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Managing Chronic Pain in Patients with Opioid Dependence

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Introduction

> "Pain is Inevitable; Suffering is Optional." [M. Kathleen Casey].

Pain is a subjective multi-dimensional experience that is influenced by physiological stimuli and the emotional, cultural, environmental and social climate surrounding an individual. Chronic pain, usually defined as lasting 12 weeks or longer, is associated with increased psychological distress, decreased mobility, obesity, decreased physical function, social isolation, financial loss, and development of chronic disability [1]. Individuals with opioid dependence may have increased vulnerabilities that influence their experience of pain, including lowered pain thresholds [2, 3], increased social stress, psychological symptoms (depression, anxiety), financial strain, and decreased coping skills. More than one-third of patients on methadone maintenance therapy have chronic severe pain [4, 5]. In some cases, patients developed opioid addiction after being given opioid medication for the treatment of acute or chronic pain [6].

Since chronic pain lasts for months to years [7], a primary goal of treatment is to **manage** pain, rather than eliminate pain altogether. This is true in patients with and without addictive diseases, but is particularly important to establish with patients with addiction. Pain is associated with increased odds of opioid misuse in opioid dependent persons [8]. Managing expectations of both clinician and patient is a mainstay of treatment. A second principle is to address the individual symptoms contributing to and resulting from chronic pain and those of importance to the patient. Lastly, self-management of pain symptoms and sequelae should

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be integrated into all aspects of pain treatment. Very little evidence exists specifically for treating pain in patients with addiction of any type, but principles of pain treatment in the general population are applicable to patients with opioid dependence.

The five pillars of treatment include

1. Improving psychosocial engagement. Cognitive behavioral therapy as well as other therapies may be helpful for pain [9, 10] but has not been proven to be helpful in opioid dependence [11-13]. Mindfulness- based therapies have been studied for pain management but have shown little efficacy to date [14, 15]. Developing a specific plan for socialization, whether it be participation in regular substance abuse treatment group, 12-step programs or other activity (perhaps with family or friends) is key to keeping the patient engaged. In particular, with pain and disability, finding a way to feel useful and engaged is essential to recovery from chronic pain. Case management or social work referral may help patients identify potential aid for financial or housing stress.
2. Physical mobility and function. A variety of methods can be used for patients to improve and maintain physical function. Increasing activity can improve mood [16, 17], increase weight loss [18], prevent deconditioning and improve pain related disability [19]. Physical therapy and other modalities (yoga) improve pain outcomes [20-28].
3. Weight loss in persons with obesity. A combination of diet and exercise for weight loss can improve pain symptoms and function [29].
4. Engagement with substance use treatment and/or relapse prevention. To treat pain optimally, patients also need to focus on their substance use, including taking accountability for their use. In the experience of the authors, some patients with substance use disorders may focus so much on the pain that they avoid doing the cognitive and emotional work required to recover from substance use problems. Full commitment to substance use disorder treatment is central to success of managing pain.
5. Medications. Medications can be used to both decrease the pain sensation but also to treat the other symptoms that occur with chronic pain. Medications from different classes of medicine may be synergistic to relieve symptoms. Opioid medications are not recommended for use to treat chronic pain in patients with opioid dependence. The exception would be a patient with terminal cancer, for whom it would be appropriate. Opioid agonist treatment for addiction may have benefits for chronic pain [30]. Opioids are appropriate for acute pain in an inpatient medical setting.

TREATMENT

Diet and lifestyle

- Weight loss has been shown to decrease disability from osteoarthritis in obese patients in combining results from several trials together [31]. An individual study found that it was the combination of

exercise plus diet together that improved function and decreased pain in osteoarthritis whereas diet alone was not effective [32]. Both strength training and aerobic walking have been shown to improve pain and function in osteoarthritis, Class I [33].

- Self-management is a process by which patients with a chronic illness or disability learn to effectively care for themselves via training, intervention, or skills acquisition. This process has been shown to improve pain, distress, and mood in patients with chronic pain in small randomized trials. Self-management using CBT has been shown to be effective in a randomized trial of 141 adults, improving pain, distress, disability, mood at one month follow up, Class II [34]. Benefits of self-management in patients with chronic neck pain were sustained over a 2 year follow up period [35].

