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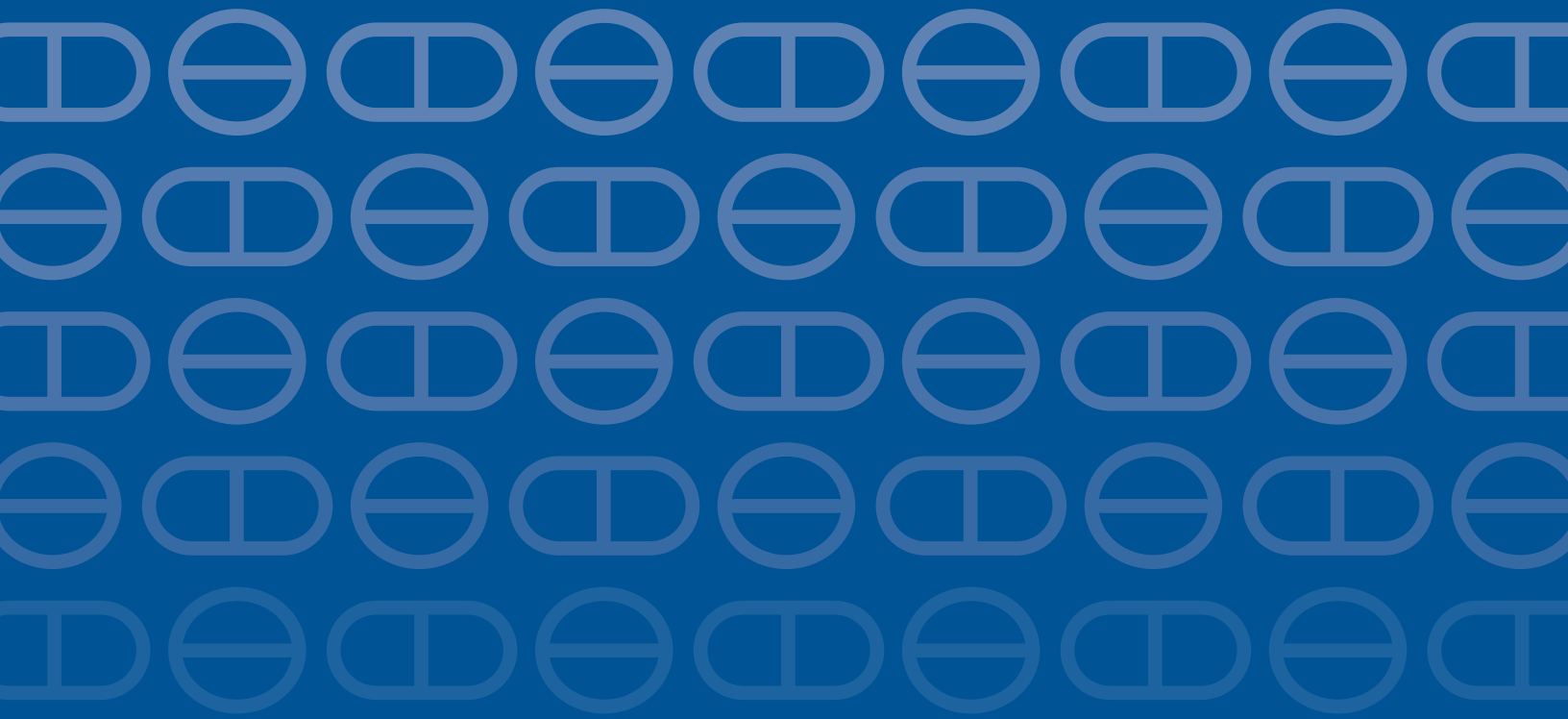
Managing chronic pain in the elderly



Managing chronic pain in the elderly

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Alosa Health

Managing chronic pain in the elderly

Accreditation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Harvard Medical School and Alosa Health. The Harvard Medical School is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.50 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Activity Overview:

The primary goal of this educational program is to address the growing problem of pain among elderly patients. Achieving functional goals that do not pose harm from side effects, encourage addiction, or contribute to drug abuse is challenging in this patient population because of issues such as altered pharmacodynamics/pharmacokinetics with increasing age, polypharmacy, potential cognitive deficits, heightened risk of fractures from falls, and organ-specific vulnerabilities.

The education program has several components, which include:

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

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

Target Audience:

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

Learning Objectives:

After completing this activity, participants will be able to:

- Set clear functional goals and realistic expectations as part of a comprehensive pain management plan.
- Optimize pain management strategy by utilizing multiple modalities, including non-pharmacologic and non-opioid pharmacologic options.

- When prescribing opioids, assess the risks and benefits of therapy, discontinuing or tapering opioids in the absence of meaningful benefit or significant harms.
- Recommend naloxone for patients with risk factors for possible overdose.
- Taper and discontinue opioids whenever possible, particularly in patients who have severe side effects or exhibit problematic behaviors.
- Refer or provide treatment for patients with suspected opioid use disorder or problematic behaviors to a specialist for medication assisted treatment.

Disclosure Policy:

Harvard Medical School has long held the standard that its continuing medical education courses be free of commercial bias.

In accord with the disclosure policy of the Medical School as well as standards set forth by the Accreditation Council for Continuing Medical Education, course planners, speakers, and content reviewers have been asked to disclose any relevant relationship they, or their spouse or partner, have to companies producing, marketing, re-selling or distributing health care goods or services consumed by, or used on, patients. In addition, faculty have been asked to list any off-label uses of pharmaceuticals and/or devices for investigational or non-FDA approved purposes that they plan to discuss. Such disclosure is not intended to suggest or condone bias in any presentation, but is elicited to provide the course director and participants with information that might be of potential importance to their evaluation of a given presentation.

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Media used:

Printed educational material.

Instructions for Participation and Credit:

There are no fees to participate in this activity. To receive credit, participants must (1) read the statements on target audience, learning objectives, and disclosures, (2) study the educational activity, and (3) complete the post−test and activity evaluation. To receive *AMA PRA Category 1 Credit*™, participants must receive a minimum score of 70% on the post−test.

Tests and evaluations should be submitted to Alosa Health via email, mail or fax.

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Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

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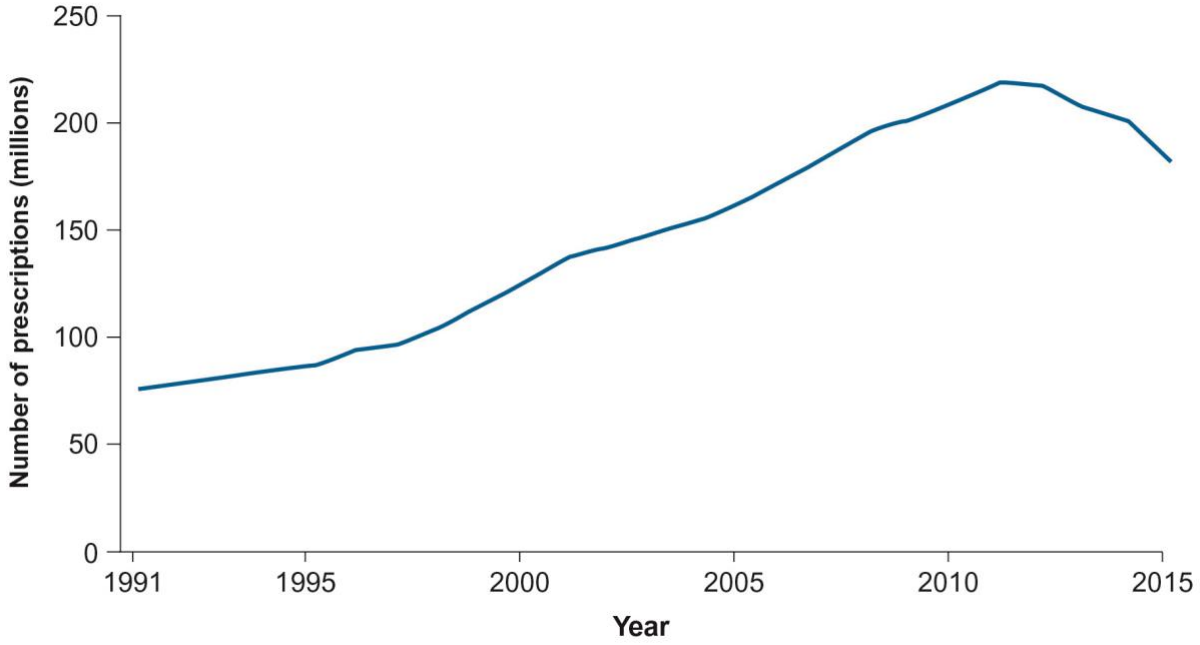
Introduction

Millions of Americans suffer from chronic debilitating pain. In a recent national estimate, about 126 million adults reported at least some pain in the previous three months, with 25 million of those adults reporting daily pain that often affects general health and increases health care utilization.[1] In 2010, the national total cost attributed to pain ranged from $560 to $635 billion, exceeding the costs attributed to heart disease and cancer combined. Direct health care costs, such as medications and office visits, ranged from $261 to $300 billion, and lost productivity due to pain ranged from $299 to $335 billion.[2]

Chronic pain is one of the most frequent reasons for office visits. For example, pain symptoms due to osteoarthritis and low back pain account for 21 million and 16 million office visits per year, respectively.[3,4] Neuropathic or complex pain syndromes such as diabetic neuropathy and fibromyalgia are also common conditions.

Because the effectiveness of non-drug and drug management options varies, depending on the chronic pain condition being treated, it is important to tailor treatment plans based on the clinical condition(s) of the patient as well as the best available evidence. In contrast, the practice of treating painful chronic conditions with opioids increased sharply over the past two decades. This change was driven largely by a campaign that minimized opioid risks, especially the risk of addiction, and exaggerated benefits of long-term use. While Figure 1 shows recent declines, the current volume of opioid prescribing remains nearly three times what it was in the late 1990s.[5]

Figure 1: Opioid prescriptions dispensed by US retail pharmacies[5]



This surge in opioid prescribing also occurred for older patients. Nearly one in three Medicare beneficiaries receive a prescription for oxycodone sustained release (OxyContin), hydrocodone-acetaminophen, oxycodone-acetaminophen, or fentanyl.[6] Medicare spending under Part D for these opioid pain medications

has grown substantially as well, exceeding $4 billion in 2015.[6] As we continue to learn more about the harms and risks associated with chronic opioid use, a shift toward alternative, evidence-based pain management options is needed.

This document discusses the management of chronic pain, focusing on four common pain syndromes which account for the majority of chronic pain in older adults: osteoarthritis, chronic low back pain, diabetic neuropathy, and fibromyalgia. It reviews evidence for non-opioid therapies, including non-drug and non-opioid drug options, as well as current evidence regarding opioid efficacy, harms, and overdose prevention with naloxone, and identifying patients with opioid use disorder for treatment referral.

Describing Pain

Acute versus chronic pain

Pain is typically classified as acute or chronic. Acute pain usually occurs suddenly and is caused by damage to tissues such as bone, muscle, or organs. Acute pain typically resolves or disappears over time with healing of the initial cause. Chronic pain lasts beyond the time of normal tissue healing or longer than 90 days.

Pain mechanisms

Determining the most plausible pain mechanism is crucial during clinical assessments and drives the selection of the most effective drug and non-drug treatment options. The types or mechanisms of pain include nociceptive, neuropathic, or mixed.

Nociceptive pain is caused by the normal activation of nociceptors and is a protective response to tissue damage, irritation, or inflammation. The pain is typically localized, constant, characterized by an aching or throbbing quality, and may occur in osteoarthritis (OA) or trauma (e.g., ankle sprain, hip fracture, or after surgery).

Neuropathic pain results from an injury to the nervous system and does not start abruptly or resolve quickly. This type of pain results from abnormal neuronal firing in the absence of active tissue damage and may be continuous or episodic. Neuropathic pain varies widely in its presentation but is usually characterized by shooting, burning, or lancinating qualities. Paresthesia (pins and needles) and loss of sensation may also occur. Examples of neuropathic pain include diabetic neuropathy, post-herpetic neuralgia, and trigeminal neuralgia.

Other pain syndromes include those that are complex and without well-understood etiology, such as fibromyalgia, non-anatomic lower back pain, phantom limb pain, and migraine.

Assessing pain

Take a history

Assessing pain is critical to effective pain management interventions. Both patient and caregiver reports of pain should be the starting points. A comprehensive pain assessment should also include evaluation of the pain quality, duration, location, aggravating or alleviating factors, and any previous treatments and their efficacy. Assessing the impact of pain on functional status and sleep and screening for any mental health conditions (e.g., depression, anxiety, and memory issues) may be useful information for pain management.[7] Depression in older patients sometimes presents with somatic complaints of pain. Pain complaints may resolve when the underlying depression is treated. Screening for comorbid depression (using the Patient Health Questionnaire-9) and anxiety (using General Anxiety Disorder) can be done using online tools available at: depts.washington.edu/anesth/education/pain/index.shtml.

Assessment tools

Many tools have been developed to document and assess pain. Initial approaches to assessing pain severity use a single visual analog scale (VAS) rating pain from 0 (no pain) to 10 (worst pain you can imagine). Multidimensional tools, such as those descried below, include questions relating to quality of life, participation in daily activities, and even pain maps, and provide a more comprehensive approach to assessing pain and response to treatment. While these tools quantify pain, the scores should be used in combination with functional goals to assess response to treatment. The selection of a pain assessment tool must balance the comprehensiveness of the assessment that is required with the usability of the tool in a real-world practice setting.

Brief pain inventory

The Brief Pain Inventory (BPI) is utilized frequently in randomized controlled trials to assess pain. Specifically developed for patients with chronic pain, the BPI more fully captures the impact of pain on patients' function and quality of life than simple 0-10 scales.[8] By including a pain map, the BPI allows tracking of the location of pain through the course of management. The BPI is self-administered but time-consuming, limiting its role in clinical practice. See Appendix I for a sample of the BPI.

PEG scale

Pain average, interference with Enjoyment of life, and interference with General activity (PEG) is a three-item scale based on the BPI. A 0 to 10 scale assesses average pain (0=no pain; 10=pain as bad as you can imagine), enjoyment of life, and general activity (0=does not interfere; 10=completely interferes). PEG scale can be self-administered or done by the clinician with its brevity lending it well to clinical practice.[9]

Figure 2: PEG scale[9]

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

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

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

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

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

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Assessing pain in the cognitively impaired

Although patients with mild to moderate dementia can report their pain and its location, those with severe dementia are often unable to communicate their pain experience or request medication. In these patients, physicians need to observe pain behaviors, including facial expressions, verbal cues, body movements, changes in interpersonal interactions, activity patterns, and mental status. Caregiver observations and reports are critical to appropriate assessment and management of chronic pain conditions.[10]

Overview of options for managing pain

For many years management of pain focused on pharmacologic interventions. While still an important consideration for some patients, non-drug options have become central to the effective management of chronic pain. The following are descriptions of common non-drug and drug options for chronic pain management.

Non-drug approaches

There are several non-drug interventions for coping with many pain syndromes such as OA, chronic low back pain, diabetic neuropathy, and fibromyalgia. Commonly used interventions across these syndromes include exercise, physical therapy, tai chi, yoga, weight loss, acupuncture, massage, cognitive behavioral therapy, mindfulness meditation, and self-management.

Movement-based options

Movement therapies may help patients suffering from chronic pain that occurs in OA, low-back pain, diabetic neuropathy, and fibromyalgia. Some health professionals believe that movement can help reduce pain by

helping patients become active again. Exercise includes muscle-strengthening, functional training, stretching and aerobic fitness (e.g., walking, aquatics). Studied exercise programs typically occur one to three times a week for a total of 60-180 minutes per week.[11-13]

Additional evidence-based movement based options include:

- **Physical therapy**: an individualized exercise program supervised by a licensed physical therapist, rather than self-directed or group exercises. It can include resistance, aerobic, balance, and flexibility exercises as well as elements of massage, manipulation, and even transcutaneous electrical nerve stimulation.
- **Tai chi**: a mind-body practice that combines controlled movements, meditation and deep breathing with the goal of balancing or restoring energy. Even for patients with limited mobility, "chair tai chi" can be a practical activity.
- **Yoga:** a set of exercises or a series of postures designed to align muscle and bones, increasing strength and flexibility. It can also harmonize the mind and body through breathing exercises and meditation. Gentler forms of yoga such as Iyengar, Hatha, or Viniyoga have been studied.

Although these interventions may cause muscle soreness, increased back pain, or falls, non-drug options are generally considered safe.[13]

Weight loss

Some pain syndromes, such as knee OA, may be made worse 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 joint(s). The goal of body weight reduction is a baseline weight loss of 7%-10% by calorie reduction using a balanced diet with less than 30% of calories from fat, 15%-20% from protein, and 45%-60% from carbohydrates.[14]

Passive options

Acupuncture involves the stimulation of specific points on the body, most often involving skin penetration by fine metallic needles manipulated by hand but sometimes also including low intensity laser therapy. Adverse events include minor bruising and bleeding at needle insertion sites.[15]

Massage is the manual manipulation of the body to promote relaxation, reduce stress and improve well-being. Swedish massage, often practiced in spas or health clubs, is done with the hands. Handheld devices may also provide relief for some patients. Some patients may report muscle soreness.[16]

Transcutaneous electrical nerve stimulation (TENS) is a machine that sends little electrical pulses into the body. The electrical stimulation from TENS blocks or disrupts pain signals from reaching the brain, reducing the perception of pain. TENS machines can be used at home or in conjunction with other interventions like physical therapy.

