Ensuring Patient Protections When Tapering Opioids: Consensus Panel Recommendations

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Abstract

Long-term opioid therapy has the potential for serious adverse outcomes and is often used in a vulnerable population. Because adverse effects or failure to maintain benefits is common with long-term use, opioid taper or discontinuation may be indicated in certain patients. Concerns about the adverse individual and population effects of opioids have led to numerous strategies aimed at reductions in prescribing. Although opioid reduction efforts have had generally beneficial effects, there have been unintended consequences. Abrupt reduction or discontinuation has been associated with harms that include serious withdrawal symptoms, psychological distress, self-medicating with illicit substances, uncontrolled pain, and suicide. Key questions remain about when and how to safely reduce or discontinue opioids in different patient populations. Thus, health care professionals who reduce or discontinue long-term opioid therapy require a clear understanding of the associated benefits and risks as well as guidance on the best practices for safe and effective opioid reduction. An interdisciplinary panel of pain clinicians and one patient advocate formulated recommendations on tapering methods and ongoing pain management in primary care with emphasis on patient-centered, integrated, comprehensive treatment models employing a biopsychosocial perspective.

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In recent years, prescribers in the United States have made considerable efforts to reduce or discontinue opioids in patients who have taken them long term. Clinicians may attempt dose reduction motivated by a range of patient-specific and environmental considerations, including minimal benefit despite stable, escalating, or high doses; state regulations; medical board rules; payer and pharmacy policies; published guidance aimed at reducing the quantity of prescribed opioids[1]; and concerns regarding adverse effects, sanctions, overdoses, and opioid use disorder (OUD).[2,3] Evidence suggests that individual and societal benefits can emerge from reduction efforts,[4-8] but adverse consequences have also occurred, necessitating greater clarity around safe opioid tapering strategies. Some patients benefit from opioid reduction when carried out skillfully in a way that minimizes pain and withdrawal symptoms[7,8]; however, reduction or discontinuation of substantial doses can be both painful and hazardous, particularly when abrupt, as attested to by growing reports from medical experts, federal agencies, and other stakeholders.[1,9-15] Resultant harms may include serious withdrawal symptoms, psychological distress, self-medicating with illicit substances, uncontrolled pain, worsening function, and suicidality.[9,11,15-19]

A complicating factor in long-term opioid therapy (LTOT) is that multiple agencies influence clinical decisions. Notably, in 2016, the Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain—United States was issued to guide primary care clinicians who were

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considering initiating or continuing opioid prescriptions.[20] It recommended avoiding opioid doses above 90 morphine milligram equivalents without careful clinical review and justification. Many states subsequently imposed fixed limits on dose and duration, measures that misapply the guideline recommendations.[21] The Centers for Medicare and Medicaid Services, as well as pharmacies and pharmacy benefit managers, have also imposed limitations that vary in their provisions for exceptions.[2] Consequently, some patients have encountered barriers to obtaining prescribed opioids or have experienced sudden dismissal from care without adequate referral, leaving them at risk for severe withdrawal and other iatrogenic harms.[2] The CDC guideline authors, warning against guideline misapplications, published a clarification that the guideline does not support abrupt tapering, sudden discontinuation, sudden dismissal of patients, or hard limits on dosages and treatment durations.[15] Such abrupt discontinuation of opioid prescribing or dismissal from care (barring extreme extenuating circumstances) raises ethical concerns regarding patient rights to participate in care decisions and be protected from abandonment and its associated risks.[1,22]

These circumstances particularly affect so-called legacy patients, patients already receiving LTOT who seek continuation of opioid therapy with a new physician after losing access elsewhere.[18] Frequently, health care systems fail to facilitate transition of care when primary opioid prescribers leave their practice; therefore, these patients, some of whom have been receiving LTOT for years, often present as desperate for a source of continuing LTOT. Concurrently, clinicians feel pressure to reduce or discontinue LTOT from health care organizations, ethical guidelines, insurance and pharmacy policies, and even the US Drug Enforcement Administration (DEA). Uncertainty about best methods for opioid reduction may compound reluctance to accept legacy patients, who need special consideration and treatment to preserve their safety and functioning. The objective of the current article is to clarify the indications and strategies for opioid reduction or elimination, to delineate the responsibilities of clinicians with current or new patients receiving LTOT, and to provide recommendations for compassionate and evidence-based care. Recommendations are informed by the recognized biopsychosocial model of pain care that optimizes individualized patient care and an interdisciplinary approach.[23]

METHODS

The American Academy of Pain Medicine Foundation convened an interdisciplinary panel of pain clinicians and a patient advocacy representative. The panel (Appendix, available online at http://www.mayoclinicproceedings.org) met in Chicago, Illinois, on April 6, 2019, to identify and discuss key questions addressing the timing, indications, ethics, and methods surrounding reduction or discontinuation of opioids prescribed for chronic pain. Panelists broke into 3 work groups to evaluate assessment, ethics, and taper methods and presented findings to the full group. Recommendations presented here are based on a survey of the existing literature and on the collective clinical expertise of panelists. Review of literature, which is sparse and generally not applicable to weaning of therapeutic opioids in a primary care setting, was not systematic. Panelists agreed on major points of discussion and were in full agreement on most statements and recommendations. When agreement was incomplete, discussion and further literature reviews were conducted via electronic communication. Deliberations continued through several rounds of manuscript drafts to reach final consensus.