Pharmacologic treatment

- The treatment aims of pharmacological therapy include reduction of pain, but also reduction of symptoms that accompany chronic pain, such as depression, anxiety, sleep, and muscle spasm. Most medications were developed and tested in populations without active addiction problems, however. Effectiveness in patients with addiction is unknown, except where noted.
- A multimodal medication regimen combines medications with different underlying mechanisms. Additive analgesia may occur and this approach allows lower doses of each of the drugs in the treatment plan, which lowers the potential for each to produce adverse effects [36]. Further, multimodal analgesia may result in comparable or greater pain relief than can be achieved with any single analgesic [37]. It may also be more effective at treating the co-occurring symptoms that accompany chronic pain and addiction.
- Patients with substance dependence who are in recovery through an abstinence-based program (e.g., Alcoholics Anonymous, Narcotics Anonymous) may be reluctant to take psychoactive medications, although these programs encourage their members to take medications that have been legitimately prescribed by their physician.

WHO's Pain Relief Ladder (WHO, 1986)

- The World Health Organization Pain Relief ladder [38] was developed and promulgated internationally as a cohesive view toward treating cancer pain. It has been also adapted for non-cancer chronic pain, but prescribers should cautiously approach its applicability in patients with co-occurring addiction and pain because opioids are a mainstay of treating severe pain. In general, opioids are not recommended to treat chronic pain in patients with addiction, even if they are in recovery.
- The analgesic ladder focuses on selecting analgesics on the basis of the intensity of the pain using analgesics from each of the analgesic groups and, to some extent, building on previously effective analgesics.
- Step 1: Simple analgesics (acetaminophen, NSAIDs)
- Step 2: Weak opioids
- Step 3: Strong opioids
- Adjuvants (anti-seizure medications, muscle relaxants, TCAs, SNRIs, SSRIs). These may be added at any of the above 3 steps.

Simple Analgesics

Acetaminophen has been shown to be better than placebo in patients with chronic pain due to osteoarthritis of the knee with respect to pain control, but not superior to NSAIDs, Class I [39]. However, Acetaminophen can be considered first-line for chronic pain because it has a better side effect profile than NSAIDs, Class I [40].

Acetaminophen:

Standard dosage:	650 mg Q6 hours (Max 2000 mg if cirrhosis or ≥ 3 alcoholic drinks/day)
Contraindications:	Patients with liver impairment and those with daily, regular alcohol intake

Main drug interactions:	Anticonvulsants, barbiturates, carbamazepine may increase the metabolism of acetaminophen; isoniazid, prilocaine. Acetaminophen increases the effects of warfarin with doses > 1.5-2g/day. Acute excessive intake of alcohol can lead to increased risk of acetaminophen hepatotoxicity.
Main side effects :	Occasional skin rash and other allergic reactions. Acute overdose can cause fatal hepatic injury.
Special points:	Well tolerated. Can be combined with other analgesics. Effective analgesic-antipyretic agent, but its anti-inflammatory activity is weak. When used as part of multimodal analgesia, can reduce the amount of opioids needed to control pain.
Cost:	Low cost

Non-Steroidal Anti-Inflammatory (NSAID)

This category of medications includes a number of over-the-counter and prescription options. Doses suggested are prescription level. This list is a sampling of widely used options. For all NSAIDs, urticaria, or allergic-type reactions following aspirin or other NSAIDS is a contraindication to use. In a systematic review of 65 RCTs including 11,237 patients, strong evidence was found to support the efficacy of NSAIDs and COX-2 inhibitors for acute and chronic low back pain, Class I [41]. All NSAIDs were found to have similar efficacy.

Naproxen:

Standard dosage:	500 mg Q12 hours or 500 Q AM plus 250 BID (Max 1000 mg/24 hours)
Contraindications:	Full-dose naproxen is not recommended in older adults because of its long half-life
Main drug interactions:	Avoid combining NSAIDS. May interact with drugs prescribed for cardiac disease including anti-hypertensive, anti-platelet and anti-coagulant medications.
Main side effects:	GI toxicity, renal toxicity, platelet dysfunction.
Special points:	First line NSAID.
Cost:	Low cost

Ibuprofen:

Standard dosage:	600 mg every 6 hours (Max 2400 mg/24 hours)
Main drug interactions:	ACE-inhibitors, aspirin, lithium, warfarin
Main side effects:	GI toxicity, renal toxicity, platelet dysfunction
Special points:	Second line NSAID. Ibuprofen can interfere with the cardioprotective effect of aspirin, so it should be taken 30 minutes to 2 hours after aspirin intake or at least 8 hours before. Pregnancy Category C.
Cost:	Low cost

Piroxicam:

Standard dosage:	10mg once daily
Contraindications:	Avoid full dose in elderly due to its long half-life and risk of GI toxicity
Main drug interactions:	ACE-Inhibitors, MAOIs, aspirin, warfarin
Main side effects:	High risk of GI toxicity, renal toxicity, platelet dysfunction
Special points:	Second line NSAID. Pregnancy Category C
Cost:	Moderate cost

