

The Next Stage of Buprenorphine Care for Opioid Use Disorder

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Buprenorphine has been used internationally for the treatment of opioid use disorder (OUD) since the 1990s and has been available in the United States for more than a decade. Initial practice recommendations were intentionally conservative, were based on expert opinion, and were influenced by methadone regulations. Since 2003, the American crisis of OUD has dramatically worsened, and much related empirical research has been undertaken. The findings in several important areas conflict with initial clinical practice that is still prevalent. This article reviews research findings in the following 7 areas: location of buprenorphine induction, combining buprenorphine with a benzodiaz-

epine, relapse during buprenorphine treatment, requirements for counseling, uses of drug testing, use of other substances during buprenorphine treatment, and duration of buprenorphine treatment. For each area, evidence for needed updates and modifications in practice is provided. These modifications will facilitate more successful, evidence-based treatment and care for patients with OUD.

Ann Intern Med. doi:10.7326/M18-1652

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This article was published at Annals.org on 23 October 2018.

Annals.org

Buprenorphine received approval from the U.S. Food and Drug Administration (FDA) in 2002 for treatment of opioid use disorder (OUD), with tight limits on patients per physician prescriber and strict guidelines by insurers and governmental agencies (1). Because buprenorphine was the first medication treatment with opioid agonist activity to be made available in the United States since methadone—with potentially similar risks for misuse and diversion (2, 3)—policymakers developed cautious recommendations. More than a decade later, sufficient data provide a better understanding of buprenorphine treatment in practice. The updated evidence argues for more individualized care. As with other health care interventions, however, inertia of past practices creates barriers to patient access, entry, and continued care (1, 4).

The purpose of this article is to contrast recent evidence with common, widespread, and outdated practices that have the paradoxical effect of potentially harming patients (Table). The core of this evidence comes from policy statements from the FDA in 2017 (5) and guidance from the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2018 (6). In addition, we searched MEDLINE from January 2014 to July 2018 to identify English-language studies of buprenorphine that also addressed induction, benzodiazepines, relapse, counseling, toxicology or drug testing, polysubstance use, or discontinuation. We examined newer studies if we believed that they added substantively to the understanding of the SAMHSA and FDA guidance.

LOCATION OF BUPRENORPHINE INDUCTION

Previous Approach

A medical setting is needed for safe and effective buprenorphine induction.

New Findings and Recommendations

Home induction is safe and effective.

Treatment Improvement Protocol (TIP) 40 for buprenorphine, released by SAMHSA in 2004, stated,

“The consensus panel recommends that physicians administer initial induction doses as observed treatment” (7). This TIP also commented on precipitated withdrawal during induction of medication for addiction treatment (MAT) (8), citing 1 buprenorphine study in which symptoms were “both mild in intensity and easily tolerated” and 1 in which a single patient receiving methadone had a “poorly tolerated withdrawal of severe intensity” when given buprenorphine (7). These 2 studies were used to substantiate practice guidelines about observed induction. A later review of buprenorphine's FDA package insert actually found *fewer* withdrawal symptoms in groups receiving buprenorphine versus placebo (9).

Home induction programs began as early as 2003 (10). Cohort studies (1, 11), observational trials (12), and reviews (13) found no adverse effects of home induction with appropriate patient education and telephone support. This adds to existing evidence that the 2 approaches are “essentially equivalent” (1).

Home induction is offered from emergency departments (14) and supported by text messaging in primary care (15). Deliberate support during home induction—including office visits, telephone or text messaging contact, close resolution of medication coverage, and patient education—can be important for successful treatment initiation. Induction from methadone may be more complicated and require closer clinical involvement (11). In TIP 63, SAMHSA recognized these research findings and advised that “[i]nduction can occur in the office or at home. Most clinical trials were conducted with office-based induction, and extant guidance recommends this approach. However, office-based induction can be a barrier to treatment initiation. Home induction is increasingly common” (6).

