

Tapering Long-term Opioid Therapy in Chronic Noncancer Pain: Evidence and Recommendations for Everyday Practice

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Learning Objectives: On completion of this article, you should be able to (1) appropriately identify circumstances when tapering chronic opioid therapy (COT) in patients with chronic noncancer pain should be considered; (2) recognize withdrawal symptoms during a COT taper, classify them for severity, and choose an adequate treatment; (3) apply strategies for medico-legal risk management during a COT taper, including using an opioid taper agreement.

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Abstract

Increasing concern about the risks and limited evidence supporting the therapeutic benefit of long-term opioid therapy for chronic noncancer pain are leading prescribers to consider discontinuing the use of opioids. In addition to overt addiction or diversion, the presence of adverse effects, diminishing analgesia, reduced function and quality of life, or the absence of progress toward functional goals can justify an attempt at weaning patients from long-term opioid therapy. However, discontinuing opioid therapy is often hindered by patients' psychiatric comorbidities and poor coping skills, as well as the lack of formal guidelines for the prescribers. The aim of this article is to review the existing literature and formulate recommendations for practitioners aiming to discontinue long-term opioid therapy. Specifically, this review aims to answer the following questions: What is an optimal opioid tapering regimen? How can the risks involved in a taper be managed? What are the alternatives to an opioid taper? A PubMed literature search was conducted using the keywords *chronic pain* combined with *opioid withdrawal*, *taper*, *wean* and *detoxification*. Six hundred ninety-five documents were identified and screened; 117 were deemed directly relevant and are included. On the base of this literature review, this article proposes evidence-based recommendations and expert-based suggestions for clinical practice. Furthermore, areas of lack of evidence are identified, providing opportunities for further research.

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Recent systematic reviews and meta-analyses suggest that long-term opioid treatment for chronic noncancer pain (CNCP) is supported by limited evidence.¹⁻¹⁰ First, the published studies of long-term opioid treatment for CNCP present the following issues, as reviewed in a recent Cochrane meta-analysis: few randomized clinical trials, a high discontinuation rate (up to 30%) of opioid therapy in the observed populations because of adverse effects or insufficient pain relief, and a relatively short observational period (6-48 months; mean, 15.15 months).⁵ Second, the results of these trials provide only weak evidence that long-term opioid therapy can provide clinically significant pain relief and fail to provide any conclusive evidence for improved quality of life or function.⁵

Among the 4.3 million American patients prescribed opioids,¹¹ often for CNCP, many present an unfavorable risk-benefit ratio for this treatment.¹² Although noting situations when a taper might be necessary, current guidelines regarding long-term opioid treatment in CNCP, whether published by multidisciplinary expert groups such as the American Pain Society and the American Academy of Pain Medicine, or regulating organizations such as the Federation of State Medical Board, focus on how to prescribe safely and effectively but do not provide practical advice on opioid treatment discontinuation.^{13,14} The burden of tapering long-term opioid treatment often falls on community pain practices and individual physician practices, where resources are relatively limited, rather than tertiary centers. Yet, practitioners face patients presenting with psychiatric comorbidities, such as personality disorders, somatic symptom disorder, substance use disorder (SUD),¹⁵⁻¹⁷ and depression,¹⁸ as well as poor coping abilities.¹⁹

The available literature was reviewed to formulate evidence-based recommendations on tapering long-term opioid treatment in CNCP, specifically aiming to answer the following questions: What is an optimal opioid tapering regimen? How can the risks involved in a taper be managed? What are the alternatives to an opioid taper?

INDICATIONS FOR TAPERING OF LONG-TERM OPIOID TREATMENT

Adverse effects often outweigh the benefits of long-term opioid treatment: sedation, decreased

concentration and memory, drowsiness, changes in mood, constipation, dry mouth, abdominal pain, nausea, hormonal changes with consequences such as sexual dysfunction, and osteopenia may limit treatment tolerability.^{4,5} The benefits of long-term opioid treatment can also be questioned when a patient reports inadequate analgesia despite high doses (tolerance), reduced function, quality of life, or absence of progress toward therapeutic goals.¹³ Table 1 presents the indications for tapering long-term opioid treatment.^{14,20} Tapering might also be considered for patients planning elective surgery. According to a retrospective trial, patients with CNCP undergoing long-term opioid treatment (N=30) experience more postoperative pain than controls without long-term opioid treatment (N=25).²¹ However, there is no research yet on the effect of preoperative tapering on postsurgical pain outcomes.

Diversion and addiction are alarming but relatively uncommon considering the number of patients undergoing long-term opioid treatment.^{7,22-24} Addiction (ie, SUD or more specifically opioid use disorder [OUD]) is a psychiatric diagnosis that involves use despite negative consequences and/or loss of control over use, compulsions, and cravings.²⁵ Among patients with chronic pain, adherence vs abuse can be seen on a spectrum,¹² and OUD is a difficult diagnosis to establish with certainty, justifying involvement of an addiction specialist for initial evaluation and follow-up.^{26,27} Although the current review aims to focus on patients with CNCP, patients with cancer pain may develop similar difficulties related to opioid use.²⁸ Diversion (ie, any act that results in another individual receiving the medication than the one it was prescribed to) is a legal issue discussed further below.

CENTRAL ISSUES DURING TAPERING OF LONG-TERM OPIOID TREATMENT

Short-term Risks

Withdrawal Syndrome. Opioid withdrawal syndrome is characterized by signs and symptoms of sympathetic stimulation (due to decreased sympathetic antagonism by opioids), which has been well described in patients with SUD: anxiety, hypertension, tachycardia, restlessness, mydriasis, diaphoresis, tremor, piloerection, nausea, abdominal cramps, diarrhea,

TABLE 1. Criteria Identifying Patients in Whom Discontinuation of Long-term Opioid Therapy Should Be Considered (Combining Those Published by the Substance Abuse Mental Health Services Agency²⁰ and by Fishman¹⁴)

1. Inability to achieve or maintain anticipated *pain relief* or *functional improvement* despite reasonable dose escalation
2. Intolerable adverse effects at the minimum dose that produces effective analgesia, with reasonable attempts at opioid rotation unsuccessful
3. Persistent nonadherence with patient treatment agreement
This can include inappropriate use, failure to comply with monitoring (after excluding this failure is due to personal cost burden), selling prescription drugs, forging prescriptions, stealing or borrowing drugs, aggressive demand for opioids, injecting oral or topical opioids, unsanctioned use of opioids, unsanctioned dose escalation, concurrent use of illicit drugs, obtaining opioids from multiple prescribers and/or multiple pharmacies, recurring emergency department visits for chronic pain management
4. Deterioration in physical, emotional, or social functioning attributed to opioid therapy
5. Resolution or healing of the painful condition

anorexia, dizziness, hot flashes, shivering, myalgias or arthralgias, rhinorrhea, sneezing, lacrimation, insomnia, and yawning.²⁹ Dysphoria is also frequently reported.³⁰ Symptoms start 2 to 3 half-lives after the last dose of opioid (eg, for oxycodone, which has a half-life of 3-4 hours; symptoms would start after 6-12 hours). In this situation, symptoms would peak at approximately 48 to 72 hours and resolve within 7 to 14 days, with variability depending on the specific dose, speed of taper, and duration of use.^{29,31} Of note, these subjective symptoms can be enhanced by anxiety, or symptoms of anxiety can be interpreted as withdrawal. When masked patients undergoing long-term opioid treatment for CNCP (N=10) were given a placebo for a 60-hour period, only 3 had symptoms of opioid withdrawal.³² A secondary abstinence syndrome, including general malaise, fatigue, decreased well-being, poor tolerance to stress, and craving for opioids, has been described in patients with SUD for up to 6 months.³³