Diclofenac:

Standard dosage:	18 or 35 mg ORALLY 3 times daily
Main drug interactions:	Concomitant use with other NSAIDS may result in enhanced gastrointestinal adverse effects (peptic ulcers, gastrointestinal bleeding and/or perforation).
Main side effects:	Increased liver function test
Special points:	Second line NSAID. Pregnancy category C
Cost:	High cost

Indomethacin:

Standard dosage:	maximum recommended oral or rectal dose is 200 mg/day
Main drug interactions:	Concurrent use of other NSAIDs may result in enhanced gastrointestinal adverse effects (peptic ulcers, gastrointestinal bleeding and/or perforation).
Main side effects:	Dizziness, headache, GI toxicity, increased liver enzymes, renal toxicity
Special points:	Use lowest effective dose for shortest possible duration this is to be used in short term only.
Cost:	Low cost

COX-2 Inhibitors

This subset of NSAID category of medications have less gastrointestinal side effects. Some formulations have been found to increase risk for cardiovascular disease and have been removed from the market. Urticaria or allergic-type reaction to aspirin or other NSAIDS is a contraindication to use. In a randomized controlled trial of 446 patients with chronic low back pain, a COX-2 inhibitor was found to be comparable to NSAIDs for pain relief, Class II [42]. In a systematic review of patients with chronic low back pain, two randomized trials compared COX-2 inhibitors with traditional NSAIDs, and no statistically significant difference was found between the two treatments, Class I [43].

Nabumetone

Standard dosage:	Arthritis 1000-2000mg PO daily. May be given once or twice daily. Max dose 2000 mg/day.
Contraindications:	Allergy or hypersensitivity to aspirin or NSAIDs.
Main side effects:	Edema, pruritus, rash, constipation, diarrhea, headache, tinnitus
Special points:	The drug is best taken with food or milk. Patient should not drink alcohol while taking this drug.
Cost:	Moderate cost

Celecoxib

Standard dosage:	200-400 mg daily in two doses.
Contraindications:	Asthma, pruritis, rhinorrhea, or other reaction after aspirin or other NSAID. Up to 21% of patients with a hypersensitivity to NSAIDs also have a hypersensitivity to COX-2 inhibitors [44].
Main drug interactions:	Concurrent use of NSAIDs may result in enhanced gastrointestinal toxicity.
Main side effects:	Hypertension, diarrhea, headache
Special points:	Instruct patients on higher doses (400 mg twice daily) to take drug with food. Lower doses may be taken with or without food. Tell patient to avoid drinking alcohol and smoking, as this may increase risk for gastrointestinal bleeding.
Cost:	Moderate cost

Muscle Relaxants

Of note, carisoprodol (Soma) is a muscle relaxant that is metabolized to a barbiturate and should not be prescribed for patients with opioid dependence. Cyclobenzaprine is the best studied muscle relaxant. A meta-analysis of 5 RCTs showed that cyclobenzaprine had efficacy for treating pain due to fibromyalgia [45], and later Kroenke et al. found that 21 RCTs show that cyclobenzaprine is effective for pain relief in patients with fibromyalgia [40]. A recent randomized trial of 36 patients showed that low-dose cyclobenzaprine improved pain associated with FM, Class II [46].

Cyclobenzaprine: (Flexeril)	
Standard dosage:	immediate release: 5 mg TID, may increase to 10 mg TID; extended release: 15 mg PO daily.
Contraindications:	Cardiac conduction disturbances, CHF, hypersensitivity, hyperthyroidism, MI (or acute recovery period).
Main drug interactions:	MAOIs, TCAs, bupropion phenothiazine, clonidine
Main side effects:	Dizziness, sedation, dry mouth, orthostatic hypotension.
Special points:	Generally well-tolerated but have sedative effects that may be additive to other centrally-acting drugs, including opioids. Muscle relaxants are not recommended in older adults as this age group has increased sensitivity to the anticholinergic and sedating effects of the drugs, and the muscle relaxant effect may contribute to falls [47].
Cost:	Low cost

Anti-Seizure Medications

Anti-seizure medications, in particular gabapentin and pregabalin, are FDA approved to treat neuropathic pain. A Cochrane Review in 2013 found that gabapentin and pregabalin were supported by 2nd tier evidence for the treatment of diabetic neuropathy and post-herpetic neuralgia, Class I [48]. Evidence also supported the use of pregabalin in fibromyalgia for pain [48].

