Annals of Internal Medicine

SPECIAL ARTICLE

The Next Stage of Buprenorphine Care for Opioid Use Disorder

Stephen A. Martin, MD, EdM; Lisa M. Chiodo, PhD; Jordon D. Bosse, MS, RN; and Amanda Wilson, MD

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 benzodiazepine, 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 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 23 October 2018.

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The purpose of this article is to contrast recent evidence with common, widespread, and outdated practices that have the paradoxical effect of potentially harming patients (**Table**).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:

Editorial comment 1

Web-Only
CME/MOC activity

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

Previous Approach	New Findings and Recommendations
A medical setting is needed for induction.	Home induction is also safe and effective (6).
Benzodiazepine and buprenorphine coprescription is toxic.	Buprenorphine should not be withheld from patients taking benzodiazepines (5).
Relapse indicates that the patient is unfit for buprenorphine-based treatment.	Relapse indicates the need for additional support and resources rather than cessation of buprenorphine treatment (43).
Counseling or participation in a 12-step program is mandatory.	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.	Drug testing is a tool to better support recovery and address relapse (56).
Use of other substances is a sign of treatment failure and grounds for dismissal from buprenorphine treatment.	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 lifesaving 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.

From University of Massachusetts Medical School and Barre Family Health Center, Barre, and CleanSlate Research and Education Foundation, Florence, Massachusetts (S.A.M.); University of Massachusetts Amherst College of Nursing, Amherst, and CleanSlate Research and Education Foundation, Florence, Massachusetts (L.M.C., J.D.B.); and CleanSlate Research and Education Foundation, Florence, Massachusetts (A.W.).

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.

Corresponding Author: Stephen A. Martin, MD, EdM, Barre Family Health Center, UMassMemorial Health Care, 151 Worcester Road, Barre, MA 01005-9099; e-mail, stmartin@gmail.com.

Current author addresses and author contributions are available at Annals.org.

References

1. **Bhatraju EP, Grossman E, Tofighi B, McNeely J, DiRocco D, Flannery M, et al.** Public sector low threshold office-based buprenorphine treatment: outcomes at year 7. Addict Sci Clin Pract. 2017; 12:7. [PMID: 28245872] doi:10.1186/s13722-017-0072-2
2. **Mund B, Stith K.** Buprenorphine MAT as an imperfect fix. J Law Med Ethics. 2018;46:279-91. [PMID: 30147005] doi:10.1177/1073110518782935
3. **Sansone RA, Sansone LA.** Buprenorphine treatment for narcotic addiction: not without risks. Innov Clin Neurosci. 2015;12:32-6. [PMID: 25973324]
4. **The Pew Charitable Trusts.** The case for medication-assisted treatment: MAT can help people with opioid use disorders, but few have access. 1 February 2017. Accessed at www.pewtrusts.org/en

