CME MOC

Roberto León-Barriera, MD
Assistant Professor of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA

Samantha Jayne Zwiebel, MD, MA
Assistant Professor of Clinical Psychiatry, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Vania Modesto-Lowe, MD, MPH
Medical Director, Hartford Behavioral Health, Hartford, CT; Department of Psychiatry, University of Connecticut, Community Faculty, University of Connecticut, Farmington, CT

A practical guide for buprenorphine initiation in the primary care setting

ABSTRACT

Buprenorphine is a safe and effective treatment for opioid use disorder but remains underutilized because a major challenge of conventional buprenorphine initiation (termed *induction*) is that the patient must already be in opioid withdrawal. Previous legal barriers and clinician lack of familiarity with the unique pharmacology of buprenorphine have also limited its use. In this review, we outline changes regarding buprenorphine prescribing laws and physician perceptions of buprenorphine. We also review buprenorphine pharmacology and novel low-dose buprenorphine induction procedures that can be adopted in primary care settings to improve treatment acceptability, retention, and outcomes.

KEY POINTS

Buprenorphine can be prescribed in the primary care setting, which can help improve treatment access and retention.

Standard induction of buprenorphine requires that patients be in mild to moderate opioid withdrawal.

Low-dose buprenorphine induction permits safe initiation of buprenorphine regardless of whether the patient is in withdrawal or has recently used opioids.

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Buprenorphine is a safe and effective treatment for opioid use disorder (OUD) but remains underutilized owing to previous prescribing limitations, lack of physician familiarity with the unique pharmacology of buprenorphine, and the need for the patient to be in opioid withdrawal before initiating treatment. Low-dose buprenorphine induction (LDBI) is a recent treatment protocol that can be adopted in primary care settings to improve treatment acceptability, retention, and outcomes.

OUD is characterized by compulsive opioid use regardless of negative consequences.[1] Individuals with OUD suffer a 15 to 20 times greater risk of mortality than that of the general population and at an unprecedented epidemic level.[2] As of 2020, the US Centers for Disease Control and Prevention reported that 2.4 million people in the United States suffer from OUD,[3,4] with only 6% to 7% likely to receive pharmacotherapy.[4]

Until recently, prescribing buprenorphine was limited by the Drug Abuse Treatment Act of 2000 and required completion of an 8-hour training course or addiction board certification to apply for a designated license (X-waiver) to treat.[1,5] In 2021, the 8-hour training requirement was removed, though an X-waiver was still required, and clinicians were still limited by monthly patient caps.[6] In December 2022, the Consolidated Appropriations Act of 2023 was signed into law, entirely eliminating the X-waiver requirement and monthly treatment caps, allowing clinicians to treat as many patients as they can support with buprenorphine.[5]

As of June 27, 2023, all who prescribe controlled substances must fulfill at least 1 of the

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following requirements before applying for or renewing their Drug Enforcement Administration registration: 8 hours of training on opioid or substance use disorders; board certification in addiction medicine or addiction psychiatry from the American Board of Medical Specialties, American Board of Addiction Medicine, or American Osteopathic Association; or graduation within 5 years in good standing from a medical, advanced practice, or physician assistant school in the United States that included at least 8 hours of opioid or substance use disorder curriculum.[5]

This easing of prescribing limitations presents an opportunity to expand buprenorphine treatment in primary care, thus increasing access to treatment for OUD. In this article, we review existing evidence supporting the use of buprenorphine in the primary care setting, provide an accessible overview of buprenorphine pharmacology, and describe buprenorphine induction protocols that can be adopted in primary care settings.

SHOULD PRIMARY CARE CLINICIANS PRESCRIBE BUPRENORPHINE?