See also:

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Table. Buprenorphine Care: Previous Approaches Compared With New Findings and Recommendations

Previous Approach	New Findings and Recommendations
A medical setting is needed for induction. Benzodiazepine and buprenorphine coprescription is toxic.	Home induction is also safe and effective (6). Buprenorphine should not be withheld from patients taking benzodiazepines (5).
Relapse indicates that the patient is unfit for buprenorphine-based treatment. Counseling or participation in a 12-step program is mandatory.	Relapse indicates the need for additional support and resources rather than cessation of buprenorphine treatment (43). Behavioral treatments and support are provided as desired by the patient (6).
Drug testing is a tool to discharge patients from buprenorphine treatment or compel more intensive settings. Use of other substances is a sign of treatment failure and grounds for dismissal from buprenorphine treatment.	Drug testing is a tool to better support recovery and address relapse (56). Buprenorphine treatment does not directly affect other substance use, and such use should be addressed in this context (43).
Buprenorphine is a short-term treatment, prescribed with tapered dosages or for weeks to months.	Buprenorphine is prescribed as long as it continues to benefit the patient (6).

Office induction has created hurdles for patients and clinicians in scheduling and has curtailed overall provision of buprenorphine (16). Current evidence supports shared decision making in selecting the best location for buprenorphine transition. Practices should broadly support home induction.

COMBINING BUPRENORPHINE WITH A BENZODIAZEPINE

Previous Approach

Benzodiazepines and buprenorphine are a toxic combination.

New Findings and Recommendations

Withholding buprenorphine because of benzodiazepine use could result in harm from untreated opioid addiction that outweighs the risks of concomitant use of these medications.

When buprenorphine was first introduced in the United States, the product insert noted “a number of reports in the post-marketing experience of coma and death associated with the concomitant intravenous misuse of buprenorphine and benzodiazepines by addicts” (17). Two years later, TIP 40 repeated this warning on the basis of 6 French patients (18, 19) in whom the combination of benzodiazepines with buprenorphine administered intravenously or in “massive oral doses” was implicated in overdose (see TIP 40 [7] for relevant early studies). On the basis of these studies, TIP 40 concluded that “[t]he use of sedative-hypnotics (benzodiazepines, barbiturates, and others) is a relative contraindication to treatment with buprenorphine because the combination (especially in overdose) has been reported to be associated with deaths” (7).

Dual prescribing of buprenorphine and benzodiazepines is prevalent, however. More than half of patients in 1 Australian sample received coprescription (20). A French cohort study reported a 75% rate of coprescribing and did not find a relationship with mortality (21). In the U.S. Department of Veterans Affairs, rates varied regionally from 11.0% to 38.5% (median, 20.2%) (22). An analysis of 2013 U.S. data found that 17.7% of patients receiving buprenorphine also received benzodiazepines (23).

If this prevalent coprescribing were dangerous, buprenorphine would be involved in a substantial number of American overdose deaths. Thankfully, this is not the case. In U.S. studies of opioid overdose deaths, buprenorphine is found in fewer than 1% to 2% (5, 24–28) of postmortem toxicology results. As TIP 63 notes, “Overdose death with buprenorphine is most often associated with intravenous benzodiazepine and heavy alcohol use” (6). Because deaths involving buprenorphine are rare, those involving buprenorphine and benzodiazepines together can be no more frequent (29). This is in contrast to the use of full agonist opioids for pain, where evidence has suggested particular risk with concomitant benzodiazepine use (30).

In 2017, the FDA issued a safety announcement concerning buprenorphine and benzodiazepines. Its review included the sensitivity analysis of a Swedish study showing an association between buprenorphine-benzodiazepine coprescription and overdose death (hazard ratio, 1.53 [95% CI, 1.11 to 1.96]). Coprescribing in this study was prevalent: Nearly a third of the sample received prescriptions for both medications (31). Weighing the evidence, the FDA advised that “[t]he combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks.” The announcement determined that “buprenorphine . . . should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS)” (5). Other studies have not found coprescription to affect overdose (32, 33), and a 2016 systematic review found no qualifying studies (34). One outlier is short-acting alprazolam: U.S. epidemiologic data show it to be the benzodiazepine most frequently involved in overdose, and clinicians should generally avoid coprescription (35).