RISKS OF LONG-TERM OPIOID THERAPY

It is axiomatic that a medical treatment should be continued only so long as benefits exceed risks and harms. However, it can be unclear whether increased pain and decreased function in a patient receiving LTOT are due to opioids, disease progression, or psychosocial and environmental factors. Eliminating opioids may create new symptoms and exacerbate existing ones, leading to the perception that the drug had been effective

when it was not. Conversely, symptoms (eg, pain) unmasked when an effective medication is reduced can erroneously be attributed to dependency and withdrawal. Reevaluating the underlying causes of pain is critical in determining if other interventions (eg, physical therapy, behavioral health, interventional, and complementary and integrative approaches) may help to reduce pain and improve psychosocial function before or in conjunction with an opioid taper.[23]

Risk is always present with LTOT and is linked to dose,[24,25] dose variability (suggesting risks for both opioid prescribing and deprescribing),[26] use of concomitant sedatives,[26-28] and other factors (Table 1).[24-31] In a cohort of almost 43,000 LTOT patients, Glanz et al[29] found 9 overdose predictors in patients on LTOT: age, mental illness, psychotropic medication, substance use disorder, tobacco use, opioid prescriptions in the year prior to initiating LTOT, long-acting/extended-release formulation, daily opioid dose, and hepatitis C. Analysis of a sample from the Veterans Health Administration confirmed that pain-related polypharmacy and individual patient characteristics such as medical, psychiatric, and substance use comorbidities exacerbate risk.[30]

INDICATIONS FOR TAPERING LONG-TERM OPIOIDS

Indications to taper in the course of LTOT (Table 2) may be as self-evident as a patient's request to try a different treatment or reduce to a safer dose. In patients who have been receiving LTOT, diminishing analgesia may be a reason to taper opioids and intensify nonopioid pain care; however, it may also be an indication for trials of alternate opioids (ie, opioid rotation),[32,33] as failure of an initial opioid trial may not predict failure with other opioids.[34] Diminishing analgesia after initial benefit may suggest a need to evaluate the patient for disease progression or for a new or previously unrecognized physical or mental health condition. It may also indicate opioid analgesic tolerance and that alternative treatments should be considered.

The targets of LTOT are improvements in pain and function, which includes physical, cognitive, vocational, social, and other valued activities. Documenting functional improvements, quantitatively and qualitatively, may justify doses and durations that exceed the current ceilings recommended by payers and others, even if such assessments are imprecise. Conversely, inadequate functional improvement suggests a need for further assessment as tapering opioids may be indicated.

Opioids should be reduced or stopped when they are harming the patient, as indicated by impaired function, unremitting aberrant behaviors, overdose,[35] or other serious adverse events.[36] It should be noted that both clinicians[37] and patients[38] may have difficulty accurately assessing the harms and benefits resulting from opioids during the conduct of LTOT, highlighting the importance of quantitatively monitoring therapeutic outcomes. In some patients, a trial taper can be the only method to determine the harm to benefit ratio. An important criterion for reduction is the presence of aberrant behaviors, typified by evidence of multiple prescribers in prescription drug-monitoring data, urine drug screen discrepancies, a pattern of stolen or lost prescriptions, frequent early refill requests, and repeated unsanctioned dose escalations. If such behaviors are multiple or severe and the patient refuses referral to an addiction specialist, clinicians may elect to discontinue or reduce opioids, concluding that their risks or harms exceed their benefits. Diverse issues such as personality changes, respiratory compromise, and sleep apnea[31] also may require reconsideration of LTOT. A substantial number of patients receiving LTOT may require tapering due to comorbid OUD, which can occur in vulnerable persons after repeated exposure to opioids and renders them unable to fully control their behavior, so that they continue to use opioids despite their causing harm.[39]

The question arises whether opioids should be tapered simply because the dose exceeds the cautionary thresholds offered by the CDC[20] or other agencies. Dose thresholds in guidelines are derived from risk calculations and do not incorporate