Different tools allow measuring withdrawal symptoms, for example, the patient self-rated Subjective Opiate Withdrawal Scale³⁴ or the objective practitioner assessment Clinical Opiate Withdrawal Scale³⁵ (Table 2). Generally, withdrawal is not life-threatening in patients without significant comorbidities. Case reports of complicated withdrawal requiring acute care, typically following abrupt cessation of opioids in the context of SUD or CNCP, include organic delusional syndromes³⁶ or stress cardiomyopathy.^{37,38}

Increased Pain. Many patients fear that their pain will increase during an opioid taper. However, according to studies of long-term opioid treatment tapers, overall, patients report improvements in function without associated worsening in pain (aggregated N=1007)³⁹⁻⁴⁴ or even decreased pain levels (aggregated N=513).^{45,46} Experimental pain testing protocols suggest that sensory hyperalgesia may appear immediately after discontinuation of long-term opioid treatment.⁴⁷⁻⁴⁹ Similar hyperalgesia has been described postoperatively, when the use of short-acting opioids is abruptly discontinued at the end of surgery.⁵⁰ In light of the functional improvement and pain reduction typically reported after discontinuation of long-term opioid treatment,³⁹⁻⁴⁶ hyperalgesia appears to be a brief, time-limited phenomenon.

Dropout. The risk that patients will refuse to taper opioids, resume long-term opioid treatment with a new prescriber, or display aggressive behavior creates concern for many clinicians. When specifically examining predictors for difficulties during tapering among 29 patients, depressive symptoms at initiation were described as a significant factor not only for drop out (rate, 34%) but also for relapse (rate, 32%).⁵¹ In a study of 42 patients randomized into 2 groups, half were informed at study initiation of a maintenance treatment option in case of taper failure, whereas the other half did not receive this option. Of the patients without an opioid maintenance option, 76% quit treatment within 3 weeks compared with 5% in the group with an opioid maintenance option.⁵² Similarly, a study of 12 patients with CNCP and OUD, randomized either to long-term buprenorphine and naloxone or a tapering protocol for 4 months, revealed a 100% dropout rate from the taper intervention, whereas 5/6 were retained in the maintenance treatment.⁵³ Finally, a review questioning the necessity for pain rehabilitation programs to taper opioids found evidence that mandatory opioid weans could be associated with increased dropout rates especially in patients taking high levels of opioids.⁵⁴

Long-term Issues

Relapse. In the long term, the goals are to reduce adverse effects and mitigate or address risks of long-term opioid treatment (opioid reliance, chemical coping, and self-medication with

TABLE 2. Opioid Withdrawal Scales

Clinical Opiate Withdrawal Scale (COWS) ^a					
Resting pulse rate: record beats per minute (measured after patient is sitting or lying for 1 minute)	Runny nose or tearing not accounted for by cold symptoms or allergies				
0 = pulse rate ≤80/min	0 = not present				
1 = pulse rate 81-100/min	1 = nasal stuffiness or unusually moist eyes				
2 = pulse rate 101-120/min	2 = nose running or tearing				
4 = pulse rate >120/min	4 = nose constantly running or tears streaming down cheeks				
Sweating: during past half hour not accounted for by room temperature or patient activity	Gastrointestinal upset: during the last half hour				
0 = no report of chills or flushing	0 = no gastrointestinal symptoms				
1 = subjective report of chills or flushing	1 = stomach cramps				
2 = flushed or observable moistness on face	2 = nausea or loose stool				
3 = beads of sweat on brow or face	3 = vomiting or diarrhea				
4 = sweat streaming off face	5 = multiple episodes of diarrhea or vomiting				
Restlessness observation during assessment	Tremor observation of outstretched hands				
0 = able to sit still	0 = no tremor				
1 = reports difficulty sitting still but is able to do so	1 = tremor can be felt but not observed				
3 = frequent shifting or extraneous movements of legs or arms	2 = slight tremor observable				
5 = Unable to sit still for more than a few seconds	4 = gross tremor or muscle twitching				
Pupil size	Yawning observation during assessment				
0 = pupils pinned or normal size for room light	0 = no yawning				
1 = pupils possibly larger than normal for room light	1 = yawning once or twice during assessment				
2 = pupils moderately dilated	2 = yawning ≥3 times during assessment				
5 = pupils so dilated that only the rim of the iris is visible	4 = yawning several times per minute				
Bone or joint aches (if patient was having pain previously, only the additional component attributed to opiate withdrawal is scored)	Anxiety or irritability				
0 = not present	0 = none				
1 = mild diffuse discomfort	1 = patient reports increasing irritability or anxiousness				
2 = patient reports severe diffuse aching of joints or muscles	2 = patient obviously irritable or anxious				
4 = patient is rubbing joints or muscles and is unable to sit still because of discomfort	4 = patient so irritable or anxious that participation in the assessment is difficult				
	Gooseflesh skin				
	0 = skin is smooth				
	3 = piloerection of skin can be felt or hairs standing up on arms				
	5 = prominent piloerection				
Subjective Opiate Withdrawal Scale (SOWS) ^b					
	Not at all (0)	A little (1)	Moderately (2)	Quite a bit (3)	Extremely (4)
I feel anxious					
I feel like yawning					
I am perspiring					
My eyes are teary					
My nose is running					
I have goose bumps					
I am shaking					
I have hot flashes					
I have cold flushes					
My bones and muscles ache					
I feel restless					
I feel nauseous					
I feel like vomiting					
My muscles twitch					
I have stomach cramps					
I feel like taking medication now					
^a Reprinted from <i>Am J Drug Alcohol Abuse</i> , ³⁴ with permission. Scoring: 5-12: mild; 13-24: moderate; 25-36: moderately severe; more than 36: severe.					
^b Reprinted from <i>J Psychoactive Drugs</i> , ³⁵ with permission. Scoring: 4-22: mild; 23-44: moderate; 45-64: high.					

risk of overdose), which imply maintaining reduced opioid consumption or abstinence. Relapse after a full taper is predicted by depressive symptoms at initiation of tapering, as described above, as well as by higher pain scores at initiation and conclusion of the taper.⁵¹ Conversely, low pain at the end of an opioid taper is predictive of long-term abstinence from opioids in CNCP (N=102; dropout rate, 24%; relapse rate, 41%).⁴⁵ In another sample of 120 patients undergoing an interdisciplinary pain program with tapering, relapse at 12 months (22.5%) was predicted solely by posttreatment depression scores, without influence of OUD or other SUD comorbidity.⁵⁵

Function. Increasing or maintaining function is a key long-term goal in treating those with chronic pain. Disability in the context of chronic pain is influenced by many psychosocial factors, including coping strategies and mood.⁵⁶ Psychiatric conditions are over-represented in samples of patients with chronic pain and disability.^{57,58} Furthermore, patients with psychiatric comorbidities seem to favor the use of opioids for self-medication of depressive or anxious symptoms,^{59,60} despite absence of evidence of long-term benefit.¹⁵ Although there is an interaction between opioid prescribing and function,^{61,62} the causality and direction of this interaction, perhaps mediated by depression,⁶³ are difficult to assess.

Medicolegal Implications. Finally, there are significant medicolegal concerns for those prescribing long-term opioid treatment for CNCP. Deaths by unintentional overdose or suicide represent the most serious consequences, leading to potential civil liability or licensing board investigations. In a study of closed malpractice claims across all medical specialties, narcotic analgesics were the most common pharmacologic class involved, representing 1% of claims.⁶⁴ Examination of closed malpractice claims among pain medicine specialists revealed that 3% were related to medication management, with claims arising mostly after patients died of opioid overdose.⁶⁵ The predominant reason for inappropriate care was a failure of the prescribing physician to adequately verify a patient's prior medical history before providing the first opioid

prescription, which could have revealed concurrent use of drugs and/or alcohol.

