Treatment Updates for Pain Management and Opioid Use Disorder

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KEYWORDS

• Opioids • Pain • Opioid use disorder • Contingency management
• Stimulant use disorder • Naloxone

KEY POINTS

- Non-opioid therapies are at least as effective as opioids for many common types of acute pain.
- Substance Abuse and Mental Health Services Administration's pandemic era flexibility with take-home methadone doses from Opioid Treatment Programs has continued after being met with strong support from both patients and providers.
- Low-dose initiation of buprenorphine can be an effective approach to treating patients with opioid use disorder. Patients do *not* need to enter withdrawal for a low-dose buprenorphine initiation.
- Concomitant opioid and stimulant use is on the increase, as are fatal overdoses involving polysubstance use. Contingency management—the practice of incentivizing patients for abstinence from drug use—has a demonstrated track record of decreasing stimulant use while increasing treatment engagement across a variety of care settings.
- Naloxone can be dispensed from pharmacies without a prescription in all states via standing order. Over-the-counter naloxone products were recently approved by the US FDA and are expected to be available in the second half of 2023.

INTRODUCTION

The number of Americans with opioid use disorder (OUD) has steadily risen over the past 2 decades, now affecting roughly 2.7 million adults.[1] The number of drug overdose deaths has risen dramatically in the past 5 years. Nearly 107,000 people died of drug overdose in the 12 months ending in April 2021, representing a nearly fivefold rate increase (32.4 vs 6.8 per 100,000 standard population) compared with 2001.

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Synthetic opioids, including fentanyl, are driving mortality[2] Evidence-based interventions are essential to combat the extraordinary challenges associated with opioid use in high-risk populations; the authors aim to review this evidence to support clinical decision-making in primary care practices.

Updates to Chronic Pain Management with Opioids

In March 2016, the US Centers for Disease Control and Prevention (CDC) published their "Guidelines for Prescribing Opioids for Chronic Pain" for primary care physicians (PCPs).[3] These guidelines were created to help PCPs decide whether to initiate and/or continue opioids for patients with chronic pain, guide opioid selection, and inform dosage recommendations. The guideline used a 4-tiered evidence-type scale based on the Agency for Healthcare Research and Quality's (AHRQ) adaptation of the Advisory Committee on Immunization Practices (ACIP) Grading of Recommendation, Assessment, Development and Evaluation method (**Table 1**).[3]

Of the 12 recommendations in the 2016 Guidelines, none cited Type 1 evidence and only one cited Type 2 evidence. Seven recommendations cited Type 4 evidence. Type 4 evidence is equivalent to AHRQs "low strength of evidence with serious limitations" with the ACIPs Type 4 evidence indicating "very little confidence in the effect estimate (high uncertainty), and the likelihood is high that the true effect differs from the estimate of the effect." The 2016 guidelines also provided specific milligram morphine equivalent (MME) recommendations to avoid exceeding based largely on expert opinion. This is notable as there is no evidence that there exists a threshold MME beyond which risk increases; rather, risk increases as dose increases.[4]

Six years later, the updated 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain continues to rely on low-quality evidence.[5] Only one recommendation draws from Type 1 evidence, one with Type 2 evidence, and seven based on Type 4 evidence. Specific MME recommendations have been removed. The updated guidelines include "acute" and "subacute" pain in several of their recommendations. The updated guidelines also offer recommendations for patients who are already receiving opioid therapy and how physicians can discuss the risks and benefits around medication tapering. The updated guidelines also attempt to address health equity with a paragraph outlining the inequalities in the introduction and a brief mention of the concept in the conclusion. However, no recommendations explicitly mention healthy equity. The omission from the recommendations means many who read solely the recommendation bullet points may miss this content. Including equity content—even those based on low-quality evidence—may valuably add to future revisions of the recommendations.