Cognitive and behavioral options

Cognitive behavioral therapy (CBT) is a structured, time-limited (3-10 weeks) intervention focused on how thoughts, beliefs, attitudes, and emotions influence pain and highlights the patient's role in controlling and adapting to pain. This therapy includes setting goals, often with recommendations to increase activity to reduce feelings of helplessness.[17]

Mindfulness meditation

Mindfulness is another structured, time-limited (8 weeks; range 3-12 weeks) option with group classes and home meditation practice. The objective of this option is to refocus the patient's mind on the present, increase awareness of self and surroundings, and reframe experiences. Adverse reactions may include anger and anxiety.[18,19]

Self-management education programs

Lorig and colleagues developed a self-management training program for patients with chronic arthritis, which was later expanded to other chronic diseases, and is generally referred to as the Stanford model.[20] 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.[21]

Drug approaches

Medications are a widely used therapeutic option to alleviate and manage pain. Categories of pain medications include the following:

- acetaminophen
- non-steroidal anti-inflammatory drugs (NSAIDs)
  - oral
  - topical
- antidepressants
  - serotonin and norepinephrine reuptake inhibitors (SNRIs)
  - tricyclic antidepressants (TCAs)
  - selective serotonin reuptake inhibitors (SSRIs)
- anticonvulsants
- topical lidocaine
- medical marijuana
- opioids

Acetaminophen

Acetaminophen's effect on pain is not well understood, though it may work by inhibiting prostaglandin synthesis in the central nervous system. Acetaminophen is available over the counter (OTC) in 325 mg, 500 mg, and 650 mg tablets. Lower doses are recommended to decrease risk of side effects. Patients should not exceed 650 mg in a single dose. The maximum dose in healthy adults is 4000 mg/day and 3000 mg/day elderly patients.[22]

The most severe side effect of acetaminophen is liver toxicity. Acetaminophen is the most common cause of acute liver failure, accounting for 46% of all cases.[23] Patients recommended to take acetaminophen should stay within recommended doses to help prevent side effects and should only be prescribed one acetaminophen-containing product at a time. Advise patients to read any over-the-counter labels to determine if the product contains acetaminophen.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce inflammation by inhibiting cycloxygenase (COX), either selectively (COX-2 predominantly) or non-selectively (COX-1 and COX-2 effects). Chronic use of NSAIDs may be limited by gastrointestinal (GI) toxicity, including GI bleeding, upper GI symptoms, ulcers, and related complications. For high risk patients, including those who are elderly, patients on warfarin, aspirin, and those with coagulopathies, adding a proton pump inhibitor (PPI) may help reduce the risk.[24,25] In addition to GI side effects, all NSAIDs have been associated with an increased risk of renal and cardiac complications.

Topical NSAIDs: Side effects with NSAIDs are significantly lower with topical formulations. The effects on coagulation and renal function are unknown, but likely not clinically significant given limited systemic absorption.[26]

Recent evidence regarding the comparative safety of celecoxib:

The Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION) study was a prospective, long-term non-inferiority trial of 24,081 patients (926 centers, 13 countries) designed to assess the cardiovascular safety of celecoxib (100-200 mg twice daily, n=8,072) compared to prescription strength doses of ibuprofen (600-800 mg three times a day, n=8,040) or naproxen (375-500 mg twice a day, n=7969) in patients with OA or rheumatoid arthritis (RA) who had established cardiovascular disease or risk factors for cardiovascular disease. The trial results provide strong evidence that cardiovascular risk with approved doses of celecoxib is not greater than that of prescription doses of ibuprofen and naproxen.

The study also showed that patients with chronic arthritic conditions and cardiovascular risk factors taking celecoxib experienced numerically fewer cardiovascular events as compared to patients receiving prescription strength doses of ibuprofen and naproxen over a median of 20 months with follow-up of 34 months. A primary outcome event 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%). The risk of gastrointestinal events was significantly lower with celecoxib than with naproxen (P=0.01) or ibuprofen (P=0.002); the risk of renal events was significantly lower with celecoxib than with ibuprofen (P=0.004) but was not significantly lower with celecoxib than with naproxen (P=0.19) The gastrointestinal safety findings were observed despite providing all patients enrolled in the study with a proton pump inhibitor.[27]

Serotonin-norepinephrine reuptake inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine (Cymbalta, generics), venlafaxine (Effexor, Effexor XR, generics) and milnacipran (Savella) are characterized by a mixed action on both major neuroamines of depression, norepinephrine and serotonin, though their exact mechanism of action for pain is unknown. Side effects (e.g., nausea, dizziness, and somnolence) limit treatment. Monitoring blood pressure is necessary for both duloxetine and venlafaxine as well as monitoring heart rate for venlafaxine and drug interactions for duloxetine.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) affect brain chemicals to ease depression symptoms, but their mechanism of action for pain is unknown. They work to inhibit reuptake of transmitter amines (e.g., norepinephrine and serotonin). Examples of TCAs studied for the management of chronic pain include amitriptyline (Elavil,

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

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs), such as citalopram (Celexa, generics), fluoxetine (Prozac, generics), and paroxetine (Paxil, generics), block the reuptake of serotonin in the brain, making more serotonin available. The mechanism of SSRIs for pain remains unknown. Side effects include weight gain and risk of QTc prolongation, especially with citalopram.

Anticonvulsants

Anticonvulsants, such as gabapentin (Neurontin, generics), pregabalin (Lyrica, Lyrica CR), oxcarbazepine (Trileptal, generics), and carbamazepine (Tegretol, generics) are prescribed for neuropathic pain. They work by inhibitory action at voltage-gated calcium channels. Side effects include sedation, dizziness, and peripheral edema. Pregabalin and gabapentin have abuse potential with misuse in the general population reported to be 1%. Misuse among people with prescriptions for pregabalin and gabapentin ranges from 40%-65% while in patients who abuse opioids misuse ranges from 15%-22%.[28] Both pregabalin and gabapentin are being tracked by some state prescription drug monitoring programs (PDMPs).[29]

Topical lidocaine

Topical lidocaine inhibits ionic fluxes required for initiation and conduction of nerve impulses. Irritation at the application site is the most noted side effect. The most common products for chronic pain management are lidocaine 5% patches (Lidoderm, generics), available by prescription, and lidocaine 4% patches available over the counter.

Medical marijuana (cannabis)

Numerous states have passed laws allowing people to use medical marijuana for pain, nausea, and other symptoms; how and when it can be used varies by state. As of June 2017, 29 states and Washington DC have enacted medical marijuana laws.

Medical marijuana contains more than 60 cannabinoids, Δ^9-tetrahydrocannabinol (THC) and cannabidiol, that act on cannabinoid receptors located throughout the body but 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. In addition to reducing pain, activating cannabinoid receptors may cause euphoria, psychosis, cognitive impairment, reduced locomotor function, and increased appetite. Medical marijuana also functions as an antiemetic and has anti-spasticity and sleep promoting effects.[30]

It is unclear what cannabinoids are active for pain or what doses and dosage forms are best for patients. A variety of dosage forms are available from most state-approved dispensaries, with the three most common presented in Table 1.

Table 1: Cannabis preparations[30]

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

Using medical marijuana poses both short-term and long-term risks. Short-term effects of medical marijuana include impaired memory, motor coordination, and judgment. Paranoid ideation and psychotic symptoms may occur with high doses of THC. Long-term effects include impaired brain development in young adults, potential for addiction, increased anxiety, depression, and psychotic illness. Cessation of marijuana may cause withdrawal syndrome with symptoms of anxiety, irritability, craving, dysphoria, and insomnia. There is an increased risk of chronic bronchitis, respiratory infections, and pneumonia.[30]

An evaluation of the association between medical cannabis laws and opioid analgesic overdose mortality found that introduction of the laws was associated with a 25% reduction in overdose mortality that generally strengthened over time.[31] FDA-approved cannaboids include dronabinol (Marinol), indicated for second-line treatment of chemotherapy-induced nausea and vomiting, anorexia associated with weight loss in HIV patients, and nabilone (Cesamet) indicated for chemotherapy-induced nausea and vomiting. While not FDA-approved for the treatment of chronic pain, it may be reasonable to trial these drugs in pain conditions where evidence for medical marijuana is present. Side effects that commonly occur with these cannaboids include dizziness/vertigo and euphoria. Dronabinol may cause nausea/vomiting, abdominal pain, and abnormal thinking. Nabilone may cause ataxia and dry mouth.[30,32,33]

Evaluating patients for medical marijuana

Criteria for determining if a patient is a candidate for medical marijuana were suggested in a medical marijuana review in JAMA and include the following:[30]

- debilitating medical condition with data to support medical marijuana would prove beneficial
- multiple failed trials of first- and second-line pharmacotherapies
- failed trial of FDA-approved cannabinoid (dronabinol or nabilone)
- no active substance use disorder, psychotic disorder, or unstable mood or anxiety disorders
- patient resides in a state with medical marijuana laws and meets the requirements of these laws

In Pennsylvania, indications for the use of medical marijuana include neuropathies, severe chronic or intractable pain of neuropathic origin, or if conventional therapies and interventions, including opioids, is contraindicated or ineffective. For a complete list of indications in Pennsylvania and a link to frequently asked questions about the Pennsylvania Medical Marijuana Program, visit AlosaHealth.org/Pain.

Opioids for chronic pain

Mechanism of Action

Opioids produce effects on neurons by acting on the mu, kappa, and delta opioid receptors. Individual agents may be classified as agonists, partial agonists and antagnoists:

- Agonists (e.g., morphine, codeine, hydromorphone, hydrocodone) stimulate at least one of the opiate receptors and provide continued analgesia with increasing doses.[34]
- Partial agonists (e.g., buprenorphine), have a high affinity/low efficacy at mu-receptor, have a ceiling for analgesic effect, and are less likely to cause respiratory depression.[34]
- Antagonists (e.g., naloxone and naltrexone), which block rather than activate with opioid receptors, do not have an analgesic effect.[34] Use of an opioid antagonist in patients taking chronic opioids may precipitate an acute withdrawal syndrome.

The Drug Enforcement Agency (DEA) assigns a schedule to each opioid based on its abuse and addiction potential. Classifications for most opioids are listed in Table 2.

Table 2: Opioids by schedule[34]

Schedule	Description	Opioid
Schedule I	No medical use, lack of accepted safety, and a high potential for abuse	Heroin Lysergic acid diethylamide (LSD)
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

Opioid formulations

Prescription opioids are available in immediate release and extended release/long acting (ER/LA) formulations. Initiation of opioids should always use immediate release products to prevent overdose in participants who are opioid naïve. 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.[35] According to the FDA, some ER/LA opioids are only for patients who tolerate 60 morphine milligram equivalents per day (MMED) for at least one week.[36]

Additional efforts to enhance opioid safety include the creation of abuse-deterrent and tamper-resistant opioid formulations, which make products more difficult to inject or snort. However, not all reformulations have proven successful. For example, Opana ER was removed from the market after reports of intravenous abuse of the oral formulation.[37] Abuse-deterrent or tamper-resistant formulations do not prevent users from

becoming addicted or taking too much of an opioid by mouth.[38,39] No prospective randomized clinical trials or rigorous observational studies have measured the impact of abuse-deterrent opioids on the risk of abuse or misuse. Abuse-deterrent formulations approved by the FDA include morphine ER + naltrexone (Embeda) and oxycodone + naloxone (Targiniq ER and Troxyca ER).

Atypical opioids

Tramadol is an atypical opioid, a partial mu agonist and a serotonin and norepinephrine reuptake inhibitor. Tramadol's exact mechanism of action is unknown, but its analgesic effect is thought to be similar to that of morphine. Patients taking tramadol should be monitored for nausea, vomiting, constipation, and drowsiness, all of which are similar to side effects with opioids.[40] There is potential risk of serotonin syndrome when combined with SSRIs and tricyclic antidepressants.[41]

Opioid side effects

In addition to risks, 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 and hallucinations. In addition, chronic opioid use will cause tolerance, requiring higher doses to achieve the same effect, and may cause hyperalgesia (paradoxical response, which is when a patient develops an abnormally heightened sensitivity to certain painful stimuli).

Gastrointestinal side effects

Constipation occurs in 40%-50% of patients taking chronic opioids and is more likely to occur in patients taking opioids for more than two years as compared with patients taking opioids for less than six months. Constipation can occur at any dose of opioid. To prevent this side effect, patients should use a mild stimulant laxative such as senna or bisacodyl and increase the dosage in 48 hours if no bowel movement occurs. Physicians should perform a rectal examination if no bowel movement occurs in 72 hours. If there is no impaction, consider other therapies such as an enema, suppository, or magnesium citrate.[42] Medications for refractory, opioid-induced constipation include naloxone derivatives: naloxegol (Movantik), methylnaltrexone (Relistor), or naldemedine (Symproic). Naloxegol is an oral tablet that is used daily while methylnaltrexone is a subcutaneous injection or oral tablet used daily. Naldemedine, a C-II agent, was approved in early 2017 and is due to be available in late 2017 or early 2018. Naldemedine is taken by mouth daily (0.2 mg) and may cause side effects such as abdominal pain or discomfort, diarrhea, and nausea.[43] In clinical trials patients not on a bowel regimen had significantly more spontaneous bowel movements (defined as ≥3 per week) than those on placebo (47.6% vs. 34.6%, p=0.002).[44]

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

Sedation

If patient complains of sedation, determine whether sedation is related to the opioid, eliminate nonessential CNS depressants (such as benzodiazepines), reduce dose by 10%-15% if analgesia is satisfactory, add or increase non-opioid or non-sedating adjuvant for additional pain to reduce opioid dose, add a stimulant in the morning, and change opioid if appropriate.

Problematic opioid use

Although evidence for the long-term effectiveness of opioids for chronic pain is insufficient, evidence does support a dose-dependent risk for serious harms.

In a 2007 study that assessed behaviors indicative of opioid misuse, most patients in primary care practices reported having engaged in aberrant behaviors one or more times.[45]

Table 3 : Behaviors indicative of opioid misuse[45]

Behavior	Frequency in patients with opioid misuse
Requested early refills	47%
Increased dose on own	39%
Felt intoxicated from pain medication	35%
Lost or had medication stolen	30%
Purposely over sedated oneself	26%
Used opioids for purpose other than pain	18%

Although opioid prescribing practices have started to trend in a more cautious direction, opioid prescribing levels and opioid-related morbidity remain high. In 2015, about 92 million (38%) non-institutionalized adults used prescription opioids, 11.5 million (4.7%) misused them, and 1.9 million (0.8%) had an opioid use disorder (OUD).[46] The most commonly reported motivation for misuse was to relieve physical pain (63%).[46] Among adults with misuse, 60% reported using opioids without a prescription, while other patients reported using larger quantities (22%), using more frequently (15%), or using for longer duration than prescribed (13%). Among adults without a prescription, 41% obtained prescription opioids from friends or relatives for their most recent episodes of misuse.[46]

To ensure clear communication regarding medical issues and avoid misunderstandings about the nature and risk of addiction, the American Society of Addiction Medicine recommends the following definitions:[47]

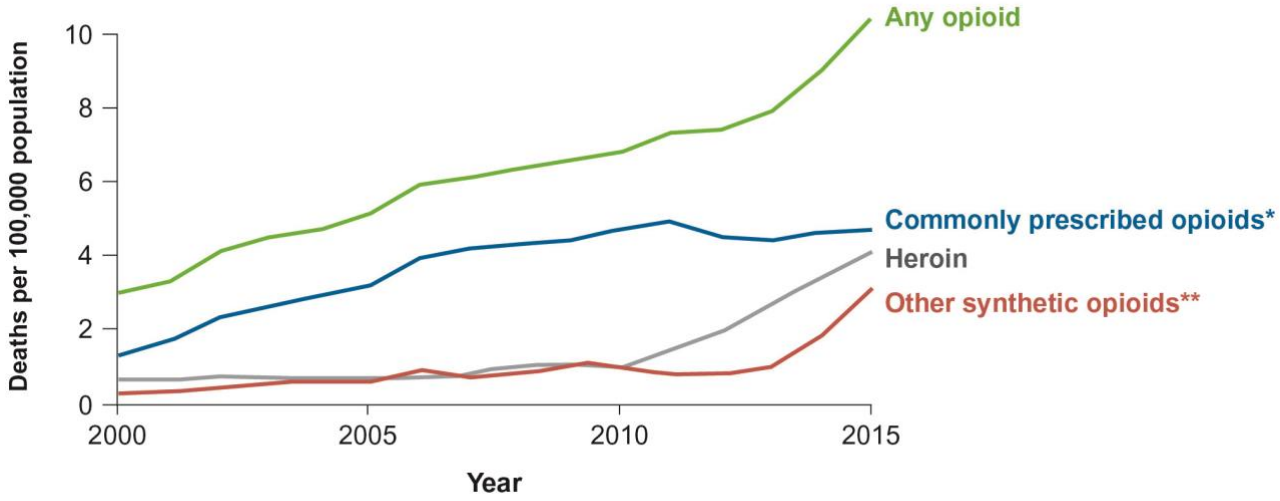
- **Abuse** - Any use of an illegal drug, or the intentional self-administration of a medication, for a non-medical purpose, such as altering one's state of consciousness (e.g., getting high).
- **Misuse** - Use of a medication other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.
- **Dependence** - A state of physical adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
- **Opioid use disorder**[48] - 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. See page 45 for complete opioid use disorder diagnostic criteria.

