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

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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 Agency[20] and by Fishman[14])

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 Scale[34] or the objective practitioner assessment Clinical Opiate Withdrawal Scale[35] (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 syndromes[36] 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

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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)
- 0 = pulse rate ≤80/min
- 1 = pulse rate 81-100/min
- 2 = pulse rate 101-120/min
- 4 = pulse rate >120/min

Sweating: during past half hour not accounted for by room temperature or patient activity
- 0 = no report of chills or flushing
- 1 = subjective report of chills or flushing
- 2 = flushed or observable moistness on face
- 3 = beads of sweat on brow or face
- 4 = sweat streaming off face

Restlessness observation during assessment
- 0 = able to sit still
- 1 = reports difficulty sitting still but is able to do so
- 3 = frequent shifting or extraneous movements of legs or arms
- 5 = Unable to sit still for more than a few seconds

Pupil size
- 0 = pupils pinned or normal size for room light
- 1 = pupils possibly larger than normal for room light
- 2 = pupils moderately dilated
- 5 = pupils so dilated that only the rim of the iris is visible

Bone or joint aches (if patient was having pain previously, only the additional component attributed to opiate withdrawal is scored)
- 0 = not present
- 1 = mild diffuse discomfort
- 2 = patient reports severe diffuse aching of joints or muscles
- 4 = patient is rubbing joints or muscles and is unable to sit still because of discomfort

Runny nose or tearing not accounted for by cold symptoms or allergies
- 0 = not present
- 1 = nasal stuffiness or unusually moist eyes
- 2 = nose running or tearing
- 4 = nose constantly running or tears streaming down cheeks

Gastrointestinal upset: during the last half hour
- 0 = no gastrointestinal symptoms
- 1 = stomach cramps
- 2 = nausea or loose stool
- 3 = vomiting or diarrhea
- 5 = multiple episodes of diarrhea or vomiting

Tremor observation of outstretched hands
- 0 = no tremor
- 1 = tremor can be felt but not observed
- 2 = slight tremor observable
- 4 = gross tremor or muscle twitching

Yawning observation during assessment
- 0 = no yawning
- 1 = yawning once or twice during assessment
- 2 = yawning ≥3 times during assessment
- 4 = yawning several times per minute

Anxiety or irritability
- 0 = none
- 1 = patient reports increasing irritability or anxiousness
- 2 = patient obviously irritable or anxious
- 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 *Am J Drug Alcohol Abuse*,[34] with permission. Scoring: 5-12: mild; 13-24: moderate; 25-36: moderately severe; more than 36: severe.
[b]Reprinted from *J Psychoactive Drugs*,[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 overrepresented 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

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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-μg/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

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when a psychosocial intervention was associated with pharmacological support; however, the nature of the psychological interventions was heterogenous.[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 limitations[88]: 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-up[42] 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-naive 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

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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 methadone[114] 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

TABLE 3. Available α_2-Adrenergic Agonists

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

[a]Use 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 *documentation,* 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 *define* the treatment as tapering or weaning; avoid the term *detoxification* unless in a licensed addiction setting.
3.	In case of doubt regarding a substance use disorder, obtain a formal opinion from an *addiction specialist* before stating a tapering program.
4.	*Collaborate* 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 *rule out criminal activity* 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 *threats* of suicide or of "buying drugs off the street".
7.	*Reassure* patients that their heath is being taken seriously, that pain will be treated, and that they will not be abandoned. Offer nonopioid treatments.
8.	Use proper *patient informed consent* and *opioid taper agreement* (Table 5).
9.	If *discharge* 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 women[114] 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: - 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): - 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

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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.

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