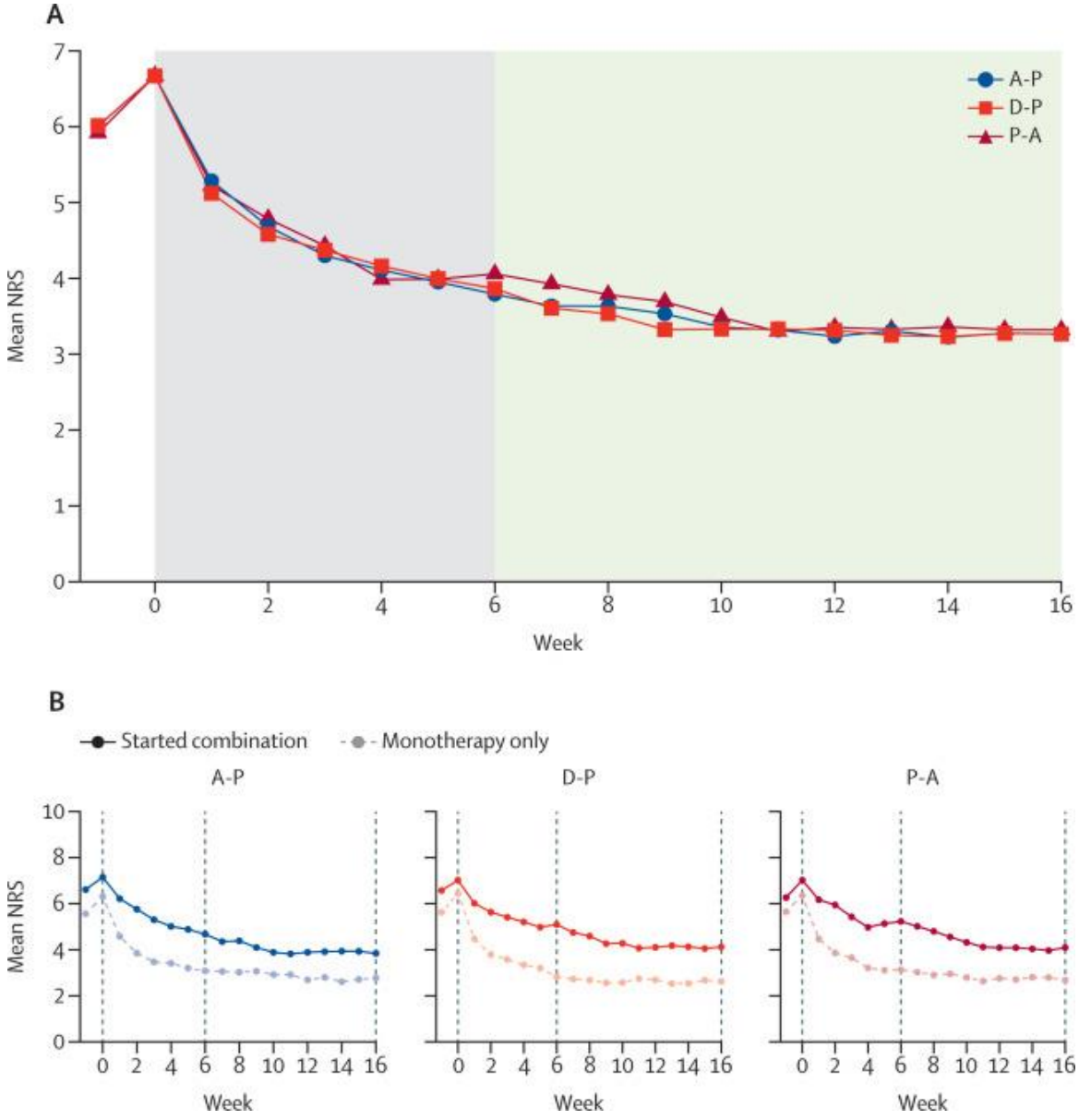
Other pharmacologic options

Evidence for the SSRIs paroxetine and citalopram is inconsistent and insufficient to recommend their use in managing pain in diabetic neuropathy. However, these medications may be effective if patients have coexisting pain and depression.[256] Earlier studies showed that treatment with topical capsaicin was beneficial for relieving pain in patients with diabetic neuropathy.[257,258] 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).[249]

Combination therapy

While a 2022 AAN meta-analysis suggests similar pain relief with SNRIs, anticonvulsants, gabapentinoids, TCAs and tramadol,[246] little is known about combination therapy. The **OPTION-DM trial** randomized 130 patients to either amitriptyline, pregabalin, or duloxetine for 6 weeks.[259] If the pain numerical rating score (NRS) was <3, patients remained on monotherapy for 10 more weeks; if the pain was ≥3, patients went on to combination therapy. Those advancing to combination therapy received one of the two options remaining, for example a patient on amitriptyline would be randomized to either pregabalin or duloxetine. The study found that monotherapy resulted in significant pain relief in only 35% of participants (40% achieved 50% reduction from baseline pain); thus, most patients required combination therapy. The combination therapies were well tolerated and similarly effective at reducing pain (Figure 19, next page).

Figure 19: Mean daily pain scores for combination treatment groups (A) or combination therapy vs. monotherapy (B)[259]



A=amitriptyline; P=pregabalin; D=duloxetine

Side effects with combination therapy were not significantly different than monotherapy, and were predictable: increase in dizziness in patients on pregabalin, nausea in patients on duloxetine, and dry mouth in patient on amitriptyline.

Pharmacologic summary for diabetic neuropathy

The American Diabetes Association recommends either pregabalin, duloxetine, or gabapentin as first-line pharmacologic treatments for diabetic neuropathic pain.[260] AAN suggests gabapentinoids, SNRIs (e.g., duloxetine), sodium channel blockers, and SNRI/opioid dual mechanism agents (such as tramadol) are all treatment options. Given similar efficacy, clinicians should balance potential adverse events, patient comorbidities, cost, and patient preferences when choosing the treatment.[246] Although tramadol or

tapentadol may be considered as third-line treatment options in some patients based on efficacy, they share the risks associated with other opioid analgesics. Other opioid analgesics are not preferred for treatment of diabetic neuropathy. For a complete summary of the pharmacologic interventions presented, see Appendix I.

Additional interventions

Spinal cord stimulation has been studied for pain relief in diabetic neuropathy but has insufficient evidence for any recommendation; most studies were single-arm with fewer than 10 patients.[261,262] 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 pairs) 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. American College of Rheumatology guidelines suggest that people with fibromyalgia have pain in at least 11 of these tender points when a doctor applies pressure.[263]

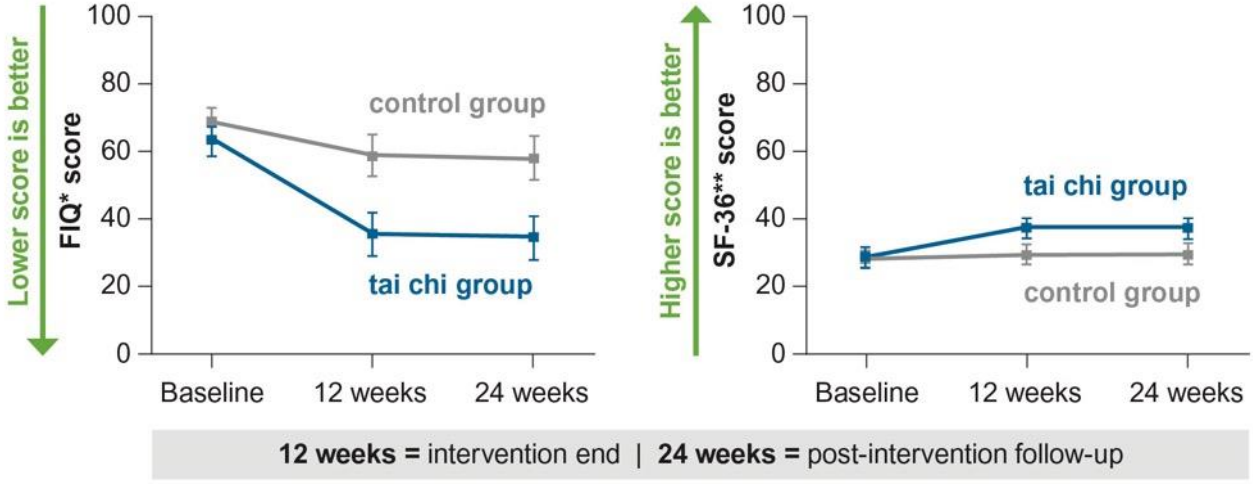
Non-pharmacologic options

Movement-based options

Exercise training is often recommended for patients with fibromyalgia,[264] 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.[265] Some reviews have concluded that the strongest evidence was in support of aerobic exercise,[266] which is the current recommendation by the American College of Rheumatology. However, resistance training can be of benefit as well.[267] 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%).[268] A separate Cochrane review of five low-quality 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.[269]