According to a 2015 meta-analysis, the prevalence of opioid abuse in primary care settings ranged from 0.6%-8%, and the prevalence of dependence ranged from 3%-26%. In a pain clinic settings, the prevalence of opioid abuse ranged from 8%-16%, and addiction ranged from 2%-14%.[49] In eastern Pennsylvania, the lifetime prevalence of opioid use dependence among chronic opioid users was 35%.[50]

Overdose

Opioids continue to be implicated in more overdose deaths than any other drug, and the trend is being driven, in part, by illicit opioid use as depicted in Figure 3.[51]

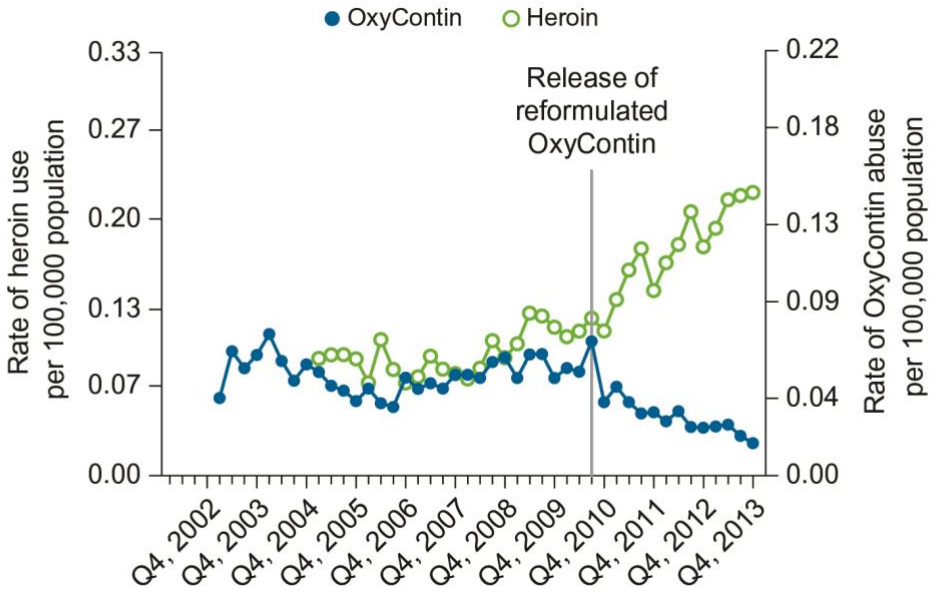
Figure 3: Overdose deaths involving opioids, U.S., 2000-2015[51]



*Natural and semi-synthetic opioids and methadone; **e.g., fentanyl, tramadol

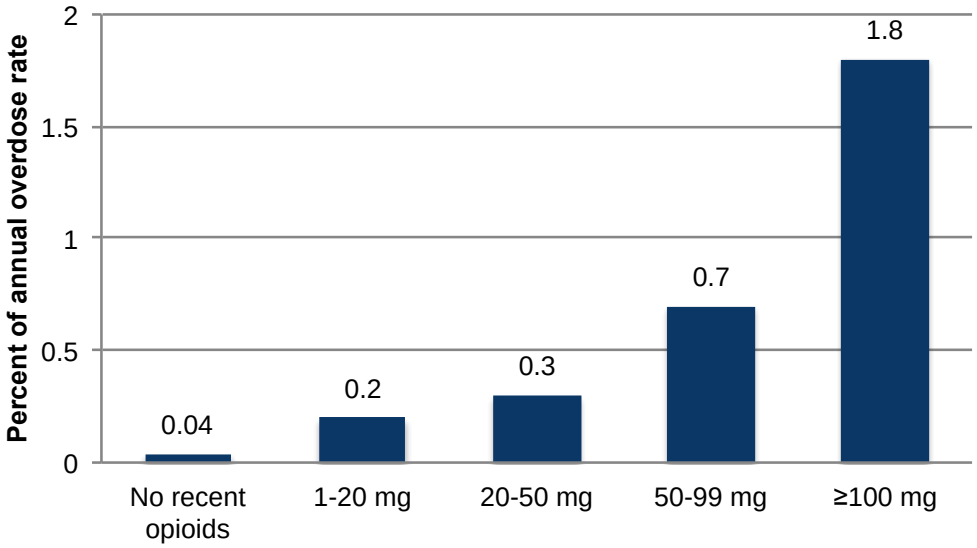
However, much of the illicit use of opioids may be attributed to prescription opioids. For example, one survey of heroin users showed that 75% began by abusing prescription opioids.[52] Ecologic data, presented in Figure 4, has also shown as association between the rapid rise in illicit heroin use after the reformulation of a long-acting prescription opioid (OxyContin).[53] The combination of illicitly manufactured fentanyl and carfentanil with heroin has also increased the mortality from illicit opioid use.

Figure 4: National poison data system and poison center, intentional abuse[53]



For prescription opioids, long-term therapy is associated with an increased risk in accidental overdose and death. A retrospective study included 9,940 patients who received three or more opioid prescriptions within 90 days for chronic pain between 1997 and 2005. The average daily opioid dose was determined from automated pharmacy data; mean follow-up was 42 months. Primary outcomes (non-fatal and fatal overdoses) were identified through diagnostic codes from inpatient and outpatient care and death certificates and confirmed by medical record review.[43] The annual rate of overdose rose exponentially when doses exceeded 50 MMED as depicted in Figure 5.

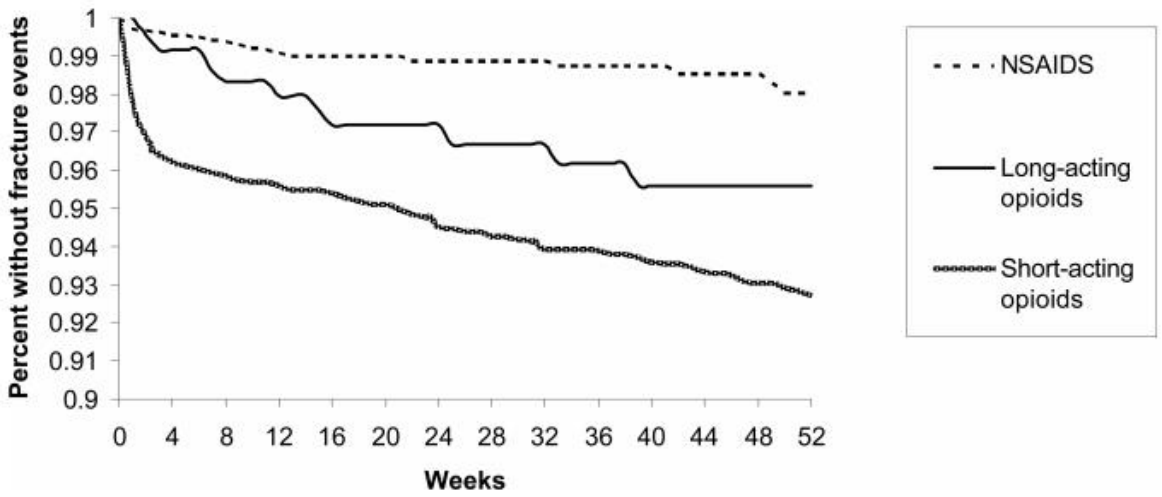
Figure 5: Risk of overdose rises with daily morphine dose.[43]



Fracture: A retrospective cohort study from pharmaceutical claims data 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 increased the risk of fracture (HR 4.9; 95% CI: 3.5-6.9) in a dose-dependent fashion. The opioid dosage form mattered (see Figure 6), with much of the risk in the first month after drug initiation for short-acting opioids, though fracture increased for both long- and short-acting opioids over time.[54]

Figure 6: Fracture risk over time for NSAIDs, short-acting and long-acting opioids[54]



Infection: Opioids may increase risk of infection in older adults. A case-controlled study of 3,061 older community dwelling adults ages 64-95 years (mean age 77) was conducted to evaluate the association between pneumonia and opioid use. Current prescription opioid users had a 38% increased risk of pneumonia (OR 1.38; 95% CI: 1.08-1.76) compared with nonusers. The risk was highest for opioid users categorized as being immunosuppressed, such as those with serious cancer, recent cancer treatment, or chronic kidney disease, or those receiving certain immunosuppressive medications or medications for human immunodeficiency virus.[55]

Myocardial Infarction (MI): A case-controlled trial 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 1.28-fold risk (95% CI: 1.19-1.37) of MI compared with non-use.[56]

Erectile Dysfunction (ED): In a cross-sectional analysis of 11,327 men with back pain, 909 received ED medications or testosterone. Long-term opioid use was associated with the 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 as compared with patients without opioid use, suggesting that dose and duration of opioid use were associated with evidence of ED.[57]

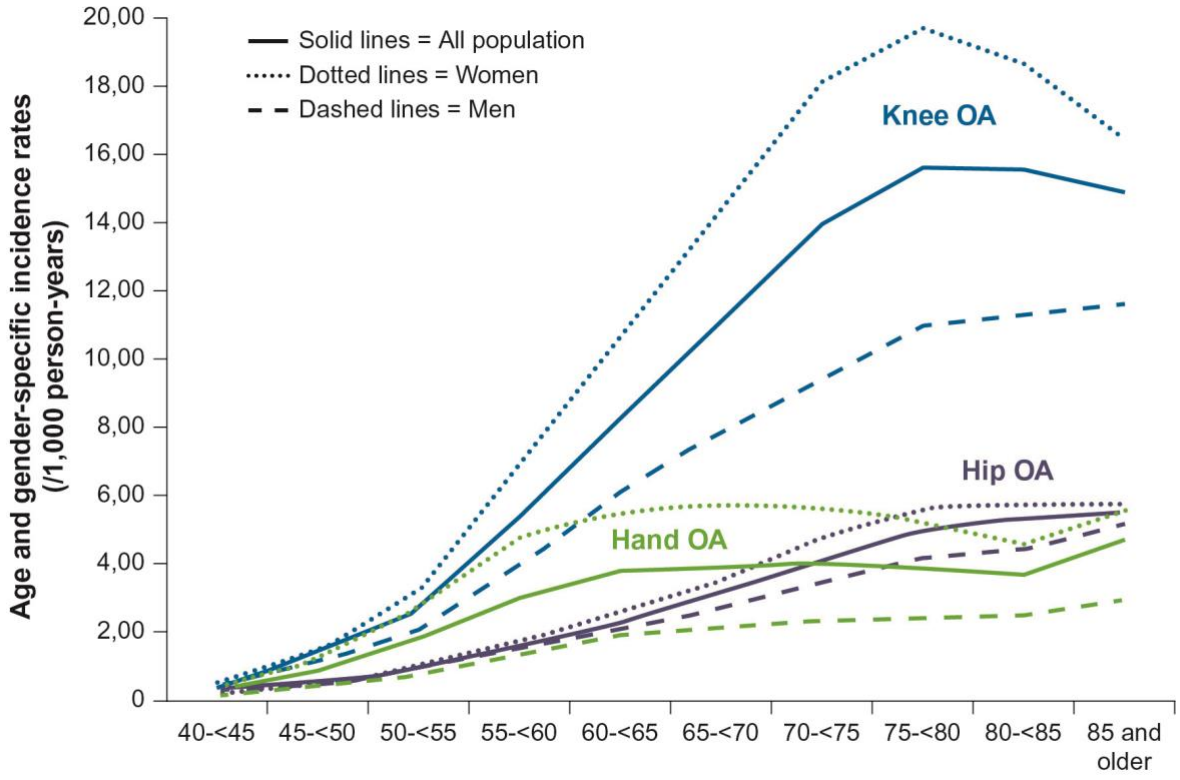
Summary of drug options

Medications to treat pain have diverse mechanisms of action and varying safety profiles. Assessing risks with the benefits discussed in the following sections is critical to determining which drugs have a role in the management of each pain syndrome. Efficacy data discussed in this document does not always align with FDA approved indications. For FDA approved indications of the medications discussed see Appendix II.

Osteoarthritis

Osteoarthritis (OA) is a common source of pain and disability that affects nearly 70% of those over 65 years of age.[58] The symptoms of OA include joint pain, tenderness, swelling, stiffness, and restricted motion in one or more joints. The joints involved tend to be the hand, hip, and knee, with knee being most common. As shown in Figure 7, more women than men suffer with OA.[59]

Figure 7: Incidence rates of OA by involved joints[60]



Non-drug options

Exercise and physical activity

Lifestyle changes are gaining increasing recognition in the management of OA. Two recent Cochrane Reviews found small to moderate benefit in the form of reduced pain and improved function with physical activity for patients with knee and hip OA, respectively, who had not undergone joint replacement. Outcomes are summarized in Table 4; exercise interventions were diverse and included tai chi, physical therapy, strength training, and aerobic exercise (e.g., walking, cycling). The reviewers concluded these benefits could be clinically important, defining a minimal clinically important treatment effect as a 20%-30% improvement from baseline.[11,61]

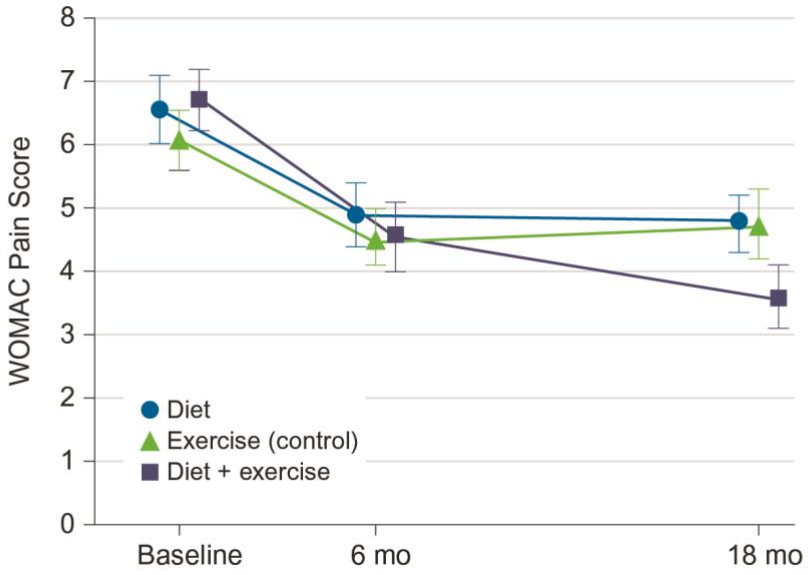
Table 4: Effect of exercise on pain and function for knee and hip OA[11,61]

		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%)

Weight loss

Weight loss interventions studied for OA typically focus on joint stress or injury rather than pain. However, one study by Messier, et al. evaluated weight loss alone and in combination with exercise. The study included 545 overweight older adults with knee OA 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 according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale at three points in time— Baseline, 6 months (end of intervention), and 18 months, as shown in Figure 8. At 18 months follow-up the diet plus exercise intervention was shown to improve pain as compared with diet or exercise alone; in the diet plus exercise group 38% of patients reported little or no pain as compared with 20% and 22% of patients with diet or exercise alone, respectively.

Figure 8: WOMAC pain scores across 18 months[14]



Function improved significantly in the diet plus exercise group versus diet and exercise alone ($p<0.001$), with no functional difference between diet and exercise groups alone. Weight loss varied. For diet plus exercise, weight loss was -10.6 kg; for diet alone weight loss was - 8.9 kg; and for exercise alone weight loss was - 1.8 kg.[14] This initial study suggests a benefit from combined weight reduction and exercise for pain and function in overweight patients with knee OA.

Tai chi

A meta-analysis of 11 randomized controlled trials (RCTs) among patients with arthritis found tai chi to be moderately effective in improving both pain (SMD -0.66; 95% CI: -0.85 to 0.48) and function (SMD -0.66; 95% CI: -0.85 to -0.46) in the short-term compared to no intervention control group. Small to moderate effects were observed in the medium to long-term but were not statistically significant with low quality of evidence.[62]

One randomized trial with 204 participants with symptomatic knee OA (mean age 62) directly compared 12 weeks of twice weekly tai chi against standard physical therapy (twice weekly physical therapy for 6 weeks followed by 6 weeks of home exercise) and followed patients for 52 weeks. Both study arms showed significant improvement from baseline pain scores but no statistically significant difference between groups in terms of pain or function.[63]

Yoga

Yoga is a popular multimodal mind-body exercise aimed at promoting flexibility. A review of 12 studies involving a total of 589 patients with OA symptoms ranged from weekly to 6 days per week yoga with sessions lasting 45 to 90 minutes over 6 to 12 weeks. Because of the diversity of interventions, the reviewers were unable to calculate effect size but found suggestions that pain, stiffness and swelling were reduced. No effect on physical function was observed.[64]

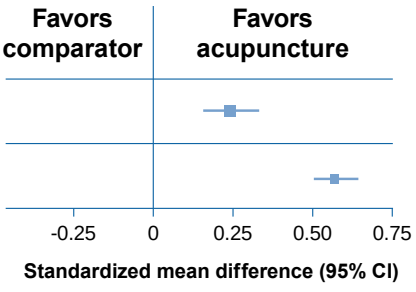
A pilot RCT published after the review of Sit 'N' Fit Chair Yoga in 112 patients (mean age 75) with lower extremity OA showed a reduction in pain interference and WOMAC pain intensity after 8 weeks of chair yoga compared to a health education program. The benefits were not sustained in assessments three months after the intervention ended.[65]

Acupuncture

A 2014 meta-analysis compared sham acupuncture with no acupuncture in a variety of pain conditions. For knee OA, there was an observed benefit for acupuncture compared with no acupuncture or sham acupuncture, which involves placing needles at sites not considered effective for pain relief. Table 5 summarizes the findings of the meta-analysis for OA.[66]

Table 5: The effectiveness of acupuncture vs. sham acupuncture or no acupuncture[66]

		Total number of participants	
Comparison	Trials	Acupuncture	Comparator
Acupuncture vs. sham	5	830	799
Acupuncture vs. no acupuncture	6	1164	1062



However, another study not included in the meta-analysis suggests that needle or laser acupuncture is no better than sham laser. The study included 282 patients with chronic knee pain (mean age 63). Treatments were delivered for 12 weeks. At the end of 12 weeks, needle and laser acupuncture reduced self-reported knee pain more than no acupuncture (control) but not more than sham acupuncture, suggesting strong placebo effects. These benefits were not sustained at 1 year follow up.[15]

When combined with the acupuncture meta-analysis results above, which indicate diminished effect sizes with more robust controls, the evidence suggests that both true acupuncture and sham acupuncture may reduce self-reported pain and improve function.