METHODS

PubMed was searched with the keywords *chronic pain* AND *opioid taper*, *wean*, *withdrawal*, and *detoxification* for articles published between January 1978 and November 2014. The bibliography and citing articles of all relevant publications were reviewed to identify additional papers. Six hundred ninety-five articles were identified and screened by the first author (C.B.). Most were relevant to opioid detoxification in patients with SUD. Finally, and after discussion with the coauthors in case of doubt, 117 sources were deemed helpful in understanding the background and answering the main questions, presenting either specific relevance to the tapering of long-term opioid treatment in CNCP or data of interest from patients with SUD. In studying the existing literature, we noted a paucity of solid evidence, favoring a topical review with critical reading of the available research to date over a systematic review. Nevertheless, the quality of the evidence presented by each individual source was graded according to the following system: A, systematic review or meta-analysis; B, high-quality study or nonsystematic review; C, studies with methodologic limitations (eg, lack of randomization); D, case reports or studies with severe methodologic limitations (eg, absence of control); and G, clinical guidelines or expert opinion ([Supplemental Table](#), available online at mayoclinicproceedings.org). The first author attributed grades, with coauthors checking them. No disagreement occurred. Doubtful cases (n=2) were discussed among authors, and a consensus was reached. Recommendations for each of the questions were formulated from this body of literature and enhanced by good clinical advice on the basis of experience with ongoing tapering in a multidisciplinary academic clinic. These recommendations were classified for scientific evidence strength with the GRADE system,⁶⁶ where a level A (high) is on the basis of several high-quality studies with consistent results, B (moderate) is on the basis of one high-quality study or several studies with some limitations, C (low) is on the basis of one or more studies with severe limitations, and D (very low) is on the basis of expert opinions or no direct research evidence studies with severe

limitations. Furthermore, suggestions for future research that would be helpful to clinicians were made.

RESULTS

Optimizing the Opioid Tapering Protocol

Taper Speed and Information. There is only scant literature examining the pace of tapering in patients receiving long-term opioid treatment for CNCP. According to literature from the addiction field, the daily dose to prevent acute withdrawal is approximately 25% of the previous day's dose (ie, 75% taper; eg, 20 mg of oxycodone for a patient taking 80 mg every day).³¹ Rapid and ultrarapid tapers (occurring during 1-7 days, usually in a hospital setting and with the patient under sedation, at times using infusions of an opioid antagonist)⁶⁷ have been frequently used in the context of OUD, with a lack of well-controlled randomized clinical trials establishing favorable outcomes compared with slower tapers.⁶⁸ There are case reports of patients treated with such protocols for opioid dependence in the context of pain from burns or cancer.^{69,70} A masked taper during a mean of 7 days has been described as part of a residential, multidisciplinary pain treatment program.⁷¹ To our knowledge, there is no trial that compares rapid or ultrarapid vs slower protocols in patients with CNCP.

In the above-mentioned study of 42 patients randomized to a 3-week tapering protocol vs a slower taper with the option for temporary maintenance therapy, abstinence was observed in 9.5% (fast group) vs 19% (slow group) at the 6-month follow-up.⁵² An 8-week taper for 11 patients taking codeine with a scheduled 50% reduction in the first 4 weeks, followed by individualized schedules for the following 4 weeks, resulted in a discontinuation in 6 patients and partial taper in 5 patients.³⁹ The Mayo Clinic Program uses a gradual, structured taper on a time-contingent basis during 3 weeks, with rates of completion that can be above 90%.^{42,54,72,73}

When open-label dose reduction controlled by patients (N=63) was compared with a masked dose reduction controlled by study staff (N=45), patients in the blinded group were more likely to not be taking opioids (89% vs 68.3%) at the 4-week outcome, but there were no significant differences in the proportion of

patients not taking medication (55% in both groups) at 6 months.⁴⁰ However, nonrandom treatment attribution and baseline differences between groups may have biased outcomes.⁴⁰

Medication Choice. Buprenorphine-naloxone and methadone are less subject to misuse (although not fully preventing intentional misuse) and are frequently used to taper patients with OUD.⁷⁴ Buprenorphine-naloxone is a combination of a partial μ -opioid receptor agonist with the antagonist naloxone. Naloxone becomes bioavailable only if the medication is dissolved and injected intravenously, blocking the agonist effect of buprenorphine. Buprenorphine-naloxone is introduced to patients in mild to moderate withdrawal because adding buprenorphine to a full opioid agonist can precipitate withdrawal (due to higher μ -opioid receptor affinity and partial antagonistic effect). It is indicated in the United States for treatment of opioid dependence.

Methadone is a long-acting full μ -opioid receptor agonist with strong analgesic potency. Methadone has a long and variable elimination half-life (8 to 59 hours), causing drug accumulation during rapid dose escalation, and can affect the cardiac cycle (QTc prolongation).⁷⁵ It is the only medication approved by the US Food and Drug Administration for detoxification treatment of OUD. A study (N=23) describes a switch to buprenorphine in patients tapered from long-term opioid treatment for CNCP, without reports of long-term outcomes.⁴¹ Methadone was used in masked "taper cocktails."^{40,76}

Recommendations

Taper Speed. There is no published comparison of speed of tapers in patients with long-term opioid treatment for CNCP, although such research would be of great interest. There is no strong evidence from the SUD literature toward rapid or ultrarapid tapers compared with slower ones,⁶⁸ and the usefulness of faster tapers for patients receiving long-term opioid treatment in the community has been questioned.⁶⁹ A fast or ultrafast taper can be considered when inpatient taper is needed because of significant coexisting psychiatric or medical illness, such as SUD or unstable cardiac disease (recommendation GRADE C).^{37,38}

In the absence of validated protocols, empirical plans have been proposed (recommendation GRADE D). Plans often first reduce the dose of the medication to the smallest commonly available unit dosage and then increase the amount of time between doses (eg, in a regimen of 60 mg of extended-release morphine every 8 hours, first decreasing to 15 mg of extended-release morphine every 8 hours, then increasing the interval between the doses).³¹ The Department of Veterans Affairs and the Department of Defense have developed a fact sheet that suggests either a taper by 20% to 50% of the original dose per week for patients who are not presenting with SUD or faster protocols with daily decreases by 20% to 50% of the initial dose down to a threshold (30-45 mg of morphine every day), followed by decreases every 2 to 5 days.⁷⁷ An Opioid Taper Plan Calculator, developed by the Washington State Medicaid in collaboration with University of Washington pain experts, can assist in calculating empirical taper plans.⁷⁸

According to our center's experience (recommendation GRADE D), a decrease of 10% of the original dose every 5 to 7 days until 30% of the original dose is reached, followed by a weekly decrease by 10% of the remaining dose, rarely precipitates withdrawal symptoms and facilitates adherence. The speed of the taper should be inversely correlated with duration of treatment to prevent withdrawal symptoms (eg, bimonthly to monthly dose adjustments can be considered in case of long-term opioid treatment exceeding 2 years).³¹ Of note, patients who take opioids as rescue doses less than once daily do not need a formal taper. Ultimately, finding a plan that an individual patient can embrace with a significant degree of personal engagement might be more important than following a specific protocol. Nevertheless, research to date did not find long-term benefits to giving patients control over their taper when compared with a masked taper.⁴⁰ Given the risk of dropout in compulsory tapers,⁵⁴ slowing the taper pace at times of intense stress or on appearance of withdrawal symptoms might, however, keep the patient engaged toward completion. This hypothesis would be worth testing in a formal study.