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 20). At 12 weeks, mean between group difference was -18.4 FIQ points (P<0.001).[270]

Figure 20: Mean changes in FIQ and SF-36 scores at 12 and 24 weeks[270]



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

As many as 35% of patients with fibromyalgia also have obesity.[271] **Weight loss** in patients with overweight or obesity improved pain and fibromyalgia symptoms in five studies, regardless of the means of achieving weight loss (i.e., low calorie diet alone, low calorie diet in combination with physical activity, gastric bypass surgery). Improvements in pain were found as early as 12 weeks and seen as long as 24 months.[271] Although amount of weight lost was not consistently reported among the studies, in one behavioral intervention pain improved with weight loss as little as 9 pounds or 4.4% body weight at six months.[272]

Yoga, acupuncture, massage, and TENS

Two RCTs suggest **yoga** may relieve pain or improve function in fibromyalgia.[273] One RCT of 53 female patients with fibromyalgia randomized subjects to receive an 8-week yoga of awareness program or wait-listed standard care. After eight weeks global FIQ scores were significantly better in patients randomized to yoga vs. control patients (post-intervention mean 35.49 vs. 48.69; p=0.003). Pain was significantly improved (p=0.0186) while function between the two groups was similar (p=0.0727).[274] The other RCT (n=40) compared yoga breathing, but not postures, to a control group that participated in recreational activities. Significant improvements in pain and function occurred at four weeks.[275]

One in five patients with fibromyalgia try **acupuncture** within two years of diagnosis,[276] Low-quality evidence suggests that acupuncture may be associated with reduced fibromyalgia-related pain. A 2013 Cochrane review of nine 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).[276]

Two systematic reviews of four trials suggest improvement for global fibromyalgia symptoms, but unclear benefit on pain and function. The first systematic review identified two small trials of myofascial **massage** that may improve pain over placebo.[277] A 2022 systematic review found two connective tissue massage RCTs that improved global FIQ score but had mixed impact on pain.[278]

Six RCTs failed to show that **TENS** reduced pain in patients with fibromyalgia.[279] A 2022 meta-analysis of RCTs that compared TENS to sham TENS (placebo) found a small, but statistically significant effect (SMD -1.09; 95% CI -2.11 to -0.07) in participants with fibromyalgia; the results were based on 3 RCTs with 307 participants and substantial heterogeneity across the three trials.[280]

Cognitive and behavioral interventions

A Cochrane review of 18 low-quality 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).[281] Controls included waitlist controls, active controls, or treatment as usual

In seven RCTs of mindfulness meditation, no reduction in pain was observed. Methods were varied and incorporated different components of mindfulness-based stress relief, CBT, and yoga.[36] In two RCTs, self-management education did not improve pain or disability, as compared to controls.[36]

Non-pharmacologic 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-pharmacologic interventions presented, see Appendix I.

Pharmacologic options

The FDA has approved three medications 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,[282] although they may be useful to treat pain triggers of fibromyalgia.[264]

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.[283] At 12 weeks, duloxetine was superior to placebo for pain reduction (RR for ≥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 (Savella) 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).[284] A similar effect on pain relief was noted with milnacipran 200 mg daily.

An updated (data through August 2017) Cochrane review identified additional seven trials of duloxetine and nine of milnacipran.[285] The updated analysis did not change findings from previous reviews: both medications were better than placebo in reducing pain by at least 30%. Both medications 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).[286]

A Cochrane review of seven RCTs comparing SSRIs to placebo found a small difference (risk difference 0.1; 95% CI: 0.01-0.20) in patients who reported a 30% pain reduction. SSRIs included in the review included citalopram, fluoxetine, and paroxetine.[287] These data are insufficient to recommend SSRIs for the treatment of pain alone in patients with fibromyalgia.

Membrane stabilizers

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).[288]

A small 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).[289]

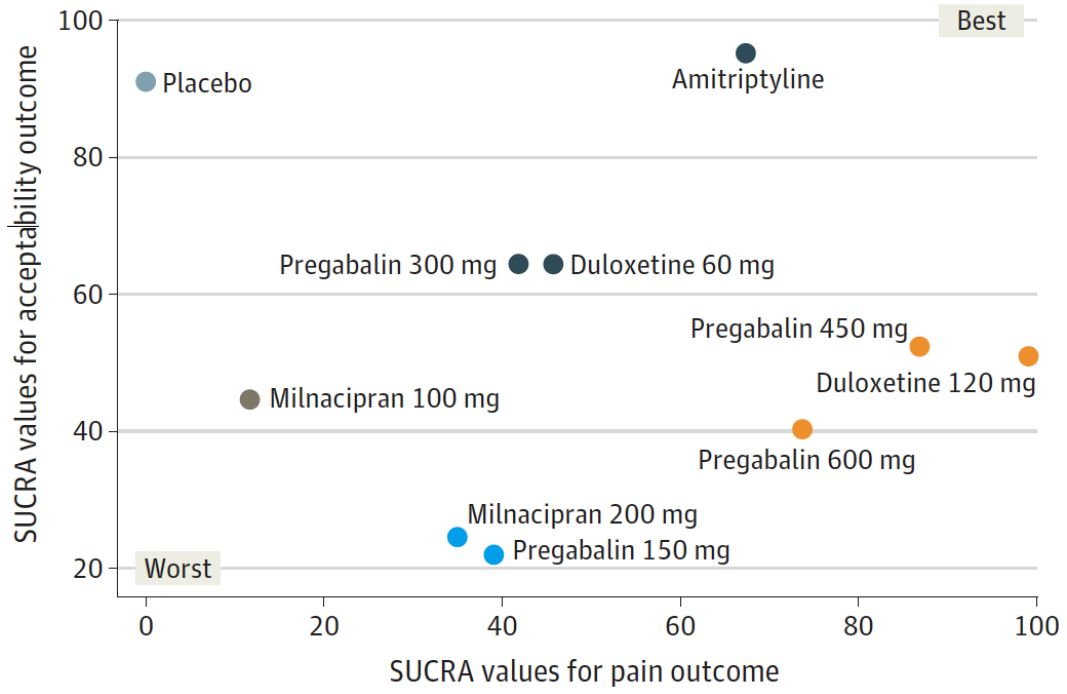
Gabapentin

Evidence supporting the use of gabapentin for fibromyalgia is very limited. In a Cochrane review of RCTs lasting eight weeks or longer (searched through May 2016) two trials were identified. One was only a conference abstract. The other trial randomized 150 patients with fibromyalgia to gabapentin 1200-2400 mg/day vs. placebo for 12 weeks.[290] 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.

Comparing medication options

A network meta-analysis of 35 RCTs in 11,423 adults with fibromyalgia evaluated pain relief with duloxetine, pregabalin, milnacipran, or amitriptyline.[291] Compared to placebo, all of these options provide small, but significant pain relief (SMD range: 0.17-33). A surface area under the cumulative ranking curve (SUCRA) score was calculated to determine the ranking of treatment options on pain relief and side effects, or patient acceptability, by dose given the available data. Plotting SUCRA scores for pain relief and acceptability highlighted the importance of optimizing doses for effect (Figure 21). Pregabalin 450 mg and duloxetine 120 mg were associated with the highest pain reduction. Milnacipran is least likely to be effective compared to other options. While amitriptyline appears very well tolerated and effective, anticholinergic and other side effects limit utility in older adults.[291] All treatments, except amitriptyline, had higher rates of discontinuation due to adverse events than placebo. Also (not in the figure), amitriptyline and duloxetine 120 mg were associated with the highest improvement in quality of life.

Figure 21: Probability of pain relief and patient acceptability by medication and dose[291]



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).[292] 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.[293] Although nabilone was associated with improved sleep quality, no significant effects were reported for pain, mood, or quality of life.

Another trial looked at whether different ratios of THC:CBD impacted pain response. Patients received a high THC option, a product with approximately a 1:1 ratio of THC:CBD, a product with higher CBD to THC ratio, or placebo. All patients received a single dose of each of the products at least two weeks apart and in random order. A significant 30% response to pain was noted with the 1:1 THC:CBD product vs. placebo, but no product provided a 50% or greater pain response that differed from placebo.[294]

Opioid options

Tramadol: 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.[295] A review of pharmacologic treatment options suggests short-term improvements in pain and quality of life with tramadol. Patients who do not respond to other treatment options may benefit from a trial of tramadol, with understanding of the limitations of evidence and risks of side effects.

Buprenorphine does not have any data to support its use in fibromyalgia.