Massage

A review of seven randomized trials with 352 participants suggests that massage as a stand-alone treatment may be better than no treatment for reducing pain. 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 improvement in the 50 foot walk test.[16,67]

Self-management education programs

Small effects were noted for self-management education programs, though the benefits were not considered clinically important (see Table 6).[68-70] 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 6: Self-management education programs[68-70]

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

Other non-drug interventions

Transcutaneous Electrical Nerve Stimulation (TENS) has been used for pain relief for decades, but studies evaluating effectiveness have shown mixed results. Data from four trials, including two randomized controlled trials, showed no statistical improvement in pain over placeo.[71]

Cognitive behavioral therapy (CBT) interventions are targeted to comorbid conditions, such as insomnia and depression; no trials have evaluated the impact of CBT on pain in OA. Data were mixed for the effect of mindfulness meditation on chronic pain with no clear benefit observed between three randomized controlled trials.[19]

Non-drug summary for OA

Across all types of non-drug interventions, most trials have been short in duration. Consequently, long-term impacts of these interventions, especially for OA, remain unknown. Evidence supporting the effectiveness of non-drug interventions is limited by lack of blinding and absence of a clinically comparable control group. However, these interventions are generally safe and therefore recommended as first-line or adjunctive treatment for chronic pain due to OA. Exercise, physical therapy, tai chi, massage and acupuncture have a favorable benefit/risk profile, with yoga and self-management also possibly favorable options. For a complete summary of the non-drug interventions presented, see Appendix III.

Drug options

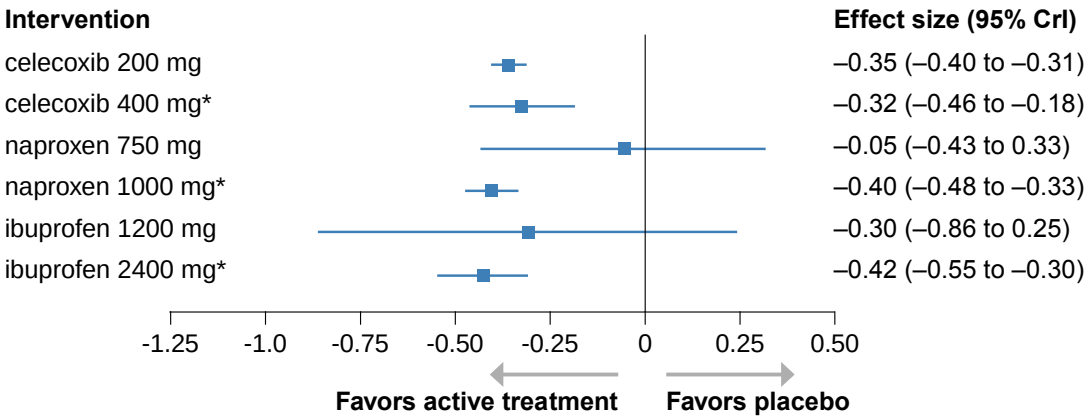
Acetaminophen

A meta-analysis of patients with OA found a small effect size of 0.21 (95% CI: 0.02-0.41) for pain relief compared with placebo.[66] Generally, scheduled dosing is better than as-needed dosing for relief of chronic pain. The recommended starting dose for elderly patients is 325 mg every 4 hours, with a maximum daily dose of 3000 mg.[26,72]

NSAIDs

Given the inflammatory mechanism of OA, NSAIDs are the first-line pharmacologic option for managing chronic pain. In a meta-analysis of 76 randomized trials, the use of oral NSAIDs was favored over placebo with a small to moderate effect size for both pain (SMD range: 0.57-0.32) and function (SMD range: 0.51-0.31). Analysis included celecoxib, a selective NSAID, as well as nonselective NSAIDs ibuprofen and naproxen, and effect sizes shown in Figure 9.[73]

Figure 9: Effect size of commonly used NSAIDs



* Maximum approved daily dose

Topical vs. Oral NSAIDs

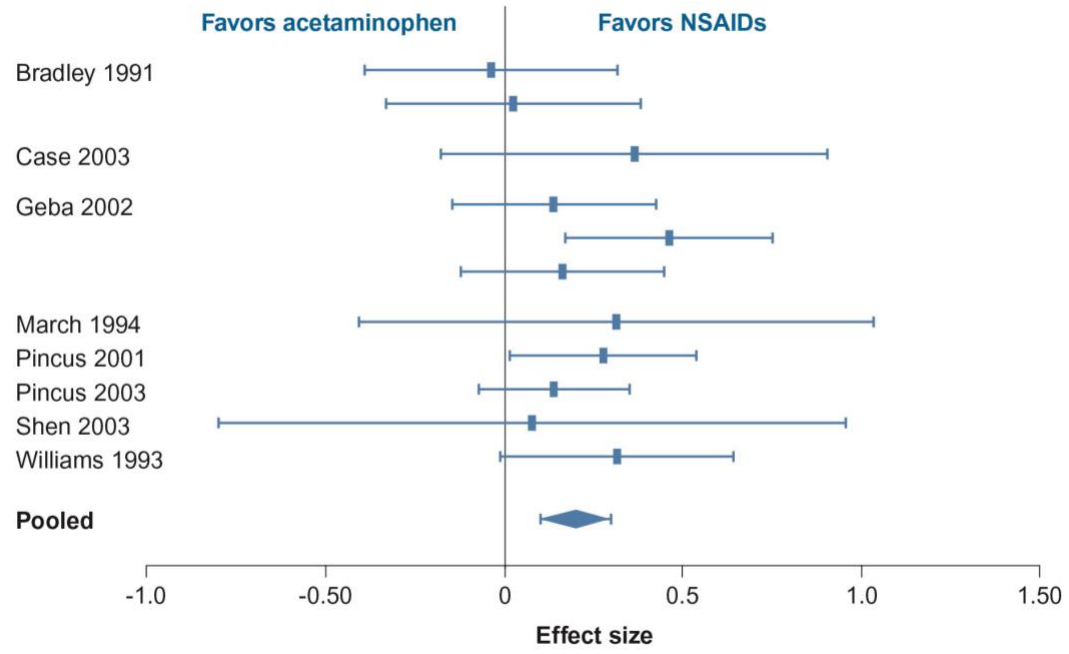
Topical NSAIDs are as effective as oral NSAIDs for OA pain. A randomized trial of 282 older patients with chronic knee pain were given advice to use oral or topical ibuprofen. In this trial, changes in the WOMAC OA index were equivalent between the two arms (topical- oral difference was 2 points, 95%CI: -2 to 6).[74] While

side effects in the study did not vary between oral and topical NSAIDs, a small though statistically significant increase in serum creatinine was observed for oral NSAIDs. Generally, topical NSAIDs are considered safer due to a lack of systemic absorption. Topical NSAIDs may be recommended over oral NSAIDs for localized, single joint pain (e.g., knee OA).[26]

Acetaminophen vs. NSAIDs

A meta-analysis of six OA trials comparing acetaminophen and NSAIDs found a small, but statistically significant treatment effect favoring NSAIDs (effect size 0.2; 95% CI: 0.1-0.3; p<0.05), as shown in Figure 10. Therefore, NSAIDs are preferred over acetaminophen unless patients have high risk for gastrointestinal, renal, and cardiovascular adverse effects.[72]

Figure 10: Effect size of pain reduction from baseline[72]



SNRIs

A meta-analysis of three trials of duloxetine for knee OA showed patients on duloxetine (60 or 120 mg daily) were 49% more likely to have a moderate pain response (≥30% reduction in pain intensity). Overall the mean difference in pain score with duloxetine compared to placebo on a scale from 0-10 was -0.88 (95% CI: -1.11 to -0.65). Physical function (assessed by the WOMAC subscale 0-68) improved by a mean difference of -4.25 (p<0.001) in the duloxetine group compared to placebo.[75] No RCT has shown evidence of efficacy with other SNRIs. A small pilot study suggests a possible role for venlafaxine XR, but further study is needed.[76] No SNRIs are FDA approved for the treatment of OA.

Anticonvulsants

A single small RCT of 89 patients with knee OA suggests pregabalin may reduce pain and improve function similarly to meloxicam, but the combination of meloxicam with pregabalin was better than either alone.[77] The study lasted four weeks, and longer term RCT data is still needed. Pregabalin is not FDA approved for OA. No RCTs have been conducted with gabapentin for OA.

Topical lidocaine

A single 12-week RCT of 143 patients with knee OA found lidocaine 5% patch had similar effects on OA pain and function as celecoxib 200 mg daily using WOMAC subscales.[78] However, lidocaine patches are not FDA approved for the treatment of OA, and more data are needed to support their use.

Opioids

A Cochrane Review of 22 trials of 8,275 patients using opioids for knee or hip OA found small, but statistically significant, 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.[79] While these short-term trials (all <16 weeks in duration) showed improvements in pain and function, there is no long-term data of benefit. In fact, there are no studies that have evaluated the efficacy of long-term opioids on pain and function for any pain condition.[49] Intermittent, as-needed use is preferred because time-scheduled use can be associated with greater total average daily opioid dosage.

Other treatment options

There is insufficient evidence to draw firm conclusions about many other pharmacologic options for managing OA. For example, no RCT data are available for TCAs, SSRIs, or medical marijuana. 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.[80] Topical capsaicin gel reduced pain 53% from baseline compared to a 27% reduction with placebo in one 12-week study. Redness and burning sensation was reported by 44% and 46% of patients, respectively, randomized to capsaicin.[81]

Steroid or hyaluronic acid injections are widely used, but their recommendation is controversial. The effects are often time-limited with study outcomes focused on cartilage and joint structure rather than pain and function.[80] Despite the controversy, the FDA approved triamcinolone extended release injection (Zilretta) for knee OA in early October 2017.

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

Drug summary for OA

NSAIDs remain the most effective pharmacologic therapy for managing OA, with duloxetine, acetaminophen, and pregabalin as second-line or potentially favorable options. Side effects and few long-term data limit the utility of other options like typical opioids. For a complete summary of the drug interventions presented, see Appendix III.

Low back pain

Chronic low back pain (LBP) is extremely common, contributing more to global disability than any other condition. In the US, 30% of adults report low back pain in the preceding three months. LBP most commonly manifests as nonspecific back pain (or back pain in the absence of a specific underlying cause). Other less common causes include pain due to mechanical causes (degenerative disks), referred pain, and neoplasia.

Imaging is of limited utility 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.[82]

Non-drug options

Exercise

In a review of 19 RCTs, exercise provided small reductions in pain with a weighted mean difference (WMD) of 10 (95% CI: 1.3-19.1 on a scale of 0-100). Small, but not statistically significant, improvements in function were also observed (WMD 3; 95% CI: -0.53 to 6.48 on a scale of 0-100).[83] Types and duration of exercise from RCTs included in the meta-analysis were not specified. Although physical therapy has a role in the management of acute low back pain, no RCTs were identified for chronic low back pain.

Weight loss

Only small, uncontrolled pilot studies suggest possible benefit from weight loss for patients with chronic low back pain.[84,85] 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).[84] Calorie restriction among obese patients suggests a reduction in pain and a significant improvement in function (n=46).[85] Randomized controlled trials are needed to provide more conclusive evidence of benefit.

Tai Chi

Two trials (n=160 and n=320) found that tai chi reduced pain versus wait list or no tai chi on a 0- to 10-point scale (MD 0.9; p<.05 and MD 1.3; p <.001). The first trial consisted of 160 volunteers who had persistent non-specific low back pain. The tai chi group (n=80) consisted of 18 sessions (40 minutes each) over a 10-week period. The waitlist control continued with their usual health care. Tai chi exercise reduced "bothersome" back symptoms by 1.7 points, reduced pain intensity by 1.3 points on the 10-point scale, and improved self-report disability by 2.6 points on the 0-24 Roland-Morris Disability Questionnaire scale (RMDQ).[83]

Yoga

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 7). For pain, a clinically meaningful reduction in pain score based on the RMDQ of 15 points was not achieved.[86]

Table 7: Yoga: improvement in pain and function

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

A review by the American College of Physicians (ACP) identified 14 RCTs with similar findings.[83]

Acupuncture

A 2013 meta-analysis of five studies suggests a moderate reduction of pain and strong improvement in function from acupuncture compared to wait list control or self-care. The overall SMD for pain was -0.72 (95%CI: -0.94 to -0.49) and -0.94 (95% CI: -1.41 to -0.47) for function. Sessions lasted about 30 minutes and acupuncture interventions ran for a duration of 5 to 12 weeks, with follow-up from 10 to 52 weeks.[87]

Massage

A review of massage for low back pain looked at two comparison groups: inactive controls (sham therapy, waiting list, or no treatment), and active controls (e.g., manipulation, mobilization, TENS, acupuncture, traction, relaxation, physical therapy, exercises or self-care education). A moderate to strong reduction in pain and improvement in function against inactive controls in the short term was not sustained in long-term studies.[88]

Table 8: Changes in pain and function with massage vs. inactive controls

	Short term (< 6 months) SMD	Long term (≥6 months)
Pain	-0.75 (-0.90 to -0.60)	0.02 (-0.15 to 0.18)
Function	-0.72 (-1.05 to -0.39)	-0.16 (-0.32 to 0.01)

For massage vs. active controls, a small to moderate reduction in pain but not function was observed in long-term follow-up (Pain: SMD -0.40; 95% CI: -0.80 to -0.01).[88]

TENS

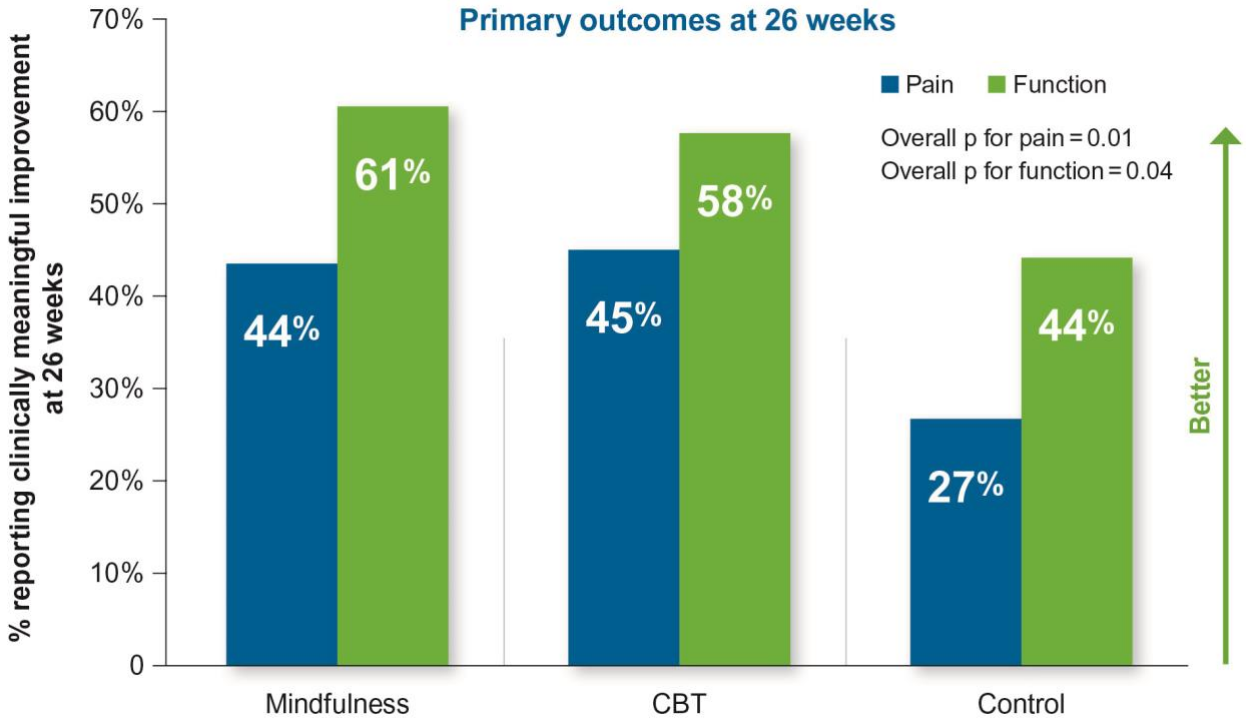
The existing clinical studies indicate that TENS has no beneficial effect on pain or function versus sham or placebo.[88,89,90]

Cognitive and behavioral therapies

A meta-analysis of five RCTs evaluating CBT found no difference in function but a moderate reduction in pain intensity compared to waitlist controls (SMD -0.6; 95% CI: -0.97 to -0.22).[83]

Newer RCT data suggests a reduction in pain and improvement in function from CBT and mindfulness-based stress reduction. A recent study 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 with post-intervention follow-up at 26 and 52 weeks. Mindfulness and CBT compared with usual care resulted in greater improvement in pain and function, with benefits persisting for both at 52 weeks, as shown in Figure 11. No statistical differences occurred between CBT and mindfulness groups throughout the study.[91]

Figure 11: Primary outcomes at 26 weeks[91]



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).[92]

Non-drug summary for chronic low back pain

Tai chi, acupuncture, massage, and cognitive behavioral therapy are effective interventions for reducing pain and improving function among patients with chronic, nonspecific LBP. Other interventions such as exercise, mindfulness meditation, and self-management have had small or mixed effects, but all of these interventions are generally considered safe. Guidelines recommend initiating non-drug therapies for managing chronic LBP as the first step in treatment.[89] For a complete summary of the non-drug interventions presented, see Appendix IV.

Drug options

Acetaminophen

No studies have evaluated acetaminophen for chronic LBP.