Gabapentin: (Neurontin)	
Standard dosage:	Titrate up to 900-1200mg TID
Contraindications:	Kidney disease, depression, pregnancy.
Main drug interactions:	Antacids
Main side effects:	Sedation, dizziness, unsteadiness, and nausea.
Special points:	Adverse effects usually lessen with time. Reports of abuse exist for gabapentin at high doses.
Cost:	Moderate cost
Pregabalin:(Lyrica)	
Standard dosage:	300-450 mg QD, divided into BID doses
Contraindications:	Caution in elderly, depressed, renal impairment, heavy alcohol consumption
Main drug interactions:	Pioglitazone (Actos) and rosiglitazone (Avandia)
Main side effects:	sedation, dizziness, unsteadiness, and nausea

Special points:	Adverse effects usually lessen with time. Approved for treatment of fibromyalgia. Should be considered the first-line drug for the treatment of post-herpetic neuralgia and other neuropathies unless a co-morbid depression suggests that a tricyclic antidepressant should be tried first [49, 50].
Cost:	High Cost

Tricyclic Antidepressants (TCAs)

TCAs have been shown to be more effective in fibromyalgia than other anti-depressants as well as other treatment options [51, 52]. In addition to the two well-studied TCAs listed below, a number of other TCAs are likely to be equally effective.

Amitriptyline: (Elavil)	
Standard dosage:	Start at 10-25 mg at bedtime; titrate to 100 mg (max 50 mg if taking an SSRI/SNRI)
Contraindications:	TCA allergies
Main drug interactions	MAOIs, St. John's Wort, clonidine. Use with caution with other medications that cause QTc prolongation
Main side effects:	sedation, orthostatic hypotension, urinary retention, and dry mouth.
Special points:	Avoid in older adults.
Cost:	Low cost
Nortriptyline:(Pamelor)	
Standard dosage:	Start at 10-25 mg, titrate to 100 mg (max 50 mg if taking an SSRI/SNRI)
Contraindications:	TCA allergies
Main drug interactions:	Alcohol can increase side effects. Use with caution with other medications that cause QTc prolongation.
Main side effects:	sedation, orthostatic hypotension, and dry mouth
Special points:	Try at least 2 TCAs but avoid in older adults (65+ years). It has less hypotension than Amitriptyline.
Cost:	Low cost

Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram

SSRIs have been used for chronic pain, although have less efficacy than TCAs for fibromyalgia. The beneficial effect on
chronic pain may be more on the co-occurring symptoms, in particular depression, associated with chronic pain rather than the pain itself. In a trial of 12 weeks of treatment with antidepressant medication (n = 123) or usual care (n = 127), at
12 months patients receiving the intervention had greater reduction in depression and pain, Class I [53].

Standard dosage:	Dosing varies based on the SSRI.
Contraindications:	hypersensitivity to sertraline, fluoxetine, paroxetine, or citalopram.
Main drug interactions:	disulfiram, MAOI within 14 days, pimozide
Main side effects:	sexual dysfunction, drowsiness, weight gain, insomnia, anxiety, dizziness, headache, dry mouth, blurry vision, nausea, rash, tremor, constipation.
Cost:	Moderate cost (variable, depending on which medication)

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

This class of medications treats both mood and a variety of other disorders- fibromyalgia, neuropathic pain, and menstrual syndromes. Duloxetine was found to be effective for treating pain due to fibromyalgia in a recent Cochrane review, Class I [54].

Venlafaxine: (Effexor)	
Standard dosage:	Start at 37.5 mg and titrate up to effective dose, with max at 225mg QD
Contraindications:	Glaucoma, heart disease, HTN, mania, seizure disorders
Main drug interactions:	MAOIs, SSRIs St John's Wort
Main side effects:	Dizziness, drowsiness, nausea and vomiting, dry mouth.
Special points:	Better adverse event profile than TCAs [55]. Use cautiously in patients with high CV risk. Should not stop abruptly. Can cause dose-related hypertension, and, if appropriate, blood pressure (BP) monitoring should be done during initiation of treatment.
Cost:	Low cost (generic available)
Duloxetine (Cymbalta)	
Standard dosage:	titrate up to 60mg QD
Contraindications:	An increase in hepatotoxicity has been linked to the use of duloxetine in individuals with pre-existing liver disease, suggesting that the drug may aggravate the disease
Main drug interactions:	MAOIs, selegiline, tranylcypromine
Main side effects:	dizziness, fatigue, and dry mouth.
Special points:	FDA-approved for fibromyalgia and diabetic neuropathy. Side effects can be reduced by starting at 30 mg daily for 1 week and then increasing to 60 mg daily. Should not be stopped abruptly. Numerous trials have shown efficacy in decreasing pain due to osteoarthritis [56, 57]. Better adverse event profile than TCAs [55].
Cost:	High cost (still on patent)

Dual Mechanism Opioids

These medications have both mu-opioid agonist and nor-epinephrine (+/−) serotonin reuptake inhibitor properties. This may improve inhibitory processes in the mid-brain to decrease pain signals. Both have abuse and addiction potential.