TABLE 1. Patient Factors That Increase Risk With Long-Term Opioid Therapy

Factor	Risk	Reference
Daily dose >90-100 MME	Overdose	VA/DoD 2017[24] Volkow & McLellan 2016[25]
Dose variability	Overdose	Glanz et al 2019[26]
Long-acting or extended-release formulation (both long-term use and within 2 wk of initiation)	Overdose	Volkow & McLellan 2016[25]
Combination with benzodiazepines, other respiratory-depressant drugs	Overdose	VA/DoD 2017[24] Volkow & McLellan 2016[25] Sullivan 2018[27] Gressler et al 2018[28]
Long-term use (>3 mo)	Overdose, OUD	VA/DoD 2017[24] Volkow & McLellan 2016[25]
Age >65 y or <30 y	Overdose, OUD	VA/DoD 2017[24] Volkow & McLellan 2016[25]
Adolescence	OUD	Volkow & McLellan 2016[25]
Renal or hepatic impairment	Overdose	Volkow & McLellan 2016[25]
Mental disorders, mental health diagnosis, psychiatric instability Current or prior depression Generalized anxiety disorder Borderline personality disorder Antisocial personality disorder Posttraumatic stress disorder	Overdose, suicidality	VA/DoD 2017[24] Volkow & McLellan 2016[25] Glanz et al 2018[29] Oliva et al 2017[30]
Respiratory compromise, including sleep apnea	Overdose	VA/DoD 2017[24] Volkow & McLellan 2016[25] Walker et al 2007[31]
Current or history of SUD	OUD	VA/DoD 2017[24]
History of drug overdose	Overdose	VA/DoD 2017[24] Volkow & McLellan 2016[25]
Psychotropic medication use	Overdose	Glanz et al 2018[29] Oliva et al 2017[30]
Smoking	Overdose, OUD	Glanz et al 2018[29]
Pain nonresponsive or worsened with opioids	Overdose, OUD	VA/DoD 2017[24]
Recent health care utilization for mental health or SUD	Overdose, suicide, suicidal behaviors	Oliva et al 2017[30]

MME = morphine milligram equivalent; OUD = opioid use disorder; SUD = substance use disorder; VA/DoD = Veterans Affairs/Department of Defense.

benefits, which are difficult to measure in pharmacoepidemiological studies. There is no inflection point above which opioids abruptly become more dangerous, provided the dose escalation is slow.[40] However, dose thresholds are reasonable as flags to indicate the need for evaluation and documentation to justify the dose. Indeed, prescribed dose correlates with overdose risk.[20,40-42] Coadministration of benzodiazepines and other sedating psychoactive medications with opioids increases the risk of overdose,[30,40] and those taking the highest doses of opioids may be most likely to use

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TABLE 2. Indications for Tapering Long-Term Opioids
Patient request
Diminishing analgesia
Diminishing function
Deteriorating quality of life not explained by medical conditions
Unacceptable medical risk
Significant risk to benefit disparity
Active harms, including opioid use disorder
High risk: dose, medication combination(s)
Aberrant behaviors

this combination.[43,44] While urging clinicians to be judicious in prescribing to reduce opioid-related harms, the American Medical Association Opioid Task Force affirmed that opioid therapy may be medically appropriate for some patients, even at doses exceeding federal agencies' recommendations.[45]

Recommendation 1: Recognizing Opioid Tapering Indications

Many patients taking higher than recommended opioid doses will be at high risk, given the established correlation of dose with other opioid-related risks, and thus may meet criteria for tapering. Most panelists agreed that high opioid doses should be reduced unless the opioid has shown benefit and alternative treatments are not beneficial or feasible. Furthermore, opioids in combination with benzodiazepines should be reduced (or the benzodiazepine reduced or discontinued) unless the combination has shown benefit and alternative treatments are not beneficial or feasible. However, exceeding recommended opioid dose limitations is not in itself a sufficient reason to taper. There is insufficient evidence to advise opioid reduction in patients who show benefit from treatment and lack evident adverse effects, aberrant behavior, or major risks. The determination that a treatment should not have been initiated is not equivalent to a decision that it should be stopped. As with all medications, the lowest effective dose is appropriate, and regular reassessment of risk and benefit is fundamental. If high-dose opioids are to be continued, the patient's awareness that the dose exceeds recommendations and is associated with higher than usual risk should be established and documented.