Medication Choice. The rationale for switching a patient treated with long-term opioid treatment for CNCP to taper with buprenorphine or methadone is not entirely clear, and

there is no evidence to support such practice (recommendation GRADE D). Empirical protocols since the 1990s favor tapers using the patient's long-term opioid treatment medication (recommendation GRADE D).³¹ Trials comparing tapers with the patient's own medication vs a switch to taper, with appropriate long-term outcome measurements, could bring forward new evidence.

Referring physicians often enquire about tapering long-acting opioid regimens. For example, transdermal fentanyl can be tapered by decrements of 12- μ g/h patches. Furthermore, a short-acting formulation can be introduced after tapering to the lowest increment of a long-acting medication (recommendation GRADE D).

Risk Management and Taper Support Symptomatic Treatment of Increased Sympathetic Activity: α_2 -Adrenergic Agonists. The α_2 -adrenergic agonists activate presynaptic α_2 -receptors in the locus coeruleus, reducing sympathetic activity and therefore reducing symptoms of withdrawal. This pharmacologic class includes clonidine, lofexidine, guanfacine, and tizanidine, and their use is well established in the treatment of withdrawal symptoms in OUD.⁷⁹ A review of trials using different α_2 -adrenergic agonists to treat withdrawal symptoms in OUD detoxification found insufficient data to draw conclusions about relative effectiveness of these agents.⁷⁹ There is anecdotal evidence for the use of α_2 -adrenergic agonists in patients undergoing long-term opioid treatment taper,^{80,81} and tizanidine is a widely used muscle relaxant in CNCP.⁸²

Other Pharmacologic Interventions. There is one anecdotal report of hospitalization for use of ketamine infusions at subanesthetic doses to support opioid tapering in 15 patients with CNCP; the doses used are not specified, and little information is given on success.⁸³ Symptomatic treatments for muscle aches and pain, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are often part of tapering protocols.^{41,83}

Psychological Management and Interdisciplinary Programs

A literature review comparing detoxification protocols for OUD found better outcomes

when a psychosocial intervention was associated with pharmacological support; however, the nature of the psychological interventions was heterogeneous.⁸⁴ Cognitive behavioral therapy (CBT) is a proven and cost-effective psychological approach in chronic pain therapy.^{85,86} Interdisciplinary programs for chronic pain (ie, a combination of physical therapy, CBT, pain management, and occupational therapy)⁸⁷ often include tapering as a mandatory or optional part of the program. The active treatment phases span approximately 1 month, on an inpatient^{40,71} or outpatient basis, such as the Mayo Clinic Pain Rehabilitation program.^{42-44,46,72,73}

A recent systematic review of the body of literature studying CBT and interdisciplinary programs for patients with CNCP tapering from long-term opioid treatment pointed out its limitations⁸⁸: only 2 studies are randomized clinical trials, both with small sample sizes or methodological issues.^{89,90} Therefore, the authors of the review renounced drawing conclusions regarding the effectiveness of psychological, alternative, or interdisciplinary interventions to support patients tapering from opioids.⁸⁸

The feasibility of providing isolated CBT support to patients with CNCP on a taper from long-term opioid treatment has been revealed in 3 studies, where weekly 90- to 120-minute group sessions were offered during 6 to 11 weeks.^{39,89,91} In one of these studies, after an initial course of CBT, patients were randomized into a follow-up group of therapeutic computer-based interactive voice response for 4 months versus usual treatment; the active group had a significant reduction in opioid use, whereas the usual care group had a significant increase.⁸⁹ The 2 other trials are small and uncontrolled (aggregated N=55), limiting conclusions.^{39,91}

Long-term outcomes from multidisciplinary programs are rarely described. One program reports 78% abstinence at 6 month follow-up⁴² and another one the same percentage at 12 months.⁵⁵ Studies of interdisciplinary programs found no differences in improvement in matters of psychological functioning, physical activity, or return to work between patients with and without opioids before the treatment,^{42,71,73} even if these medications were not tapered.⁹² This literature can be interpreted in favor of opioid tapering (patients improve after the program, despite less medication) or against it

(patients improve despite continuing to take opioids).

Medicolegal Risks

Attempting tapering appears to carry low risks, with only rare medicolegal actions arising in a number of specific situations, which include diversion, unclear documentation or terms, and failure to collaborate with appropriate specialists.⁹³⁻⁹⁸ For instance, when a clinician is certain that a patient is diverting medication, continuation of long-term opioid treatment is problematic because a partial taper could allow continued diversion.⁹⁹ Erroneous terms can lead to issues: a prescription opioid *taper* or *wean* is distinct from *detoxification*. *Detoxification* implies a diagnosis of SUD and requires special licensure in the United States. Risk of death by suicide can be a concern for patients with primary affective symptoms, especially in the context of a complicated pharmacotherapy regimen.⁶⁵

Complementary and Alternative Medicine

Acupuncture is frequently used in OUD to manage withdrawal symptoms; however, the evidence supporting this practice is weak.^{100,101} Two trials studied the effects of electroacupuncture in the context of long-term opioid treatment for CNCP,^{90,102} without clear benefits.

Recommendations

Preventing Taper Failure (Dropout and Relapse). Depression, high pain scores, high opioid doses, and the absence of provision for taper failure are key predictors of opioid-tapering dropout or relapse.^{45,51-55} Addressing these factors through pharmacologic and psychological support might improve outcomes, although there is no research yet to validate this hypothesis (recommendation GRADE D).

Withdrawal Symptom Management. Use of α_2 -adrenergic agonists is well supported by the OUD literature (recommendation GRADE A).⁷⁹ However, comparative studies have not determined an advantage for one of them.⁷⁹ There is no similar research in patients tapering from long-term opioid treatment. Pharmacologic particularities of the different agents are presented in Table 3. A well-designed study of the relative benefits of α_2 -adrenergic agonists in a significant sample of patients tapering from

long-term opioid treatment would be especially interesting to assist clinical decision making.

Acupuncture has not been found to provide significant relief from withdrawal symptoms in long-term opioid treatment tapering and is supported by weak evidence in OUD (Recommendation GRADE C).^{90,100,102} Further research could investigate alternative medicine approaches.

On the basis of our center's experience, knowledge of the expected time course of withdrawal signs, complemented by the use of a symptomatic scale, will best determine whether a taper should be slowed down, adjunctive therapy introduced, or reassurance alone provided (recommendation GRADE D).

Pain Management. Convincing evidence (from an aggregated population of 1520 patients)³⁹⁻⁴⁶ suggests stable or improved pain reports after an opioid taper, although short-term withdrawal can lead to transitory increased pain and hyperalgesia.⁴⁷⁻⁴⁹ Continued pain management, including optimized nonopioid regimens and interventional approaches, should be offered (recommendation GRADE D). In parallel, teaching patients about expected pain outcomes might provide reassurance and would be the topic of an interesting study.

Psychological Management and Interdisciplinary Programs. To date, there is strong evidence supporting CBT and interdisciplinary approaches in patients with chronic pain,^{85,86} moderate evidence for patients with OUD,⁸⁴ and low evidence specifically for taper support from long-term opioid treatment in CNCP.^{39,40,42-44,46,71-73,89,91} However, considering the risks factors for dropout and adverse functional outcomes in these patients, as reviewed above, psychological support may be needed to address possible anxiety related to the taper, underlying depression, deficient pain- and stress-coping strategies (recommendation GRADE C). Simply removing a patient's main strategy for dealing with pain and perhaps mood (ie, their opioids) is unlikely to be well tolerated or allow for increased function if learning of adaptive coping mechanisms and treatment of any underlying negative affect are not encouraged. Further research is needed to assess the different

approaches individually and comparatively or to determine predictors and mediators of success.