NSAIDs

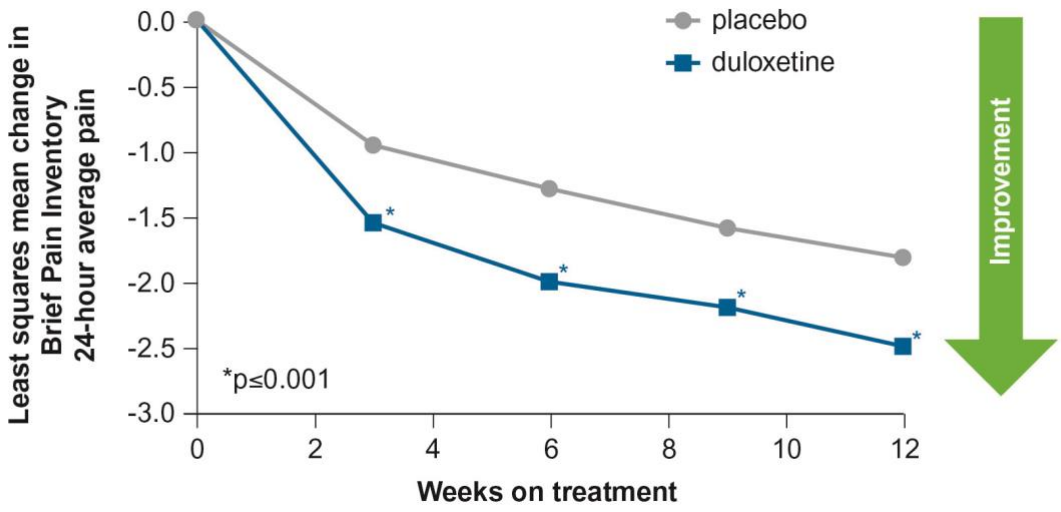
Six of the 13 RCTs in a review showed that oral NSAIDs are more effective than placebo regarding pain intensity, with a small to moderate reduction in pain observed at 12 weeks (WMD -12.4; 95% CI -15.53 to -9.26 on a 0-100-point scale). Little to no effect was observed on function.[93] No data evaluated the difference between non-selective and selective COX2 inhibitors for patients with chronic LBP. No RCTs evaluated the efficacy of topical NSAIDs on chronic LBP.[89]

Antidepressants

Duloxetine

An analysis of three moderate quality RCTs found small improvements in pain and function when compared to placebo. One of the studies involved 401 patients randomized to duloxetine 60 mg daily or placebo. Compared with placebo-treated patients, duloxetine-treated patients reported a significantly greater reduction (p≤0.001) in average pain as measured by the Brief Pain Inventory (BPI), as shown in Figure 12.[94]

Figure 12: Duloxetine change in BPI[94]



SSRIs and TCAs were found to be no different than placebo for pain or function.[95]

Other therapies

Other drug options such as gabapentin, pegabalin, topical lidocaine, muscle relaxants, typical opioids and even medical marijuana have little or no data for use in managing chronic low back pain. For anticonvulsants, pregabalin and gabapentin, a small number of low quality RCTs failed to show a reduction in pain or improvement in function compared to placebo.[96] No data exists to support the use of topical lidocaine for low back pain without a neuropathic component. While widely prescribed, use of skeletal muscle relaxants for chronic LBP is not supported by evidence.[95] Medical marijuana does not have RCTs to recommend its use. Open label trial data from 30 patients, 20 of whom had low back pain and other pain locations, noted a small improvement in pain when dronabinol was added to opioids. However, there is insufficient data to recommend use.[32]

Opioids

The risks associated with using opioids for chronic LBP are likely to outweigh potential benefits. All opioids provided a small 10% reduction in pain versus placebo with a small SMD. No studies evaluated the long-term effect (>1 year) of opioids on pain and function. Six RCTs found no difference in pain response from using either immediate release or ER/LA opioid products.[95] However, tramadol had a moderate reduction in pain (SMD -0.55; 95% CI: -0.66 to -0.44) and a small improvement in function (SMD -0.18; 95% CI: -0.29 to -0.07) compared to placebo.[83]

Additional interventions

Epidural steroid injections

LESS (Lumbar Epidural Steroid Injections for Spinal Stenosis) was a federally funded randomized trial (400 patients with lumbar spinal stenosis and back/leg pain) that compared the efficacy of epidural injections with glucocorticoid plus lidocaine against lidocaine alone. At 6 weeks, patients randomized to steroid plus lidocaine did no better on a pain-related functional disability score than those randomized to lidocaine alone. Differences between the groups at three weeks were not considered clinically significant.

Table 9: Primary outcomes according to treatment group and injection approach[97]

	Lidocaine			Glucocorticoid-lidocaine			Treatment comparison	
Overall	**# of patients**	**Overall Mean**	**Mean change from baseline**	**# of patients**	**Overall Mean**	**Mean change from baseline**	**Adjusted difference (95% CI)**	**p-value**
RMDQ score								
Baseline	200	15.7	--	200	16.1	--	--	--
3 weeks	189	13.1	-2.6	195	11.7	-4.4	-1.8	<0.001
6 weeks	193	12.5	-3.1	193	11.8	-4.2	-1.0	0.07
Score on numerical rating scale for leg pain								
Baseline	200	7.2	--	200	7.2	--	--	--
3 weeks	188	5.0	-2.2	195	4.4	-2.9	-0.6	0.02
6 weeks	193	4.6	-2.6	193	4.4	-2.8	-0.2	0.48

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 -4.1 (95% CI: -8.1 to -0.1; p=0.045). The range of ODI is 0 to 100 (totally disabled or bedridden), and the minimum clinically important change is estimated to be between 4 and 17. Those assigned to surgery had more complications (dural tears, excessive bleeding, repeat surgery).[98]

Drug summary for chronic low back pain

Guidelines from the American College of Physicians recommend initiating pharmacologic management after insufficient response to non-drug options. When selecting treatment, NSAIDs are first-line pharmacologic option. Duloxetine and tramadol are considered second-line treatments, though vary in side effects.[89] Tramadol has many of the adverse effects associated with typical opioids; duloxetine has a more favorable side effect profile. For a complete summary of the drug interventions presented, see Appendix III.

Diabetic neuropathy

A long-term complication of diabetes, diabetic neuropathy has a lifetime prevalence of 30%-50 and most commonly affects the distal extremities in a symmetric fashion. The disabling condition is characterized by numbness, tingling, pain (sensory symptoms), loss of vibratory sensation, and altered proprioception. Improved glucose control may reduce the incidence, and pain management may improve quality of life.[99]

Non-drug options

Movement-based options and weight loss

Studies of exercise focus on prevention of neuropathy, but no human studies focus on exercise for treatment of diabetic neuropathy.[99] A single small RCT of 39 patients 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. For example, total symptom score was reduced by 1.64 SD ($P < 0.042$).[100] No RCT data are available for weight loss or yoga.

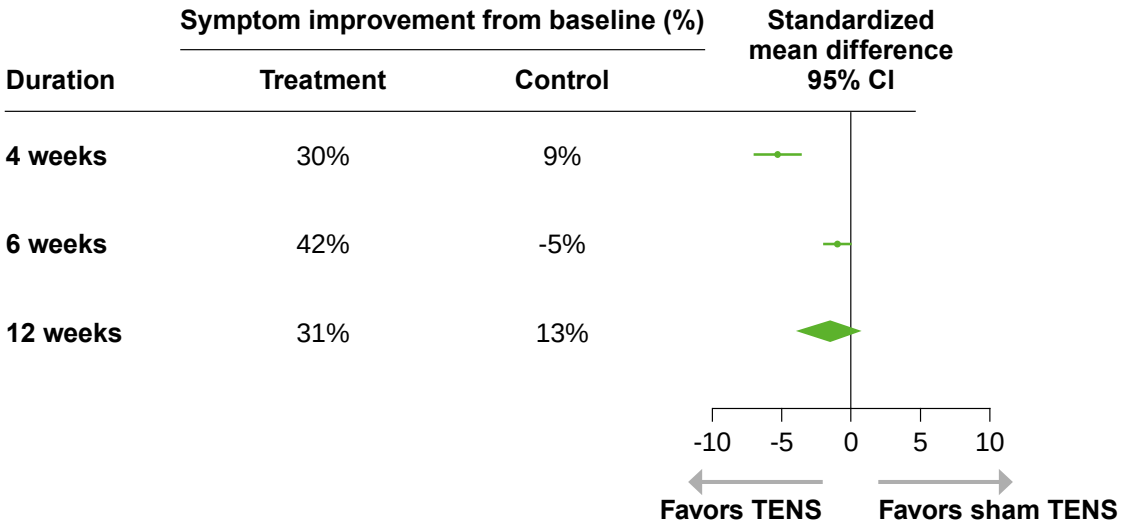
Acupuncture and massage

Small studies suggest a possible effect of acupuncture and massage on pain and function. A pilot study of 46 patients found overall symptom improvement with acupuncture in 77% of patients from baseline with 67% discontinuing medication. However, the study didn't have a control group nor did it specifically identify pain as an endpoint.[101] A 4-week trial involving 46 patients who received aromatherapy and massage had reduced pain and improved quality of life compared to usual care.[102] Further studies are required to provide a more clear understanding of the role of acupuncture and massage in managing pain in diabetic neuropathy.

TENS

A meta-analysis of three trials involving 92 patients with chronic pain due to diabetic neuropathy found improvement in pain severity at four and six weeks but not at 12 weeks.[103]

Figure 13: Improvement in pain with TENS at 4 and 6 weeks[103]



However, a separate analysis by the Agency for Healthcare Research and Quality (AHRQ) did not find significant or compelling evidence to suggest TENS was more effective than placebo for diabetic neuropathy.[104]

Cognitive and behavioral interventions

Little data support cognitive and behavioral interventions for patients with diabetic neuropathy. A small trial of 20 patients receiving CBT had a small decrease in pain scores as compared with treatment as usual after 11 weeks.[105] Similarly, a small study of 20 patients found no difference with mindfulness meditation versus placebo on pain or quality of life.[106] Self-management education focus primarily on glycemic control and foot care for patients with diabetes. No programs have examined the impact of self-management on pain.

Non-drug summary for diabetic neuropathy

Fewer non-drug options have been studied or shown to be possibly effective for diabetic neuropathy. Tai chi and TENS are potentially beneficial. For a complete summary of the non-drug interventions presented, see Appendix V.

Drug options

Acetaminophen and NSAIDs

No RCTs support the use of acetaminophen alone or NSAIDs, either oral or topical, for diabetic neuropathy.

SNRIs

Both duloxetine and venlafaxine reduce pain when compared against placebo. A network meta-analysis of four RCTs found a large effect from duloxetine (SMD -1.33; 95% CI: -1.82 to -0.86).[107] In one 12-week study of 457 patients, duloxetine reduced pain by 50% in 49% of patients receiving 60 mg daily compared to

placebo. Duloxetine 120 mg daily increased side effects, with drop-out rates four times that of the placebo group.[108] Three low to moderate quality RCTs evaluated venlafaxine vs. placebo at three months, finding a large effect size in a network meta-analysis.[107] One of the studies found that at six weeks venlafaxine ER 150-225 mg reduced pain 50% from baseline ($p<0.001$ vs. placebo), but venlafaxine 75 mg was no different from placebo. Baseline pain intensity was moderately severe at 67.3–69.9 mm for the three treatment groups. By week six, pain intensity had dropped to 31 mm with higher dose venlafaxine therapy.[109]

TCAs

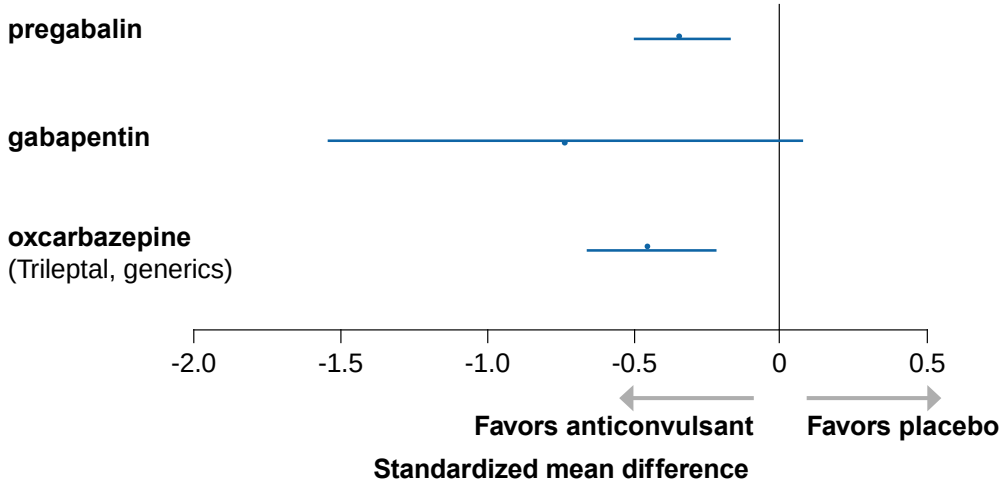
TCAs studied for diabetic neuropathy include amitriptyline, imipramine, and desipramine. A meta-analysis of five RCTs found a moderate to large effect size for pain reduction for TCAs (SMD -0.78; 95% CI: -1.24 to -0.33).[110] However, efficacy must be balanced against safety, especially given adverse effects common in older adults.

Anticonvulsants

Pregabalin and oxcarbazepine reduce pain, but the effects of other anticonvulsants are less clear. In a meta-analysis looking at 16 RCTs, pregabalin was effective at reducing pain compared with placebo (SMD -0.34; 95% CI: -0.50 to -0.18).[111] Similarly, oxcarbazepine had a small effect size compared to placebo (SMD -0.45; 95% CI: -0.68 to -0.21).[111]

Gabapentin is a commonly prescribed off-label to treat diabetic neuropathy. Based on a review of five RCTs, 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, crossing the null effect size of 0). These effect sizes are summarized in Figure 14.

Figure 14: Effect size of anticonvulsants for diabetic neuropathy compared to placebo



The American Diabetes Association recommends using pregabalin, reserving gabapentin for patients unable to afford pregabalin. Other anticonvulsants (e.g., carbamazepine, topiramate, valproic acid, lacosamide, lamotrigine) lack clear findings of benefit but have documented harms or are ineffective.[29]

Topical lidocaine

FDA approved for post-herpetic neuralgia, no RCTs of lidocaine patches have been conducted in diabetic neuropathy. One open label, 4-week trial of 300 patients with painful diabetic polyneuropathy or post-herpetic neuralgia looked at 5% lidocaine medicated plaster was compared to pregabalin. In post-herpetic neuralgia more patients responded to 5% lidocaine medicated plaster treatment than to pregabalin (PPS: 62.2% vs. 46.5%), while response was comparable for patients with painful diabetic polyneuropathy (PPS: 66.7% vs. 69.1%).[112]

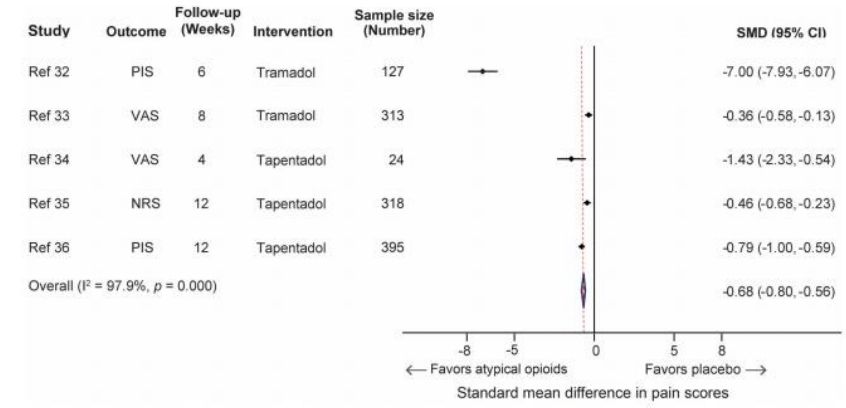
Cannabinoids for diabetic neuropathy

Medical marijuana and cannabinoids have limited data to suggest efficacy in reducing pain. A study of one-time use of high and low potency cannabis cigarettes (7% or 3.5% THC) in 44 patients showed reduced pain scores in both cannabis cigarette groups vs. placebo cigarettes.[113] Over 4 weeks, 70% of patients had at least a 30% reduction in pain with oral cannabinoid, nabilone (Cesamet) versus placebo. An open-label 5-week extension treatment period found a dose of 3 mg (range 1-4 mg) effective for continued pain reduction.[114] While encouraging, it is difficult to draw clinically meaningful conclusions from these studies, in part due to the fact that dosages have not been standardized.

Opioids

Typical opioids are ineffective for pain in diabetic neuropathy based on data from four RCTs (SMD -0.58; 95% CI: -1.53 to 0.36). This analysis excludes tramadol and tapentadol.[111] Due to their effect on serotonin and norepinephrine receptors, tramadol and tapentadol may be more effective than other opioids at reducing pain in diabetic neuropathy (see Figure 15). However, follow-up was short term, with the longest study lasting 12 weeks and both medications are subject to opioid tolerance, dependence, and addiction.

Figure 15: Studies comparing an atypical opioid with placebo for pain outcome[111]



CI = confidence interval; NRS = Numeric Rating Scale; PIS = Philadelphia Pain Intensity Scale; VAS = Visual Analog Scale.

Other drug options

Data for use of the SSRIs paroxetine and citalopram are inconsistent and insufficient to recommend their use in managing pain in diabetic neuropathy. However, these drugs may be effective if patients have coexisting pain and depression.[115]

Earlier studies showed that treatment with topical capsaicin was beneficial for relieving pain in patients with diabetic neuropathy.[116,117] However, a recent meta-analysis found that capsaicin cream was ineffective.[111]

Additional interventions

Spinal cord stimulation has been studied for pain relief in diabetic neuropathy but has insufficient evidence for any recommendation and most studies are single-arm, prospective studies with fewer than 10 patients.[118,119] RCTs are needed to determine efficacy.