Clinicians should be aware that buprenorphine (usually combined with naloxone) given as medication-assisted treatment (MAT) of OUD should not be reduced or discontinued in an attempt to comply with analgesia guidelines. Similarly, there may be less argument for taper of buprenorphine (with or without naloxone) when used as a plausible lower-risk alternative to traditional opioids. This partial mu agonist has unique properties that create a plateau in respiratory-depressant effects. Furthermore, most patients with OUD who are tapered from buprenorphine relapse to the use of more dangerous opioids.[46]

Although it is essential to consider and document input from the patient and family, the final responsibility for the tapering decision rests with the prescriber, who should not continue a medically contraindicated

TABLE 3. Common Opioid Withdrawal Symptoms
Physical symptoms
Tremor
Diaphoresis
Agitation
Insomnia
Myoclonus
Diffuse pain/hyperalgesia
Hyperthermia
Hypertension
Cramping/diarrhea
Pupillary dilation
Piloerection
Release of stress hormones
Pain increase
Affective symptoms
Dysphoria
Anhedonia
Anxiety
Depression
Hopelessness/suicidal ideation

Such symptoms as seizures, delirium, and death, which are known risks of sedative withdrawal, occur only rarely in opioid withdrawal, except in seriously ill patients.

TABLE 4. Ensuring Patient Safety During Opioid Taper

Decision Point	Method	Follow-up
Opioid risk outweighs benefit Dose Combinations Aberrant behaviors Active harms Insufficient analgesia Psychiatric/medical comorbidities	• Systematic assessment • Input from patient/family • Gain patient consent and collaboration • Clinician decision determinative	At each clinic visit
Before initiating taper	• Opioid taper agreement • Address depression, anxiety, insomnia • Consider OUD *DSM-V* checklist • Offer support • Offer other pain treatment modalities • Discuss rate of taper, possible withdrawal • Slow taper If noncollaborative • Explain decision • Rapid reduction only if imminent danger • Continue to offer decreasing doses	
Initiate taper	• Close observation, support • Ensure availability (team approach if possible) • Manage withdrawal symptoms (adjuvants) • Rate, based on tolerability: 10% of previous week's dose (faster) and 10% of previous month's dose (slower) have been recommended; slower preferred with long-term use	Week 1 Daily, or as needed (virtual visits, phone) ≥ Week 2 Every 2 wk, as needed Weekly, if symptoms are severe (team based) Slow or pause taper as needed
Poor response to taper	• OUD Buprenorphine/naloxone • Poor response to taper without OUD Buprenorphine OR slow taper	Initiation: Every 3-4 d to optimize dosing

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TABLE 4. Continued

Decision Point	Method	Follow-up
	• Advise patient of possible withdrawal • Set target/follow-up buprenorphine dose(s) • Start behavioral program	

DSM-V = Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition); OUD = opioid use disorder.

treatment solely on the basis of patient request. Tapering is essential if patients are in serious danger because of medical complications, overdose,[35] or hazardous (eg, injecting) behaviors. Clinicians should offer care to all patients who are dependent or who have OUD, or else should obtain agreement from others to provide this care. Simply giving the patient the name of another health care professional is inadequate and ineffective.

Risks Associated With Opioid Tapering

Numerous studies have documented that most patients who agree to taper either benefit or are unharmed.[7,8,47-49] Most studies, however, lacked randomization and blinding and did not investigate the consequences of nonconsensual tapering. Viewed differently, credible evidence suggests that voluntary, patient-centered opioid reduction mostly yields good results with minimal to no documented harms; however, these results cannot be generalized to other opioid tapering strategies. Furthermore, preliminary data from patients undergoing consensual opioid taper indicate that a subgroup worsened with dose reduction.[8] This finding may indicate that the LTOT benefit was significant and justifies continuing opioid treatment in a minority of LTOT patients. Or, it may indicate psychiatric comorbidity that needs evaluation and treatment. More research is needed in larger, diverse populations to draw generalizable conclusions.

Reports of harms after involuntary opioid discontinuation include overdoses, termination of care, emergent hospital or emergency department utilization, and suicidal ideation or behavior.[9,17-19,50] However, these reports are difficult to interpret regarding causality because reasons for opioid stoppage are either not reported[17,50] or include worrisome patient behaviors.[17,19,51] Thus, it could be that patient-related factors (eg, substance use disorder) that precipitated opioid discontinuation played an independent causal role in the harms that followed. That said, the poor outcomes make it hard to argue that stopping opioids resulted in benefit. In practice, patients who are unwilling to reduce opioids are likely to drop out of treatment.[50,52]

The problems of tapering dropouts and early opioid resumption are often triggered by difficulty tolerating withdrawal when symptoms are inadequately addressed, and fear of withdrawal is one reason patients continue LTOT.[53] Dropouts also occur due to patients' fear that pain will worsen and possibly become intolerable with opioid cessation. This fear must be taken seriously and addressed. It often goes unrecognized that pain itself may be a withdrawal symptom and not simply an exacerbation of the original chronic pain.[53] The increased pain associated with withdrawal may be new or amplified preexisting pain, as descending pain facilitatory tracts originating in the rostral ventral medulla show increased firing and amplify pain during early abstinence.[54] Anxiety and depressive symptoms may emerge or intensify during withdrawal. A 2018 study of voluntary opioid tapering found that greater depressive symptoms predicted taper discontinuation.[8]