Tramadol:	
Standard dosage:	100 mg PO once daily; titrate up by 100 mg every 2-3 days as needed for moderate pain. For severe pain, 100 mg PO daily, titrate up by 100 mg every 5 days as needed with a maximum of 300 mg /day.
Contraindications:	Hypercapnia, acute or severe bronchial asthma, respiratory depression, hypersensitivity to opioids.
Main drug interactions:	Acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, or psychotropic drugs (may worsen CNS and respiratory depression).
Main side effects:	Flushing, pruritis, constipation, nausea, vomiting, dizziness, headache, insomnia, somnolence. Rarely, seizure, dyspnea, pancreatitis.
Special points:	Patients should be tapered if they are on tramadol chronically.
Cost:	Low cost
Tapentadol:	

Standard dosage:	For severe chronic pain, 50 mg PO extended release q12h. Titrate up by 50 mg q3d, up to therapeutic range of 100-250 mg PO q12h. Maximum dose of 500 mg/day.
Contraindications:	Hypercapnia, bronchial asthma, hypersensitivity to tapentadol, GI obstruction, respiratory depression.
Main drug interactions:	MAOIs, sedatives.
Main side effects:	Constipation, nausea, vomiting, dizziness, Headache, somnolence, hypotension, left bundle branch block, anaphylaxis, seizure, respiratory depression.
Special points:	Seizure potential
Cost:	Moderate cost

Opioids

Although opioids are a common treatment for chronic pain, they are not recommended for patients with active addiction of any type. They can be cautiously recommended for patients in stable recovery, although even then have to be closely monitor. Use of opioids may become problematic in patients with prior addiction. High quality studies on use of opioids for chronic non-cancer pain are not available, and most available trials of opioids for chronic pain are limited by the exclusion of patients with addiction, sponsorship by pharmaceutical industry, small sample sizes, and short duration. A Cochrane review combining the largest trials with 8-13 month follow up found that only 44% of patients treated with opioids experienced a 50% reduction in pain [58]. In certain patients, the underlying pain condition may warrant use of opioids, in which case, they should be under the care of someone with both addiction and pain expertise who has the ability to do close monitoring with pills counts, and urine drug testing.

Two opioids used in the treatment of opioid dependence have potential analgesic properties. A study of patients with addiction on chronic opioid therapy who were randomized to low dose methadone or buprenorphine/naloxone produced moderate analgesia [30].

Methadone:

Standard Dosage:	**For chronic pain treatment:** methadone should be started at very low doses and increased slowly over weeks. Since the analgesic half-life is 6-8 hours, it should be given 3-4 times daily. It can be started at 2.5-5 mg 3-4 times per day, with increases done at weekly intervals. For chronic pain, 30-60 mg total daily dose is typical range. *For opioid dependence*, methadone should be prescribed by programs and providers with federal licensure to treat opioid dependence with methadone. It should not be initiated for this purpose without enrollment in such a program. For opioid dependence, methadone is started at a dose of 20-300mg/day, with a maximum dose of 30 mg [59, 60]. An additional 10 mg can be given on the first day if withdrawal symptoms persist hours later. If the initial dose of methadone is too high, patients may experience respiratory depression, urinary retention, edema, and abdominal distension. After the first day, the dose is then increased at 5-10 mg increments daily until 60-80 mg/day is reached. Dose increases after 80 mg /day should proceed slowly based on the individual patient's cravings and withdrawal symptoms. Most patients are stable on doses 80-120mg/day [59].
Main drug interactions:	Phenytoin, phenobarbital, carbamazepine, rifamycins, benzodiazepines. Concomitant use with MAOI's can induce serotonin syndrome.
Main side effects:	Constipation, sedation, potential QTc prolongation.
Special points:	Methadone serum half-life ranges from 20-100 hours, and is dosed every 24 hours for opioid replacement therapy. The analgesic effects of methadone are much shorter (6-8 hours) and it is given more frequently for pain relief. . The peak

	respiratory depression due to methadone occurs at 12-14 hours after the dose, and lasts longer than the analgesic effects, which contributes to the risk of overdose [60]. Respiratory depression has been implicated as the cause of death in most methadone-related deaths [60]. Even if the patient has a history of opioid tolerance, it should be started at low doses and increased slowly. If the patient is already taking other opioids, those medications can be tapered while the methadone is being titrated up. It can also cause QT prolongation, particularly at higher doses and when combined with other medications with QT prolongation effects. No neurotoxic metabolites. Chronic low-dose methadone may be safe for pain and have the side benefit of suppressing opioid cravings [30].
Cost:	Low cost