Table 1
Centers for Disease Control and Prevention opioid prescribing guideline tiers of evidence quality

Evidence Quality	Type	Description
Strongest	1	Randomized clinical trials or overwhelming evidence from observational studies.
	2	Randomized clinical trials with important limitations or exceptionally strong evidence from observational studies.
	3	Observational studies or randomized clinical trials with notable limitations.
	4	Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.
Weakest		

Two recommendations in the 2022 Practice Guideline are based on strong data support. The recommendations advising providers to start with non-opioid analgesic agents before moving to opioids (#2, Type 2 evidence) and to refer patients with OUD to evidence-based treatment (#12, Type 1 evidence) have a more rigorous evidence base than the other guidelines. Both recommendations improved their evidence grade from the previous guidelines. This improvement is encouraging and highlights the potential for other recommendations to similarly develop in future iterations of the guidelines. Indeed, the CDC guidelines read: "Although the strength of the evidence is sometimes low quality and research gaps remain, clinical scientific evidence continues to advance and supports the recommendations in this clinical practice guideline." A major challenge in studying the use of opioids for pain is that not all types of pain are the same, and the subjective experience of pain makes it difficult to quantify.

CLINICS CARE POINTS

- Updates to Guidelines:
  - Acute pain (duration <1 month): Non-opioid therapies are at least as effective as opioids for many common types of acute pain.
  - Subacute pain (duration 1–3 months): Non-opioid therapies are preferred for subacute and chronic pain (duration >3 months).
  - Many noninvasive non-pharmacologic approaches, including physical and behavioral therapy, can improve pain and function with very low risk.
  - Clinicians, practices, health systems, and payers should be mindful of health equity and implicit bias in managing the pain of all kinds of patients.
  - For patients already receiving opioid therapy:
    - Be careful when changing opioid dosage and avoid rapid dose decreases.
    - Opioid therapy should not be discontinued abruptly.
    - Use the lowest effective opioid dose in treating pain whenever opioids are indicated and maximize concomitant non-opioid therapy.

Updates to Opioid Use Disorder Treatment in Primary Care Settings

The early stages of the COVID-19 pandemic presented several challenges for Opioid Treatment Programs (OTPs). OTPs, federally licensed clinics that dispense methadone, are required to offer in-person care. Pre-pandemic patients who began treatment at an OTP were required by federal regulation to attend the clinic in-person 6 days per week for the first several months of treatment, with the possibility of receiving take-home doses slowly increasing thereafter. The prospect of mandating in-person clinic attendance daily during an era of social distancing proved sufficiently concerning for regulators to change this requirement. In March 2020, the Substance Abuse and Mental Health Services Administration (SAMHSA) issued an exemption allowing states to request that their OTPs can provide up to 28 days of take-home doses of methadone for patients meeting certain criteria.[6] Three years later, states, OTPs, and patients continue to support this exemption. Advocates identify an increase in treatment engagement, improved patient satisfaction, and fewer incidents of misuse associated with greater methadone take-home flexibility.[7,8] The exemption remains in place today, and SAMHSA has indicated that it may become permanent; however, a final decision has yet to be announced.[9]

On the coattails of the successful changes around methadone dispensed from OTPs, advocates have called for reform to the methadone regulatory framework. The National Institute on Drug Abuse convened a Methadone Access Research Task Force to develop a research agenda to increase access to methadone treatment

for OUD. One prong of this agenda includes exploring the risks and benefits of expanded methadone access in the United States.[10] The support of a federal agency in exploring this topic is significant, suggesting an openness to reforming a system largely unchanged since the 1970s.

The pandemic also improved access to substance use disorder care by increasing availability and awareness of telemedicine. Telemedicine offers safe, accessible health care and delivers outcomes similar to "care as usual" for OUD.[11,12] One study found patients with Medicare had increased retention in care and a reduced odds of medically treated overdose when receiving medication management for OUD via telehealth services.[12] Another study found video observation of methadone take-home doses as an effective alternative to in-person dosing.[13]

Although telemedicine has certainly increased access to care, the reintroduction of mobile treatment units has brought medicine straight to the people. Many persons seeking treatment for OUD must travel long distances to receive methadone at a brick-and-mortar OTP, with longer travel distances associated with worse treatment outcomes.[14] To address this disparity, the drug enforcement administration (DEA) allowed mobile methadone units to provide legally dispensed methadone to people in need at specified parking locations. For 2 decades, mobile methadone mobile units provided care. From 2007 to 2021, the approval of new units was paused by the DEA and ultimately resumed in July 2021.[15] DEA-registered OTPs may once again obtain and deploy mobile methadone units, with the goal of increasing access to care in underserved areas.