Prior studies have found that primary care physicians (PCPs) regularly encounter patients with OUD and believe buprenorphine is an effective treatment for OUD, but do not always feel prepared to prescribe buprenorphine.[7,8] One investigation found that 82% of individuals newly diagnosed with OUD had visited a PCP in the preceding 12 months.[7] Another study in rural New England found that more than 80% of family physicians regularly encountered patients with OUD in their practice.[8] Most of these physicians (73%) believed that they had a professional responsibility to treat OUD.[8] More recently, a survey of physicians' perceptions of pharmacotherapy for OUD found that 53 and 52 of 127 respondents indicated that buprenorphine decreases opioid cravings and fatal overdoses, respectively.[9] Despite the interest of PCPs in treating OUD with buprenorphine and having some knowledge of this medication, they may not yet feel comfortable prescribing buprenorphine.[10] A cross-sectional survey of PCPs found that approximately 80% of respondents were very or somewhat comfortable identifying OUD.[10] However, only 36.9% were very or somewhat comfortable treating OUD with pharmacotherapy.[10] Physician respondents identified lack of access to behavioral treatments and lack of experience with pharmacotherapy for OUD as the main reasons for feeling uncomfortable.[10] The authors concluded that identifying comprehensive models of care and improving physicians' sense of self-efficacy (one's belief that one can succeed at a certain task) could help expand access to buprenorphine treatment through PCPs.[10]

The treatment of OUD in primary care clinics typically involves medications such as buprenorphine in conjunction with services to address psychosocial needs.[7] Data from rural and community primary care settings that prescribe buprenorphine demonstrate superior treatment retention relative to designated buprenorphine clinics.[6,11–13] Though this model has been implemented in the United States to varying degrees, 91% to 99% of opioid agonist treatment is prescribed by PCPs in France.[6] French primary care settings have improved OUD outcomes with decreased fatal opioid overdoses and overall mortality,[8] suggesting that PCPs with proper buprenorphine training are well poised to have an enormous impact on the trajectory of patients with OUD.

BUPRENORPHINE: PHARMACOLOGY AND FORMULATIONS

Pharmacology

Successful buprenorphine induction requires familiarity with its unique pharmacologic properties. Buprenorphine is a semisynthetic opioid with partial agonism at the mu-opioid receptor (MOR), antagonism at the kappa-opioid receptor, and agonism at the opioid receptor-like 1 receptor.[2] There is controversy about the action of buprenorphine on the delta-opioid receptor, with some sources describing it as an agonist and others as an antagonist.[2,14] Kappa-opioid receptor antagonism is thought to play a role in the antidepressant and antiaddictive properties of buprenorphine.[15] Human and animal models show that kappa-opioid receptor activation by stress neuropeptides produces dysphoria and drug-seeking behaviors.[15] There is current interest in studying buprenorphine and other kappa-opioid receptor antagonists as adjuncts to treat depression and drug-seeking behaviors.[15] Buprenorphine's actions at the MOR and opioid receptor-like 1 likely account for its rewarding and analgesic properties, while its action at the MOR decreases opioid cravings and withdrawal[2] and is therefore considered the most pharmacodynamically significant in the treatment of OUD.

When binding to the MOR, buprenorphine acts as a partial agonist with high receptor affinity and potency, which can pose both clinical advantages and challenges.[2,16] Because of the partial agonism

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TABLE 1
Buprenorphine formulations and indications

Generic name and administration route	Brand name	Dose formulations	US Food and Drug Administration indication
Buprenorphine hydrochloride for intravenous or intramuscular administration	Buprenex injection	0.3 mg/mL	Acute moderate-to-severe pain
Buprenorphine transdermal system	Butrans	5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour	Chronic pain
Buprenorphine buccal film	Belbuca	75 µg 150 µg 300 µg 450 µg 600 µg 750 µg 900 µg	Chronic pain
Buprenorphine extended-release injection for subcutaneous use	Sublocade	300 mg/1.5 mL monthly after induction for first 2 months 100 mg/0.5 mL maintenance dose monthly (can increase to 300 mg)	Opioid use disorder
Buprenorphine sublingual tablets	Subutex	2 mg 8 mg	Opioid use disorder
Buprenorphine/naloxone sublingual film	Suboxone	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	Opioid use disorder
Buprenorphine/naloxone sublingual tablets	Suboxone	2 mg/0.5 mg 8 mg/2 mg	Opioid use disorder
Buprenorphine/naloxone sublingual rapid-dissolve tablets	Zubsolv	0.7 mg/0.18 mg 1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg 8.6 mg/2.1 mg 11.4 mg/2.9 mg	Opioid use disorder

Based on information in references 22 and 23.