TABLE 5. Buprenorphine Initiation in Patients Taking Opioids for Pain
• Buprenorphine may produce acute opioid withdrawal in patients on full mu agonists
• Patients discontinue all opioids the night before initiation (time depending on duration of action)
• After mild withdrawal is present, initiate 2-4 mg (repeated at 2-hour intervals, if well tolerated, until resolution of withdrawal symptoms)
• Typically, 4-8 mg will be needed the first day
• Reevaluate on day 2 and increase dose if needed
• Total dose given on day 2 can then be prescribed as the daily dose
• Unlike treatment for opioid use disorder, buprenorphine for analgesia should be given in 3-4 daily doses

These realizations, along with a US Food and Drug Administration (FDA) safety alert[12] warning of serious withdrawal symptoms in patients abruptly discontinued from opioids, underscore the importance of helping all patients avoid such symptoms (Table 3). Thus, withdrawal distress should be preempted and treated with liberal use of adjuvant agents along with adequate clinician time and support. Clinicians should also convey that many patients receiving LTOT actually feel and function better following opioid tapering.[48,55-57]

Less recognized than acute withdrawal is a syndrome that has been called *protracted withdrawal*.[58-60] Months after opioid elimination, patients may experience dysphoria, irritability, insomnia, anhedonia, or a vague sense of being unwell.[59,61] These symptoms must be expected, discussed with the patient, and either preempted or treated. Importantly, these symptoms cannot be easily differentiated from what is seen in patients with chronic pain who have not been treated with opioids and may reflect an unmasking of the original chronic pain problem.

Recommendation 2: Reducing Risk During Taper

Reducing opioids comes with risks that should be appreciated and reviewed carefully with the patient and their family (Table 4). Patients who agree to taper tolerate it better. Some patients become upset when changes are suggested. If the patient is depressed and is opposed to taper, treatment for depression should be instituted before taper or taper should only be undertaken when the patient's potential for self-harm is recognized and addressed. The panel agreed that taper should include a declared commitment to work with the patient on a safe, comfortable process with assurance that there will be no abandonment. Optimally, there should be a team-based approach that addresses psychosocial as well as medical issues. It is recognized, however, that access to such a team is unavailable in many locations. The process may require considerable education, time, and counseling. Consideration may also be given to referral to a pain specialist at this time to help ensure that nonopioid treatments are optimized and that the patient does not feel abandoned. Most symptoms of opioid withdrawal can be mitigated or eliminated with the use of adjuvants. Because poor results from outpatient tapers may result from insufficient physician expertise as well as the inaccessibility of services, clinicians must develop expertise or refer to another health care professional with specialized skills.

METHODS OF OPIOID REDUCTION

There is no established best way to reduce or eliminate opioids, and evidence to support a particular taper rate is weak. Working with voluntary patients, Darnall et al[8] provided initial reductions of 5% and continued slow reductions, usually in 10% decrements, over 4 months. Not all patients chose this approach, and for a minority, doses did not decline but increased. The Washington State Agency Medical Directors' Group guideline recommended for most patients an initial reduction of 10% or less per week with further adjustments based on patient status.[62] The CDC recommended 10% per

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week reduction as a starting point.[36] More recently, a guide from the US Department of Health and Human Services[63] suggested individualized tapering plans that range from 10% per month (or slower) to faster tapers of 10% per week until 30% of the original dose is reached, followed by 10% weekly reductions of the remaining dose. Slow tapers may require several months or years and are more appropriate than faster tapers for patients who have been receiving prolonged LTOT.[63] Because of complex and variable pharmacokinetics, nonlinear morphine equivalency, multiple drug interactions, and documented high lethality, outpatients should not be converted to methadone for weaning in the absence of special justification and clinician experience. This recommendation is especially true in those taking high doses of opioids.

Several authors described beneficial outcomes with treatment in chronic pain rehabilitation programs based on an interdisciplinary model that incorporated opioid tapering in a context of psychosocial treatments (cognitive behavioral therapy, mindfulness stress reduction, relaxation training, and pain education) and rehabilitation (physical and occupational therapy and graded exercise).[47,55,64-68] Taper (often to zero) commonly was completed in 3 to 4 weeks, and dropouts were typically less than those reported in much slower outpatient approaches. Notably, program participation was voluntary, taper was consensual in the setting of specialized programs, and patients were often seen daily throughout the process.

Collectively, these reports and studies suggest that the tolerability and success of opioid tapering may depend less on the opioid dose than on the intensity of support and observation and the ability of staff to provide immediate intervention when there is patient distress. This issue poses a major challenge for primary care clinicians and for health systems. Importantly, the goal is rarely the rapidity of reduction but rather its durability over time, which is likely to be contingent on maintaining patient comfort and valued activities.