Management of Medicolegal Risks. Risk mitigation strategies learned from legal cases and governmental or clinical guidelines can be found in Table 4 (recommendation GRADE C).^{14,64,65,93-99,103-105} A taper agreement, including the collaboratively formulated plan (Table 5), may help to foster an effective therapeutic relationship and minimize the risk of breaking trust (recommendation GRADE D).

Alternatives to Tapering

A diagnosis of persistent opioid dependence can be established with a new patient undergoing long-term opioid treatment or when facing a taper failure.²⁷ Long-term opioid treatment is often maintained with possible associated risk management strategies.^{106,107}

Opioid Maintenance. A literature review comparing short- and long-acting opioid regimens has not found a clear advantage of either of these strategies in matters of analgesia, quality of life, or risk for misuse, except in specific circumstances.¹⁰⁸ In parallel, there are specific maintenance treatment options in the forms of buprenorphine and methadone.

A review underlines the absence of consensus to support buprenorphine as an effective treatment in opioid-naïve patients with CNCP, and this might be explained by the weak analgesic effects of buprenorphine and its ceiling effects.¹⁰⁹ However, in patients with opioid dependence, buprenorphine may reverse opioid-induced hyperalgesia and reduce opioid tolerance, and convincing evidence from 8 studies (aggregated N=14,224), including 3 randomized clinical trials and a large open-label observational study, supports the benefits from this practice.¹⁰⁹ Nevertheless, important dropout from treatment with buprenorphine needs to be underlined as a limiting factor to trials and a possible source of bias.¹⁰⁹

Methadone as a specific opioid for long-term opioid treatment in patients with CNCP is supported by limited evidence.¹¹⁰ Its possible usefulness after a problematic course with other opioids is suggested by 3 small studies.^{52,111,112} Methadone was one of the options for long-term treatment in a taper vs maintenance study

described above (section about dropouts).⁵² Relevance is further supported by a small pilot study (N=4) in patients with CNCP and SUD.¹¹¹ Finally, patients with CNCP (N=60) with OUD were followed up (mean of 34 months, 68% retention rate) after a switch to methadone (mean dose, 99.5 mg/d), reporting satisfying pain control and physical function in all 42 patients who were still in the program.¹¹² The use of different scales at baseline and outcome limit the interpretation of the results.

Finally, a randomized clinical trial in patients with OUD and chronic pain (N=54) comparing methadone with buprenorphine-naloxone did not find a significant difference in pain reduction or dropouts; however, fewer in the methadone group used nonprescribed opioids.¹¹³ Nevertheless, buprenorphine-naloxone led to higher birth weight and fewer neonatal abstinence syndromes in infants born to women with OUD compared with methadone¹¹⁴ and does not present a risk for accumulating in renal dysfunction.¹¹⁵

Risk Reduction Programs

An uncontrolled study examined 85 patients with significant psychiatric comorbidity before and after 3 months in a heavily monitored, multidisciplinary outpatient primary care program, revealing encouraging trends on mood and pain scores, with substance misuse being the main reason for subject dropout (23%).¹⁰⁶ In a randomized clinical trial, patients with chronic low back pain and a high-risk profile for prescription drug misuse (N=21) were assigned to an intervention that included monthly electronic diaries, urine toxicology screens, and medication adherence counseling. Outcomes were compared at 6 months to a high-risk no-intervention group (N=21) and low-risk comparison control (N=20) group.¹⁰⁷ After the intervention, nonadherence in the high-risk group was similar to that in the low-risk group.¹⁰⁷ Dropout rate was low across groups, and the intervention group reported good satisfaction.

Recommendations

The options presented above have the common goal of risk reduction during continued opioid prescription, which requires a solid

Medication ^a	Marketed Indications	Dosing	Contraindications	Adverse Effects
Tizanidine	Muscle relaxant	Start with 2 mg orally at night and, if well tolerated, increase by 2-4 mg every day up to 8 mg every 8 hours	When prescribed in conjunction with methadone, there is an increased risk of prolonged QTc. Concomitant use of CYP1A2 inhibitors (eg, oral contraceptives). Dose reduction and monitoring recommended for hepatic and renal impairment. Pregnancy class C, breastfeeding: infant risk cannot be ruled out.	Sedation, hypotension, dry mouth, asthenia, dizziness, somnolence, hepatotoxicity.
Clonidine	Antihypertensive	0.1-0.2 mg orally every 6 hours OR 0.1 mg transdermal patch, applied once every 7 days, possible increase to 0.2 mg patch	Pregnancy class C, milk effects possible. Caution in case of cardiovascular disease.	Hypotension, sedation or somnolence, dizziness, dry mouth, headache, fatigue, erythema, atrioventricular block
Guanfacine	Antihypertensive, treatment of attention-deficit disorder	0.03-1.75 mg/d orally at night for 5-15 days	Interactions with CYP3A4 inhibitors and inducers. Caution in case of history of bradycardia, heart block, or cardiovascular disease. Avoid in case of concomitant use of alcohol. Dose reduction and monitoring recommended for hepatic impairment. Pregnancy category B. Breastfeeding: infant risk cannot be ruled out.	Hypotension, bradycardia, abdominal pain, constipation, dry mouth, dizziness, headache, somnolence, insomnia, erectile dysfunction, fatigue
Lofexidine	Antihypertensive	0.1 mg orally every 8-12 hours, can be increased up to 0.4 mg every 6 hours	Dose reduction and monitoring recommended for hepatic impairment Note: not marketed in the United States (not Food and Drug Administration approved), approved only in the United Kingdom	Hypotension, dry mouth, sedation, (all less frequent and less severe than with clonidine); headache, dizziness, rhinitis

^aUse of these agents should not be stopped abruptly if used for more than 9 weeks, especially if the patient is taking a high dose; decrease progressively to decrease risks of rebound hypertension, tachycardia, and hypertonia.

TABLE 4. Medicolegal Risk Mitigation Strategies for Opioid Tapering

1.	Provide detailed case <i>documentation</i> , including diagnosis, physical examination, substance abuse risk assessment, review of prior records, review of prescription monitoring data, and all of the efforts below.
2.	Narrowly <i>define</i> the treatment as tapering or weaning; avoid the term <i>detoxification</i> unless in a licensed addiction setting.
3.	In case of doubt regarding a substance use disorder, obtain a formal opinion from an <i>addiction specialist</i> before stating a tapering program.
4.	<i>Collaborate</i> legitimately with relevant medical or mental health specialists, including referrals for addiction and psychiatric care. Consider making prescriptions conditional to attendance at specialized consultations.
5.	Make every effort to <i>rule out criminal activity</i> if this suspicion is present. In case of known diversion, the physician should not prescribe even at lower or decreasing doses.
6.	Involve a psychiatrist or legal counsel in case of <i>threats</i> of suicide or of “buying drugs off the street”.
7.	<i>Reassure</i> patients that their health is being taken seriously, that pain will be treated, and that they will not be abandoned. Offer nonopioid treatments.
8.	Use proper <i>patient informed consent</i> and <i>opioid taper agreement</i> (Table 5).
9.	If <i>discharge</i> occurs, communicate with the patient about the cause and the end of treatment.

therapeutic relationship and, in case of suspicion of SUD, involvement of an addiction specialist. In such a situation, a direct discussion with the patient should occur, identifying the practitioner’s reasons for concern and underscoring the fact that pain therapy alone cannot fully meet the patient’s needs (recommendation GRADE D).^{105,116,117}