Another recent policy change was the elimination of the DATA-Waiver through the Consolidated Appropriations Act of 2023—which includes elements of Mainstreaming of Addiction Treatment Act and the Medication Access and Training Expansion Act.[16] The DATA-Waiver (also called the X-Waiver) required additional training for DEA-licensed providers—8 hours for physicians, 24 hours for advanced practice providers—as well as administrative burden and patient limits to prescribe buprenorphine for OUD. With the X-Waiver removal, providers with a DEA registration with Schedule III authority can prescribe buprenorphine to patients with OUD without any limitations, including no limitations on the number of patients treated. The DEA and SAMHSA plan to implement new training requirements for all DEA-licensed prescribers, which are expected to go into effect in June 2023.[17]

Another update related to OUD treatment involves a novel change in clinical practice in response to the increasing concentration of fentanyl in the non-pharmaceutical opioid supply. Low-dose initiation of buprenorphine is a relatively new approach for transitioning patients from full opioid agonists to buprenorphine. Buprenorphine, a partial mu-opioid agonist with high affinity for the receptor, can cause precipitated withdrawal (PW) if a full dose is administered to a patient who has recently used full agonist opioids. In a traditional buprenorphine initiation, patients using full agonist opioids must abstain from opioid use until entering mild-to-moderate withdrawal—an unappetizing prospect for many patients—then begin buprenorphine slowly. The emergence of widespread illicit fentanyl use, and fentanyl's high lipophilicity, has led to increased concerns related to traditional initiations causing more PW. This phenomenon is not universal, with data on the incidence of PW related to buprenorphine initiation somewhat limited: ED-based studies have shown an incidence of ~1%, and other data based on patient self-reported data have shown an incidence of 35% to 40% depending on a variety of factors.[18,19] In response, prescribers have embraced low-dose buprenorphine initiation. Multiple studies have demonstrated its effectiveness and tolerability.[20] The process begins with a small dose of buprenorphine and increasing dose gradually, all while the patient continues to use the full agonist opioids (**Table 2**).

Table 2
Example schedule for low dose initiation of buprenorphine

Day	Buprenorphine Dose	Continue Other Opioid?
1	0.5 mg once a day	Yes
2	0.5 mg twice a day	Yes
3	1 mg twice a day	Yes
4	2 mg twice a day	Yes
5	3 mg twice a day	Yes
6	4 mg twice a day	Yes
7	4 mg thrice a day (stop other opioids)	No
8	12–20 mg total daily dose	No

During this time, the patient continues to use full agonist opioids.[20] On reaching 12 mg, the patient is instructed to stop their full agonist opioid and is given a full dose of buprenorphine (typically 12–24 mg) aiming to avoid PW and successfully transitioning to buprenorphine. This approach has been studied most extensively in the inpatient setting; however, positive data exist from the ambulatory setting as well.

CLINICS CARE POINTS

- SAMHSAs pandemic era flexibility with take-home methadone doses from OTPs has continued after being met with strong support from OTPs and patients.
- Telemedicine and mobile methadone units are two proven strategies to improve access to OUD treatment.
- The X-Waiver has been eliminated; providers are able to prescribe buprenorphine for OUD with a standard DEA registration.
- Low-dose initiation of buprenorphine can be an effective approach to treating patients with OUD, particularly if there is concern about PW or inability to tolerate withdrawal. Patients do *not* need to enter withdrawal for a low-dose buprenorphine initiation.

Concomitant Stimulant and Opioid Use and Increased Access to Contingency Management

Concomitant stimulant and opioid use continues to increase in the United States with some researchers deeming our current era the "fourth wave" of the opioid epidemic.[21–23] At present, there are no FDA-approved medications to treat methamphetamine or cocaine use disorders.[24] Providers must rely on psychosocial treatments to treat patients with stimulant use disorders, and the behavioral intervention with the strongest evidence base to treat stimulant use disorders is contingency management.