Other opioids: A Cochrane review found no RCTs of opioid therapy in patients with fibromyalgia lasting more than eight weeks.[296] 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.[297] 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.[298]

Pharmacologic summary for fibromyalgia

The European League Against Rheumatism (EULAR) guidelines for managing fibromyalgia-related pain recommend beginning with non-pharmacologic 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.[265] A recent meta-analysis of evidence showed that amitriptyline, duloxetine, pregabalin, and milnacipran had similar effects in patients with fibromyalgia, with some medications (i.e., pregabalin, duloxetine) showing higher pain reduction with higher doses. In the elderly, duloxetine and pregabalin may be the more favorable pharmacologic options. For a complete summary of the pharmacologic interventions presented, see Appendix I.

Putting it all together

Managing chronic pain is always challenging, and more so in those with comorbidities, polypharmacy, or physical or cognitive impairments. Clinicians and caregivers need to develop individualized pain treatment plans identifying realistic functional goals and the type 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-pharmacologic options (which can be as effective as pharmacologic options) should be tried first. When pharmacologic 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, close monitoring, and careful tapering.

Appendix I: Evidence for non-pharmacologic and pharmacologic approaches to managing pain

	INTERVENTION	Osteoarthritis	Low back pain	Diabetic neuropathy	Fibromyalgia
Non-pharmacologic options	exercise	●	●	—	●
	physical therapy	●	●	—	—
	tai chi	●	●	—	●
	weight loss	○	○	—	●
	yoga	●	●	—	○
	acupuncture	●	●	—	○
	massage	●	●	—	●
	TENS*	○	○	●	○
	cognitive behavioral therapy	○	●	●	●
	mindfulness meditation	○	●	○	○
	self-management	●	●	—	○
Non-opioid pharmacologic options	acetaminophen	●	○	—	—
	NSAIDs—oral	●	●	—	—
	NSAIDs—topical	●	○	—	—
	duloxetine (Cymbalta, generics)	●	●	●	●
	tricyclic antidepressants (TCAs)	—	●	●	●
	pregabalin (Lyrica, Lyrica CR)	●	—	●	●
	gabapentin (Neurontin, generics)	—	○	●	●
	topical lidocaine (Lidoderm, generics)	○	—	●	—
	cannabis/cannabinoids	—	—	●	○
Opioids	tramadol (Ultram)	○	●	●	○
	buprenorphine (Belbuca, Butrans)	○	●	○	—
	other opioids	●	●	●	●

Risk/benefit: ● = favorable; ● = potentially favorable; ● = unfavorable; ○ = no clear benefit; — = insufficient data
***TENS:** transcutaneous electrical nerve stimulation

Appendix II: Dosing suggestions for selected analgesics

Class	Medication	Starting dose	Frequency	Requires slow titration*	Therapeutic daily dose	Maximum daily dose
Acetaminophen	acetaminophen	325 – 650 mg	every 4-6 hours	No	3000 – 4000 mg	4000 mg (adults – acute) 3250 mg (acute - elderly) 3000 mg (chronic)**
NSAID - oral	celecoxib (Celebrex, generics)	100 mg	twice daily	No	200 - 400 mg	400 mg
	ibuprofen (Advil, generics)	200-400 mg	every 8 hours	No	2400 mg	3200 mg (acute) 2400 mg (chronic) 1200 mg (OTC)
	naproxen (Aleve, generics)	220 -500 mg	every 12 hours	No	1000 mg	1500 mg
NSAID - topical	diclofenac gel 1% # (Voltaren, generics - OTC)	2-4 grams	every 6 hours	No	16 grams	32 grams (chronic)
	diclofenac patch (Flector)	1 patch	twice daily	No		2 patches (acute)
SNRI	duloxetine (Cymbalta, generics)	20-30 mg	daily	Every 2 weeks	60-120 mg	120 mg
	milnacipran (Savella)	12.5 mg	daily or twice daily	Every 2 days	100 – 200 mg	200 mg
TCAs	amitriptyline	10 - 25 mg	nightly	Every 2 weeks	25 – 150 mg	150 mg
	nortriptyline	10 - 25 mg	nightly	Every 2 weeks	25 - 100 mg	200 mg
Anticonvulsants	pregabalin (Lyrica, generics)	50-75 mg	Twice or thrice daily	Every 1-2 weeks	300-600 mg	600 mg
	gabapentin (Neurontin, generics)	100-300 mg	nightly to every 8 hours	Daily or longer interval as tolerated	900 - 3600 mg	3600 mg
Topicals	lidocaine 5% patch	1 patch	daily	No	1 – 3 patches	3 patches
	lidocaine 4% patch (OTC)	1 patch	daily	No	1 patch	1 patch
	capsaicin (OTC)	1 application	three to four times daily	No	3-4 applications	3-4 applications
	capsaicin patch (OTC)	1 patch for up to 8 hours	daily	No	1 – 4 patches	4 patches per day

References[47,171,223,299-302]

* If No, the dose may be changed with each administration based on patient symptoms ** lower doses may be required in older adults and patients taking certain medications (e.g., anticoagulants) # Diclofenac 3% gel has an indication for actinic keratosis, not pain.

References

1. Yong RJ, Mullins PM, Bhattacharyya N. Prevalence of chronic pain among adults in the United States. *Pain.* 2022;163(2):e328-e332.
2. Zelaya CE, Dahlhamer JM, Lucas JW, Connor EM. Chronic pain and high-impact chronic pain among U.S. adults, 2019. *NCHS Data Brief.* 2020(390):1-8.
3. Centers for Disease Control & Prevention. Prescription painkiller overdoses in the US. *Vital Signs.* 2011.
4. Centers for Disease Control & Prevention. Understanding the epidemic. 2019; https://www.cdc.gov/drugoverdose/epidemic/index.html. Accessed April 1 2019.
5. Centers for Disease Control & Prevention. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morbidity and mortality weekly report.* 2011;60(43):1487-1492.
6. Centers for Disease Control & Prevention. U.S. overdose deaths in 2021 increased half as much as in 2020 - but are still up 15%. May 11, 2022; https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm#print. Accessed Oct 31, 2022.
7. National Center for Health Statistics. Provisional drug overdose death counts. Oct 10, 2022; www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Accessed Oct 31, 2022.
8. Centers for Disease Control & Prevention. Opioid data analysis and resources. June 2, 2022; https://www.cdc.gov/opioids/data/analysis-resources.html. Accessed Oct 31, 2022.
9. Substance Abuse and Mental Health Services Administration. *Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health.* Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration;2021. HHS Publication No. PEP21-07-01-003, NSDUH Series H-56.
10. IQVIA. Prescription opioid trends in the United States. Dec 16, 2020; https://www.iqvia.com/insights/the-iqvia-institute/reports/prescription-opioid-trends-in-the-united-states. Accessed Oct 3, 2022.
11. Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: A systematic review and meta-analysis. *JAMA.* 2018;320(23):2448-2460.
12. Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. *JAMA.* 2018;319(9):872-882.
13. Carr DB, Goudas LC. Acute pain. *Lancet.* 1999;353(9169):2051-2058.
14. Wells N PC, McCaffery M. *Improving the quality of care through pain assessment and management.* Rockville, MD2008.
15. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10(2):113-130.
16. Alexander J, Black A. Pain mechanisms and the management of neuropathic pain. *Curr Opin Neurol Neurosurg.* 1992;5(2):228-234.
17. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. *Lancet.* 2021;397(10289):2098-2110.
18. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin J Pain.* 2008;24(6):479-496.
19. Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain.* 1988;33(1):11-23.
20. Covington EC. Anticonvulsants for neuropathic pain and detoxification. *Cleve Clin J Med.* 1998;65 Suppl 1:SI21-29.
21. Gordon DB, Dahl JL, Miaskowski C, et al. American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. *Arch Intern Med.* 2005;165(14):1574-1580.
22. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *J Gen Intern Med.* 2009;24(6):733-738.
23. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain.* 2004;20(5):309-318.