/research-and-analysis/fact-sheets/2017/02/the-case-for-medication-assisted-treatment on 25 February 2018.
5. **U.S. Food and Drug Administration.** FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. 2017. Accessed at www.fda.gov/Drugs/DrugSafety/ucm575307.htm on 30 November 2017.
6. **Substance Abuse and Mental Health Services Administration.** TIP 63: Medications for Opioid Use Disorder. Rockville: Substance Abuse and Mental Health Services Administration; 2018. Accessed at https://store.samhsa.gov/product/SMA18-5063FULLDOC on 22 February 2018.
7. **Center for Substance Abuse Treatment.** Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Rockville: Substance Abuse and Mental Health Services Administration; 2004.
8. **Wakeman SE.** Medications for addiction treatment: changing language to improve care. J Addict Med. 2017;11:1-2. [PMID: 27898497] doi:10.1097/ADM.0000000000000275
9. **Ruan X, Luo J, Kaye AD.** Efficacy and tolerability of co-administering full μ-opioid receptor agonists with buprenorphine and mixed opioid agonists [Letter]. Drug Res (Stuttg). 2017;67:189-90. [PMID: 27926949] doi:10.1055/s-0042-119946
10. **Alford DP, LaBelle CT, Richardson JM, O'Connell JJ, Hohl CA, Cheng DM, et al.** Treating homeless opioid dependent patients with buprenorphine in an office-based setting. J Gen Intern Med. 2007; 22:171-6. [PMID: 17356982]
11. **Cunningham CO, Giovanniello A, Li X, Kunins HV, Roose RJ, Sohler NL.** A comparison of buprenorphine induction strategies: patient-centered home-based inductions versus standard-of-care office-based inductions. J Subst Abuse Treat. 2011;40:349-56. [PMID: 21310583] doi:10.1016/j.jsat.2010.12.002
12. **Sohler NL, Li X, Kunins HV, Sacajiu G, Giovanniello A, Whitley S, et al.** Home- versus office-based buprenorphine inductions for opioid-dependent patients. J Subst Abuse Treat. 2010;38:153-9. [PMID: 19801178] doi:10.1016/j.jsat.2009.08.001
13. **Lee JD, Vocci F, Fiellin DA.** Unobserved "home" induction onto buprenorphine. J Addict Med. 2014;8:299-308. [PMID: 25254667] doi:10.1097/ADM.0000000000000059
14. **D'Onofrio G, O'Connor PG, Pantalon MV, Chawarski MC, Busch SH, Owens PH, et al.** Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. JAMA. 2015;313:1636-44. [PMID: 25919527] doi:10.1001/jama.2015.3474
15. **Tofighi B, Grossman E, Sherman S, Nunes EV, Lee JD.** Mobile phone messaging during unobserved "home" induction to buprenorphine. J Addict Med. 2016;10:309-13. [PMID: 26933874] doi:10.1097/ADM.0000000000000198
16. **Gunderson EW.** Buprenorphine induction: a major barrier for physician adoption of office-based opioid dependence treatment [Letter]. J Addict Med. 2011;5:304-5. [PMID: 22027906] doi:10.1097/ADM.0b013e31821ee8fe
17. **Reckitt Benckiser Healthcare.** SUBOXONE (CIII) (buprenorphine HCl and naloxone HCl dihydrate sublingual tablets)/SUBUTEX (CIII) (buprenorphine HCl sublingual tablets) [package insert]. Hull, United Kingdom: Reckitt Benckiser Healthcare. Accessed at www.naabt.org/documents/packageinsert.pdf on 11 February 2017.
18. **Reynaud M, Petit G, Potard D, Courty P.** Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addiction. 1998;93:1385-92. [PMID: 9926544]
19. **Reynaud M, Tracqui A, Petit G, Potard D, Courty P.** Six deaths linked to misuse of buprenorphine-benzodiazepine combinations [Letter]. Am J Psychiatry. 1998;155:448-9. [PMID: 9501765]
20. **Nielsen S, Dietze P, Lee N, Dunlop A, Taylor D.** Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment. Addiction. 2007;102: 616-22. [PMID: 17286641]
21. **Dupouy J, Palmaro A, Fatséas M, Auriacombe M, Micallef J, Oustric S, et al.** Mortality associated with time in and out of buprenorphine treatment in French office-based general practice: a 7-year cohort study. Ann Fam Med. 2017;15:355-8. [PMID: 28694272] doi:10.1370/afm.2098