Partial Opioid Agonists

Buprenorphine:	
Standard dosage:	8-16 mg sublingual daily for opioid agonist treatment for opioid dependence, but doses as low as 2 mg a day or as high as 32 mg a day have been used successfully
Contraindications:	Concurrent use of other opioids. Attaches tightly to mu receptor, limiting the ability of other opioids to act
Main drug interactions:	CNS depressants, azole antifungals, macrolide antibiotics, HIV antivirals, and protease inhibitors
Main side effects:	Taste aversion, sedation in opioid naïve individuals.
Special points:	Has a ceiling effect at the mu receptor. Respiratory depression not easily reversed with naloxone. It has some analgesic properties, and preliminary data suggests it can be used to decrease pain (off-label) and to concomitantly treat opioid dependence [30]. Because the analgesic effects are shorter than the serum half-life, analgesic dosing should be every 6 hours
Cost:	High cost

Topical medications

Topical medications have shown efficacy for decreasing musculoskeletal pain and often have fewer side effects than systemic therapy. Lidocaine has been proven to be effective for chronic pain due to post-herpetic neuralgia [61] and diabetic neuropathy [62], and limited evidence exists for the use of lidocaine with other chronic pain conditions, Class I [62]. Topical capsaicin is useful as an adjunct to other medications for chronic pain patients, Class I [63]. Topical NSAIDs, such as diclofenac, have also proven efficacy for osteoarthritis, but not for chronic low back pain [64].

Capsaicin:	
Standard dosage:	3-4 times per day for arthritis and musculoskeletal pain
Contraindications:	Specific contraindications have not been determined
Main drug interactions:	None
Main side effects:	Erythema, pain, rash, or pruritis of application site; nausea; nasopharyngitis; hypertension
Special points:	Treatment area may be heat-sensitive, and patient should not apply cream directly before bathing, swimming, sun bathing, or exercise.
Cost:	Low cost

Lidocaine Cream and Patch (Lidoderm):

Standard dosage:	5% ointment, maximum dose of 17-20 g of ointment daily; apply up to 3 patches topically at one time, for up to 12 hours within a 24-hour period.
Contraindications:	Hypersensitivity to local anesthetics of the amide type.
Main drug interactions:	None for topical lidocaine.
Main side effects:	Rare for topical application.
Cost:	High cost patch, low cost cream

BenGay (Camphor 4%, Menthol 10%, Methylsalicylate 30%):

Standard dosage:	Apply to affected area 3-4 times daily
Contraindications:	hypersensitivity to Camphor, hypersensitivity to peppermint, menthol, or any other member of the mint family, topical application should not be used on the face or chest of infants or small children or on open skin areas.
Main drug interactions:	No drug interaction data available.
Main side effects:	Nausea, vomiting, warmth, headache, confusion, vertigo, delirium, hallucinations, tremors, elevated LDH, contact eczema, contact dermatitis.
Cost:	Low cost

Diclofenac (topical)

Standard dosage:	(1% gel) 2-4 gm applied daily around joint (1.5% solution) 10 drops around affected joints 4 times daily
Contraindications:	NSAID or aspirin allergy
Main drug interactions:	Concomitant use of Ketoralac (Strong NSAID) or Cyclosporine
Main side effects:	Local site reaction, blood coagulation disorder [65]
Cost:	High cost

Physical/speech therapy and exercise

• Exercise, including physical therapy, aerobic exercise, and yoga, has been evaluated to treat various chronic pain syndromes, including fibromyalgia and chronic low back pain. Although there is currently no evidence to support the use of exercise in patients with concurrent opioid dependence, the exercise interventions below will likely have a positive effect on these patients.