Maintenance with a long-acting opioid (eg, extended-release morphine or transdermal fentanyl) is an option, although there is no evidence to date favoring in general such a regimen over a

short-acting one.¹⁰⁸ There is growing evidence, including randomized clinical trials, supporting maintenance with buprenorphine for patients with CNCP and opioid dependence, inadequate analgesia, or OUD (recommendation GRADE B).¹⁰⁹ There is low evidence to support methadone use in these populations, and further research is needed (recommendation GRADE C).^{52,111,112} However, methadone could be favored in patients likely to take nonprescribed medications,¹¹³ whereas buprenorphine could be favored in pregnant women¹¹⁴ or patients

TABLE 5. Key Points to Include in an Opioid Taper agreement

Opioid taper formulated due to ... (formal rationale)
The taper starts _____ and is planned to end _____
Weekly/monthly reduction plan: 1)..., 2)..., 3)..., etc.
Outline risks (withdrawal symptoms, fluctuations in pain, anxiety) and management thereof
Patient agrees to: <ul style="list-style-type: none"> - Keep all regularly scheduled appointments with the treatment staff - Comply with other consultations as requested by the physician - Contact the treatment physician immediately to discuss continuation or changes in the plan if an issue occurs - Engage in relevant pain management strategies concurrent with the taper (eg, multidisciplinary functional restoration program, [detail]) - Regular urine toxicology and prescription monitoring program checks - No changes to plan without conferring with the prescribing physician - No controlled substances from other physicians without prenotification of treating physician - No new medication without agreement of prescribing physician - Notify the physician of any factors, such as development of increasing depression symptoms, that may be an barrier to success - Where appropriate, involve actively the significant other to provide support
Provisions for taper failure (could include some of the following elements, depending on the reason for taper and likely cause of failure): <ul style="list-style-type: none"> - New taper attempt with revised schedule - Referral to structured inpatient taper - Referral for consultation with addiction medicine or cognitive therapy specialists - No more opioid prescriptions, no more prescriptions of a certain medication, or no more prescriptions above a certain dose beyond date... - Long-term maintenance opioid therapy (with current or other prescriber), can include specific substance or maximum dose - Long-term as needed opioid rescue doses (eg, limited 10 doses supply per month)
List state-specific locations where remaining opioids can be appropriately disposed of

with kidney disease (recommendation GRADE C).¹¹⁵ Direct assessment of such a strategy would be needed. Pragmatically, the comfort levels of the prescriber, ceiling effects of buprenorphine, regulations surrounding prescription of these opioids, and costs often determine which agent is chosen.

Opioid maintenance for treating CNCP requires close monitoring, support, and reassessment over time, as underlined by expert panels and regulatory instances.^{13,14,27} If available, adherence counseling could be offered in conjunction with opioid maintenance, although the long-term effects of these interventions are unknown (recommendation GRADE C).^{106,107} Motivational interviewing, which is included in the adherence counseling,¹⁰⁷ might help prepare readiness for a future taper, although this hypothesis has yet to be studied (recommendation GRADE D).

CONCLUSION

There is mounting concern regarding the use of long-term opioid therapy for patients with CNCP, and increasing numbers of physicians are contemplating tapering for their patients. Although some evidence can be translated from the field of SUD to inform care in patients with CNCP, little specific and high-quality research has focused on guiding tapering from long-term opioid treatment and on specific support needed to manage risks and issues in this process. Important questions remain to be studied, as emphasized in the sections above. In the meantime, drawing on the available literature and our own clinical experience, we have put forth some suggestions to help guide physicians. Although some of these recommendations may be challenged by future evidence, we hope most will be validated and strengthened by further research. Overall, we suggest aiming to find the best possible equilibrium for each patient, balancing the risks and benefits of opioids in a way that optimizes function, and establishing realistic opioid taper or maintenance goals accordingly.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>.

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The Symposium on Pain Medicine will continue in an upcoming issue.

REFERENCES

- Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349(20):1943-1953.
- Manchikanti L, Ailani H, Koyyalagunta D, et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain Physician*. 2011;14(2):91-121.
- Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380.
- Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ*. 2006;174(11):1589-1594.
- Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010;1:CD006605.
- Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA*. 2005;293(24):3043-3052.
- Martell BA, O'Connor PG, Kems RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007;146(2):116-127.
- McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. *Cochrane Database Syst Rev*. 2013;8:CD006146.
- Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev*. 2013;8:CD004959.
- Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage*. 2008;35(2):214-228.
- Parsells Kelly J, Cook SF, Kaufman DW, Anderson T, Rosenberg L, Mitchell AA. Prevalence and characteristics of opioid use in the US adult population. *Pain*. 2008;138(3):507-513.
- Passik SD. Issues in long-term opioid therapy: unmet needs, risks, and solutions. *Mayo Clin Proc*. 2009;84(7):593-601.
- Chou R, Fanciullo GJ, Fine PG, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. *J Pain*. 2009;10(2):113-130.e122.
- Fishman SM. *Responsible Opioid Prescribing, A Clinician's Guide*. 2nd ed. Euless, TX: Federation of State Medical Boards; 2014.
- Howe CQ, Sullivan MD. The missing 'P' in pain management: how the current opioid epidemic highlights the need for psychiatric services in chronic pain care. *Gen Hosp Psychiatry*. 2013;36(1):99-104.
- Sullivan MD, Edlund MJ, Steffick D, Unutzer J. Regular use of prescribed opioids: association with common psychiatric disorders. *Pain*. 2005;119(1-3):95-103.

17. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006;166(19):2087-2093.
18. Braden JB, Sullivan MD, Ray GT, et al. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. *Gen Hosp Psychiatry*. 2009;31(6):564-570.
19. Jensen MK, Thomsen AB, Hojsted J. 10-year follow-up of chronic non-malignant pain patients: opioid use, health related quality of life and health care utilization. *Eur J Pain*. 2006;10(5):423-433.
20. Substance Abuse and Mental Health Services. Managing Chronic Pain in Adults with or in Recovery from Substance Use Disorder. <http://store.samhsa.gov/shin/content/SMA12-4671/SMA12-4671.pdf>. Accessed May 11, 2012.
21. Chapman CR, Davis J, Donaldson GW, Naylor J, Winchester D. Postoperative pain trajectories in chronic pain patients undergoing surgery: The effects of chronic opioid pharmacotherapy on acute pain. *J Pain*. 2012;12(12):1240-1246.
22. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129(3):235-255.
23. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis*. 2011;30(3):185-194.
24. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? a structured evidence-based review. *Pain Med*. 2008;9(4):444-459.
25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.
26. Morasco BJ, Gritzner S, Lewis L, Oldham R, Turk DC, Dobscha SK. Systematic review of prevalence, correlates, and treatment outcomes for chronic non-cancer pain in patients with comorbid substance use disorder. *Pain*. 2011;152(3):488-497.
27. Ballantyne JC, Sullivan MD, Kolodny A. Opioid dependence vs addiction: a distinction without a difference? *Arch Intern Med*. 2012;172(17):1342-1343.
28. Del Fabbro E. Assessment and management of chemical coping in patients with cancer. *J Clin Oncol*. 2014;32(16):1734-1738.
29. Farrell M. Opiate withdrawal. *Addiction*. 1994;89(11):1471-1475.
30. Kanof PD, Aronson MJ, Ness R. Organic mood syndrome associated with detoxification from methadone maintenance. *Am J Psychiatry*. 1993;150(3):423-428.
31. Fishbain DA, Rosomoff HL, Cutler R. Opiate detoxification protocols: a clinical manual. *Ann Clin Psychiatry*. 1993;5(1):53-65.
32. Cowan DT, Wilson-Barnett J, Griffiths P, Vaughan DJ, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain Med*. 2005;6(2):113-121.
33. Mattick RP, Hall W. Are detoxification programmes effective? *Lancet*. 1996;347(8994):97-100.
34. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse*. 1987;13(3):293-308.
35. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35(2):253-259.
36. Fishbain DA, Goldberg M, Rosomoff RS, Rosomoff H. Atypical withdrawal syndrome (organic delusional syndrome) secondary to oxycodone detoxification. *J Clin Psychopharmacol*. 1988;8(6):441-442.
37. Spadotto V, Zorzi A, Elmaghawry M, Meggiolaro M, Pittoni GM. Heart failure due to 'stress cardiomyopathy': a severe manifestation of the opioid withdrawal syndrome. *Eur Heart J Acute Cardiovasc Care*. 2013;2(1):84-87.
38. Rivera JM, Lockett AJ, Fritz KD, et al. "Broken heart syndrome" after separation (from OxyContin). *Mayo Clin Proc*. 2006;81(6):825-828.
39. Nilsen HK, Stiles TC, Landro NI, Fors EA, Kaasa S, Borchgrevink PC. Patients with problematic opioid use can be weaned from codeine without pain escalation. *Acta Anaesthesiol Scand*. 2010;54(5):571-579.
40. Ralphs JA, Williams ACDC, Richardson PH, Pither CE, Nicholas MK. Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods. *Pain*. 1994;56(3):279-288.
41. Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. *J Opioid Manag*. 2006;2(5):277-282.
42. Townsend CO, Kerkvliet JL, Bruce BK, et al. A longitudinal study of the efficacy of a comprehensive pain rehabilitation program with opioid withdrawal: Comparison of treatment outcomes based on opioid use status at admission. *Pain*. 2008;140(1):177-189.
43. Hooten WM, Townsend CO, Bruce BK, et al. Effects of smoking status on immediate treatment outcomes of multidisciplinary pain rehabilitation. *Pain Med*. 2009;10(2):347-355.
44. Crisostomo RA, Schmidt JE, Hooten WM, Kerkvliet JL, Townsend CO, Bruce BK. Withdrawal of analgesic medication for chronic low-back pain patients: Improvement in outcomes of multidisciplinary rehabilitation regardless of surgical history. *Am J Phys Med Rehabil*. 2008;87(7):527-536.
45. Krumova EK, Bennemann P, Kindler D, Schwarzer A, Zenz M, Maier C. Low pain intensity after opioid withdrawal as a first step of a comprehensive pain rehabilitation program predicts long-term nonuse of opioids in chronic noncancer pain. *Clin J Pain*. 2013;29(9):760-769.
46. Darchuk KM, Townsend CO, Rome JD, Bruce BK, Hooten WM. Longitudinal treatment outcomes for geriatric patients with chronic non-cancer pain at an interdisciplinary pain rehabilitation program. *Pain Med*. 2010;11(9):1352-1364.
47. Younger J, Barelka P, Carroll I, et al. Reduced cold pain tolerance in chronic pain patients following opioid detoxification. *Pain Med*. 2008;9(8):1158-1163.
48. Hooten WM, Mantilla CB, Sandroni P, Townsend CO. Associations between heat pain perception and opioid dose among patients with chronic pain undergoing opioid tapering. *Pain Med*. 2010;11(11):1587-1598.
49. Wang H, Akbar M, Weinsheimer N, Gantz S, Schiltenswolf M. Longitudinal observation of changes in pain sensitivity during opioid tapering in patients with chronic low-back pain. *Pain Med*. 2011;12(12):1720-1726.
50. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology*. 2006;104(3):570-587.
51. Heiwe S, Lonnquist I, Kallmen H. Potential risk factors associated with risk for drop-out and relapse during and following withdrawal of opioid prescription medication. *Eur J Pain*. 2011;15(9):966-970.
52. Tennant FS Jr, Rawson RA. Outpatient treatment of prescription opioid dependence: comparison of two methods. *Arch Intern Med*. 1982;142(10):1845-1847.
53. Blondell RD, Ashrafouf L, Dambra CM, Foschio EM, Zielinski AL, Salcedo DM. A clinical trial comparing tapering doses of buprenorphine with steady doses for chronic pain and co-existent opioid addiction. *J Addict Med*. 2010;4(3):140-146.
54. Vowles KE, Ashworth J. Is opioid withdrawal necessary within comprehensive pain rehabilitation programs? *Pain*. 2011;152(9):1948-1950.
55. Huffman KL, Sweis GW, Gase A, Scheman J, Covington EC. Opioid use 12 months following interdisciplinary pain rehabilitation with weaning. *Pain Med*. 2013;14(12):1908-1917.