24. Garg A, Pathak H, Churyukanov MV, Uppin RB, Slobodin TM. Low back pain: critical assessment of various scales. *Eur Spine J.* 2020;29(3):503-518.
25. Olsen MF, Bjerre E, Hansen MD, Tendal B, Hilden J, Hrobjartsson A. Minimum clinically important differences in chronic pain vary considerably by baseline pain and methodological factors: systematic review of empirical studies. *J Clin Epidemiol.* 2018;101:87-106 e102.
26. Bjoro K, Herr K. Assessment of pain in the nonverbal or cognitively impaired older adult. *Clin Geriatr Med.* 2008;24(2):237-262.
27. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2015;9(1).
28. Kang JW, Lee MS, Posadzki P, Ernst E. T'ai chi for the treatment of osteoarthritis: a systematic review and meta-analysis. *BMJ Open.* 2011;1(1):2010-000035.
29. Sherman KJ, Cherkin DC, Wellman RD, et al. A randomized trial comparing yoga, stretching, and a self-care book for chronic low back pain. *Arch Intern Med.* 2011;171(22):2019-2026.
30. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. *JAMA.* 2013;310(12):1263-1273.
31. Eisenberg D, Shikora SA, Aarts E, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for metabolic and bariatric surgery. *Surg Obes Relat Dis.* 2022;18(12):1345-1356.
32. Hinman RS, McCrory P, Pirotta M, et al. Acupuncture for chronic knee pain: a randomized clinical trial. *JAMA.* 2014;312(13):1313-1322.
33. Perlman AI, Sabina A, Williams AL, Njike VY, Katz DL. Massage therapy for osteoarthritis of the knee: a randomized controlled trial. *Arch Intern Med.* 2006;166(22):2533-2538.
34. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. *BMJ.* 2015;13(350).
35. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain.* 1999;80(1-2):1-13.
36. Hilton L, Hempel S, Ewing BA, et al. Mindfulness meditation for chronic pain: Systematic review and meta-analysis. *Ann Behav Med.* 2017;51(2):199-213.
37. Lorig KR, Sobel DS, Stewart AL, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: A randomized trial. *Medical Care.* 1999;37(1):5-14.
38. Haas M, Groupp E, Muench J, et al. Chronic disease self-management program for low back pain in the elderly. *J Manipulative Physiol Ther.* 2005;28(4):228-237.
39. Food and Drug Administration. Questions and answers about oral prescription acetaminophen products to be limited to 325 mg per dosage unit. 2016; https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm239871.htm.
40. Tylenol adult dosing. https://www.tylenol.com/safety-dosing/dosage-for-adults. Accessed Jan 4, 2023.
41. Lee WM. Acetaminophen (APAP) hepatotoxicity-Isn't it time for APAP to go away? *J Hepatol.* 2017;20(17):32148-32147.
42. Hawkey CJ, Svedberg LE, Naesdal J, Byrne C. Esomeprazole for the management of upper gastrointestinal symptoms in patients who require NSAIDs: a review of the NASA and SPACE double-blind, placebo-controlled studies. *Clin Drug Investig.* 2009;29(10):677-687.
43. Desai JC, Sanyal SM, Goo T, et al. Primary prevention of adverse gastroduodenal effects from short-term use of non-steroidal anti-inflammatory drugs by omeprazole 20 mg in healthy subjects: a randomized, double-blind, placebo-controlled study. *Dig Dis Sci.* 2008;53(8):2059-2065.
44. Food and Drug Administration. FDA Briefing Document: Joint meeting of the arthritis advisory committee and the drug safety and risk management advisory committe April 24 and 25 2018. 2018.
45. Brown T. CV safety of celecoxib similar to naproxen, ibuprofen, FDA panels say. 2018; https://www.medscape.com/viewarticle/895722. Accessed April 19 2019.
46. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med.* 2016;375(26):2519-2529.
47. Makris UE, Abrams RC, Gurland B, Reid MC. Management of persistent pain in the older patient: a clinical review. *JAMA.* 2014;312(8):825-836.
48. U.S. Food and Drug Administration. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR).

Jan 19, 2022; https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin. Accessed Nov 2, 2022.
49. Bykov K, Bateman BT, Franklin JM, Vine SM, Patorno E. Association of gabapentinoids with the risk of opioid-related adverse events in surgical patients in the United States. *JAMA Netw Open.* 2020;3(12):e2031647.
50. Gomes T, Greaves S, van den Brink W, et al. Pregabalin and the risk for opioid-related death: A nested case-control study. *Ann Intern Med.* 2018;169(10):732-734.
51. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. *PLoS Med.* 2017;14(10):e1002396.
52. Peet ED, Dana B, Sheng FY, Powell D, Shetty K, Stein BD. Trends in the concurrent prescription of opioids and gabapentin in the US, 2006 to 2018. *JAMA Intern Med.* 2022.
53. Evoy KE, Covvey JR, Peckham AM, Reveles KR. Gabapentinoid misuse, abuse and non-prescribed obtainment in a United States general population sample. *Int J Clin Pharm.* 2021;43(4):1055-1064.
54. Derry S, Rice AS, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2017;1:CD007393.
55. ProCon.org. State-by-state medical marijuana laws. https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc/. Accessed Nov 3, 2022.
56. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. *JAMA.* 2015;313(24):2474-2483.
57. Williams AR, Hill KP. Care of the patient using cannabis. *Ann Intern Med.* 2020;173(9):Itc65-itc80.
58. Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain.* 2018;159(10):1932-1954.
59. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA.* 2015;313(24):2456-2473.
60. National Academies of Sciences E, Medicine, Health, et al. The National Academies Collection: Reports funded by National Institutes of Health. In: *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.* Washington (DC): National Academies Press (US); 2017.
61. Harlow AF, Leventhal AM, Barrington-Trimis JL. Closing the loophole on hemp-derived cannabis products: A public health priority. *JAMA.* 2022;328(20):2007-2008.
62. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain physician.* 2008;11(2 Suppl):S133-153.
63. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health *HHS Publication No SMA 18-5068, NSDUH Series H-53.* 2018.
64. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. *MMWR Recomm Rep.* 2022;71(3):1-95.
65. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology.* 2006;104(3):570-587.
66. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. *MMWR Recomm Rep.* 2016;65(1):1-49.
67. Pedersen L, Borchgrevink PC, Breivik HP, Fredheim OM. A randomized, double-blind, double-dummy comparison of short- and long-acting dihydrocodeine in chronic non-malignant pain. *Pain.* 2014;155(5):881-888.
68. FDA blueprint for prescriber education for extended-release and long-acting opioid analgesics. In. Silver Springs, MD: US Department of Health and Human Services, Food and Drug Administration; 2017.
69. Food and Drug Administration. Extended-release and long-acting opioid analgesics shared system. 2015; http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf.
70. Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin.
71. Chronis Manolis CBG, and William Shrank. Mandating coverage of abuse-deterrent opioids would be a costly distraction from more effective solutions. In. *Health Affairs*2017.

72. Food and Drug Administration. Abuse-deterrent opioid analgesics. 2021; https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics. Accessed Nov 15, 2022.
73. Guenther SM, Mickle TC, Barrett AC, Roupe KA, Zhou J, Lam V. Relative bioavailability, intranasal abuse potential, and safety of benzhydrocodone/acetaminophen compared with hydrocodone bitartrate/acetaminophen in recreational drug abusers. *Pain Med.* 2018;19(5):955-966.
74. Mickle TC, Guenther SM, Barrett AC, et al. Pharmacokinetics and abuse potential of benzhydrocodone, a novel prodrug of hydrocodone, after intranasal administration in recreational drug users. *Pain Med.* 2018;19(12):2438-2449.
75. Benzhydrocodone/acetaminophen (Apadaz) [package insert]. Newtown, PA: KVK-Tech, Inc.; 2021 https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208653s007lbl.pdf Accessed Nov 15, 2022.
76. Mustafa AA, Rajan R, Suarez JD, Alzghari SK. A review of the opioid analgesic benzhydrocodone-acetaminophen. *Cureus.* 2018;10(6):e2844.
77. Centers for Disease Control & Prevention. Commonly used terms. 2021; https://www.cdc.gov/opioids/basics/terms.html. Accessed February 23, 2023.
78. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th - text revision ed. Washington, DC.2022.
79. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain.* 2007;8(7):573-582.
80. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* 2015;162(4):276-286.
81. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med.* 2010;152(2):85-92.
82. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug Alcohol Depend.* 2012;125(1-2):8-18.
83. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines. 2016; https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-serious-risks-and-death-when-combining-opioid-pain-or. Accessed June 27 2019.
84. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain physician.* 2008;11(2 Suppl):S105-120.
85. Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil.* 2010;22(4):424-430.
86. Rivkin A, Chagan L. Lubiprostone: chloride channel activator for chronic constipation. *Clin Ther.* 2006;28(12):2008-2021.
87. Miller M, Sturmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. *J Am Geriatr Soc.* 2011;59(3):430-438.
88. Yoshikawa A, Ramirez G, Smith ML, et al. Opioid use and the risk of falls, fall injuries and fractures among older adults: A systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci.* 2020;75(10):1989-1995.
89. Dublin S, Walker RL, Jackson ML, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. *J Am Geriatr Soc.* 2011;59(10):1899-1907.
90. Hamina A, Taipale H, Karttunen N, et al. Hospital-treated pneumonia associated with opioid use among community dwellers with Alzheimer's disease. *J Alzheimers Dis.* 2019;69(3):807-816.
91. Edelman EJ, Gordon KS, Crothers K, et al. Association of prescribed opioids with increased risk of community-acquired pneumonia among patients with and without HIV. *JAMA Intern Med.* 2019;179(3):297-304.
92. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. *J Intern Med.* 2013;273(5):511-526.
93. Deyo RA, Smith DH, Johnson ES, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. *Spine.* 1976;38(11):909-915.
94. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43(13):879-923.