Pharmacological Adjuvants to Opioid Reduction

A number of medications mitigate physical and psychological withdrawal symptoms. α_2-Agonists directly attenuate opioid withdrawal.[69] Clonidine suppresses withdrawal symptoms but may cause orthostasis or hypotension in some, necessitating small initial doses and careful titration. Tizanidine is less effective but also less likely to cause hypotension. Lofexidine is FDA approved for control of opioid withdrawal symptoms.[63]

An old and generally weak scientific literature confirms the usefulness of agents that do not specifically counteract the physiologic changes of opioid withdrawal but do mitigate anxiety, insomnia, and irritability. Drugs reported to have benefit for short-term use include trazodone,[70] tricyclic antidepressants,[71] gabapentin,[72] and mirtazapine.[73] Gastrointestinal discomfort may respond to loperamide; however, clinicians should know that it can be abused and, in high doses, can cause dangerous arrhythmias.[74]

The Role of Buprenorphine

Buprenorphine, a partial mu-receptor agonist, is approved in sublingual form for treatment of OUD in combination with naloxone. As noted at a 2018 National Academies of Sciences, Engineering, and Medicine workshop on MAT of OUD, "Medications are irrefutably the most effective way to treat OUD—reducing the likelihood of overdose death by up to threefold…"[75]

Buccal and cutaneous patches of low-dose buprenorphine are FDA-approved for the treatment of pain, and buprenorphine/naloxone has been used off-label as an analgesic for chronic pain.[76-78] Buprenorphine has safety advantages over full mu agonists because respiratory depression tends to plateau as dose increases, and it is also less subject to dose escalation. Although use of buprenorphine/naloxone to treat OUD requires training and a waiver from the DEA, no federal restrictions apply to its use as an analgesic (although payers often deny coverage for off-label use). Studies have

suggested efficacy in patients with comorbid chronic pain and OUD.[79,80] Daitch et al,[80] in a small retrospective review, found that patients taking high doses of opioids for pain experienced substantial improvements in pain and quality of life when switched from a full mu opioid receptor agonist to buprenorphine.

Buprenorphine has been suggested for certain patients who, despite substantial opioid doses, continue to manifest poor analgesia and function, yet worsen when opioids are either reduced or increased. They often have comorbid mood disorders or psychiatric diagnoses but do not meet criteria for OUD.[58] Typically, such patients experience prolonged symptoms from opioid reduction, even when supported, that may include hyperalgesia and anhedonia. Their sufferings engender a desire to continue LTOT, yet, unlike patients with OUD, they do not crave opioids or use them compulsively.[53,58] The situation has been described as *complex persistent dependence* or *complex persistent opioid dependence*, terms intended to help guide research and treatment of these challenging patients but not proposed as diagnostic nomenclature. (Importantly, one should avoid the error of assuming that all deterioration resulting from opioid reduction is due to dependence given that the processes that originally engendered the pain are likely to remain active and could be unmasked by opioid reduction.)

Although large studies are lacking, such patients have responded well to buprenorphine/naloxone.[58,77,79] In support of this finding, the recent US Department of Health and Human Services guide suggests a buprenorphine trial in persons failing to benefit from high opioid doses yet responding poorly to taper.[63] Therefore, the panel agreed that this difficult to handle situation may warrant a trial of buprenorphine/naloxone, given that (1) neither opioid escalation nor reduction seem viable, (2) buprenorphine/naloxone may reduce urges for dose escalation, and (3) the combination is demonstrably safer than high doses of mu agonists, which these patients are typically taking. (Because it has abuse-deterrent properties, buprenorphine/naloxone is preferred over buprenorphine alone.) An alternative treatment track is a very slow opioid dose taper, which may be selected when patients cannot tolerate buprenorphine, among other rationales.

Recommendation 3: Initiating Taper

The panel suggested the use of an opioid taper agreement or informed consent to be discussed and signed by the patient and physician and to contain such items as a statement of collaboration, a statement of commitment to treatment and teamwork, description of clinician responsibilities (eg, patient nonabandonment and commitment to treat withdrawal and pain), and descriptions of patient responsibilities (eg, adherence to the collaborative treatment plan and communication regarding difficulties) (Table 4). Before and during reduction, depression, anxiety, and insomnia should be addressed. The panel recommended that addiction assessment be conducted before tapering because patients with OUD are unlikely to tolerate abstinence and are at heightened risk for using hazardous substitutes. This assessment may include administering the OUD checklist of the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).[39] If used, the clinician should be aware that many criteria for the diagnosis of OUD can also occur as a result of chronic pain, thus risking false-positives. The panel endorsed making available buprenorphine with or without naloxone in all delivery systems and dosages for treatment of pain without the necessity of an OUD diagnosis. Panelists agreed that OUD can be difficult to diagnose in those receiving LTOT and that consultation or comanagement with an addiction specialist is helpful if available.