Physical Therapy

- Exercise has been used to improve pain in patients with chronic low back pain. In a Cochrane review including 43 randomized trials pertaining to chronic low back pain, exercise therapy was found to be slightly effective at decreasing pain and improving function in adults, Class I [20]. A systematic review by Hayden et al states that healthcare personnel supervision during physiotherapy for chronic low back pain may further improve pain and function, Class I [21].
- Exercise has also been used as a treatment for fibromyalgia. Moderate quality evidence from a Cochrane Review supports aerobic-only exercise training for improving global well-being and physical function for patients with fibromyalgia, Class I [22]. A lack of evidence precludes the evaluation of the benefits of strength-only and flexibility-only training for patients with fibromyalgia in the same Cochrane Review. Additionally, a meta-analysis that examined 33 trials in which physical therapy and exercise were used as treatment for fibromyalgia indicated a moderate effect on pain [23].

Yoga

- A systematic review including 10 randomized controlled trials and a total of 967 patients concluded that strong evidence supported short-term

effectiveness of yoga for low back pain patients and moderate evidence for the long-term effectiveness, Class I [25].

- In a randomized trial of 313 patients with chronic low back pain, Tilbrook et al found that patients offered yoga (n = 156) v. usual care (n = 157) had better back function (measured with the Roland-Morris Disability Questionnaire), and higher pain self-efficiency scores at 3, 6, and 12 months, Class I [27].
- In another randomized controlled trial of 228 adults with chronic low back pain, Sherman et al found that yoga was superior to a self-care book at 12 weeks (mean difference for function, −2.5 [95% CI, −3.7 to −1.3], P < 0.001) and at 26 weeks (mean difference, −1.8 [95% CI, −3.1 to −0.5]; P < .001) but not to conventional stretching at any time [26].
- In a systematic review of yoga for rheumatic diseases, Cramer et al found two randomized controlled trials pertaining to yoga for fibromyalgia. Based on these data, only a weak recommendation could be made, Class I [28].

Other treatments

• Clinical trials have investigated acupuncture, Cognitive Behavioral Therapy (CBT), and massage as effective treatment options for chronic pain in general populations, with limited evidence in populations with addiction or opioid dependence. Mindfulness and qigong have not been shown to be effective for pain conditions. CBT, while effective for pain, has not been shown to be effective for addiction. It is not clear how it would work in populations with opioid dependence.

Acupuncture for Chronic Pain

- Acupuncture uses thin needles inserted into specific points on the body. Acupuncture has been used in China for centuries to treat many disorders. A more modern type of acupuncture, transcutaneous electric acupoint stimulation (TEAS), uses electrodes placed on the skin to apply electrical stimulation at acupoints.
- Acupuncture has been shown to be effective in reducing pain in patients with chronic pain conditions. A Cochrane review of 9 randomized controlled trials indicates low to moderate quality evidence supports the use of acupuncture to improve pain and stiffness in patients with fibromyalgia, Class I [66].
- In a meta-analysis including 29 RCTs and data for 17, 922 patients, Vickers et al found that acupuncture improved pain in back and neck pain, chronic headache, and shoulder pain (P < 0.001), Class I [67].
- Cherkin et al performed a four-arm randomized trial of 638 patients with chronic low back pain and determined that improvements in back-related dysfunction (measured with the Roland-Morris Disability Questionnaire score) were greater in patients receiving individualized, standardized, or simulated acupuncture as compared with controls, Class I [68]. These improvements were present at 1 year.
- Acupuncture may also play a role in decreasing opioid use in chronic pain patients. In a small randomized controlled trial of 35 chronic pain patients receiving opioids for pain, short-term reduction in opioid-like medications (codeine, methadone, oxycodone, morphine and tramadol) was found in those who received acupuncture (39% v. 25% reduction in opioid use), Class II [69]. However, the reduced consumption of opioids did not last beyond 8 weeks after treatment. A Cochrane review including this study stated that no conclusions could be made about the efficacy of the acupuncture treatment for reducing opioid use in chronic non-cancer pain patients, Class I [70].

Cognitive Behavioral Therapy (CBT)

- In a Cochrane review of patients with chronic pain, CBT was found to have small to moderate effects on disability, pain, mood, and catastrophizing when compared with treatment as usual, but only mild improvements in disability and catastrophizing when compared with active controls, Class I [10].