The FDA announcement also noted that “[c]essation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use with MAT medicines. . . . In [other cases], gradually tapering off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose is appropriate” (5). The announcement added that “careful medication

management can reduce risks" (5), echoing the advice of others (36, 37). As TIP 63 observes, "Some patients may have taken appropriately prescribed benzodiazepines for years with limited or no evidence of misuse. For such patients, tapering benzodiazepines may be contraindicated and unrealistic. Others may require treatment for a benzodiazepine use disorder" (6).

RELAPSE DURING BUPRENORPHINE TREATMENT

Previous Approach

Patients who experience relapse have failed buprenorphine treatment.

New Findings and Recommendations

Patients who experience relapse should be provided additional support and resources rather than cessation of buprenorphine treatment.

Over the long term, stable complete abstinence from opioid use is low (<30% in a cohort review with 10 to 30 years of observation [38]). Iterative relapse is the most common path, an expectation to be managed and addressed, and an indication to refine problem-solving strategies and care.

Iterative relapse is also common in other chronic diseases (such as hypertension and type 2 diabetes), and only a minority of patients follow medical recommendations (39). This is true worldwide: The World Health Organization estimates that adherence to long-term therapy for chronic illness is at most 50% (40). Adherence rates are even lower among persons who experience poverty or lack social support, suggesting that a shortage of resources is a contributing factor. In other chronic conditions, we speak not of "relapse" but of "noncompliance," "nonadherence," and "uncontrolled disease." Because clinically shaming or discharging patients who are nonadherent is not customary, punitive consequences should not exist for OUD patients who relapse.

The National Institute on Drug Abuse (41), public health departments (42), and specialty professional organizations (43) recognize relapse as a common, expected part of care for substance use disorders. This does not mean that relapse should be ignored; rather, it should lead to thoughtful, patient-centered refinements in care, such as avoidance of social media, family supervision of buprenorphine administration, and support as patients seek employment or stable housing. Keeping a range of options and approaches available—including alternative types (for example, methadone and long-acting naltrexone) and intensities of care—is an important part of ongoing treatment. Patients who experience relapse should not be identified as "failing medical treatment."

REQUIREMENTS FOR COUNSELING

Previous Approach

Traditional counseling is needed to benefit from buprenorphine treatment.

New Findings and Recommendations

Traditional counseling is not necessary for successful outcomes in buprenorphine treatment.

Some patients find counseling incredibly helpful; others do not. Some instead find benefit in peer support, in a spiritual home, or from family. Behavioral health support comes in many forms and should be tailored to the patient's needs. To mandate that all patients need a particular kind of behavioral support (such as 1:1 counseling [8]) is short-sighted and impractical (44). As with other chronic diseases (such as congestive heart failure), the use of ancillary or additional professional support staff and resources should be customized. Patients with congestive heart failure may need home nursing, remote monitoring, and the support of a nutritionist. Some simply need regular visits with a primary care provider.

A systematic review of psychosocial counseling provided with MAT found that "support for the efficacy of delivering concurrent psychosocial interventions was less robust for buprenorphine" (45). Evidence for additional benefit was marginal, and the accompanying editorial concluded that patients reduced their opioid use regardless of whether they received additional psychosocial treatment (46). A separate review found that "pharmacotherapy alone is effective treatment for opioid dependence with minimal to no drug-abuse counseling" (47). The authors recommended that, as with other chronic conditions, counseling be offered rather than mandated to receive pharmacologic intervention.

Despite the lack of evidence for counseling, insurers prohibit many patients from continuing to receive MAT if not in dedicated counseling (48). This lack of evidence combined with inadequate access to behavioral health providers drastically limits MAT access (49, 50). The World Health Organization has reversed the message on MAT, calling effective treatment of opioid dependence "psychosocially assisted pharmacological treatment" (51).