- For patients with OUD, treatment with MAT is essential: clinicians should treat with buprenorphine/naloxone if authorized by the DEA Drug Addiction Treatment Act of 2000 waiver for treating OUD or should refer the patient for addiction treatment.

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- For patients with poor pain control, poor functioning, and poor response to taper but without OUD, 2 treatment paths may be considered: (1) treatment with or referral for treatment with buprenorphine/naloxone or (2) slow opioid dose taper that may take months or years.

The manufacturer has provided guidelines for safe buprenorphine initiation that exceed the scope of this paper.[81] These guidelines are for patients initiating MAT for addiction but are also applicable to patients taking therapeutic opioids (Table 5 contains panel recommendations).

Clinicians should initiate slow, reasonable, collaborative taper with adjuvant treatments as needed for withdrawal symptoms, counseling patients that such symptoms, should they occur, can be safely managed. Patients should be encouraged to share ownership of the collaborative process and to understand that the health care professional is not dismissing them, withdrawing from their treatment, or giving up on managing their pain effectively. Clinicians should set patients up for success by communicating at the start regarding individualized goals, expectations, patient fears, and the contingency plans should problems arise (eg, slow or pause taper, clonidine, and other options).

Taper rate is determined by patients' ability to tolerate it. It may be helpful to implement very small dose decreases at first to address patient anxiety and to increase patient confidence in the process. Percentage reductions should not be understood as a straight-line taper from the starting dose (which, in the case of 10% reductions, would subject a person starting at 1000 morphine milligram equivalents to a reduction from 100 mg to zero at the last decrement); rather, each new dose should be 90% of the previous dose. The target dose may not be zero, and some patients whose regimens have been tapered to elimination may benefit from resumption at lower doses. Close observation and support during the taper are critical to the process as is clinician availability to treat symptoms and manage fears.

There may be a role for "virtual visits" via video in situations of limited access to the caregiver. There is also a need for long-term follow-up, as periods of increased pain can be expected at some point in time and may require increased nonopioid strategies.

Recommendation 4: Avoiding Abandonment

Such practices as abrupt withdrawal or major dose reduction and "cold referrals" to clinicians who have not agreed to accept the patient are unacceptable medical care except in extreme cases, such as confirmed diversion or serious medical toxicity, and even then, there may be risk of overdose in such points of care transition.[82] Sudden cessation is no more appropriate with opioids than with antihypertensives or antihyperglycemics. To reduce or discontinue LTOT, the clinician is obligated to (1) offer a comfortable and safe tapering regimen, (2) obtain agreement from another physician to offer care, or (3) replace full mu agonists with buprenorphine. These considerations apply even more in the case of benzodiazepines, baclofen, carisoprodol, barbiturates, and other central nervous system depressants whose abrupt cessation can cause significant morbidity and even death (Supplemental Table, available online at http://www.mayoclinicproceedings.org).[83-85]

It is acceptable to continue higher than recommended doses of LTOT when there are neither adverse effects nor aberrant behaviors and the patient demonstrates functional and analgesic benefits.

Nonpharmacological Strategies for Opioid Reduction

Little research specifically examines the role of psychosocial treatments in reducing opioids in patients receiving LTOT.[7,49] Furthermore, a Cochrane review found only 11 studies (1592 patients) in which pharmacological treatment of addiction was compared with pharmacological plus psychosocial interventions.[86] Only a small number of psychosocial interventions were studied, and data were inadequate to compare them. Yet the addition of psychosocial care was found

to significantly reduce dropouts, rate of opioid use during treatment and at follow-up, and clinical absences during treatment. Moore et al[87] found that cognitive behavioral therapy improved outcomes among prescription opioid users with OUD who were being treated with buprenorphine/naloxone but had no effect on heroin users similarly treated. A recent American Society of Addiction Medicine practice guideline proposes offering patients psychosocial treatment as determined by individual need but without allowing patient refusal or treatment unavailability to preclude or delay pharmacotherapy.[88] Exercise and fitness training are known to reduce both chronic pain and anxiety, suggesting that they may be useful in therapeutic opioid reductions; however, there are no available data on this topic. In animal models of opioid withdrawal, treadmill exercise reduced physical signs of opioid abstinence.[89,90] It may be significant that many of the studies showing patient improvement with opioid elimination incorporated intensive psychosocial treatments and physical rehabilitation.