22. **Park TW, Bohnert AS, Austin KL, Saitz R, Pizer SD.** Datapoints: regional variation in benzodiazepine prescribing for patients on opioid agonist therapy. Psychiatr Serv. 2014;65:4. [PMID: 24382761] doi:10.1176/appi.ps.201300419
23. **Zhu Y, Coyle DT, Mohamoud M, Zhou E, Eworuke E, Dormitzer C, et al.** Concomitant use of buprenorphine for medication-assisted treatment of opioid use disorder and benzodiazepines: using the Prescription Behavior Surveillance System. Drug Alcohol Depend. 2018;187:221-6. [PMID: 29680678] doi:10.1016/j.drugalcdep.2018.02.019
24. **Rees VW.** Summary of opioid overdose deaths: Massachusetts, January–June, 2014. 2015. Accessed at http://s3.amazonaws.com/media.wbur.org/wordpress/15/files/2015/11/Brief-report-MA-opioid-OD-deaths-2014.pdf on 25 February 2018.
25. **Paone D, Tuazon E, Stajic M, Sampson B, Allen B, Mantha S, et al.** Buprenorphine infrequently found in fatal overdose in New York City. Drug Alcohol Depend. 2015;155:298-301. [PMID: 26305073] doi:10.1016/j.drugalcdep.2015.08.007
26. **Visconti AJ, Santos GM, Lemos NP, Burke C, Coffin PO.** Opioid overdose deaths in the city and county of San Francisco: prevalence, distribution, and disparities. J Urban Health. 2015;92:758-72. [PMID: 26077643] doi:10.1007/s11524-015-9967-y
27. **Howland RH.** A question about the safety of buprenorphine/naloxone and benzodiazepine drugs. J Psychosoc Nurs Ment Health Serv. 2015;53:11-4. [PMID: 26653090] doi:10.3928/02793695-20151117-01
28. **Lofwall MR, Walsh SL.** A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. J Addict Med. 2014;8:315-26. [PMID: 25221984] doi:10.1097/ADM.0000000000000045
29. **Tversky A, Kahneman D.** Extensional versus intuitive reasoning: the conjunction fallacy in probability judgment. Psychol Rev. 1983; 90:293-315.
30. **U.S. Food and Drug Administration.** FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. 2016. Accessed at www.fda.gov/Drugs/DrugSafety/ucm518473.htm on 24 August 2017.
31. **Abrahamsson T, Berge J, Öjehagen A, Håkansson A.** Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment–a nation-wide register-based open cohort study. Drug Alcohol Depend. 2017;174:58-64. [PMID: 28315808] doi:10.1016/j.drugalcdep.2017.01.013
32. **Schuman-Olivier Z, Hoeppner BB, Weiss RD, Borodovsky J, Shaffer HJ, Albanese MJ.** Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes. Drug Alcohol Depend. 2013;132:580-6. [PMID: 23688843] doi:10.1016/j.drugalcdep.2013.04.006
33. **Bakker A, Streel E.** Benzodiazepine maintenance in opiate substitution treatment: good or bad? A retrospective primary care case-note review. J Psychopharmacol. 2017;31:62-6. [PMID: 28072037] doi:10.1177/0269881116675508
34. **Ding KY, Mosdøl A, Hov L, Staumann GH, Vist GE.** The effects of concurrent prescription of benzodiazepines for people undergoing opioid maintenance treatment: a systematic review. Report 2016. Oslo: Norwegian Institute of Public Health; 2016.
35. **Warner M, Trinidad JP, Bastian BA, Minino AM, Hedegaard H.** Drugs most frequently involved in drug overdose deaths: United States, 2010-2014. Natl Vital Stat Rep. 2016;65:1-15. [PMID: 27996932]
36. **Posternak MA, Mueller TI.** Assessing the risks and benefits of benzodiazepines for anxiety disorders in patients with a history of substance abuse or dependence. Am J Addict. 2001;10:48-68. [PMID: 11268828]
37. **Park TW.** Debate: are benzodiazepines appropriate treatments for patients with substance use disorders? Yes. J Addict Med. 2017; 11:87-9. [PMID: 28301370] doi:10.1097/ADM.0000000000000292