Drug summary for diabetic neuropathy

The American Diabetes Association recommends selecting either pregabalin or duloxetine as the initial pharmacologic approach. Gabapentin may also be considered as an effective approach, but the patient's socioeconomic status, comorbidities, and potential drug interactions should be taken into consideration. TCAs are effective but should be used with caution because of the higher risk of serious side effects, especially in the elderly. Opioids are not recommended as first- or second-line options, considering the risk of addiction and other harms.[120] Although based on efficacy, tramadol may be considered as a treatment option in some patients, although it has all the risks associated with opioid analgesics. For a complete summary of the drug interventions presented, see Appendix V.

Fibromyalgia

Fibromyalgia is the second most common "rheumatic" disorder after OA and can be thought of as a centralized pain state. Patients will have lifelong pain throughout their bodies. Fibromyalgia should be suspected in patients having multifocal pain not fully explained by injury or inflammation. Chronic headaches, sore throats, visceral pain, and sensory hyper-responsiveness are very common.

Checking 18 tender points (9 pair) on the body may aid in diagnosing fibromyalgia. These tender points are sometimes confused with trigger points, which are associated with chronic myofascial pain. The primary difference between tender points and trigger points is that trigger points can produce referred pain. Guidelines suggest that people with fibromyalgia have pain in at least 11 of these tender points when a doctor applies a certain amount of pressure.[121]

Non-drug options

Movement-based options and weight loss

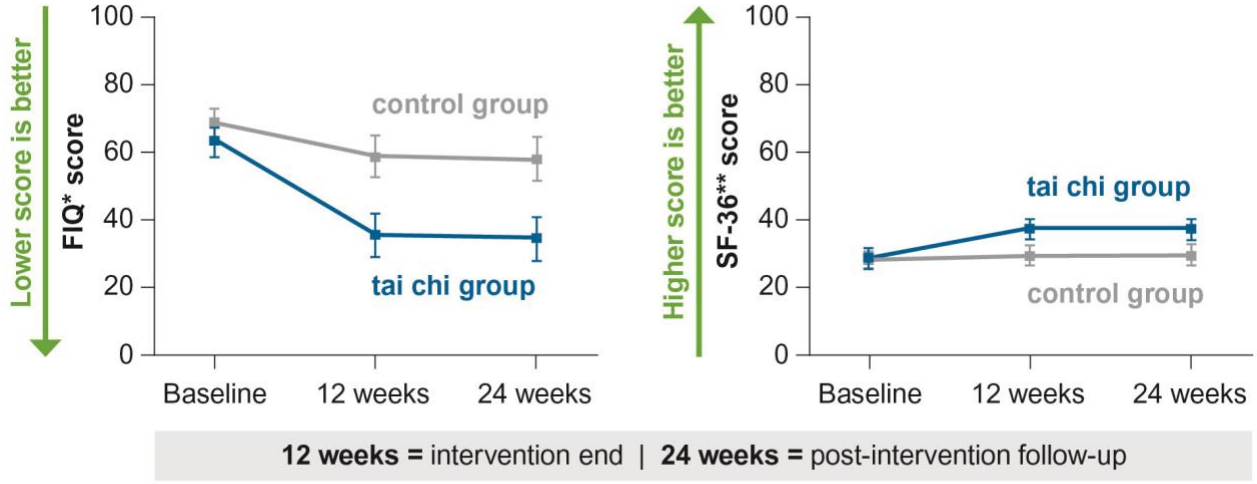
Exercise training is often recommended for patients with fibromyalgia. The benefits of aerobic exercise include strengthening the heart and improving circulation, lowering blood pressure, and helping control blood sugar and weight. In eight RCTs (n=456), small clinical improvements were noted in pain (18%) and function (22%) with aerobic exercise compared to placebo. Benefits for pain and function persisted after intervention (24 to 208 weeks). Also, patients who exercised rated their fatigue as 63 points versus 68 points in the control group after 14 to 24 weeks.[122] Based on three small trials (n=100) aerobic exercise was better for pain than resistance training.[123]

There are no data for **physical therapy** alone.

In one RCT (n=83), obese patients were assigned to 6-month dietary **weight loss** (n = 41) and no weight loss (n = 42) groups. Patients in the dietary weight loss group were instructed to follow a conventional energy-restricted diet of approximately 1,200 kcal/day for six months with 15– 20% of energy intake in the form of protein, 50–55% in the form of carbohydrates, and approximately 30% in the form of fat divided in three meals. Study results showed that six months of dietary weight loss led to significant improvement in quality of life as shown by a decrease in Fibromyalgia Impact Questionnaire (FIQ) scores (between group difference, 51.6 vs. 47) but small clinical effect.[124]

Tai chi is considered a complex multicomponent intervention that integrates physical, emotional, and behavioral elements and with its mind-body attribute, may be well-suited to the treatment of fibromyalgia. One RCT of 66 patients compared the physical and psychological benefits of tai chi with those of a control intervention that consisted of wellness education and stretching. The tai chi intervention took place twice a week for 12 weeks (60-minute sessions). Tai chi improved scores on the FIQ (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 the follow-up period (24-weeks) as shown in Figure 16. At 12 weeks, between group difference was -18.4 FIQ points.[125]

Figure 16: Mean change in FIQ and SF-36 scores at 12 and 24 weeks[125]



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

There is conflicting evidence about the benefit of **yoga** from small, low quality trials.[126]

Acupuncture, massage, and TENS

One in five patients with fibromyalgia use **acupuncture** within two years of diagnosis.[127] In a RCT (n=13), acupuncture had a moderate reduction in pain (mean difference of -22.4 on a scale of 0-100) at 1 month compared with placebo and no difference in pain reduction vs. sham. Mean pain in the non-treatment control group was 70 points on a 100-point scale. Acupuncture improved well-being (15 points) and fatigue (1 point). There was no difference in sleep quality, and physical function was not reported.[127]

Based on two small trials, myofascial **massage** may improve pain over placebo.[128] Although data recommending other forms of massage for reducing pain are limited, most styles of massage therapy consistently improved quality of life for patients with fibromyalgia.

Six low-quality RCTs failed to show that **TENS** reduced pain in fibromyalgia.[129]

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)[130]

In seven RCTs of mindfulness, no reduction in pain was observed. Methods were varied and incorporated different components of mindfulness based stress relief, CBT, and yoga.[19] In two low quality RCT, self-management education did not improve pain or disability vs. controls.[19]

Non-drug summary for fibromyalgia

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

Drug options

Acetaminophen and NSAIDs

There are no data demonstrating efficacy in treating pain in patients with fibromyalgia.[131]

SNRIs

Duloxetine

A review of duloxetine included six RCTs, involving 2249 participants with fibromyalgia aged 18 or older. Four studies tested duloxetine for 12 weeks and 2 for 6 months. Five of the six studies stipulated minimum entry criteria: significant pain at entry (≥ 4 on the pain intensity item of the Fibromyalgia Impact Questionnaire or Brief Pain Inventory). One study did not stipulate any criteria for pain at entry and participants could have, or not have, major depressive disorder. One study included only women, and the other five included over 90% women, despite being open to males and females, reflecting the epidemiology of this condition. Duloxetine 120 mg daily reduced pain scores by ≥30% in more patients vs. placebo at ≤12 weeks. Doses <60 mg daily did not improve pain vs. placebo. Studies >12 weeks also found similar benefits from duloxetine 60 or 120 mg daily vs. placebo. The magnitude of improvement in pain at 12 weeks was similar to that seen in participants with diabetic peripheral neuropathy.[132]

Milnacipran

Three RCTs that evaluated 100 mg daily vs. placebo favored milnacipran for at least 30% pain relief (RR 1.38; 95% CI: 1.22-1.57). A similar effect on pain relief was noted with milnacipran 200 mg daily.[133]

Antidepressants

Nine trials of the **TCA** amitriptyline found a small improvement in pain (SMD -0.43; 95% CI: -0.75 to -0.11).[134]

A Cochrane review of seven low quality RCTs found a small (10%) difference in patients who reported a 30% pain reduction between **SSRIs** (33%) and placebo (23%). SSRIs included in review included citalopram, fluoxetine, and paroxetine.[135] These data are insufficient to recommend SSRIs for the treatment of pain alone in patients with fibromyalgia.

Anticonvulsants

Pregabalin

A systematic review of five RCTs found pregabalin had a small effect on pain (SMD -0.28; 95% CI: -0.35 to -0.20). Low doses of 150 mg per day were no different than placebo, but doses of 300 mg daily or greater, reduced pain scores more than placebo. Doses of 300 mg daily were more likely to result in a 50% reduction in pain than placebo (RR 1.45; 95% CI: 1.03-2.05).[136]

Gabapentin

Only two RCTs with duration of eight weeks or more were conducted with gabapentin. A study of 150 patients found 49% (38/75) had a 30% reduction in pain with gabapentin vs. 31% (23/75) with placebo.[137]

Other options

Topical lidocaine

Other drug options such as topical lidocaine, medical marijuana have no evidence to support their use in patients with fibromyalgia.

Opioids

A Cochrane review found no RCTs of opioid therapy in patients with fibromyalgia lasting more than eight weeks.[138] A cohort of fibromyalgia patients treated with opioids vs. non-opioids found the opioid cohort had no difference in pain severity and poorer pain interference scores vs. non-opioid cohort.[139] One RCT suggests that tramadol + acetaminophen may reduce pain over 91 days, but long-term evidence is not available.[140]

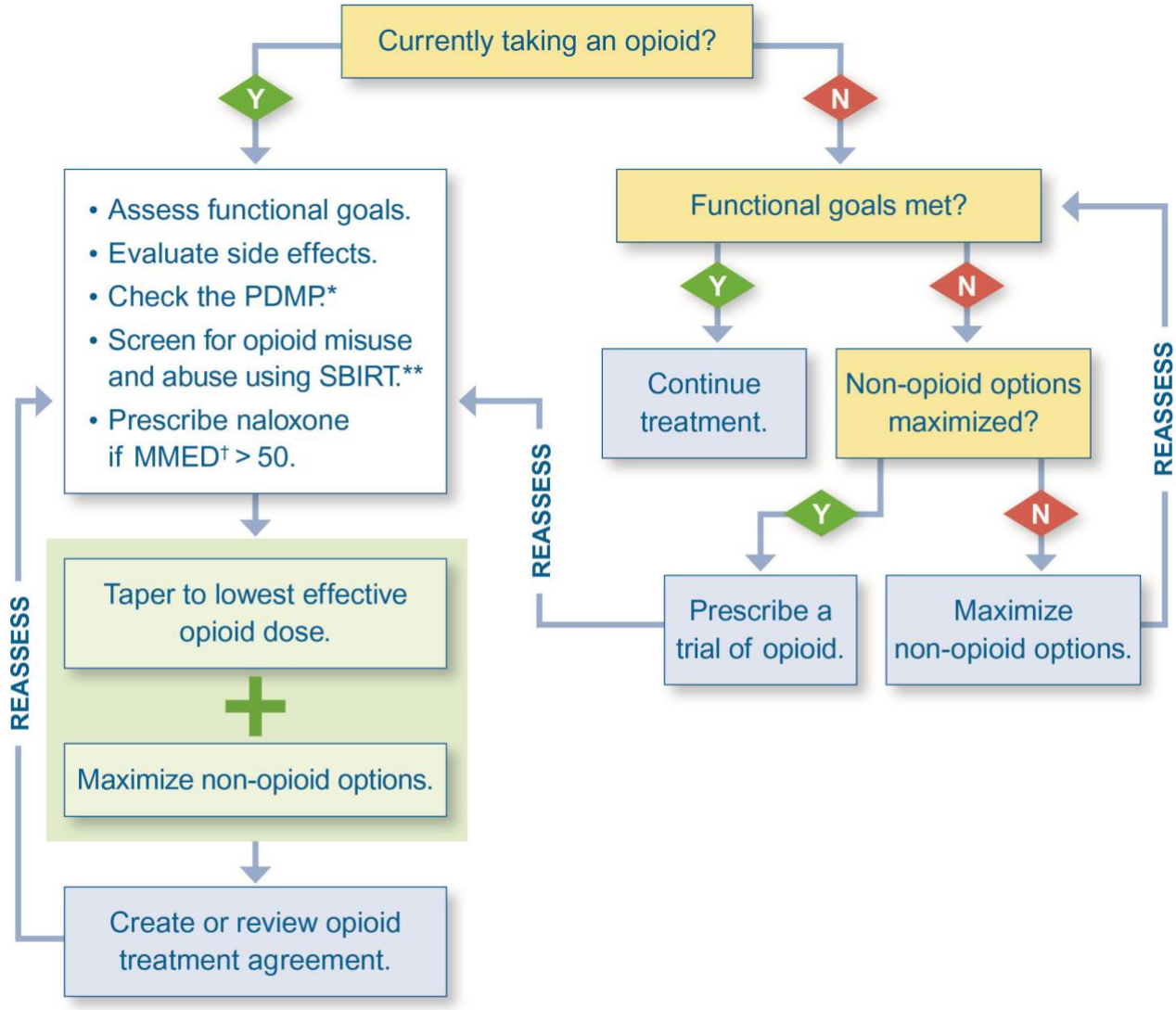
Drug summary for fibromyalgia

The European League Against Rheumatism (EULAR) guidelines recommend beginning with non-drug approaches (exercise, CBT, acupuncture, yoga, tai chi, and mindfulness) and then advancing to pharmacologic options (low dose amitriptyline, duloxetine or milnacipran, tramadol, pregabalin). Most recommendations were considered weak.[141] However, in the elderly, duloxetine or milnacipran and pregabalin or gabapentin may be the more favorable pharmacologic options. For a complete summary of the drug interventions presented, see Appendix VI.

Creating a chronic pain management plan

Managing chronic pain is a balance between safety and efficacy with a strong focus on establishing functional goals and monitoring progress toward those goals. Many patients with OA, chronic low back pain, diabetic neuropathy, and fibromyalgia have been struggling with the challenge of managing their pain for years and may already be on opioids. For those patients, improving safety and exploring non-opioid coping techniques to help reduce daily opioid doses are two important yet challenging considerations. For those who have not yet started opioids, exploring other therapeutic options before starting a trial of opioids is the optimal treatment approach. One approach for managing these different patient populations is presented in Figure 17 below. For overall recommendations of non-opioid options for each of the four chronic pain conditions, see Appendix VII.

Figure 17: Algorithm for managing chronic pain



* **PDMP:** prescription drug monitoring program
****SBIRT:** Screening, Brief Intervention, and Referral to Treatment
† **MMED:** morphine milligram equivalents per day

For all patients with chronic pain, management begins by establishing treatment goals, exploring non-opioid treatment options, and addressing comorbid depression and anxiety. Pain management goals may include both pain and functional targets, but the ultimate goal to be entire pain free is often not realistic and should not be an acceptable target. Instead, patient goals should be established by focusing on activities that are meaningful and attainable based on the severity of the individual pain condition. A multi-modal approach that includes non-drug and drug interventions is essential for a pain management plan. Select evidence-based options based on the pain condition being managed. Be aware that comorbid conditions such as depression and anxiety can impact pain management. In a study of 250 patients with low back, hip and knee pain and moderate depression, using antidepressant therapy reduced pain interference in completing daily task before

interventions targeting pain were added.[142] Ensure effective treatment of depression and anxiety while initiating pain management options.

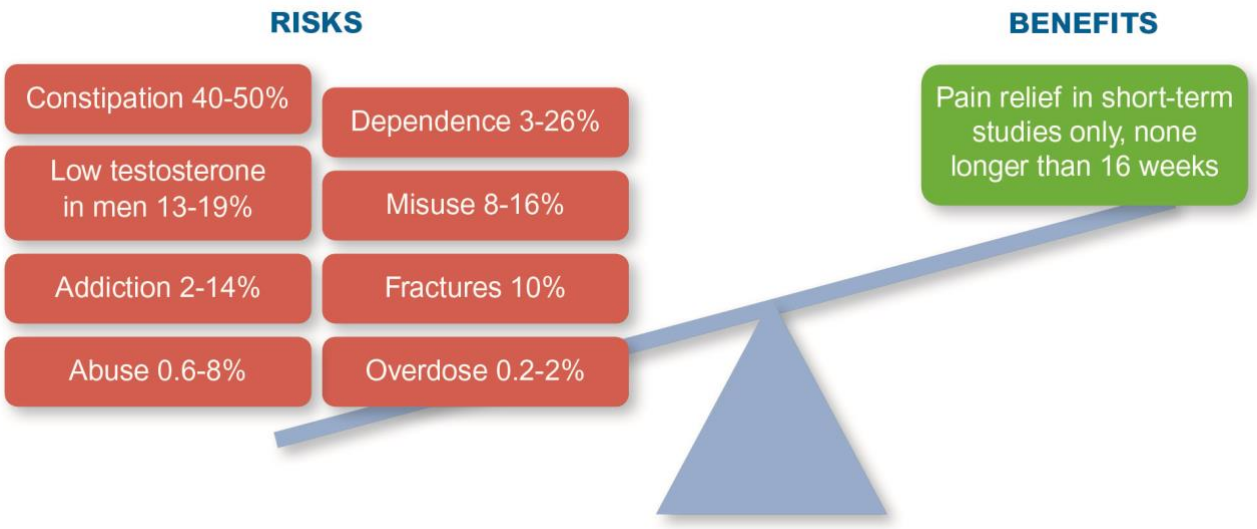
For patients with intractable, severe pain with an etiology that may be responsive to opioids who have optimized non-opioid treatment options, a trial of opioids may be indicated. However, expert opinion has shifted in recent years, suggesting that opioids are rarely the best treatment option for patients with chronic pain. Key following steps are recommended to ensure safe opioid prescribing:

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

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 many patients, the risks of opioid therapy, as shown in Figure 18, outweigh the benefits. However, for some patients with nociceptive chronic pain, intermittent use of low-dose opioids on an as-needed basis may be a reasonable approach.