at the MOR, buprenorphine demonstrates beneficial ceiling effects for respiratory depression, euphoria, and physiologic dependence that offer high clinical safety with relatively infrequent overdoses reported.[2,16–19] Buprenorphine's affinity for the MOR is about 120 times higher than that of oxycodone and 6.2 times higher than that of fentanyl[16,20,21] and can therefore quickly and easily displace these opioids from the MOR.[20] As a result of the ability of buprenorphine to displace almost all other opioids, in conjunction with its partial opioid-agonist activity, patients starting buprenorphine are at high risk of experiencing precipitated withdrawal.[16] Precipitated withdrawal is characterized by the rapid onset of opioid withdrawal and occurs when the partial MOR agonist buprenorphine displaces a full MOR agonist, such as heroin, leading to a relative withdrawal despite a high percentage of MORs still being occupied.[2,16]

Formulations

Buprenorphine is available in a wide variety of formulations (**Table 1**)[22,23] and is often paired with naloxone (an opioid antagonist) as a deterrent for

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misuse.[2,22] Though naloxone has very limited oral bioavailability, it becomes highly bioavailable through insufflation ("snorting") or intravenous injection, thus precipitating opioid withdrawal and reversing opioid overdose.[2,22] It was believed that naloxone would therefore precipitate withdrawal if consumed intranasally or intravenously in combination with buprenorphine, but it should be noted that buprenorphine still has a binding affinity that is 10 times higher than naloxone.[24] Although selecting the ideal formulation of buprenorphine for induction can seem daunting for the novice prescriber, we describe below a practical guide for induction.

STANDARD BUPRENORPHINE INDUCTION: METHOD AND CHALLENGES

Clinicians face a peculiar challenge in initiating buprenorphine for OUD using a standard induction approach. If buprenorphine is started in the setting of recent opioid use, as is expected in patients with OUD, it will cause precipitated withdrawal as the partial MOR agonist buprenorphine displaces almost all other opioids, including full MOR agonists.[16] Successful induction is therefore difficult, but can be accomplished when patients abstain from opioids before initiating buprenorphine or when LDBI guidelines are followed.

Method

Standard buprenorphine induction requires that patients abstain from opioids and present with moderate withdrawal to initiate buprenorphine.[19] Withdrawal should be measured by the clinical opiate withdrawal scale, an 11-item scale that is readily available online and in many clinical calculator applications.[25] The patient's clinical opiate withdrawal scale score should be greater than 12 prior to giving the first buprenorphine dose.[2,17,19,26] Another challenge of the standard induction approach is that a 2-day process is recommended, with a maximum total dose of 8 mg on the first day.[19]

Guidelines from the Substance Abuse and Mental Health Services Administration suggest giving a single starting dose of 2 mg to 4 mg buprenorphine sublingual if the patient is in adequate withdrawal,[19] though we recommend starting with 2 mg. If the patient experiences precipitated withdrawal (marked by an abrupt worsening of withdrawal), symptoms should be treated, and induction reattempted 24 hours later.[19] However, if withdrawal symptoms are instead partially relieved, another 2-mg or 4-mg dose is given after 2 to 4 hours.[19] This process can be repeated until withdrawal symptoms are controlled, up to a total of 8 mg daily on the first day.[19] The total dose received on the first day should then be prescribed for the next day, and the patient should return to clinic for the second day of induction.[19] If the patient reports adequate symptom relief, the induction is complete.[19] If symptoms are not yet controlled, the patient will resume the induction process of taking repeated 2-mg or 4-mg doses, with assessment of withdrawal symptoms every 2 to 4 hours.[19] This process can be repeated as needed until a total of 16 mg of buprenorphine has been given on the second day, or until symptoms are controlled.[19]

Challenges

At a dose of 16 mg buprenorphine, it is believed that approximately 80% to 90% of MORs are occupied, and withdrawal symptoms should theoretically be controlled.[27] Yet there is evidence that 16 mg may not suppress opioid cravings in severely dependent patients.[27] Patients with severe OUD may require doses up to 24 to 32 mg (maximum approved dose) or even higher for adequate control of withdrawal and cravings.[27–29]