New standards should focus on appropriate referral to care based on individual patient needs; TIP 63 does just this, as SAMHSA explains:

Drug Addiction Treatment Act of 2000 legislation requires that buprenorphine prescribers be able to refer patients to counseling, but making referrals is not mandatory. Many patients benefit from referral to mental health services or specialized addiction counseling and recovery support services. However, four randomized trials found no extra benefit to adding adjunctive counseling to well-conducted medical management visits delivered by the buprenorphine prescriber. (6)

In TIP 63's algorithm for referring patients to behavioral health therapies, the first question asks, "Is the patient willing to engage in additional [to medication management] behavioral health strategies?" (6). If "No," the algorithm recommends, "Offer best advice and ongoing motivational interviewing; revisit offer for behavioral health therapies." If "Yes," it recommends peer support groups, case management, vocational training, social supports, and counseling. Patients should receive appropriate medical management of buprenorphine and be provided with counseling choices.

USES OF DRUG TESTING

Previous Approach

Drug testing indicates which patients are unsuccessful and should be removed from buprenorphine treatment.

New Findings and Recommendations

Drug testing is a tool for supporting recovery rather than a method of punishment.

Clinical and nonclinical use of drug testing (for example, employment drug screening) has led to poor outcomes based on misinterpretation and test limitations (52-55). As with any medical test, the operating characteristics of drug testing are critical for clinicians to understand. Interpretation may be complicated by difficulty in assessing the pretest probability of a positive result, flawed interpretation of metabolite concentrations, and use of point-of-care drug "screens" with lower sensitivity and specificity. Unfortunately, misinterpretation often means penalties for a patient and increased barriers to care. Stigma remains widespread in addiction treatment, which can result in discharge if a patient continues to struggle in early phases of stabilization or have relapse in later stages.

The most recent guidance from the American Society of Addiction Medicine recommends that "[d]rug testing should be used as a tool for supporting recovery rather than exacting punishment" (56). Clinicians are advised in TIP 63 to "[e]xplain to patients that testing will help them meet treatment goals and is not performed to render punishments" (6).

To this end, positive findings on drug tests should not be called "dirty." Although this is a common term describing test results that show use of addictive substances (57), it is not how we describe abnormal levels of hemoglobin A_{1c} or thyroid-stimulating hormone. Guidance from the American Society of Addiction Medicine urges use of the nonjudgmental terminology "expected" or "unexpected" results and advises that when results contradict self-reported use, therapeutic discussions should take place (56). Drug testing should be accurately interpreted, used to support positive patient outcomes rather than cause patient harm, and discussed in a nonjudgmental manner. In addition, technologies such as oral fluid (saliva) testing can improve the testing process by allowing full observation and reducing rates of adulterated samples while addressing patient concerns about privacy and exposure.

USE OF OTHER SUBSTANCES DURING BUPRENORPHINE TREATMENT

Previous Approach

Patients who use other substances are not appropriate candidates for buprenorphine treatment.

New Findings and Recommendations

Buprenorphine does not have a direct effect on other substance use, and this use should generally not influence care for OUD.

Opioids share the same broad categorization of "substance use disorder" with alcohol, marijuana, cocaine, and other drugs. Polysubstance use is common: Nearly one third of U.S. residents who received substance abuse treatment in 2013 reported treatment for both alcohol and drugs (58). A Clinical Trials Network survey from the National Institute on Drug Abuse found a 38% prevalence of alcohol use disorder among persons seeking OUD treatment (59); other analyses found alcohol involvement in approximately one fifth of opioid-related deaths (60, 61). Lumping varied substances under the common heading of "use disorders," however, belies how substances and their use disorders differ and require different treatment strategies.

Although inadequate MAT dosing has been related to increased polysubstance use (62), expecting OUD treatment to affect other substance use is unreasonable (38). As a comparison, patients not meeting type 2 diabetes goals would not have their asthma inhalers discontinued. Similarly, other substance use should not affect the decision whether to continue effective OUD care. Substance use disorders involving cocaine, alcohol, methamphetamine, and opioids can result in similar psychosocial penalties (such as job loss) and physical consequences (including death) but are very different diseases and require specific clinical approaches. Patients can succeed with MAT in the presence of other substance use. In a study comparing patients who did and did not use cocaine, those entering buprenorphine treatment who reported concomitant use at baseline (nearly 40%) had similar retention and reduction in opioid use (63).