Contingency management (CM) is a psychosocial intervention where participants are rewarded for positive behavior.[25] In relation to stimulant use disorders, CM is used to incentivize abstinence from drug use. In practice, patients who provide a negative toxicology test are rewarded, and this reward builds on itself with repeated negative toxicology tests over time. Rewards may be a coupon, gift card, or a cash prize.

Critics argue CM is a poor use of limited resources, stating it is unethical to pay people for what they "should be doing anyway."[26] However, CM is both clinically effective

and cost beneficial. A recent systematic review examined the practice of CM among patients with methamphetamine use disorder, finding the intervention not only decreased non-prescribed substance use but also lower rates of medical utilization and risky sexual behaviors.[27] Other studies of methamphetamine and cocaine use disorders have supported this evidence with similar results: CM is consistently associated with improved clinical outcomes and is more effective than other behavioral interventions.[28,29] An economic analysis of stimulant use disorder treatments in a community setting found CM was an overall cost saving intervention when used in conjunction with other psychosocial interventions, such as cognitive behavioral therapy.[29]

Despite its efficacy, CM has not been widely adopted by providers and treatment centers. One reason for this low uptake is the lack of a mechanism for reimbursement. However, state Medicaid programs have leveraged Section 1115 of the Social Security Act to request waivers creating pilot programs that increase availability of CM by using Medicaid funding.[30] Montana and California Medicaid plans now offer a CM benefit.[31,32] The California program—named the Recovery Incentives Program—began in the first quarter of 2023 for eligible California Medicaid beneficiaries. It is expected to run for 24 weeks with an upgraded incentive change in the latter 12 weeks pending patient participation.[32] Although models may vary across states, the California program caps the yearly reimbursement at $599 per patient.[33] Other states, including Washington and West Virginia, are also piloting CM programs.[34,35]

CLINICS CARE POINTS

- Concomitant opioid and stimulant use is on the rise, as are fatal overdoses involving polysubstance use.
- There are no FDA-approved medications for cocaine or methamphetamine use disorders.
- CM—the practice of incentivizing patients for abstinence from drug use—has a demonstrated track record of decreasing stimulant use while increasing treatment engagement across a variety of care settings.
- CM will likely continue to be implemented in the future as more payors offer reimbursement.

Updates on Naloxone Access

Naloxone, an opioid receptor antagonist used as an antidote to opioid overdoses, is an essential tool in the medical management of OUD. Policymakers, pharmacists, patients, and providers all support increasing access to naloxone; however, the optimal path to this outcome is debated. Removing the requirement for an individual prescription has proven effective: Ohio's dispensed naloxone orders increased by 2328% over a 3 year time period following the removal of this requirement.[36] Other studies have found similar increases in Medicaid recipient dispensing following similar changes.[37] Currently, pharmacists in all 50 states can dispense naloxone without a patient-specific prescription through the use of statewide standing orders.[38] Pharmacy access may be particularly important for communities that do not have local harm reduction programs.

Although this policy change has allowed greater access to naloxone, medication cost remains a barrier to widespread distribution. The drugmaker Kaleo famously raised the cost of its naloxone auto-injector Evzio by 600% to $4100 per dose; the drugmaker later entered into a $12.7 million settlement with the Department of Justice to resolve allegations of false claims related to falsified prior authorizations related to

its extraordinary price hike.[39,40] The overwhelming majority of naloxone dispensed in the United States is as a nasal spray. The out-of-pocket cost for naloxone can range from $60 to $140 (for one box containing two doses).[41–43] With Medicaid, generic naloxone averages around $20 with state-to-state variability.[43] Price is not the only barrier; 10 states have monthly prescription limits, seven having top-10 per-capita opioid prescribing rates nationwide.[44]

Of note, a federal advisory committee recommended the US Food and Drug Administration authorize over-the-counter naloxone in February 2023, paving the way for even greater access to the drug.[45] Many states also have third party prescribing, which allows someone to receive naloxone with the intention of using the product on someone else.[46] In addition to government efforts, nonprofit organizations have developed resources aiming to link providers and patients with freely dispensed naloxone nationwide.[47,48] Medication cost is particularly important for nonprofit organizations focusing on harm reduction: the cheaper the product, the more units that can be purchased and distributed to high-need populations.