It is important to note that when the standard induction protocol was developed, heroin (a short-acting opioid) dominated the illicit opioid supply.[17,19] Patients only needed to abstain from heroin for 4 to 12 hours before experiencing adequate withdrawal to safely start buprenorphine.[17,19] However, with the shift from heroin to fentanyl as the current prevalent illicit opioid, the abstinence time required has dramatically increased.[2,16,17,21,26] The total abstinence time required depends on the type of opioid used, and ranges from 4 hours for heroin to 36 to 48 hours for methadone, and 3 days or more is often needed for fentanyl.[2,16,17,21,26,30] Notably, fentanyl users may experience buprenorphine-precipitated withdrawal even after prolonged abstinence.[16,21,31] Fentanyl is stored in adipose tissue with chronic high-dose use,[2,16,21,26,31] and therefore demonstrates an unexpectedly long renal clearance time despite a half-life comparable to that of heroin.[30] Fentanyl's prolonged clearance time as the drug is slowly released from adipose tissue likely accounts for why patients using fentanyl are at higher risk of precipitated withdrawal compared with other opioids.[32] The prolonged clearance time and requirement of multiple days of abstinence can prove difficult for patients and may lead to treatment dropout or relapse.[2,16,17,21,31]

LOW-DOSE BUPRENORPHINE INDUCTION

LDBI strategies are designed to avoid precipitated withdrawal and are feasible to implement in the pri-

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TABLE 2
Options for home buprenorphine induction

Day	Complex home induction	Simplified home induction	Precise induction (may be better suited for inpatient use)
1	Cut 2-mg buprenorphine/naloxone film into 4 pieces, take 1 piece every 6 hours	Cut 8-mg buprenorphine/naloxone film into 8 pieces, take 1 piece every 1–2 hours	150-µg buprenorphine buccal film every 3 hours for 8 doses
2	Cut 2-mg buprenorphine/naloxone film into 2 pieces, take 1 piece every 6 hours	Take 8-mg buprenorphine/naloxone film twice daily	450-µg buprenorphine buccal film every 6 hours for 2 doses; then 900-µg buprenorphine buccal film for 2 doses
3	Take 2-mg buprenorphine/naloxone film every 6 hours	Follow up with primary care physician	2-mg buprenorphine/naloxone film every 4 hours for 4 doses
4	Take 8-mg buprenorphine/naloxone film twice daily		8-mg buprenorphine/naloxone film 2 or 3 times per day
5	Follow up with primary care physician		Follow up with primary care physician

Based on information in reference 36.

mary care setting.[6,11,16] LDBI was first described (in English) in 2016 by Hämmig et al.[17] This method was based on previous research showing that doses of 0.2 mg of buprenorphine did not precipitate withdrawal in patients taking methadone for OUD.[33] LDBI involves giving very small doses of buprenorphine, with gradual dose increases. When the patient continues using full-agonist opioids or illicit opioids concurrently with LDBI, this approach is called the Bernese method.[2,16,17] Hämmig et al described 2 cases in which this approach was taken.[17] In case 1, the patient received an initial buprenorphine dose of 0.2 mg, followed by slowly increasing incremental doses of buprenorphine while tapering heroin use.[17] After multiple attempts with conventional induction, the patient was weaned with the Bernese method, and on day 9, the patient had been 4 days without heroin while taking 12 mg/day of buprenorphine, and tolerated this process much better.[17] In case 2, the patient was titrated slowly to a dose of 24 mg of buprenorphine with ongoing full-opioid-agonist use over 29 days.[17] On day 29, full agonists were stopped without any symptoms of withdrawal.[17]

Buprenorphine films or tablets are often cut to make these smaller doses.[34,35] Off-label use of the buprenorphine transdermal patch (dosed in micrograms) has also been reported.[18] LDBI takes advantage of buprenorphine's higher affinity for and slower dissociation from the MOR with commonly used full agonists (eg, heroin, fentanyl, oxycodone).[2,16,17] In this manner, small doses of buprenorphine slowly displace full agonists at the MOR, without precipitating withdrawal.[2,16,17]