Figure 18: Balancing the risks and benefits of opioid therapy



Establish a written treatment agreement

Prepare a written agreement when opioids are initiated. A written agreement or treatment plan should clarify how opioids will be prescribed, goals of patient-centered therapy (i.e., more than pain and function and include emotional and social dimensions), include side effects and risks of treatment, monitoring requirements, and a discontinuation or tapering plan.[143] Agreements may specify a single pharmacy and a

commitment that prohibits using other providers. Patients should be informed that opioid prescriptions are tracked and will be monitored. Additional monitoring may be included in the contract including, pill counts, urine drug screens, and other interventions. Visit AlosaHealth.org/Pain for a link to a sample treatment agreement from the National Institute of Drug Abuse (NIDA) and other useful resources.

Monitoring opioid use

Many strategies to assess opioid use and ensure patient safety have been recommended. However, simply asking patients questions about how they are using the medication, how often they take it, how many pills they take at one time, and what triggers them to take the medication, can identify patients who may be misusing opioids or need changes to their pain management plan. Other ways to objectively monitor opioid use are checking prescription drug monitoring programs, completing urine drug screens, agreements regarding pharmacy utilization, random pill counts and other interventions. Many of these safety checks are described in a comprehensive treatment agreement so patients are aware of the increased monitoring that accompanies opioid prescriptions.

Prescription drug monitoring programs (PDMP)

All 50 states have a mandate for a PDMP, a database where prescribers can review prescriptions for controlled substances for a patient. Information available through the PDMP varies based on reporting requirements and restrictions, such as schedules reported, timeliness of pharmacy dispensing information, access, and required reviews. Recommendations regarding use of the PDMP include:

- Check the PDMP before starting anyone on opioid therapy.
- Review the PDMP periodically throughout opioid therapy (at least every 3 months).
- Look for opioids and other controlled substances, like benzodiazepines, that can increase risk of overdose.
- Review the total MMED to discuss tapering or initiating naloxone.
- Discuss any concerning information with patients.
- Check a urine screen, if diversion is suspected.

Some states have specific requirements for PDMP use, such as requiring review prior to initial prescription or any time a specific prescription is written, such as hydrocodone ER (Zohydro). Be aware of your state's requirement. For more information regarding the requirements for Pennsylvania visit doh.pa.gov/PDMP. States are permitting or enacting permissions for interstate sharing of data to reduce doctor shopping potential across state lines.

PDMPs identify patients who may be at increased risk of overdose. Combining opioids with other agents, such as benzodiazepines, increases the risk of respiratory depression.[143] Benzodiazepines have been linked with opioids in overdose fatalities, 50-80% in heroin overdoses, and 40-80% in methadone related deaths.[143,144] Patients on benzodiazepines who are being initiated on opioids should have their benzodiazepine tapered and discontinued whenever possible. For patients being co-managed by mental health professionals, coordinate a plan regarding continuing or tapering benzodiazepines in the setting of opioid co-prescribing.

In Pennsylvania, requirements include reviewing the PDMP before starting anyone on opioid therapy (prescribers practicing in emergency room settings are exempt). Documentation is required for first-time prescriptions and new patients. For example, if there are no red flags when checking the PA PDMP, then it is

safe to proceed with the prescription. If a prescriber checks the PA PDMP and opts not to prescribe an opioid, the findings from the PDMP that support the decision not to prescribe an opioid must be documented and discussed with the patient. An example may be: “Checked the PA PDMP; opted not to prescribe an opioid after determining patient had filled six prescriptions from four different prescribers over the past five weeks. Discussed findings with patient."[145]

Urine drug screens

Urine drug screens are recommended before prescribing an opioid. No clear evidence supports a specific monitoring schedule, but experts believe at least annual testing may be reasonable. Providers using urine drug screens should be knowledgeable about expected results, such as being familiar with the metabolites and expected positive results based on the opioid prescribed. For example, a patient taking oxycodone may have a test positive for both oxycodone and oxymorphone (a metabolite). Discuss use of prescribed (including when the last dose was taken) and other drugs prior to obtaining a urine screen, as this will help interpret testing results.[143]

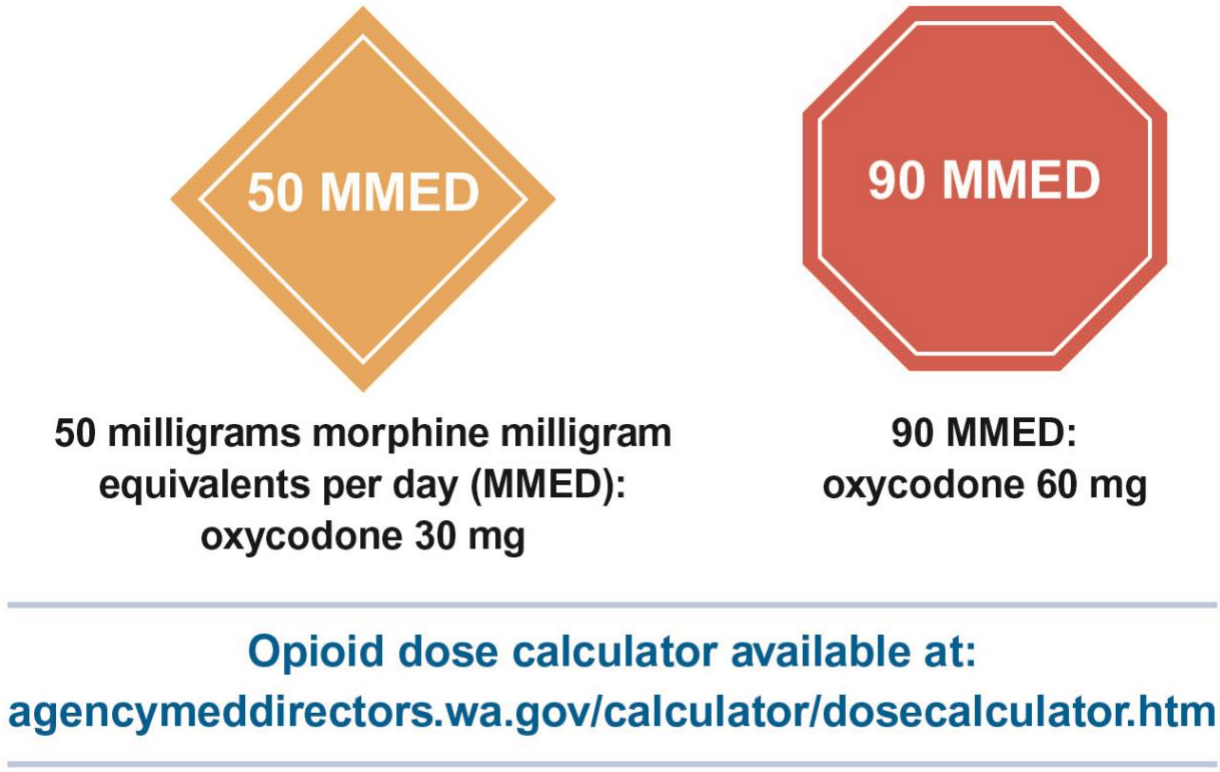
If the prescribed opioid is not detected, and the patient admits to diverting, re-evaluate the specific pain management strategy and discontinue opioids. If other drugs, not prescribed are positive, schedule more frequent follow-up visits, offer naloxone, or refer for treatment for substance use disorder. Decision tools and help with interpreting urine drug testing results are available at mytopcare.org/.

Caution with dose escalation

When initiating a trial of opioids, start with immediate release opioids. These short-acting opioids are safer because of a shorter half-life and lower risk of inadvertent overdose. Prescribe low doses on an intermittent, as needed basis. Except in palliative care, dose escalation should be avoided. For elderly patients who have comorbidities, start at an even lower dose (25-50% of usual adult dose). Follow-up appointments should occur one to four weeks after initiation of opioids or with dose changes; maintenance therapy visits should occur at least every three months. Each visit should include an assessment using a pain and function tool, questions about side effects, evaluation the risk of overdose, and discussions regarding how the medication is being used.[143]

When escalating opioid doses, beware of critical daily thresholds—50 and 90 morphine milligram equivalents per day (MMED).[143] According to the CDC, doses >50 MMED increase the risk without increasing the benefit,[43,143] with a more than doubling in risk of overdose in patients on more than 50 MMED than patients on <50 MMED. For patients on >90 MMED, a 9-fold increase in mortality risk was observed compared with the lowest opioid doses. Experts recommend 90 MMED as a maximum daily dose, requiring careful assessment and documentation of the benefits of treatment beyond this dose. The total MMED for all prescribed opioids should be used to determine the overall MMED. MMED is calculated on many state Prescription Drug Monitoring Programs (PDMPs) reports.

Figure 19: Morphine equivalents for 50 and 90 MMED



Role of ER/LA opioids and methadone

Based on expert recommendations from the CDC, patients should not be initiated on ER/LA opioids and they should be prescribed only on a schedule (no PRN doses). Given a dose caution at 50 MMED, the continued role for ER/LA opioids in chronic, non-cancer pain should be limited.

The use of methadone for chronic pain in primary care should generally be avoided. QTc prolongation and fatal arrhythmias may occur. Equianalgesic dose ratios are highly variable, making conversion from other opioids to methadone difficult and increasing the risk of overdose. While methadone related death rates decreased 9% from 2014 to 2015 for most adults, the rate increased in people ≥65 years of age.[146] If methadone is being considered, refer patients to pain management specialists with expertise in using this medication.

Prescribe naloxone

Naloxone, an opioid antagonist, reverses the effects of taking too much of an opioid such as respiratory depression. Widespread distribution to first responders occurred in many states as a way to combat the spike in opioid related overdose deaths. Primary care providers should also prescribe naloxone to patients at risk of overdose, including those:

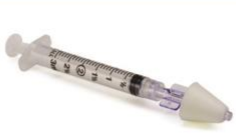
- with renal or hepatic dysfunction,

- taking opioid doses >50 MMED,
- co-prescribed benzodiazepines or other sedating medications,
- with a history of overdose or opioid use disorder, or
- starting addiction treatment.

Friends and family members may also request naloxone. In many states, including Pennsylvania, a standing order allows patients, family members, caregivers, and/or friends to request naloxone from their local pharmacist.

All who receive naloxone should be counseled about appropriate use of the device. Signs of overdose include slow or shallow breathing, gasping for air or unusual snoring, pale or bluish skin, not waking up or responding, pin point pupils, and a slow heart rate. A variety of naloxone products are available (see Table 10). The intranasal with atomizer and intramuscular (IM) shots require the most manipulation in order to administer. Intranasal naloxone (Narcan) and the auto-IM injector are easier to use, but vary greatly in terms of price and insurance coverage.

Table 10: Dosage forms available for naloxone

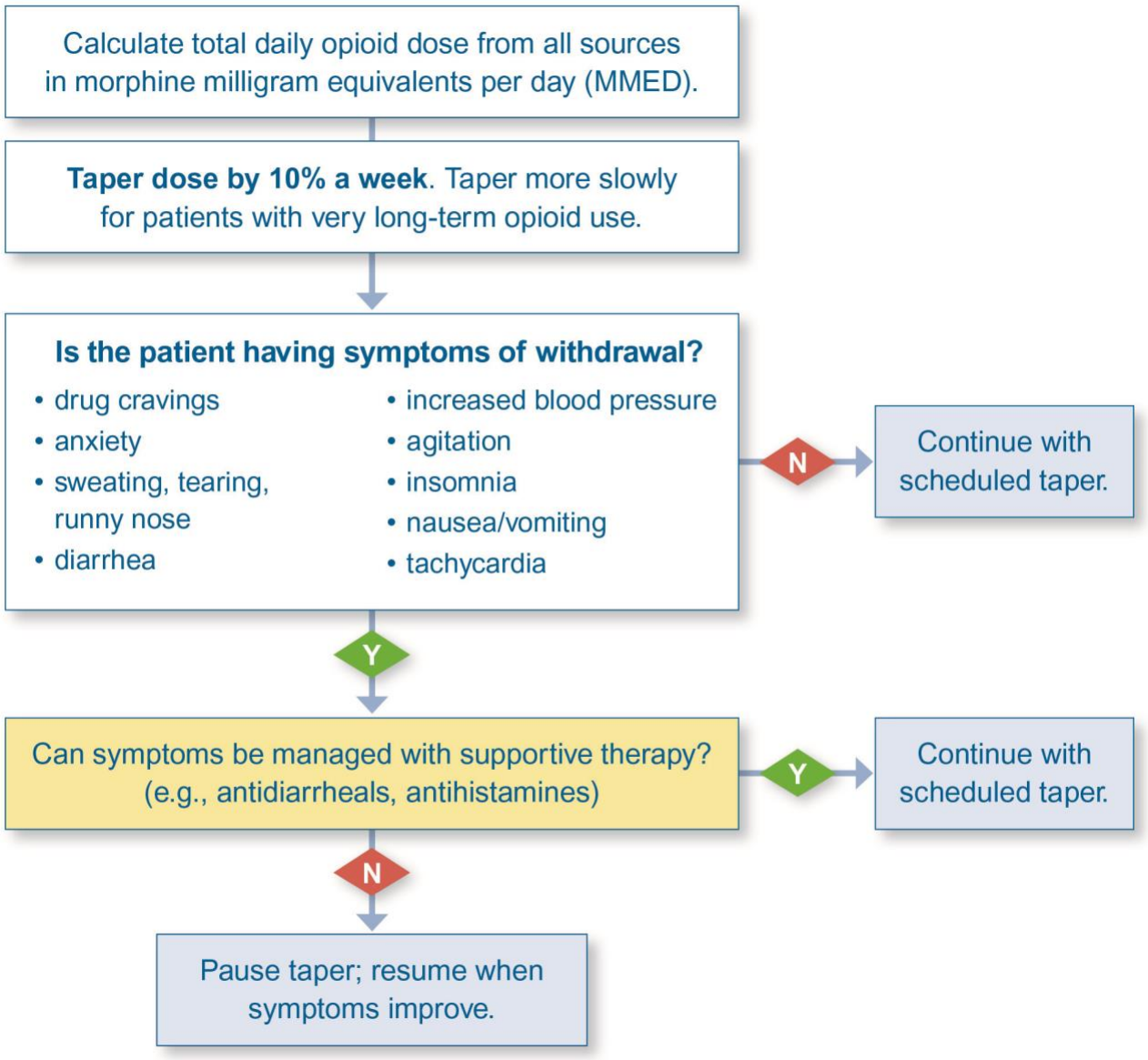
	Intranasal (w/atomizer)	Intranasal	Intramuscular (IM)	Auto-IM
				
Brand name		Narcan		Evzio
Strength	1 mg/1 mL	4 mg/ 0.1 mL	0.4 mg/1 mL	0.4 mg/1 mL
Sig for suspected overdose	Spray 1 mL into each nostril.	Spray full dose into one nostril.	Inject 1 mL into shoulder or thigh.	Use as directed by voice-prompt.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

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

Tapering and discontinuing opioids

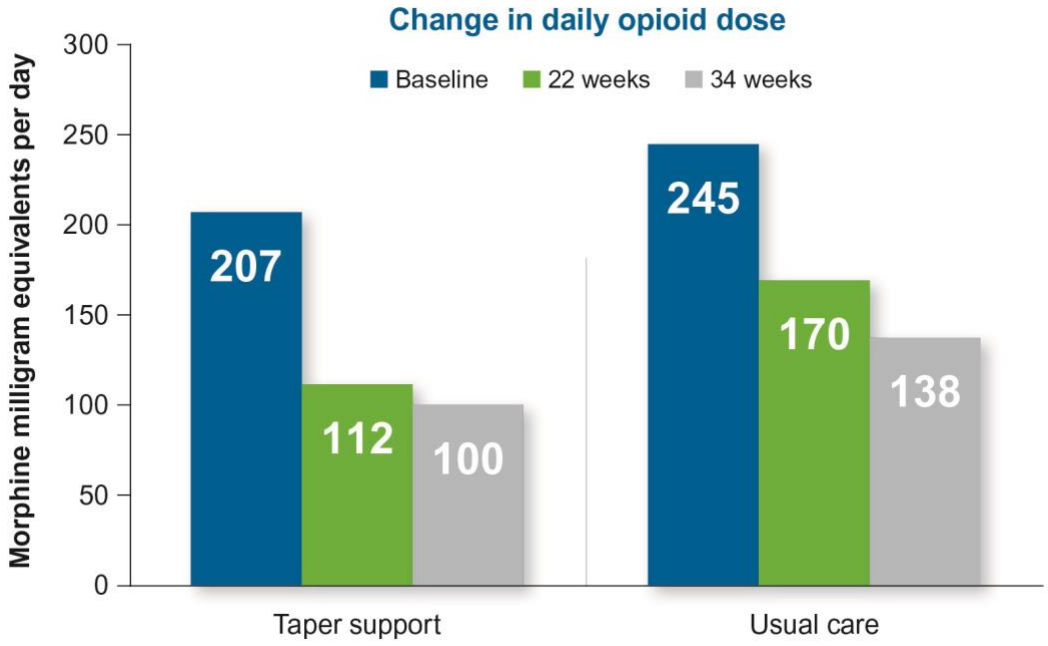
For all patients, but especially those who are on high opioid doses, not achieving functional goals despite increasing opioid doses or those with side effects, tapering and discontinuing opioids should be discussed. Patient resistance to tapering and discontinuing opioids centers around the belief that lower opioid doses will increase their pain. However, a 2017 systematic review found that dose reduction or discontinuation resulted in reduced pain (eight studies) and improved function (five studies) and quality of life (three studies).[147] Given the heterogeneity across interventions and the overall poor quality of studies, data on the comparative effectiveness of different models of care or opioid tapering protocols are lacking. Conservative recommendations vary based on the duration of opioid use. A 10% decrease weekly is recommended, based on years of opioid use (i.e., 10% decrease monthly for patients using opioids ≥4 years). For patients on high-dose opioids (i.e. ≥90 MMED), taper 10% until patient is taking 30% of the total initial dose, then recalculate 10% taper based on new total opioid dose to slow taper.[147,148] An approach to managing an opioid taper is presented in Figure 20.