- In a systematic review and meta-analysis including 14 randomized trials and 910 patients with fibromyalgia, CBT was found to reduce depressed mood after treatment (SMD −0.24, 95% CI −0.40, −0.08; P = 0.004), and the number of physician visits (SMD −1.57, 95% CI −2.00, −1.14; P<0.001), but no effect was found on pain, fatigue, sleep, and healthrelated quality of life, Class I [71].
- In a trial of 701 adults, patients with chronic low back pain were randomized to six sessions of group CBT (n = 468) or control (n = 233). The outcomes of a Roland Morris disability questionnaire (difference between groups 1.3 points, 0.56-2.06, p = 0.0008) and modified Von Korff disability (difference 8.4%, 4.47-12.32, p < 0.0001) and pain scores (difference 7.0%, 3.12-10.81, p<0.0001) at 12 months showed continued improvement on chronic low back pain in patients who received the intervention compared with controls [9].
- In a Cochrane review of any psychosocial intervention plus pharmacological standard v. pharmacological standard treatment of opioid dependence, 34 randomized trials including 3777 patients were included, Class I [11]. The authors concluded that adding psychosocial support does not change retention in treatment or opiate use during treatment.
- In a trial of 141 opioid dependent patients receiving buprenorphine/naloxone in a primary care setting, patients were randomized to physician management or physician management and CBT. No difference in effectiveness for addiction was found between the two groups, Class II [12].
- In Cochrane review of psychosocial treatment only for opioid abuse and dependence, five randomized trials including 389 patients were analyzed. Mayet et al found that psychosocial treatments are not currently proved to be effective alone and are not superior to any other type of treatment, Class I [13].

Mindfulness

- In a trial of 99 patients with chronic pain, patients were randomized to receive a mindfulness-based stress reduction (MBSR) program (n=51) or a multidisciplinary intervention (n=48), and no significant difference in pain intensity or pain-related distress was found between the two groups, Class II [15].
- In a three-armed randomized controlled trial of 177 female patients with fibromyalgia, patients were randomized to MBSR (n = 53), active control (n = 56), or a wait list (n = 59). No significant differences between groups in health-related quality of life (HRQoL) was found (p = 0.004), Class II [14]. Post-hoc analysis showed that patients receiving MBSR had the greatest pre- to- post improvements in HRQoL (p = 0.02).

Qigong

• Qigong is a form of Chinese medicine that includes deep breathing exercises and meditation. Qigong has been investigated as a treatment for pain due to fibromyalgia. In a systematic review of 7 articles and 395 fibromyalgia patients, Lauche et al. found low-quality evidence to support the use of qigong to improve pain, quality of life, and sleep. No evidence was found for superiority of qigong over usual care of patients with fibromyalgia, Class I [72].

Massage

- In a systematic review, Kumar et al concluded that massage may have some increased benefit for patients with chronic pain compared with relaxation, but no statement could be made about spinal manipulation, Class I [73].
- In a trial of 401 patients randomized to structural massage (n = 132), relaxation massage (n = 136) or usual care (n = 133), the adjusted Roland Disability Questionnaire score was lower in both the relaxation and structural massage groups after 10 weeks, Class II [74].

Multidisciplinary Therapy

• Multidisciplinary treatment for pain conditions has been shown in

individual trials, meta-analyses and systematic reviews to be more effective than control conditions [75]. Inpatient treatment programs tend to be more intense that outpatient but do not have strong advantage over outpatient treatment when accounting for intensity. In particular, chronic back pain benefit from multidisciplinary treatment. A Cochrane review of multidisciplinary treatment for fibromyalgia showed mixed results without evidence of efficacy in low quality studies [76]. Behavioral treatment and stress reduction as well as physical training appear to be beneficial aspects of multidisciplinary treatment [76]. Class II

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Opinion statement

Chronic pain may last for months to years, and is often heightened by co-morbid opioid dependence; thus, setting realistic expectations for both patient and physician is a key step in formulating treatment plans. Chronic pain is influenced by psychological, social and environmental factors in addition to somatic pathology, and thus, treatment needs to encompass more than just analgesia. The specific treatments should address contributors to and sequelae of chronic pain and addiction (e.g. social isolation, physical disability, depression, anxiety, obesity, financial stress, housing instability) and include multimodal interventions: psychosocial engagement, physical mobility and conditioning, weight loss, substance use treatment, and medications. Psychosocial treatments include evidence-based cognitive behavioral therapies, substance abuse treatment groups, 12-step programs and other social activities. Physical mobility and conditioning can be accomplished with physical therapy, yoga, or other exercise programs, and are essential to avoid loss of function and a negative functional spiral. In the setting of obesity, diet in combination with exercise can decrease pain and improve function. Substance abuse treatment is essential for patients with comorbid pain and opioid dependence. Opioid replacement therapies may have some added analgesic benefit. Medication can help decrease the pain level and alleviate some of the complicating conditions but is unlikely to be effective used in isolation. Opioid analgesics are generally not recommended in cases of patient with opioid dependence because of mixed evidence for efficacy and high risk.