The American Society of Addiction Medicine advises that use of other substances should not result in suspension of OUD treatment (43). Providing MAT for OUD is often a critical point of entry into ongoing health care and provides an opportunity to reduce harms associated with polysubstance use. Opioids are often the most hazardous substance patients use, and helping patients remain in treatment reduces their risk for harm. When nonopioid substance use occurs, practices should focus on treating it rather than punitively discontinuing buprenorphine care.

DURATION OF BUPRENORPHINE TREATMENT

Previous Approach

Buprenorphine treatment can readily be discontinued.

New Findings and Recommendations

Patients should receive buprenorphine as long as it provides benefit.

Early cessation of buprenorphine treatment can have catastrophic effects, including death (21, 64). A review of buprenorphine therapy discontinuation found that “rates of relapse to illicit opioid use exceeded 50% in every study” (65). A 2010 analysis found no reduction in mortality until 20 weeks of treatment; opioid substitution treatment for 12 months or longer was needed to achieve a chance greater than 85% of reducing overall mortality (66). When asked, more than 80% of patients intend to continue buprenorphine treatment for 1 year or more (67). Together with a randomized controlled trial showing high failure rates with tapering (68), these data argue against buprenorphine dosage tapering or cessation of therapy until patients have at least 1 year of treatment, have attained clinical stability, and wish to discontinue treatment.

Buprenorphine should not be considered a short-duration treatment, similar to antibiotics. Some patients who have had treatment for more than 1 year may feel ready to taper their dosage, much like those who receive antidepressant treatment may taper after achieving stability. For others, buprenorphine is similar to thyroid replacement (that is, providing benefit indefinitely). The decision to discontinue any medical treatment should be a shared process between the patient and clinician. Nonetheless, some states and insurers continue to mandate lifetime limits on OUD treatment, leaving local advocates to petition agencies on the basis of mental health parity (69, 70).

Fewer than 10% of patients stop treatment because they want to continue illicit use or do not like buprenorphine treatment. Instead, most cessation is due to involuntary discharge based on missed treatments, ongoing substance use, logistic conflicts, or interpersonal conflicts with staff (71). Given the lethality of OUD and the potential harm of arbitrary limits on treatment duration, early medication discontinuation should be questioned (72). Health centers should work to remove barriers and allow patients to remain in potentially life-saving treatment. As TIP 63 advises, “[P]atients should take buprenorphine as long as they benefit from it and wish to continue” (6).

CONCLUSION

Buprenorphine, the most commonly used evidence-based treatment of OUD (73, 74) in the United States, is associated with reduced mortality (75, 76). Although buprenorphine has risks, common overly restrictive approaches—high barriers to entry and low barriers to dismissal—can cause patient harm and contrast with the National Institute on Drug Abuse principle that “[d]rug abuse treatment is not ‘one size fits all’” (77) (Box). Of note, nearly all evidence guiding current practice was found before the lethality of heroin and illicitly produced fentanyl appeared at scale, making updated, evidence-based treatment all the more critical.

Box. Take-home points.

Initial U.S. recommendations for buprenorphine treatment were unintentionally restrictive. These restrictions have been associated with a shortfall of prescribers and barriers to care for patients. Recent evidence-based recommendations more readily support initial and ongoing individualized care. Practices and policymakers should update their approaches on the basis of this evidence.

Patient safety depends on care that is evidence-based, emphasizes harm reduction, has a low barrier to entry, and is longitudinal (1). When we shift our focus to providing individualized care that incorporates patient-centered outcomes, we can better help our patients with OUD achieve remission and lead improved lives.

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Financial Support: By the CleanSlate Research and Education Foundation.

Disclosures: Dr. Martin reports personal fees from CleanSlate Research and Education Foundation during the conduct of the study and personal fees from CleanSlate Addiction Treatment Centers outside the submitted work. Dr. Chiodo reports that her spouse has stock in CleanSlate Addiction Treatment Centers. Dr. Wilson reports owning stock in CleanSlate Addiction Treatment Centers. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-1652.

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