Figure 20: Tapering algorithm



A small trial of 35 patients with over 10 years of opioid use (taper group: n=18; usual care group: n=17) found reduced opioid doses in the intervention group compared to the placebo group (see Figure 21 on next page). The taper group was provided weekly consultations modeled after chronic pain CBT interventions while the usual care group continued to receive care from their usual physician, but with the restriction that buprenorphine could not be prescribed. Pain scores as assessed using the BPI, decreased by 1 point in the taper support group vs. no change in usual care. All patients were evaluated to determine if antidepressant doses were optimized. Between group differences in opioid dose were not statistically significant, but were lower in the intervention group. Opioid taper did not cause any adverse events.

Figure 21: Change in daily opioid dose [149]



Encouraging patient tapers should include identifying harms or risks that resonate with patients. Find social supports to encourage opioid dose reductions. Locate opportunities for peer support to address fear of taper and benefits of not using opioids. Be supportive, nonjudgmental, flexible, and accessible. The CDC recommends going slowly and consulting with experts if patients have OUD or are pregnant, providing support by consulting or referring to mental health providers, offering naloxone, and encouragement by considering any dose reduction as a success.[150]

Screen for opioid abuse

Screening, Brief Intervention, and Referral to Treatment (SBIRT) assists primary care providers in identifying patients with problematic opioid use or potential opioid use disorder. SBIRT assess the severity of opioid use, is brief (typically 5-10 minutes), and targets behaviors specific to substance use. In a study of patients with opioid use disorder presenting to the emergency room, SBIRT resulted in increased retention in addiction treatment at 30 days compared to screening alone, 45% and 37%, respectively.[151] SBIRT is a billable service, visit AlosaHealth.org/Pain for more information on SBIRT.

Opioid use disorder

Nearly 2 million people have opioid use disorder.[46] Opioid use disorder (OUD) is defined as a problematic pattern of opioid use leading to clinically significant impairment or distress, with at least two of the following, occurring within a 12-month period:

- opioids often taken in larger amounts or over a longer period than was intended
- persistent desire or unsuccessful efforts to cut down or control opioid use
- a great deal of time spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects
- craving, or a strong desire or urge to use opioids

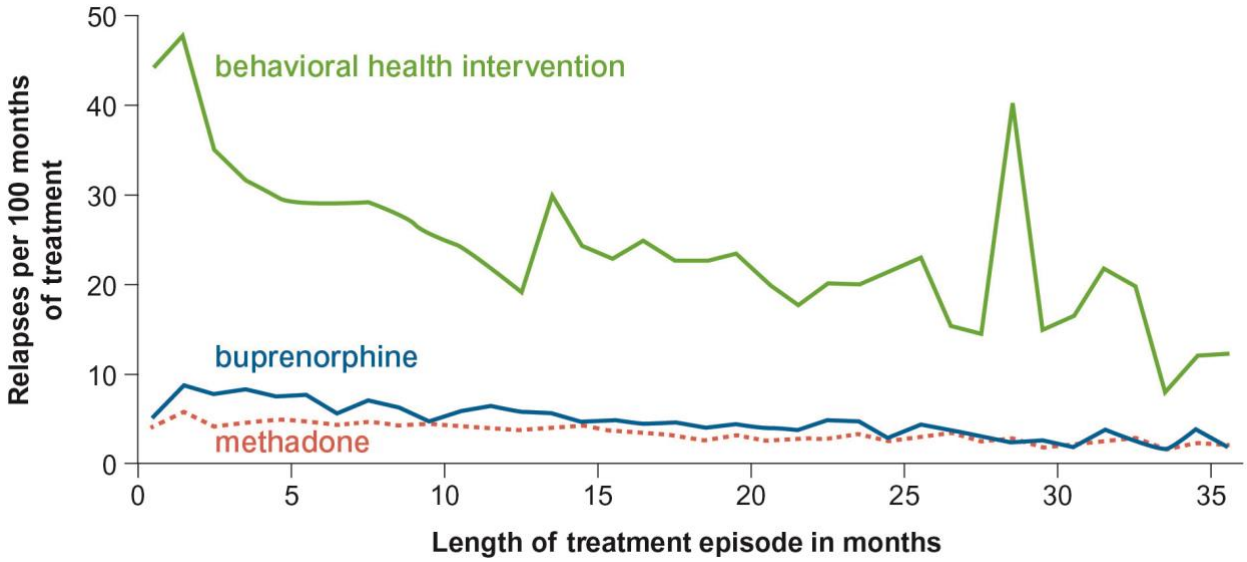
- recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home
- continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the opioids
- important social, occupational, or recreational activities are given up or reduced because of opioid use
- recurrent opioid use in situations in which it is physically hazardous
- continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been cause or exacerbated by the substance
- tolerance – either a need for markedly increased amounts of opioids to achieve intoxication or desired effect OR a markedly diminished effect with continued use of the same amount of an opioid*
- withdrawal – characteristic opioid withdrawal syndrome OR opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms*[48]

* These criteria are not considered to be met for individuals taking opioids solely under appropriate medical supervision

The severity of OUD is classified by the number of symptoms with the presence of 2-3 symptoms classified as mild, 4-5 symptoms as moderate and 6 or more symptoms as severe.

Patients with identified OUD can be effectively treated in primary care settings with buprenorphine/naloxone (Suboxone) or they can be referred to specialty addiction treatment. Medication options include methadone, buprenorphine as buprenorphine/naloxone (Suboxone), naltrexone extended-release (ER) injection (Vivitrol), and a newly approved buprenorphine monthly injection (Sublocade). Medications have been shown to be better at maintaining abstinence than behavioral interventions alone (see Figure 22).

Figure 22: Relapses were less common with patients on methadone and buprenorphine than with behavioral health intervention



Each medication option has benefits and challenges. Addiction treatment programs have the longest experience with methadone. However, it is dispensed only from methadone clinics and many patients are required to attend the clinic daily for their medication. Buprenorphine can be prescribed by primary care providers who complete eight hours of training for a DEA-X waiver, potentially increasing patient access to treatment and removing the stigma of attending a methadone clinic daily. A systematic review found no

difference in terms of treatment retention between patients prescribed methadone compared to buprenorphine.[152] Naltrexone ER injection requires seven days of detoxification prior to starting. Injections are given monthly, so compliance with treatment can be monitored and assessed more easily in these patients. New data suggest naltrexone ER is not inferior to buprenorphine (Suboxone).[153] The new buprenorphine subcutaneous injection is an option for patients who have successfully been treated with buprenorphine (Suboxone).

Putting it all together

Chronic pain is, and will continue to be, a concern as the elderly population grows, and for this population of adults who live independently, chronic pain can have devastating and widespread effects. Chronic pain is often considered a health condition in itself.

Managing chronic pain is challenging. As the healthcare team, physicians and caregivers need to develop a plan to address the patient's chronic pain, focusing on identifying realistic patient goals and the level of pain management needed to reach the desired functional ability with the patient's direct input in the pain management plan and implementation. Although different pain syndromes have varied options, it is important that the treatment plan should minimize harm from treatment-related side effects, addiction, or drug abuse. For most syndromes, non-drug options, which can be as effective as drug options, should be tried first. When drug options are considered, it is important to maximize non-opioid options before prescribing opioids. For selected patients requiring opioids, the risk of long-term opioid treatment should be minimized through patient education, screening of high-risk patients for OUD, continuous monitoring, use of alternative non-opioid options, and careful tapering.

Appendix I: Brief Pain Inventory

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

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

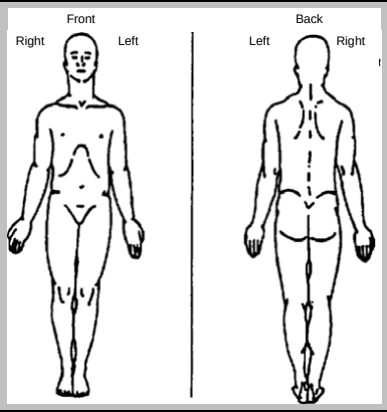
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2

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

Date:___/____/____ Time:_____

Name:_____ _____ _____

Last First Middle Initial

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

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

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

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

Appendix II: FDA approved indications for medications to manage pain

Medication	Brand name	FDA-approved indication
acetaminophen	Tylenol, generics	Pain relief / fever reduction
NSAIDs		
Ibuprofen	Advil, generics	Pain relief / fever reduction
Naproxen	Aleve (OTC), Naprosyn, generics	Pain relief / fever reduction
Celecoxib	Celebrex, generics	Relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis in adults
Serotonin norepinephrine reuptake inhibitors (SNRIs)		
Duloxetine	Cymbalta, generics	Major depressive disorder Generalized anxiety disorder Diabetic peripheral neuropathy pain Fibromyalgia Chronic musculoskeletal pain
Milnacipran	Savella	Fibromyalgia
Venlafaxine	Effexor, Effexor XR, generics	Major depressive disorder Generalized anxiety disorder Social anxiety disorder Panic disorder
Tricyclic antidepressants (TCAs)		
Amitriptyline	Elavil, generics	Depression
Nortriptyline	Pamelor, generics	Depression
Anticonvulsants		
Pregabalin	Lyrica, Lyrica CR	Diabetic peripheral neuropathy Postherpetic neuralgia Partial onset seizures Fibromyalgia Neuropathic pain associated with spinal cord injury
Gabapentin	Neurontin, generics	Postherpetic neuralgia Epilepsy (partial onset seizures)

Oxcarbazepine	Trileptal, generics	Partial onset seizures in adults and children
Lidocaine patches	Lidoderm, generics	Postherpetic neuralgia
Opioids		
Tramadol	Ultram, Ultram ER, generics	Pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
Tapentadol ER	Nucynta ER	Pain associated with diabetic peripheral neuropathy AND general pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Tapentadol	Nucynta	Acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
Oxycodone		Moderate to moderately severe pain
Fentanyl patch Hydrocodone ER Methadone Oxycodone ER	Duragesic, generics Zohydro ER Dolophine, Methadose, generics OxyContin, generics	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Appendix III: Non-drug and drug summary for OA

	INTERVENTION	Duration	Effect size	Data quality	Safety	Overall
NON-DRUG OPTIONS	exercise	4 wks–30 mo (mode 8 wks)	◎	●	●	●
	physical therapy	4 wks–30 mo (mode 8 wks)	◎	●	●	●
	tai chi	8 wks–18 mo	◎	●	●	●
	weight loss	6-20 wks	○	◎	●	○
	yoga	6-12 wks	●	◎	●	●
	acupuncture	2-6 mo	◎	◎	●	●
	massage	4-12 wks	◎	●	●	●
	TENS*	3 mo	○	●	●	○
	cognitive behavioral therapy	—	—	—	●	○
	mindfulness meditation	8-10 wks	○	●	●	○
	self-management	—	●	●	●	●
DRUG OPTIONS	acetaminophen	1-6 wks	●	●	●	●
	NSAIDs—oral	1-56 wks	◎	●	●	●
	NSAIDs—topical	6-12 wks	◎	●	●	●
	duloxetine (Cymbalta, generics)	10-13 wks	●	●	●	●
	tricyclic antidepressants (TCAs)	—	—	—	◎	◎
	pregabalin (Lyrica, Lyrica CR)	4 wks	●	●	●	●
	gabapentin (Neurontin, generics)	—	—	—	●	○
	topical lidocaine (Lidoderm, generics)	12 wks	○	●	●	○
	medical marijuana	—	—	—	●	○
	opioids	—	●	●	◎	○
	tramadol	—	●	●	◎	○

* TENS: transcutaneous electrical nerve stimulation

Effect size: ● = large (cohen 0.8) ◎ = moderate (cohen 0.5) ● = small (cohen 0.2) ○ = no effect

Data quality: ● = high ◎ = moderate ● = low ◎ = very low

Safety: ● = generally recognized as safe ● = risk of significant side effects ◎ = significant harms

Overall risk/benefit profile: ● = favorable ● = potentially favorable ◎ = unfavorable ○ = unknown

Appendix IV: Non-drug and drug summary for chronic LBP

	INTERVENTION	Duration	Effect size	Data quality	Safety	Overall
NON-DRUG OPTIONS	exercise	—	●	◎	●	●
	physical therapy	—	—	—	●	○
	tai chi	—	◎	●	●	●
	weight loss	1 year	○	○	●	○
	yoga	—	○	●	●	○
	acupuncture	—	◎	◎	●	●
	massage	—	○	●	●	○
	TENS*	—	○	●	●	○
	cognitive behavioral therapy	—	◎	●	●	●
	mindfulness meditation	26-52 wks	●	◎	●	●
	self-management	—	●	●	●	●
DRUG OPTIONS	acetaminophen	—	—	—	●	○
	NSAIDs—oral	—	◎	◎	●	●
	NSAIDs—topical	—	—	—	●	○
	duloxetine (Cymbalta, generics)	—	●	◎	●	●
	tricyclic antidepressants (TCAs)	—	○	◎	◎	◎
	pregabalin (Lyrica, Lyrica CR)	—	○	●	●	○
	gabapentin (Neurontin, generics)	—	○	●	●	○
	topical lidocaine (Lidoderm, generics)	—	—	—	●	○
	medical marijuana	—	—	—	●	○
	opioids	—	●	◎	◎	○
	tramadol	—	◎	◎	◎	●

* TENS: transcutaneous electrical nerve stimulation

Effect size: ● = large (cohen 0.8) ◎ = moderate (cohen 0.5) ● = small (cohen 0.2) ○ = no effect

Data quality: ● = high ◎ = moderate ● = low ◎ = very low

Safety: ● = generally recognized as safe ● = risk of significant side effects ◎ = significant harms

Overall risk/benefit profile: ● = favorable ● = potentially favorable ◎ = unfavorable ○ = unknown

Appendix V: Non-drug and drug summary for diabetic neuropathy

	INTERVENTION	Duration	Effect size	Data quality	Safety	Overall
NON-DRUG OPTIONS	exercise	—	—	—	●	○
	physical therapy	—	—	—	●	○
	tai chi	3 mo	●	●	●	●
	weight loss	—	—	—	●	○
	yoga	—	—	—	●	○
	acupuncture	1 year	○	○	●	○
	massage	4 wks	○	●	●	○
	TENS*	<12 wks	●	●	●	●
	cognitive behavioral therapy	11 wks–4 mo	○	○	●	○
	mindfulness meditation	4 wks	○	○	●	○
	self-management	—	—	—	●	○
DRUG OPTIONS	acetaminophen	—	—	—	●	○
	NSAIDs—oral	—	—	—	●	○
	NSAIDs—topical	—	—	—	●	○
	duloxetine (Cymbalta, generics)	6-8 wks	●	◎	●	●
	tricyclic antidepressants (TCAs)	—	◎	●	○	●
	pregabalin (Lyrica, Lyrica CR)	—	●	●	●	●
	gabapentin (Neurontin, generics)	—	○	●	●	○
	topical lidocaine (Lidoderm, generics)	4 wks	●	●	●	●
	medical marijuana	0-5 wks	●	●	●	●
	opioids	—	○	●	○	○
	tramadol	—	◎	●	○	●

* TENS: transcutaneous electrical nerve stimulation

Effect size: ● = large (cohen 0.8) ◎ = moderate (cohen 0.5) ● = small (cohen 0.2) ○ = no effect

Data quality: ● = high ◎ = moderate ● = low ○ = very low

Safety: ● = generally recognized as safe ● = risk of significant side effects ○ = significant harms

Overall risk/benefit profile: ● = favorable ● = potentially favorable ○ = unfavorable ○ = unknown

Appendix VI: Non-drug and drug summary for fibromyalgia

	INTERVENTION	Duration	Effect size	Data quality	Safety	Overall
NON-DRUG OPTIONS	exercise	6-24 wks	●	●	●	●
	physical therapy	—	—	—	●	○
	tai chi	12-24 wks	◎	●	●	●
	weight loss	6 mo	●	●	●	●
	yoga	8 wks	○	●	●	○
	acupuncture	4 wks	○	●	●	○
	massage	—	●	●	●	●
	TENS*	—	○	●	●	○
	cognitive behavioral therapy	—	●	●	●	●
	mindfulness meditation	6-30 wks	○	●	●	○
	self-management	—	○	●	●	○
DRUG OPTIONS	acetaminophen	—	—	—	●	○
	NSAIDs—oral	—	—	—	●	○
	NSAIDs—topical	—	—	—	●	○
	duloxetine/	<12 wks	●	◎	●	●
	milnacipran	8-24 wks	◎	●	●	●
	tricyclic antidepressants (TCAs)	—	●	●	◎	○
	pregabalin (Lyrica, Lyrica CR)	8-14 wks	●	●	●	●
	gabapentin (Neurontin, generics)	12 wks	●	●	●	●
	topical lidocaine (Lidoderm, generics)	—	—	—	●	○
	medical marijuana	—	—	—	●	○
	opioids	—	—	—	◎	◎
	tramadol	—	●	●	◎	○

* TENS: transcutaneous electrical nerve stimulation

Effect size: ● = large (cohen 0.8) ◎ = moderate (cohen 0.5) ● = small (cohen 0.2) ○ = no effect

Data quality: ● = high ◎ = moderate ● = low ◎ = very low

Safety: ● = generally recognized as safe ● = risk of significant side effects ◎ = significant harms

Overall risk/benefit profile: ● = favorable ● = potentially favorable ◎ = unfavorable ○ = unknown

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

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

Risk/benefit profile: ● = favorable ● = potentially favorable ◎ = unfavorable ○ = unknown

* **TENS:** transcutaneous electrical nerve stimulation

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About this publication

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

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