38. **Hser YI, Evans E, Grella C, Ling W, Anglin D.** Long-term course of opioid addiction. Harv Rev Psychiatry. 2015;23:76-89. [PMID: 25747921] doi:10.1097/HRP.0000000000000052
39. **McLellan AT, Lewis DC, O'Brien CP, Kleber HD.** Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA. 2000;284:1689-95. [PMID: 11015800]
40. **Sabaté E, ed.** Adherence to Long-Term Therapies: Evidence for Action. World Health Organization. 2003. Accessed at www.who.int/chp/knowledge/publications/adherence_report/en on 21 September 2018.
41. **National Institute on Drug Abuse.** Principles of effective treatment. Principles of drug addiction treatment: a research-based guide. 3rd ed. 2012. Accessed at www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/principles-effective-treatment on 16 May 2017.
42. **Massachusetts Department of Public Health Bureau of Substance Abuse Services.** Practice guidance: responding to relapse. 2013. Accessed at www.mass.gov/eohhs/docs/dph/substance-abuse/care-principles/care-principles-guidance-responding-to-relapses.pdf on 16 May 2017.
43. **American Society of Addiction Medicine.** National practice guideline for the use of medications in the treatment of addiction involving opioid use. 2015. Accessed at www.asam.org/quality-practice/guidelines-and-consensus-documents/npg/complete-guideline on 25 February 2018.
44. **Knopf A.** No proof that buprenorphine treatment requires counseling. Alcoholism & Drug Abuse Weekly. 2017;29:3-5.
45. **Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D.** A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. J Addict Med. 2016;10:93-103. [PMID: 26808307] doi:10.1097/ADM.0000000000000193
46. **Schwartz RP.** When added to opioid agonist treatment, psychosocial interventions do not further reduce the use of illicit opioids: a comment on Dugosh et al. J Addict Med. 2016;10:283-5. [PMID: 27471920] doi:10.1097/ADM.0000000000000236
47. **Friedmann PD, Schwartz RP.** Just call it "treatment." Addict Sci Clin Pract. 2012;7:10. [PMID: 23186149] doi:10.1186/1940-0640-7-10
48. **Burns RM, Pacula RL, Bauhoff S, Gordon AJ, Hendrikson H, Leslie DL, et al.** Policies related to opioid agonist therapy for opioid use disorders: the evolution of state policies from 2004 to 2013. Subst Abus. 2016;37:63-9. [PMID: 26566761] doi:10.1080/08897077.2015.1080208
49. **Andrilla CHA, Coulthard C, Larson EH.** Barriers rural physicians face prescribing buprenorphine for opioid use disorder. Ann Fam Med. 2017;15:359-62. [PMID: 28694273] doi:10.1370/afm.2099
50. **Hutchinson E, Catlin M, Andrilla CH, Baldwin LM, Rosenblatt RA.** Barriers to primary care physicians prescribing buprenorphine. Ann Fam Med. 2014;12:128-33. [PMID: 24615308] doi:10.1370/afm.1595
51. **World Health Organization.** Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. 2009. Accessed at www.who.int/substance_abuse/activities/treatment_opioid_dependence/en on 23 July 2017.
52. **Glass I.** Very tough love. This American Life. 25 March 2011. Accessed at www.thisamericanlife.org/radio-archives/episode/430/very-tough-love on 23 March 2017.
53. **Gabrielson R, Sanders T.** How a $2 roadside drug test sends innocent people to jail. The New York Times. 7 July 2016:MM34.
54. **Starrels JL, Fox AD, Kunins HV, Cunningham CO.** They don't know what they don't know: internal medicine residents' knowledge and confidence in urine drug test interpretation for patients with chronic pain. J Gen Intern Med. 2012;27:1521-7. [PMID: 22815062] doi:10.1007/s11606-012-2165-7
55. **Heit HA.** Patient-centered urine drug testing: facts you should know. Providers Clinical Support System. 2014. Accessed at http://pcssnow.org/wp-content/uploads/2014/06/Heit-ASAM-PCSS-MAT-Online-Module-2.pdf on 23 March 2017.
56. **American Society of Addiction Medicine.** The ASAM appropriate use of drug testing in clinical addiction medicine. 2017. Accessed at www.asam.org/resources/guidelines-and-consensus-documents/drug-testing on 15 May 2017.
57. **Kelly JF, Wakeman SE, Saitz R.** Stop talking 'dirty': clinicians, language, and quality of care for the leading cause of preventable death in the United States [Editorial]. Am J Med. 2015;128:8-9. [PMID: 25193273] doi:10.1016/j.amjmed.2014.07.043
58. **Substance Abuse and Mental Health Services Administration.** Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. NSDUH Series H-48. HHS Publication no. (SMA) 14-4863. Rockville: Substance Abuse and Mental Health Services Administration; 2014.
59. **Hartzler B, Donovan DM, Huang Z.** Comparison of opiate-primary treatment seekers with and without alcohol use disorder. J Subst Abuse Treat. 2010;39:114-23. [PMID: 20598831] doi:10.1016/j.jsat.2010.05.008
60. **Jones CM, Paulozzi LJ, Mack KA; Centers for Disease Control and Prevention (CDC).** Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths–United States, 2010. MMWR Morb Mortal Wkly Rep. 2014;63:881-5. [PMID: 25299603]
61. **Bebinger M.** It's not just heroin: drug cocktails are fueling the overdose crisis. WBUR CommonHealth. 13 November 2015. Accessed at www.wbur.org/commonhealth/2015/11/13/drug-overdose-cocktails on 21 September 2018.
62. **Heikman PK, Muhonen LH, Ojanperä IA.** Polydrug abuse among opioid maintenance treatment patients is related to inadequate dose of maintenance treatment medicine. BMC Psychiatry. 2017;17:245. [PMID: 28683783] doi:10.1186/s12888-017-1415-y
63. **Cunningham CO, Giovanniello A, Kunins HV, Roose RJ, Fox AD, Sohler NL.** Buprenorphine treatment outcomes among opioid-dependent cocaine users and non-users. Am J Addict. 2013;22:352-7. [PMID: 23795874] doi:10.1111/j.1521-0391.2013.12032.x
64. **Kakko J, Svanborg KD, Kreek MJ, Heilig M.** 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet. 2003;361:662-8. [PMID: 12606177]
65. **Bentzley BS, Barth KS, Back SE, Book SW.** Discontinuation of buprenorphine maintenance therapy: perspectives and outcomes. J Subst Abuse Treat. 2015;52:48-57. [PMID: 25601365] doi:10.1016/j.jsat.2014.12.011
66. **Cornish R, Macleod J, Strang J, Vickerman P, Hickman M.** Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010;341:c5475. [PMID: 20978062] doi:10.1136/bmj.c5475
67. **Bentzley BS, Barth KS, Back SE, Aronson G, Book SW.** Patient perspectives associated with intended duration of buprenorphine maintenance therapy. J Subst Abuse Treat. 2015;56:48-53. [PMID: 25899872] doi:10.1016/j.jsat.2015.04.002
68. **Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG.** Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern Med. 2014;174:1947-54. [PMID: 25330017] doi:10.1001/jamainternmed.2014.5302
69. **The BDN Editorial Board.** Maine robs patients of addiction treatment as feds stress greater fairness. Bangor Daily News. 21 April 2016. Accessed at https://bangordailynews.com/2016/04/21/opinion/editorials/maine-robs-patients-of-addiction-treatment-as-feds-stress-greater-fairness on 25 February 2018.
70. **Volkow ND, Frieden TR, Hyde PS, Cha SS.** Medication-assisted therapies–tackling the opioid-overdose epidemic. N Engl J Med. 2014;370:2063-6. [PMID: 24758595] doi:10.1056/NEJMp1402780
71. **Gryczynski J, Mitchell SG, Jaffe JH, O'Grady KE, Olsen YK, Schwartz RP.** Leaving buprenorphine treatment: patients' reasons for cessation of care. J Subst Abuse Treat. 2014;46:356-61. [PMID: 24238714] doi:10.1016/j.jsat.2013.10.004