95. Malonne H, Coffiner M, Sonet B, Sereno A, Vanderbist F. Efficacy and tolerability of sustained-release tramadol in the treatment of symptomatic osteoarthritis of the hip or knee: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther.* 2004;26(11):1774-1782.
96. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc.* 2009;57(8):1331-1346.
97. Substance Abuse and Mental Health Services Administration. 2020 NSDUH detailed tables. 2022; samhsa.gov/data/report/2020-nsduh-detailed-tables. Accessed Nov 10, 2022.
98. Zeng C, Dubreuil M, LaRochelle MR, et al. Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA.* 2019;321(10):969-982.
99. Tramadol (Ultram) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2021; www.accessdata.fda.gov/drugsatfda_docs/label/2021/020281s049lbl.pdf Accessed Nov 15, 2022.
100. Ryan NM, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clin Toxicol (Phila).* 2015;53(6):545-550.
101. Drug Enforcement Administration. Tramadol information. *Diversion Control Division, Drug & Chemical Evaluation Section.* 2018.
102. Gudin J, Fudin J. A narrative pharmacological review of buprenorphine: A unique opioid for the treatment of chronic pain. *Pain Ther.* 2020;9(1):41-54.
103. Fishman MA, Kim PS. Buprenorphine for chronic pain: a systemic review. *Curr Pain Headache Rep.* 2018;22(12):83.
104. Khanna IK, Pillarisetti S. Buprenorphine - an attractive opioid with underutilized potential in treatment of chronic pain. *J Pain Res.* 2015;8:859-870.
105. Webster L, Gudin J, Raffa RB, et al. Understanding buprenorphine for use in chronic pain: Expert opinion. *Pain Med.* 2020;21(4):714-723.
106. Buprenorphine (Belbuca) [package insert]. Raleigh, NC: BioDelivery Sciences International, Inc.; 2022; https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207932s019s020lbl.pdf Accessed Feb 19, 2023.
107. Buprenorphine (Butrans) [package insert]. Stamford, CT: Purdue Pharm L.P.; 2022; https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021306s039lbl.pdf Accessed Feb 19, 2023.
108. Pergolizzi JV, Jr., Raffa RB. Safety and efficacy of the unique opioid buprenorphine for the treatment of chronic pain. *J Pain Res.* 2019;12:3299-3317.
109. Fishman S. *Responsible opioid prescribing: A clinician's guide, 2nd Ed.* Washington, DC: Waterford Life Sciences; 2012.
110. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth.* 1997;78(5):606-617.
111. Pengel LH, Herbert RD, Maher CG, Refshauge KM. Acute low back pain: systematic review of its prognosis. *BMJ.* 2003;327(7410):323.
112. OPEN. Patient counseling. 2022; michigan-open.org/healthcare-professionals/patient-counseling/. Accessed Nov 9, 2022.
113. Traeger AC, Hübscher M, Henschke N, Moseley GL, Lee H, McAuley JH. Effect of primary care-based education on reassurance in patients with acute low back pain: Systematic review and meta-analysis. *JAMA Intern Med.* 2015;175(5):733-743.
114. Kroenke K, Bair MJ, Damush TM, et al. Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. *JAMA.* 2009;301(20):2099-2110.
115. Chang AK, Bijur PE, Esses D, Barnaby DP, Baer J. Effect of a single dose of oral opioid and nonopioid analgesics on acute extremity pain in the emergency department: A randomized clinical trial. *JAMA.* 2017;318(17):1661-1667.
116. Flynn DM. Chronic musculoskeletal pain: Nonpharmacologic, noninvasive treatments. *Am Fam Physician.* 2020;102(8):465-477.
117. Lipman AG, Jackson K. Opioid pharmacotherapy. In: Warfield CA BZ, ed. *Principles and practice of pain medicine, 2nd Edition.* New York, NY: McGraw-Hill Companies, Inc.; 2004.
118. Kim N, Matzon JL, Abboudi J, et al. A prospective evaluation of opioid utilization after upper-extremity surgical procedures: Identifying consumption patterns and determining prescribing guidelines. *J Bone Joint Surg Am.* 2016;98(20):e89.

119. Chu J, Farmer B, Ginsburg B, et al. New York City emergency department discharge opioid prescribing guidelines. 2013; https://www1.nyc.gov/site/doh/providers/health-topics/opioid-prescribing-resources-for-emergency-departments.page. Accessed November 9 2018.
120. Cheng D, Majlesi N. *Clinical practice statement: emergency department opioid prescribing guidelines for the treatment of noncancer related pain.* Milwaukee, WI: American Academy of Emergency Medicine;2013.
121. Thorson D, Biewen P, Bonte B, et al. Acute pain assessment and opioid prescribing protocol. 2014; https://www.icsi.org. Accessed November 9 2018.
122. Paone D, Dowell D, Heller D. Preventing misuse of prescription opioid drugs. *City Health Information.* 2011;30:23-30.
123. Cantrill SV, Brown MD, Carlisle RJ, et al. Clinical policy: critical issues in the prescribing of opioids for adult patients in the emergency department. *Ann Emerg Med.* 2012;60(4):499-525.
124. Washington State Agency Medical Directors Group. *Interagency guideline on opioid dosing for chronic non-cancer pain.* 2010.
125. American Society of Addiction Medicine. *Consensus statement on appropriate use of drug testing in clinical addiction medicine.* 2017.
126. Centers for Disease Control & Prevention. *Quality improvement and care coordination: Implementing the CDC guideline for prescribing opioids for chronic pain.* National Center for Injury Prevention and Control, Division of Unintentinal Injury Prevention, Atlanta, GA;2018.
127. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med.* 2015;175(4):608-615.
128. Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths - United States, 2010-2015. *MMWR Morbidity and mortality weekly report.* 2016;65(5051):1445-1452.
129. Legislative Analysis and Public Policy Association. *Naloxone access: Summary of state laws.* 2022.
130. Guy GP, Jr., Khushalani JS, Jackson H, Sims RSC, Arifkhanova A. Trends in state-level pharmacy-based naloxone dispensing rates, 2012-2019. *Am J Prev Med.* 2021;61(6):e289-e295.
131. Cremer LJ, Board A, Guy GP, Jr., Schieber L, Asher A, Parker EM. Trends in pharmacy-based dispensing of buprenorphine, extended-release naltrexone, and naloxone during the COVID-19 pandemic by age and sex - United States, March 2019 - December 2020. *Drug and alcohol dependence.* 2022;232:109192.
132. O'Donoghue AL, Biswas N, Dechen T, et al. Trends in filled naloxone prescriptions before and during the COVID-19 pandemic in the United States. *JAMA Health Forum.* 2021;2(5):e210393.
133. NIDA. Overview. National Institute on Drug Abuse website. https://nida.nih.gov/publications/research-reports/medications-to-treat-opioid-addiction/overview. December 2, 2021 Accessed November 17, 2022.
134. Substance Abuse and Mental Health Services Administration. *Medications for Opioid Use Disorder Treatment Improvement Protocol 63. Publication No. PEP21-02-01-002.* Rockville, MD: Substance Abuse and Mental Health Services Administration;2021.
135. American Society of Addiction Medicine. *National Practice Guideline for the use of medications in the treatment of addiction involving opioid use.* 2015.
136. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. Prescribing opioids for pain - The new CDC clinical practice guideline. *N Engl J Med.* 2022;387(22):2011-2013.
137. U.S. Department of Health and Human Services. HHS guide to clinicians on appropriate dosage reduction of discontinuation of long-term opioid analgesics. 2019; https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf. Accessed Nov 17, 2022.
138. Mackey K, Anderson J, Bourne D, Chen E, Peterson K. Benefits and harms of long-term opioid dose reduction or discontinuation in patients with chronic pain: A rapid review. *J Gen Intern Med.* 2020;35(Suppl 3):935-944.
139. McPherson S, Lederhos Smith C, Dobscha SK, et al. Changes in pain intensity after discontinuation of long-term opioid therapy for chronic noncancer pain. *Pain.* 2018;159(10):2097-2104.
140. Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan YF. Prescription opioid taper support for outpatients with chronic pain: A randomized controlled trial. *J Pain.* 2017;18(3):308-318.