There are multiple LDBI protocols but no current standard protocols, with some more suitable protocols used in the supervised inpatient setting.[2,16–18,26,34,36] Ahmed et al[16] noted an excellent review of studied techniques. A 2022 case report of a patient with a 3-year history of treatment with a 72-mg daily dose of methadone who needed to switch treatments owing to age, excessive sedation, and inability to come into clinic regularly detailed LDBI over 3 days in the outpatient setting.[34] A 2-mg/0.5-mg buprenorphine/naloxone sublingual film was cut into 4 parts (approximately 0.5 mg of buprenorphine each), and each piece was given in intervals of 30 minutes to 1 hour on the first day.[34] On the second day, buprenorphine was increased to 4 mg, and on the third day, buprenorphine was increased to 8 mg.[34] A methadone dose of 72 mg was administered after every successful induction of buprenorphine for the day for 3 days. Mild withdrawal was treated symptomatically. Methadone was fully discontinued on day 4 once stabilization was confirmed.[34]

Recommended protocols

For patients using fentanyl in the outpatient setting, we recommend one of the 3 induction protocols that are available online from Penn Medicine's Center for Addiction Medicine and Policy and summarized in **Table 2**.[36] The first protocol is more complex and occurs over the course of 4 days.[36] For patients who may benefit from simpler dosing, patients can also complete a 2-day induction.[36] Because cutting films or tablets can be cumbersome and may lead to less-precise

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TABLE 3
Symptomatic management of opioid withdrawal

Symptom	Drug	Dose
Anxiety	Hydroxyzine	25–100 mg orally every 6–8 hours as needed (maximum 400 mg/day)
	Lorazepam	1 mg every 4–6 hours as needed (maximum 6 mg/day)
Hypertension, tachycardia	Clonidine	0.1–0.2 mg every 6–8 hours, taper if given for > 7 days
Diarrhea	Loperamide	4 mg initial dose followed by 2 mg after each loose stool (maximum 16 mg/day)
Myalgias, arthralgias	Acetaminophen	1,000 mg every 6–8 hours
	Ibuprofen	600 mg every 6 hours for up to 7 days (maximum 2,400 mg/day)
Nausea, vomiting	Ondansetron	4 mg every 6 hours as needed (maximum 16 mg/day)
Insomnia	Trazodone	25–100 mg nightly (maximum 300 mg)
Muscle cramps	Cyclobenzaprine	5–10 mg every 8 hours as needed (maximum 30 mg/day)
Gastrointestinal cramps	Dicyclomine	10–20 mg every 6–8 hours as needed (maximum 160 mg/day)

Based on information in references 36, 39, and 40.

dosing,[37] some institutions have endorsed off-label use of buprenorphine buccal films (dosed in micrograms and approved for pain).[36] Penn Medicine's Center for Addiction Medicine and Policy also describes this approach.[36] There is no current consensus on optimal time to fully discontinue MOR agonists,[2] though a cross-titration from the full MOR agonist to buprenorphine is most desirable. Once the patient is on 16 mg of buprenorphine or higher and 90% of MORs are occupied, abrupt cessation of full agonists should theoretically not cause clinically significant withdrawal.[25,35]

Though LDBI can seem complicated, it offers many clinical advantages. It decreases the risk of precipitated withdrawal, does not require that the patient already be in withdrawal to start buprenorphine, and may thus provide better treatment outcomes for patients, especially those using fentanyl.[16] Additionally, the Bernese method of treating with LDBI while reducing full-agonist opioids is gaining popularity among patients.[38]

TIPS FOR MANAGING PRECIPITATED WITHDRAWAL

Even with appropriate precautions, precipitated withdrawal may occur during buprenorphine initiation. One theory of the mechanism of precipitated withdrawal proposes that an abrupt reduction in opioid tone in certain brain areas, including the locus coeruleus and mesolimbic areas, occurs and causes withdrawal.[2] More specifically, neuroadaptations in MOR signaling caused by chronic exposure to high-dose opioids, followed by a sudden reduction of MOR occupancy by full MOR agonists, likely causes precipitated opioid withdrawal.[2] Precipitated withdrawal—much dreaded and called "precip" by patients—constitutes a major risk to overcome during early induction.[2,17]