72. **Salsitz E.** Frequently asked question. Buprenorphine: clinical management. Treatment duration. Providers Clinical Support System. 2017. Accessed at http://pcssmat.org/mentoring/frequently-asked-questions on 26 February 2017.
73. **Jones CM.** The opioid epidemic: HHS response. U.S. Department of Health and Human Services. Accessed at www.pdmpassist.org/pdf/06-B1_Jones.pdf on 21 September 2018.
74. **Alderks CE.** Trends in the use of methadone, buprenorphine, and extended-release naltrexone at substance abuse treatment facilities: 2003-2015 (update). The CBHSQ Report. 22 August 2017. Accessed at www.samhsa.gov/data/sites/default/files/report_3192/ShortReport-3192.html on 29 August 2018.
75. **Schwartz RP, Gryczynski J, O'Grady KE, Sharfstein JM, Warren G, Olsen Y, et al.** Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009. Am J Public Health. 2013; 103:917-22. [PMID: 23488511] doi:10.2105/AJPH.2012.301049
76. **Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, et al.** Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. Ann Intern Med. 2018;169:137-45. [PMID: 29913516] doi:10.7326/M17-3107
77. **National Institute on Drug Abuse.** Seeking drug abuse treatment: know what to ask. 2013. Accessed at www.drugabuse.gov/publications/seeking-drug-abuse-treatment-know-what-to-ask/introduction on 21 May 2017.

Current Author Addresses: Dr. Martin: Barre Family Health Center, UMassMemorial Health Care, 151 Worcester Road, Barre, MA 01005-9099.
Dr. Chiodo and Mr. Bosse: College of Nursing, University of Massachusetts, 228 Skinner Hall, 651 North Pleasant Street, Amherst, MA 01003-9299.
Dr. Wilson: 46 Sovereign Way, Florence, MA 01062.

Author Contributions: Conception and design: S.A. Martin, L.M. Chiodo, A. Wilson.
Analysis and interpretation of the data: S.A. Martin, L.M. Chiodo, J.D. Bosse, A. Wilson.
Drafting of the article: S.A. Martin, J.D. Bosse, A. Wilson.
Critical revision of the article for important intellectual content: S.A. Martin, L.M. Chiodo, J.D. Bosse, A. Wilson.
Final approval of the article: S.A. Martin, L.M. Chiodo, J.D. Bosse, A. Wilson.
Obtaining of funding: A. Wilson.
Administrative, technical, or logistic support: J.D. Bosse, A. Wilson.
Collection and assembly of data: S.A. Martin, L.M. Chiodo.