56. Fordyce WE. On the nature of illness and disability: an editorial. *Clin Orthop Relat Res*. 1997;(336):47-51.
57. Dersh J, Gatchel RJ, Polatin P, Mayer T. Prevalence of psychiatric disorders in patients with chronic work-related musculoskeletal pain disability. *J Occup Environ Med*. 2002;44(5):459-468.
58. Dersh J, Gatchel RJ, Mayer T, Polatin P, Temple OR. Prevalence of psychiatric disorders in patients with chronic disabling occupational spinal disorders. *Spine (Phila Pa 1976)*. 2006;31(10):1156-1162.
59. Schieffer BM, Pham Q, Labus J, et al. Pain medication beliefs and medication misuse in chronic pain. *J Pain*. 2005;6(9):620-629.
60. Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain*. 2007;23(4):307-315.
61. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: a prospective, population-based study among injured workers in Washington state, 2002-2005. *Clin J Pain*. 2009;25(9):743-751.
62. Dersh J, Mayer TG, Gatchel RJ, Polatin PB, Theodore BR, Mayer EA. Prescription opioid dependence is associated with poorer outcomes in disabling spinal disorders. *Spine (Phila Pa 1976)*. 2008;33(20):2219-2227.
63. Valkanoff TA, Kline-Simon AH, Sterling S, Campbell C, von Korff M. Functional disability among chronic pain patients receiving long-term opioid treatment. *J Soc Work Disabil Rehabil*. 2012;11(2):128-142.
64. Troxel DB. *REMS: Opioid-Related Patient Safety and Liability*. Richardson, TX: The Doctors Company; 2012.
65. Fitzgibbon DR, Rathmell JP, Michna E, Stephens LS, Posner KL, Domino KB. Malpractice claims associated with medication management for chronic pain. *Anesthesiology*. 2010;112(4):948-956.
66. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
67. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA*. 2005;294(8):903-913.
68. Singh J, Basu D. Ultra-rapid opioid detoxification: current status and controversies. *J Postgrad Med*. 2004;50(3):227-232.
69. Maani CV, DeSocio PA, Jansen RK, et al. Use of ultra rapid opioid detoxification in the treatment of US military burn casualties. *J Trauma*. 2011;71(1 suppl):S114-S119.
70. Monterubbiansi MC, Capuccini J, Ferioli I, Tassinari D, Sarti D, Raffaelli W. High opioid dosage rapid detoxification of cancer patient in palliative care with the Raffaelli model. *J Opioid Manag*. 2012;8(5):292-298.
71. Murphy JL, Clark ME, Banou E. Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment. *Clin J Pain*. 2013;29(2):109-117.
72. Hooten WM, Townsend CO, Sletten CD, Bruce BK, Rome JD. Treatment outcomes after multidisciplinary pain rehabilitation with analgesic medication withdrawal for patients with fibromyalgia. *Pain Med*. 2007;8(1):8-16.
73. Rome JD, Townsend CO, Bruce BK, Sletten CD, Luedtke CA, Hodgson JE. Chronic noncancer pain rehabilitation with opioid withdrawal: Comparison of treatment outcomes based on opioid use status at admission. *Mayo Clin Proc*. 2004;79(6):759-768.
74. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2009;3:CD002025.
75. Fredheim OMS, Moksnes K, Borchgrevink PC, Kaasa S, Dale O. Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand*. 2008;52(7):879-889.
76. Buckley FP, Sizemore WA, Charlton JE. Medication management in patients with chronic non-malignant pain: a review of the use of a drug withdrawal protocol. *Pain*. 1986;26(2):153-165.
77. Department of Veterans Affairs. *Tapering and Discontinuing Opioids*. Washington, DC: Dept of Veterans Affairs; 2013.
78. Webcalculator. <http://www.hca.wa.gov/medicaid/pharmacy/documents/taperschedule.xls>. Accessed May 14, 2014.
79. Gowing L, Farrell MF, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2014;3:CD002024.
80. Bakris GL, Cross PD, Hammarsten JE. The use of clonidine for management of opiate abstinence in a chronic pain patient. *Mayo Clin Proc*. 1982;57(10):657-660.
81. Jimenez AC, Gusmorino P, Pinter I, Snow B. The use of clonidine for the treatment of meperidine withdrawal in a multidisciplinary pain program setting: a case presentation. *Bull Hosp Jt Dis Orthop Inst*. 1987;47(1):72-77.
82. See S, Ginzburg R. Choosing a skeletal muscle relaxant. *Am Fam Physician*. 2008;78(3):365-370.
83. Quinlan J. The use of a subanesthetic infusion of intravenous ketamine to allow withdrawal of medically prescribed opioids in people with chronic pain, opioid tolerance and hyperalgesia: outcome at 6 months. *Pain Med*. 2012;13(11):1524-1525.
84. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev*. 2011;(9):CD005031.
85. Lamb SE, Hansen Z, Lall R, et al. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. *Lancet*. 2010;375(9718):916-923.
86. Chou R, Huffman LH. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med*. 2007;147(7):492-504.
87. Guzman J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary rehabilitation for chronic low back pain: systematic review. *BMJ*. 2001;322(7301):1511-1516.
88. Windmill J, Fisher E, Eccleston C, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. *Cochrane Database Syst Rev*. 2013;9:CD010323.
89. Naylor MR, Naud S, Keefe FJ, Helzer JE. Therapeutic interactive voice response (TIVR) to reduce analgesic medication use for chronic pain management. *J Pain*. 2010;11(12):1410-1419.
90. Zheng Z, Guo RJ, Helme RD, Muir A, Da Costa C, Xue CCL. The effect of electroacupuncture on opioid-like medication consumption by chronic pain patients: a pilot randomized controlled clinical trial. *Eur J Pain*. 2008;12(5):671-676.
91. Currie SR, Hodgins DC, Crabtree A, Jacobi J, Armstrong S. Outcome from integrated pain management treatment for recovering substance abusers. *J Pain*. 2003;4(2):91-100.
92. MacLaren JE, Gross RT, Sperry JA, Boggess JT. Impact of opioid use on outcomes of functional restoration. *Clin J Pain*. 2006;22(4):392-398.
93. Fishbain DA, Cutler RB, Cole B, Lewis J, Rosomoff RS, Rosomoff HL. Medico-legal rounds: medico-legal issues and alleged breaches of "standards of medical care" in opioid rotation to methadone: a case report. *Pain Med*. 2003;4(2):195-201.
94. Fishbain DA. Medico-legal rounds: medico-legal issues and breaches of "standards of medical care" in opioid tapering for alleged opioid addiction. *Pain Med*. 2002;3(2):135-146.
95. Germaine RM. Revocation of Registration, Registrant Actions 2007. *Fed Regist*. 2007;72(174):51665-51668. http://www.deadiversion.usdoj.gov/fed_regs/actions/2007/fr0910.htm. Accessed December 3, 2014.
96. Cochran M. Revocation of Registration. *Fed Regist*. 2012;77(58):17505-17522. http://www.deadiversion.usdoj.gov/fed_regs/actions/2012/fr0326.htm. Accessed December 3, 2014.

97. McNichol TJ. Decision and Order. *Fed Regist*. 2012;77(180):57133-57154. http://www.deadiversion.usdoj.gov/fed_regs/actions/2012/fr0917_3.htm. Accessed December 3, 2014.
98. Hassman J. Denial of Application Notice. *Fed Regist*. 2010;75(35):8201:8210. http://www.deadiversion.usdoj.gov/fed_regs/actions/2010/fr0223.pdf. Accessed December 6, 2014.
99. Herbert RA. Decision and Order. 2011;76(168):53942-53961. <http://www.gpo.gov/fdsys/pkg/FR-2011-08-30/html/2011-22093.htm>. Accessed December 6, 2014.
100. Cui CL, Wu LZ, Li YJ. Acupuncture for the treatment of drug addiction. *Int Rev Neurobiol*. 2013;111:235-256.
101. Beam J, Swami A, Stewart D, Atnas C, Giotto L, Gossop M. Auricular acupuncture as an adjunct to opiate detoxification treatment: effects on withdrawal symptoms. *J Subst Abuse Treat*. 2009;36(3):345-349.
102. Kroening RJ, Oleson TD. Rapid narcotic detoxification in chronic pain patients treated with auricular electroacupuncture and naloxone. *Int J Addict*. 1985;20(9):1347-1360.
103. Jamison RN, Senraillier J, Michna E. Assessment and treatment of abuse risk in opioid prescribing for chronic pain. *Pain Res Treat*. 2011;2011:941808.
104. National Conference of State Legislatures. *Prevention of Prescription Drug Overdose and Abuse*. Washington, DC: National Conference of State Legislatures; June 2, 2014.
105. Savage SR. Management of opioid medications in patients with chronic pain and risk of substance misuse. *Curr Psychiatry Rep*. 2009;11(5):377-384.
106. Chelminski PR, Ives TJ, Felix KM, et al. A primary care, multidisciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. *BMC Health Serv Res*. 2005;5(1):3.
107. Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: a randomized trial. *Pain*. 2010;150(3):390-400.
108. Argoff CE, Silvershein DI. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clin Proc*. 2009;84(7):602-612.
109. Chen KY, Chen L, Mao J. Buprenorphine-naloxone therapy in pain management. *Anesthesiology*. 2014;120(5):1262-1274.
110. Haroutiunian S, McNicol ED, Lipman AG. Methadone for chronic non-cancer pain in adults. *Cochrane Database Syst Rev*. 2012;11:CD008025.
111. Kennedy JA, Crowley TJ. Chronic pain and substance abuse: a pilot study of opioid maintenance. *J Subst Abuse Treat*. 1990;7(4):233-238.
112. Rhodin A, Grönbladh L, Nilsson LH, Gordh T. Methadone treatment of chronic non-malignant pain and opioid dependence: a long-term follow-up. *Eur J Pain*. 2006;10(3):271-278.
113. Neumann AM, Blondell RD, Jaanimagi U, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *J Addict Dis*. 2013;32(1):68-78.
114. Boyer EW, McCance-Katz EF, Marcus S. Methadone and buprenorphine toxicity in children. *Am J Addict*. 2010;19(1):89-95.
115. Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J Support Oncol*. 2012;10(6):209-219.
116. Clark MR, Stoller KB, Brooner RK. Assessment and management of chronic pain in individuals seeking treatment for opioid dependence disorder. *Can J Psychiatry*. 2008;53(8):496-508.
117. Morasco BJ, Duckart JP, Dobscha SK. Adherence to clinical guidelines for opioid therapy for chronic pain in patients with substance use disorder. *J Gen Intern Med*. 2011;26(9):965-971.