Withdrawal symptoms can include diarrhea, abdominal cramps, anxiety, yawning, rhinorrhea, lacrimation, myalgias, arthralgias, diaphoresis, and mydriasis,[31,39] and can be quantified using the Clinical Opiate Withdrawal Scale.[25] The medications noted in **Table 3** can be used to alleviate symptoms of precipitated withdrawal and can also be used to facilitate induction.[36,39,40] One current recommendation for managing precipitated withdrawal is to give 2 mg of buprenorphine every 1 to 2 hours, a strategy that may have limited utility in patients using fentanyl.[26,31]

Another approach involves using high-dose buprenorphine, often referred to as macroinduction.[21,31,39] This method relies on using repeated doses of 4 to 8 mg of buprenorphine to saturate MORs and reverse withdrawal symptoms.[31,39] A recent case report from an emergency department setting detailed using a total dose of 20 mg of buprenorphine on the day of induction as a rescue strategy for precipitated withdrawal.[31] Alternatively, macroinduction itself has also been described as an induction strategy, with a rela-

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tively low risk of precipitated withdrawal when given in various dose increments up to 32 mg in a single day.[41] Macroinduction is typically used in emergency medicine settings and merits further study as it may not be suitable for the outpatient primary care setting given the intense monitoring that is required.[39]

TAKE-HOME MESSAGES

The increasing prevalence of OUD in the United States has led to mortality rates increasing to epidemic proportions. Buprenorphine is a MOR partial agonist approved for treatment of OUD. Advantages of induction with buprenorphine include its partial agonist properties that provide a ceiling effect and decrease the risk of overdose. Historically, buprenorphine treatment has been underutilized owing to prescribing restrictions and legal and pharmacologic barriers. While restrictions have been removed, thus positioning PCPs to be key prescribers of buprenorphine, pharmacologic challenges such as the risk of precipitated withdrawal still exist. Hence, standard induction guidelines suggest that patients take their first buprenorphine dose only after the onset of opioid withdrawal, which can be challenging with many patients now using fentanyl and experiencing complex, prolonged withdrawal.

LDBI is an alternate strategy that involves starting at and repeating small doses of buprenorphine and slowly titrating to therapeutic doses. These protocols can be implemented in primary care settings, with patients being able to complete most of the induction at home. Initiation in the primary care setting can help patients continue treatment and improves access to much needed OUD treatment.