Providers and organizations are striving to increase naloxone access in ambulatory and emergency department settings. Co-prescription of naloxone with opioids has increased over the past decade.[49] The 2016 CDC Guideline for Prescribing Opioids for Chronic Pain recommended providers consider co-prescribing naloxone to patients taking greater than 50 MME opioids per day; however, the updated 2022 guidelines offer no specific recommendations for MME dosages above which naloxone co-prescribing should occur, instead leaving the decision to the judgment of the provider.[3,5] Naloxone co-prescribing has increased across all states, but individual state rates vary and co-prescribed naloxone rates nationally are low overall.[50–51] Importantly, evidence supporting co-prescription as an effective means to reduce opioid overdose on a population level is limited.[51] Nevertheless, given potential benefit and limited risk, greater distribution of naloxone among people who need it is a promising approach.

Naloxone prescriptions are inconsistently picked up by patients, particularly patients at high risk of overdose seen in the ED.[52,53] Providers and hospitals have attempted to overcome this obstacle by dispensing naloxone directly to patients while in the ED.[54] Implementation barriers exist, including training, costs, means of distribution, and patient education, but the idea may be a novel and successful approach in reducing overdose deaths.[54–56] There are reimbursement barriers related to naloxone *dispensed but not administered* in the ED, further impeding distribution and underscoring the need for system-level change to advance public health initiatives.[55,56] In addition, state laws may limit dispensing of medications from inpatient pharmacies.

CLINICS CARE POINTS

- Naloxone is an effective medication for opioid overdose reversal.
- Naloxone can be dispensed without a prescription in all states via standing order.
- The cost of naloxone continues to be a barrier to its community distribution.
- Co-prescribing naloxone with opioids and dispensing take-home naloxone from EDs aim to increase naloxone access, though there are barriers to both practices.
- The people most likely to save a life with naloxone are people who use opioids themselves—as such, they are a priority population to receive naloxone.

Looking Forward

This article's aim is to provide primary care providers with pertinent updates on opioid use and chronic pain management. The number of overdose deaths caused by opioids continues to increase, with ultra-potent fentanyl analogs saturating the drug supply. Although fentanyl is currently used primarily via inhalation, it is not unreasonable to expect a transition to intravenous fentanyl use in the coming years. This represents an enormous increase in risk to an already hazardous practice.

In the face of this challenging landscape, the medical community must continue to implement the essential practice of harm reduction. Harm reduction aims to mitigate the negative consequences of risks of drug use without condemning or endorsing said use. Examples of harm reduction include syringe access programs, overdose prevention centers, and fentanyl testing strips.[57] Harm reduction practices have a proven track record of reducing infectious disease transmission, decreased risk of overdose, and enhanced engagement in treatment.

The medical community must address opioid initiation and use across the spectrum of prevention.[58] The prevention of opioid use initiation and promotion of harm reduction practices—especially to high-risk populations—using a multilevel approach may decrease negative outcomes at a public health level while decreasing stigma around drug use as well. The coordinated implementation of primary, secondary, and tertiary prevention strategies will mitigate the impact of adverse outcomes associated with opioid use. The American College of Preventive Medicine strongly supports this approach and endorses population-level interventions.[58]

As health care providers, we must strive to keep our patients safe and healthy using every available tool in our toolkit. We hope that this review helps the reader accomplish this goal.

DISCLOSURE

The authors report no actual or perceived conflicts of interest. The viewpoints presented in this article represent the opinion of the authors and do not reflect the position of their employers. This article has not been published elsewhere.

AUTHOR CONTRIBUTIONS

E. Salisbury-Afshar, D.T. Coyle, and T. Locke conceptualized the initial commentary. T. Locke conducted supporting research and authored the article. E. Salisbury-Afshar, D.T. Coyle, and T. Locke provided critical feedback and contributed to the writing of the article.

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