Recommendation 5: Optimizing Nonpharmacological Opioid Reduction Strategies

Patients undergoing opioid reduction should be referred for or encouraged to seek behavioral therapies as a strategy for reducing withdrawal-related anxiety and increasing treatment retention. It is likely but not documented that such measures as meditation, yoga, and aerobic exercises may attenuate discomfort related to opioid reduction.

SYSTEMIC CHANGES NEEDED

Delineation of the Problem

One reason for the prescribing of dangerous doses and combinations is the lack of alternatives. Current incentives promote a brief visit that ends with a prescription, and, unsurprisingly, this is what many patients want and expect. It is not productive to educate health care professionals on the importance of optimizing nonopioid therapies while disincentivizing their provision. Interdisciplinary pain rehabilitation programs have repeatedly found that severely impaired patients with chronic pain can achieve good function and reasonable comfort with a combination of psychosocial treatments, physical reconditioning, and nonopioid analgesics.[49] Yet, such treatments are available only to a small percentage of those who could benefit.

Recommendation 6: Aligning Health Care Incentives With Optimal Patient Care

The incentive structure of office practice should be aligned with optimal care. A major strategy for opioid reduction must be the provision of access to integrated comprehensive pain care that utilizes multiple disciplines within a biopsychosocial framework. The time required for education and counseling of patients with chronic pain suggests that reimbursement codes should provide for treatment analogous to diabetic education, the nursing care code for depression, or Centers for Medicare and Medicaid Services payment for cardiac rehabilitation.[91]

For reasons previously detailed, payers, pharmacies, pharmacy benefit managers, medical boards, and legislatures must recognize that rigid adherence to dose limitations is not supported scientifically.

STATEMENT OF LIMITATIONS

The evidence for the recommendations set forth is suboptimal. Patients have rarely been randomized to opioid reduction or discontinuation. It is conceivable that those who improved were those whose conditions no longer required opioids. It is possible that those who did poorly after opioid elimination were discontinued from opioids because of aberrant behaviors or other factors that led to poor outcomes. The larger discussion regarding long-term benefits of opioids for chronic, nonmalignant pain is controversial and beyond the scope of this article. The panel believed that the available data supported the conclusions reached but acknowledged that subsequent investigations could point to different conclusions.

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CONCLUSION

System-wide initiatives to decrease opioid prescribing have had mixed results. Although population studies have suggested benefit, reports of individual harms suggest increased suffering, procurement of illicit substances, and suicides. These results highlight the importance of assessing the whole person when considering opioid reduction or discontinuation. Dose reduction in a collaborative environment is indicated when opioid risks or harms outweigh demonstrated benefits in pain and function.

Among the criteria for reduction in LTOT, daily dose is important but not determinative because neither a ceiling nor average effective dose has been established. Therefore, each patient's dose should be individualized. Dose reduction is indicated when a patient is in significant danger with the provision that alternative care is available and offered if tapering results in a worsening clinical status. Dose reduction may not be indicated in the absence of serious risk when there is evidence of benefit. Although data are limited, voluntary opioid reduction appears to have the best outcomes to date. Patient preferences in opioid tapering should be documented. A written opioid reduction or discontinuation agreement may be useful to confirm the patient's responsibility to adhere to the plan and the clinician's commitment to provide facilitated access and support during taper. Nonconsensual dose reduction is justifiable when the current treatment involves significant danger to the patient, there are no benefits sufficient to justify this risk, and the patient cannot be brought to understand this. With confirmed diversion of controlled substances, immediate stoppage is justified.

Opioid monotherapy is rarely optimal care. Nonopioid pharmaceuticals, interventional pain management, psychosocial treatments for pain control and improved coping, and rehabilitation strategies should be utilized for best outcomes. Regular documentation of treatment response, including quantitative assessments of pain and function and ongoing risk-benefit analysis, is essential to facilitate decisions by patients and clinicians as well as to justify those decisions to others.

It is contingent on payers, suppliers, and regulators to recognize and support flexibility in LTOT dosage and duration. It is contingent on payers and regulators to promote access to nonopioid treatments for chronic pain and to incentivize their provision.

Key takeaway points for practicing health care professionals include:

- Do not abruptly stop LTOT, except for reasons of diversion or extreme patient danger
- Do not abandon patients or make "cold" referrals to other clinicians
- Consider high dose a risk factor but not determinative for taper
- Seek patient consent and collaboration during tapering
- Consider buprenorphine when tapering is indicated but poorly tolerated
- Monitor patients closely and provide support, including referrals, during taper
- Diagnose and treat OUD when present
- Document treatment response

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles

has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CDC** = Centers for Disease Control and Prevention; **DEA** = Drug Enforcement Administration; **FDA** = Food and Drug Administration; **MAT** = medication-assisted treatment; **OUD** = opioid use disorder; **LTOT** = long-term opioid therapy

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