141. Food and Drug Administration. FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering. 2019; https://www.fda.gov/Drugs/DrugSafety/ucm635038.htm. Accessed April 19 2019.
142. Coffin PO, Barreveld AM. Inherited patients taking opioids for chronic pain - Considerations for primary care. *N Engl J Med.* 2022;386(7):611-613.
143. Powell VD, Rosenberg JM, Yaganti A, et al. Evaluation of buprenorphine rotation in patients receiving long-term opioids for chronic pain: A aystematic review. *JAMA Netw Open.* 2021;4(9):e2124152.
144. Spreen LA, Dittmar EN, Quirk KC, Smith MA. Buprenorphine initiation strategies for opioid use disorder and pain management: A systematic review. *Pharmacotherapy.* 2022;42(5):411-427.
145. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. *Osteoarthritis Cartilage.* 2005;13(1):20-27.
146. Allen KD, Golightly YM. State of the evidence. *Curr Opin Rheumatol.* 2015;27(3):276-283.
147. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Ann Rheum Dis.* 2014;73(9):1659-1664.
148. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev.* 2014;22(4).
149. Hurley M, Dickson K, Hallett R, et al. Exercise interventions and patient beliefs for people with hip, knee or hip and knee osteoarthritis: a mixed methods review. *Cochrane Database Syst Rev.* 2018;4:CD010842.
150. Gohir SA, Eek F, Kelly A, Abhishek A, Valdes AM. Effectiveness of internet-based exercises aimed at treating knee osteoarthritis: The iBEAT-OA randomized clinical trial. *JAMA Netw Open.* 2021;4(2):e210012.
151. Nelligan RK, Hinman RS, Kasza J, Crofts SJC, Bennell KL. Effects of a self-directed web-based strengthening exercise and physical activity program supported by automated text messages for people with knee osteoarthritis: A randomized clinical trial. *JAMA Intern Med.* 2021;181(6):776-785.
152. Hall A, Copsey B, Richmond H, et al. Effectiveness of tai chi for chronic musculoskeletal pain conditions: Updated systematic review and meta-analysis. *Phys Ther.* 2017;97(2):227-238.
153. Wang C, Schmid CH, Iversen MD, et al. Comparative effectiveness of tai chi versus physical therapy for knee osteoarthritis: A randomized trial. *Ann Intern Med.* 2016;165(2):77-86.
154. Messier SP, Resnik AE, Beavers DP, et al. Intentional weight loss in overweight and obese patients with knee osteoarthritis: Is more better? *Arthritis Care Res (Hoboken).* 2018;70(11):1569-1575.
155. Messier SP, Newman JJ, Scarlett MJ, et al. Changes in body weight and knee pain in adults with knee osteoarthritis three-and-a-half years after completing diet and exercise interventions: Follow-up study for a single-blind, single-center, randomized controlled trial. *Arthritis Care Res (Hoboken).* 2022;74(4):607-616.
156. Dowsey MM, Brown WA, Cochrane A, Burton PR, Liew D, Choong PF. Effect of bariatric surgery on risk of complications after total knee arthroplasty: A randomized clinical trial. *JAMA Netw Open.* 2022;5(4):e226722.
157. Cheung C, Park J, Wyman JF. Effects of yoga on symptoms, physical function, and psychosocial outcomes in adults with osteoarthritis: A focused review. *Am J Phys Med Rehabil.* 2016;95(2):139-151.
158. Park J, McCaffrey R, Newman D, Liehr P, Ouslander JG. A pilot randomized controlled trial of the effects of chair yoga on pain and physical function among community-dwelling older adults with lower extremity osteoarthritis. *J Am Geriatr Soc.* 2017;65(3):592-597.
159. Manheimer E, Cheng K, Wieland LS, et al. Acupuncture for hip osteoarthritis. *Cochrane Database Syst Rev.* 2018;5:CD013010.
160. White P, Bishop FL, Prescott P, Scott C, Little P, Lewith G. Practice, practitioner, or placebo? A multifactorial, mixed-methods randomized controlled trial of acupuncture. *Pain.* 2012;153(2):455-462.
161. Perlman A, Fogerite SG, Glass O, et al. Efficacy and safety of massage for osteoarthritis of the knee: a randomized clinical trial. *J Gen Intern Med.* 2019;34(3):379-386.
162. Nelson NL, Churilla JR. Massage therapy for pain and function in patients with arthritis: A systematic review of randomized controlled trials. *Am J Phys Med Rehabil.* 2017;96(9):665-672.

163. Helminen EE, Sinikallio SH, Valjakka AL, Väisänen-Rouvali RH, Arokoski JP. Effectiveness of a cognitive-behavioural group intervention for knee osteoarthritis pain: a randomized controlled trial. *Clin Rehabil.* 2015;29(9):868-881.
164. Hausmann LRM, Youk A, Kwoh CK, et al. Effect of a positive psychological intervention on pain and functional difficulty among adults with osteoarthritis: A randomized clinical trial. *JAMA Netw Open.* 2018;1(5):e182533.
165. Chodosh J, Morton SC, Mojica W, et al. Meta-analysis: chronic disease self-management programs for older adults. *Ann Intern Med.* 2005;143(6):427-438.
166. Warsi A, LaValley MP, Wang PS, Avorn J, Solomon DH. Arthritis self-management education programs: a meta-analysis of the effect on pain and disability. *Arthritis Rheum.* 2003;48(8):2207-2213.
167. Forster A, Young J, Lambley R, Langhorne P. Medical day hospital care for the elderly versus alternative forms of care. *Cochrane Database Syst Rev.* 2008;8(4).
168. Canadian Agency for Drugs and Technologies in Health. *Home transcutaneous electrical nerve stimulation for chronic pain: A review of the clinical effectiveness.* Ottawa Ontario 2016.
169. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus placebo for knee and hip osteoarthritis. *Cochrane Database Syst Rev.* 2019;2:CD013273.
170. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis.* 2004;63(8):901-907.
171. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet.* 2017;390(10090):e21-e33.
172. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 2017;5:CD008609.
173. Underwood M, Ashby D, Cross P, et al. Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. *BMJ.* 2008;336(7636):138-142.
174. Wang ZY, Shi SY, Li SJ, et al. Efficacy and safety of duloxetine on osteoarthritis knee pain: A meta-analysis of randomized controlled trials. *Pain Med.* 2015;16(7):1373-1385.
175. Sullivan M, Bentley S, Fan MY, Gardner G. A single-blind placebo run-in study of venlafaxine XR for activity-limiting osteoarthritis pain. *Pain Med.* 2009;10(5):806-812.
176. Ohtori S, Inoue G, Orita S, et al. Efficacy of combination of meloxicam and pregabalin for pain in knee osteoarthritis. *Yonsei Med J.* 2013;54(5):1253-1258.
177. Kivitz A, Fairfax M, Sheldon EA, et al. Comparison of the effectiveness and tolerability of lidocaine patch 5% versus celecoxib for osteoarthritis-related knee pain: post hoc analysis of a 12 week, prospective, randomized, active-controlled, open-label, parallel-group trial in adults. *Clin Ther.* 2008;30(12):2366-2377.
178. Toupin April K, Bisaillon J, Welch V, et al. Tramadol for osteoarthritis. *Cochrane Database Syst Rev.* 2019;5(5):Cd005522.
179. da Costa BR, Nuesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev.* 2014;17(9).
180. AHRQ. *Treatment of osteoarthritis of the knee: an update review #19.* Rockville MD 2017.
181. Guedes V, Castro JP, Brito I. Topical capsaicin for pain in osteoarthritis: A literature review. *Reumatol Clin.* 2016;26(16):30089-30084.
182. Persson MSM, Stocks J, Walsh DA, Doherty M, Zhang W. The relative efficacy of topical non-steroidal anti-inflammatory drugs and capsaicin in osteoarthritis: a network meta-analysis of randomised controlled trials. *Osteoarthritis Cartilage.* 2018;26(12):1575-1582.
183. Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for osteoarthritis of the knee: A systematic review of the evidence. *J Bone Joint Surg Am.* 2015;97(24):2047-2060.
184. Altman RD, Akermark C, Beaulieu AD, Schnitzer T, Durolane International Study G. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *Osteoarthritis Cartilage.* 2004;12(8):642-649.
185. Arden NK, Akermark C, Andersson M, Todman MG, Altman RD. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. *Curr Med Res Opin.* 2014;30(2):279-286.
186. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet.* 2019;393(10182):1745-1759.

187. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of P. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2017;166(7):514-530.
188. Last AR, Hulbert K. Chronic low back pain: evaluation and management. *Am Fam Physician.* 2009;79(12):1067-1074.
189. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med.* 2007;147(7):478-491.
190. Ballantyne JC. Opioid therapy in chronic pain. *Phys Med Rehabil Clin N Am.* 2015;26(2):201-218.
191. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic therapies for low back pain: A systematic review for an American College of Physicians clinical practice guideline. *Ann Intern Med.* 2017;166(7):493-505.
192. Fritz JM, Lane E, McFadden M, et al. Physical therapy referral from primary care for acute back pain with sciatica : A randomized controlled trial. *Ann Intern Med.* 2021;174(1):8-17.
193. Hall AM, Maher CG, Lam P, Ferreira M, Latimer J. Tai chi exercise for treatment of pain and disability in people with persistent low back pain: a randomized controlled trial. *Arthritis Care Res (Hoboken).* 2011;63(11):1576-1583.
194. Weifen W, et al. Effectivenes of tai chi practice for non-specific chronic low back pain on retired athletes: a randomized controlled study. *J Musculoskeletal Pain.* 2013;21(1):37-45.
195. Khoueir P, Black MH, Crookes PF, Kaufman HS, Katkhouda N, Wang MY. Prospective assessment of axial back pain symptoms before and after bariatric weight reduction surgery. *Spine J.* 2009;9(6):454-463.
196. Roffey DM, Ashdown LC, Dornan HD, et al. Pilot evaluation of a multidisciplinary, medically supervised, nonsurgical weight loss program on the severity of low back pain in obese adults. *Spine J.* 2011;11(3):197-204.
197. Robson EK, Hodder RK, Kamper SJ, et al. Effectiveness of weight-loss interventions for reducing pain and disability in people with common musculoskeletal disorders: A systematic review with meta-analysis. *J Orthop Sports Phys Ther.* 2020;50(6):319-333.
198. Saper RB, Lemaster C, Delitto A, et al. Yoga, physical therapy, or education for chronic low back pain: A randomized noninferiority trial. *Ann Intern Med.* 2017;167(2):85-94.
199. Bussing A, Ostermann T, Ludtke R, Michalsen A. Effects of yoga interventions on pain and pain-associated disability: a meta-analysis. *J Pain.* 2012;13(1):1-9.
200. Wieland LS, Skoetz N, Pilkington K, Vempati R, D'Adamo CR, Berman BM. Yoga treatment for chronic non-specific low back pain. *Cochrane Database Syst Rev.* 2017;12(1).
201. Zhu F, Zhang M, Wang D, Hong Q, Zeng C, Chen W. Yoga compared to non-exercise or physical therapy exercise on pain, disability, and quality of life for patients with chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. *PLoS One.* 2020;15(9):e0238544.
202. Mu J, Furlan AD, Lam WY, Hsu MY, Ning Z, Lao L. Acupuncture for chronic nonspecific low back pain. *Cochrane Database Syst Rev.* 2020;12(12):Cd013814.
203. Furlan AD, Giraldo M, Baskwill A, Irvin E, Imamura M. Massage for low-back pain. *Cochrane Database Syst Rev.* 2015;1(9).
204. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. *N Engl J Med.* 1990;322(23):1627-1634.
205. Caldas VVA, Maciel DG, Cerqueira MS, et al. Effect of pain education, cryotherapy, and transcutaneous electrical nerve stimulation on the pain, functional capacity, and quality of life in patients with nonspecific chronic low back pain: A single-blind randomized controlled trial. *Am J Phys Med Rehabil.* 2021;100(3):243-249.
206. Petrucci G, Papalia GF, Russo F, et al. Psychological approaches for the integrative care of chronic low back pain: A systematic review and metanalysis. *Int J Environ Res Public Health.* 2021;19(1):60.
207. Lamb SE, Hansen Z, Lall R, et al. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. *Lancet.* 2010;375(9718):916-923.
208. Burns JW, Jensen MP, Thorn B, et al. Cognitive therapy, mindfulness-based stress reduction, and behavior therapy for the treatment of chronic pain: randomized controlled trial. *Pain.* 2022;163(2):376-389.

209. Cherkin DC, Sherman KJ, Balderson BH, et al. Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: A randomized clinical trial. *JAMA.* 2016;315(12):1240-1249.
210. Zeidan F, Salomons T, Farris SR, et al. Neural mechanisms supporting the relationship between dispositional mindfulness and pain. *Pain.* 2018;159(12):2477-2485.
211. Foster G, Taylor SJ, Eldridge SE, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database Syst Rev.* 2007;17(4).
212. Rubinstein SM, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. *BMJ.* 2019;364:l689.
213. Foster NE, Anema JR, Cherkin D, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *Lancet.* 2018;391(10137):2368-2383.
214. Skelly AC CR, Dettori JR, et al. In: Noninvasive nonpharmacological treatment for chronic pain: A systematic review update. Rockville (MD):2020.
215. Hickey RF. Chronic low back pain: a comparison of diflunisal with paracetamol. *N Z Med J.* 1982;95(707):312-314.
216. Stein D, Peri T, Edelstein E, Elizur A, Floman Y. The efficacy of amitriptyline and acetaminophen in the management of acute low back pain. *Psychosomatics.* 1996;37(1):63-70.
217. Davies RA, Maher CG, Hancock MJ. A systematic review of paracetamol for non-specific low back pain. *Eur Spine J.* 2008;17(11):1423-1430.
218. Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Abdel Shaheed C, Maher CG. Paracetamol for low back pain. *Cochrane Database Syst Rev.* 2016(6):CD012230.
219. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev.* 2016;10(2).
220. Kolber MR, Ton J, Thomas B, et al. PEER systematic review of randomized controlled trials: Management of chronic low back pain in primary care. *Can Fam Physician.* 2021;67(1):e20-e30.
221. Flurbiprofen tape for treatment of chronic low back pain (LBP). Oct 6, 2016; https://clinicaltrials.gov/ct2/show/results/NCT00759330?view=results. Accessed Oct 8, 2022.
222. Chou R, Deyo R, Friedly J, et al. Systemic pharmacologic therapies for low back pain: A systematic review for an American College of Physicians clinical practice guideline. *Ann Intern Med.* 2017;166(7):480-492.
223. Skljarevski V, Zhang S, Desaiah D, et al. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. *J Pain.* 2010;11(12):1282-1290.
224. Skljarevski V, Desaiah D, Liu-Seifert H, et al. Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine (Phila Pa 1976).* 2010;35(13):E578-585.
225. Skljarevski V, Ossanna M, Liu-Seifert H, et al. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. *Eur J Neurol.* 2009;16(9):1041-1048.
226. Ferreira GE, McLachlan AJ, Lin CC, et al. Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analysis. *BMJ.* 2021;372:m4825.
227. Enke O, New HA, New CH, et al. Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis. *Cmaj.* 2018;190(26):E786-e793.
228. Santana JA, Klass S, Felix ER. The efficacy, effectiveness and safety of 5% transdermal lidocaine patch for chronic low back pain: A narrative review. *Pm r.* 2020;12(12):1260-1267.
229. Boya C, Bansal D, Kanakagiri S, Ghai B. Efficacy and safety of opioid wnalgesics for the management of chronic low back pain: An evidence from bayesian network meta-analysis. *Pain physician.* 2021;24(1):73-82.
230. Cashin AG, Folly T, Bagg MK, et al. Efficacy, acceptability, and safety of muscle relaxants for adults with non-specific low back pain: systematic review and meta-analysis. *BMJ.* 2021;374:n1446.
231. Rivera CE. Lumbar epidural steroid injections. *Phys Med Rehabil Clin N Am.* 2018;29(1):73-92.
232. Staal JB, de Bie R, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev.* 2008(3):CD001824.
233. Fairbank J, Frost H, Wilson-MacDonald J, Yu LM, Barker K, Collins R. Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. *BMJ.* 2005;330(7502):23.
234. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care.* 2019;42(Suppl. 1):S124-138.

235. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. *Lancet Neurol.* 2012;11(6):521-534.
236. Draznin B, Aroda VR, Bakris G, et al. 12. Retinopathy, neuropathy, and foot Care: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022;45(Suppl 1):S185-s194.
237. Ahn S, Song R. Effects of Tai Chi Exercise on glucose control, neuropathy scores, balance, and quality of life in patients with type 2 diabetes and neuropathy. *J Altern Complement Med.* 2012;18(12):1172-1178.
238. Abuaisha BB, Costanzi JB, Boulton AJ. Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. *Diabetes Res Clin Pract.* 1998;39(2):115-121.
239. Gok Metin Z, Arikan Donmez A, Izgu N, Ozdemir L, Arslan IE. Aromatherapy massage for neuropathic pain and quality of life in diabetic patients. *J Nurs Scholarsh.* 2017;49(4):379-388.
240. Garrow AP, Xing M, Vere J, Verrall B, Wang L, Jude EB. Role of acupuncture in the management of diabetic painful neuropathy (DPN): a pilot RCT. *Acupunct Med.* 2014;32(3):242-249.
241. Gibson W, Wand BM, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst Rev.* 2017;9(9):Cd011976.
242. Jin DM, Xu Y, Geng DF, Yan TB. Effect of transcutaneous electrical nerve stimulation on symptomatic diabetic peripheral neuropathy: a meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract.* 2010;89(1):10-15.
243. Gossrau G, Wahner M, Kuschke M, et al. Microcurrent transcutaneous electric nerve stimulation in painful diabetic neuropathy: a randomized placebo-controlled study. *Pain Med.* 2011;12(6):953-960.
244. Otis JD, Sanderson K, Hardway C, Pincus M, Tun C, Soumekh S. A randomized controlled pilot study of a cognitive-behavioral therapy approach for painful diabetic peripheral neuropathy. *J Pain.* 2013;14(5):475-482.
245. Teixeira E. The effect of mindfulness meditation on painful diabetic peripheral neuropathy in adults older than 50 years. *Holist Nurs Pract.* 2010;24(5):277-283.
246. Price R, Smith D, Franklin G, et al. Oral and topical treatment of painful diabetic polyneuropathy: Practice guideline update summary. *Report of the AAN Guideline Subcommittee.* 2022;98(1):31-43.
247. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. *Ann Intern Med.* 2014;161(9):639-649.
248. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain.* 2005;116(1-2):109-118.
249. Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. *Neurology.* 2017;88(20):1958-1967.
250. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. *Cochrane Database Syst Rev.* 2019;1:CD007076.
251. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. *Curr Med Res Opin.* 2009;25(7):1663-1676.
252. Mucke M, Phillips T, Radbruch L, Petzke F, Hauser W. Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2018;3:CD012182.
253. Allan GM, Finley CR, Ton J, et al. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. *Can Fam Physician.* 2018;64(2):e78-e94.
254. Sommer C, Klose P, Welsch P, Petzke F, Häuser W. Opioids for chronic non-cancer neuropathic pain. An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration. *Eur J Pain.* 2020;24(1):3-18.
255. Simpson RW, Wlodarczyk JH. Transdermal buprenorphine relieves neuropathic pain: A randomized, double-blind, parallel-group, placebo-controlled trial in diabetic peripheral neuropathic pain. *Diabetes Care.* 2016;39(9):1493-1500.
256. Mendell JR, Sahenk Z. Clinical practice. Painful sensory neuropathy. *N Engl J Med.* 2003;348(13):1243-1255.
257. Treatment of painful diabetic neuropathy with topical capsaicin: A multicenter, double-blind, vehicle-controlled study. *Arch Intern Med.* 1991;151(11):2225-2229.
258. Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. *Diabetes Care.* 1992;15(1):8-14.

259. Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. *Lancet.* 2022;400(10353):680-690.
260. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: A position statement by the American Diabetes Association. *Diabetes Care.* 2017;40(1):136-154.
261. Dworkin RH, O'Connor AB, Kent J, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. *Pain.* 2013;154(11):2249-2261.
262. Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. *Lancet.* 1996;348(9043):1698-1701.
263. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33(2):160-172.
264. American College of Rheumatology. Fibromyalgia treatment. 2019; https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Fibromyalgia. Accessed May 24 2019.
265. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis.* 2017;76(2):318-328.
266. Jones KD, Adams D, Winters-Stone K, Burckhardt CS. A comprehensive review of 46 exercise treatment studies in fibromyalgia (1988-2005). *Health Qual Life Outcomes.* 2006;4:67.
267. Andrade A, de Azevedo Klumb Steffens R, Sieczkowska SM, Peyre Tartaruga LA, Torres Vilarino G. A systematic review of the effects of strength training in patients with fibromyalgia: clinical outcomes and design considerations. *Adv Rheumatol.* 2018;58(1):36.
268. Bidonde J, Busch AJ, Schachter CL, et al. Aerobic exercise training for adults with fibromyalgia. *Cochrane Database Syst Rev.* 2017;21(6).
269. Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. *Cochrane Database Syst Rev.* 2013;20(12).
270. Wang C, Schmid CH, Rones R, et al. A randomized trial of tai chi for fibromyalgia. *N Engl J Med.* 2010;363(8):743-754.
271. D'Onghia M, Ciaffi J, Lisi L, et al. Fibromyalgia and obesity: A comprehensive systematic review and meta-analysis. *Semin Arthritis Rheum.* 2021;51(2):409-424.
272. Shapiro JR, Anderson DA, Danoff-Burg S. A pilot study of the effects of behavioral weight loss treatment on fibromyalgia symptoms. *J Psychosom Res.* 2005;59(5):275-282.
273. Cramer H, Lauche R, Langhorst J, Dobos G. Yoga for rheumatic diseases: a systematic review. *Rheumatology (Oxford).* 2013;52(11):2025-2030.
274. Carson JW, Carson KM, Jones KD, Bennett RM, Wright CL, Mist SD. A pilot randomized controlled trial of the Yoga of Awareness program in the management of fibromyalgia. *Pain.* 2010;151(2):530-539.
275. Ide MR, Laurindo IMM, Rodrigues-Junior AL, Tanaka C. Effect of aquatic respiratory exercise-based program in patients with fibromyalgia. *Int J Rheum Dis.* 2008;11(2):131-140.
276. Deare JC, Zheng Z, Xue CC, et al. Acupuncture for treating fibromyalgia. *Cochrane Database Syst Rev.* 2013;31(5).
277. Yuan SL, Matsutani LA, Marques AP. Effectiveness of different styles of massage therapy in fibromyalgia: a systematic review and meta-analysis. *Man Ther.* 2015;20(2):257-264.
278. Kundakci B, Kaur J, Goh SL, et al. Efficacy of nonpharmacological interventions for individual features of fibromyalgia: a systematic review and meta-analysis of randomised controlled trials. *Pain.* 2022;163(8):1432-1445.
279. Salazar AP, Stein C, Marchese RR, Plentz RD, Pagnussat AS. Electric stimulation for pain relief in patients with fibromyalgia: A systematic review and meta-analysis of randomized controlled trials. *Pain physician.* 2017;20(2):15-25.
280. Johnson MI, Paley CA, Jones G, Mulvey MR, Wittkopf PG. Efficacy and safety of transcutaneous electrical nerve stimulation (TENS) for acute and chronic pain in adults: a systematic review and meta-analysis of 381 studies (the meta-TENS study). *BMJ Open.* 2022;12(2):e051073.
281. Bernardy K, Klose P, Busch AJ, Choy EH, Hauser W. Cognitive behavioural therapies for fibromyalgia. *Cochrane Database Syst Rev.* 2013;10(9).
282. Derry S, Wiffen PJ, Hauser W, et al. Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. *Cochrane Database Syst Rev.* 2017;27(3).

283. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev.* 2014;1:CD007115.
284. Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. *Cochrane Database Syst Rev.* 2015(10):CD008244.
285. Welsch P, Uceyler N, Klose P, Walitt B, Hauser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev.* 2018;2:CD010292.
286. Hauser W, Petzke F, Uceyler N, Sommer C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. *Rheumatology.* 2011;50(3):532-543.
287. Walitt B, Urrutia G, Nishishinya MB, Cantrell SE, Hauser W. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. *Cochrane Database Syst Rev.* 2015;5(6).
288. Uceyler N, Sommer C, Walitt B, Hauser W. Anticonvulsants for fibromyalgia. *Cochrane Database Syst Rev.* 2013;16(10).
289. Gilron I, Chaparro LE, Tu D, et al. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. *Pain.* 2016;157(7):1532-1540.
290. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum.* 2007;56(4):1336-1344.
291. Farag HM, Yunusa I, Goswami H, Sultan I, Doucette JA, Eguale T. Comparison of amitriptyline and US Food and Drug Administration-approved treatments for fibromyalgia: A systematic review and network meta-analysis. *JAMA Netw Open.* 2022;5(5):e2212939.
292. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain.* 2008;9(2):164-173.
293. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg.* 2010;110(2):604-610.
294. van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. *Pain.* 2019;160(4):860-869.
295. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *Am J Med.* 2003;114(7):537-545.
296. Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for pain in fibromyalgia in adults. *Cochrane Database Syst Rev.* 2016;1(9).
297. Peng X, Robinson RL, Mease P, et al. Long-term evaluation of opioid treatment in fibromyalgia. *Clin J Pain.* 2015;31(1):7-13.
298. Franklin GM, American Academy of N. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. *Neurology.* 2014;83(14):1277-1284.
299. Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. *Cochrane Database of Systematic Reviews.* 2017(1).
300. McQuay HJ, Tramèr M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain.* 1996;68(2-3):217-227.
301. Lexi-Drugs. Hudson, OH: Lexicomp, 2019. http://online.lexi.com/. Accessed February 14, 2023.
302. Tauben D, Stacey BR. Pharmacologic management of chronic non-cancer pain in adults. 2023; https://www.uptodate.com/contents/pharmacologic-management-of-chronic-non-cancer-pain-in-adults. Accessed February 23, 2023.

Continuing education

CMEO evaluation links

To complete your activity posttest, evaluation and print your certificate or statement of credit immediately, please visit:

www.cmeoutfitters.com/ah008p/

Credit request forms, and activity evaluations must be completed online (requires free account activation), and participants can print their certificate or statement of credit immediately. This website supports all browsers except Internet Explorer for Mac. For complete technical requirements and privacy policy, visit www.cmeoutfitters.com/privacy-and-confidentiality-policy

Questions about this activity?

Alosa Health,
419 Boylston Street, 6th Floor,
Boston, MA 02116
Email: cme@alosahealth.org
Fax: 857-350-9155