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REFERENCES

1. **Modesto-Lowe V, Swiezbin K, Chaplin M, Hoefer G.** Use and misuse of opioid agonists in opioid addiction. Cleve Clin J Med 2017; 84(5):377–384. doi:10.3949/ccjm.84a.16091
2. **De Aquino JP, Parida S, Sofuoglu M.** The pharmacology of buprenorphine microinduction for opioid use disorder. Clin Drug Investig 2021; 41(5):425–436. doi:10.1007/s40261-021-01032-7
3. **Centers for Disease Control and Prevention.** The drug overdose epidemic: behind the numbers. Updated May 8, 2023. https://www.cdc.gov/opioids/data/index.html. Accessed August 21, 2023.
4. **Williams AR, Nunes EV, Bisaga A, et al.** Developing an opioid use disorder treatment cascade: a review of quality measures [published correction appears in J Subst Abuse Treat 2018; 92:99]. J Subst Abuse Treat 2018; 91:57–68. doi:10.1016/j.jsat.2018.06.001
5. **Substance Abuse and Mental Health Services Administration.** Waiver elimination (MAT Act). Updated June 7, 2023. https://www.samhsa.gov/medications-substance-use-disorders/waiver-elimination-mat-act. Accessed August 21, 2023.
6. **Leiser A, Robles M.** Expanding buprenorphine use in primary care: changing the culture. Perm J 2022; 26(2):177–180. doi:10.7812/TPP/21.203
7. **Gertner AK, Rotter JS, Holly ME, Shea CM, Green SL, Domino ME.** The role of primary care in the initiation of opioid use disorder treatment in statewide public and private insurance. J Addict Med 2022; 16(2):183–191. doi:10.1097/ADM.0000000000000860
8. **DeFlavio JR, Rolin SA, Nordstrom BR, Kazal LA Jr.** Analysis of barriers to adoption of buprenorphine maintenance therapy by family physicians. Rural Remote Health 2015; 15:3019. pmid:25651434
9. **Haffajee RL, Andraka-Christou B, Attermann J, Cupito A, Buche J, Beck AJ.** A mixed-method comparison of physician-reported beliefs about and barriers to treatment with medications for opioid use disorder. Subst Abuse Treat Prev Policy 2020; 15(1):69. doi:10.1186/s13011-020-00312-3
10. **Foti K, Heyward J, Tajanlangit M, et al.** Primary care physicians' preparedness to treat opioid use disorder in the United States: a cross-sectional survey. Drug Alcohol Depend 2021; 225:108811. doi:10.1016/j.drugalcdep.2021.108811
11. **Mirer AG, Tiemstra JD, Hammes NE, Cloum HM, LaFavor KJ.** Integrating buprenorphine treatment for opioid use with primary care is associated with greater retention in treatment. J Am Board Fam Med 2022; 35(1):206–208. doi:10.3122/jabfm.2022.01.210292
12. **Bailey SR, Lucas JA, Angier H, et al.** Associations of retention on buprenorphine for opioid use disorder with patient characteristics and models of care in the primary care setting. J Subst Abuse Treat 2021; 131:108548. doi:10.1016/j.jsat.2021.108548
13. **Hsu YJ, Marsteller JA, Kachur SG, Fingerhood MI.** Integration of buprenorphine treatment with primary care: comparative effectiveness on retention, utilization, and cost. Popul Health Manag 2019; 22(4):292–299. doi:10.1089/pop.2018.0163
14. **Kumar R, Viswanath O, Saadabadi A.** Buprenorphine. In: StatPearls. Treasure Island, FL: StatPearls Publishing; February 27, 2023.
15. **Chavkin C.** Kappa-opioid antagonists as stress resilience medications for the treatment of alcohol use disorders. Neuropsychopharmacology 2018; 43(9):1803–1804. doi:10.1038/s41386-018-0046-4
16. **Ahmed S, Bhivandkar S, Lonergan BB, Suzuki J.** Microinduction of buprenorphine/naloxone: a review of the literature. Am J Addict 2021; 30(4):305–315. doi:10.1111/ajad.13135
17. **Hämmig R, Kemter A, Strasser J, et al.** Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Subst Abuse Rehabil 2016; 7:99–105. doi:10.2147/SAR.S109919
18. **De Aquino JP, Fairgrieve C, Klaire S, Garcia-Vassallo G.** Rapid transition from methadone to buprenorphine utilizing a micro-dosing protocol in the outpatient Veteran Affairs setting. J Addict Med 2020; 14(5):e271–e273. doi:10.1097/ADM.0000000000000618
19. **Substance Abuse and Mental Health Services Administration.** Buprenorphine quick start guide. https://www.samhsa.gov/sites/default/files/quick-start-guide.pdf. Accessed August 21, 2023.
20. **Volpe DA, McMahon Tobin GA, Mellon RD, et al.** Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol 2011; 59(3):385–390. doi:10.1016/j.yrtph.2010.12.007
21. **Jain L, Morrisroe K, Modesto-Lowe V.** To use or not to use buprenorphine for illegally manufactured fentanyl. Fam Pract 2023; 40(2):428–430. doi:10.1093/fampra/cmac098

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22. **Poliwoda S, Noor N, Jenkins JS, et al.** Buprenorphine and its formulations: a comprehensive review. Health Psychol Res 2022; 10(3):37517. doi:10.52965/001c.37517
23. **Orexo US Inc.** Zubsolv dosage and administration. https://www.zubsolv.com/healthcareprofessionals/about-zubsolv/dosage-administration/. Accessed August 21, 2023.
24. **Blazes CK, Morrow JD.** Reconsidering the usefulness of adding naloxone to buprenorphine. Front Psychiatry 2020; 11:549272. doi:10.3389/fpsyt.2020.549272
25. **Wesson DR, Ling W.** The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 2003; 35(2):253–259. doi:10.1080/02791072.2003.10400007
26. **Antoine D, Huhn AS, Strain EC, et al.** Method for successfully inducting individuals who use illicit fentanyl onto buprenorphine/naloxone. Am J Addict 2021; 30(1):83–87. doi:10.1111/ajad.13069
27. **Greenwald MK, Comer SD, Fiellin DA.** Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend 2014; 144:1–11. doi:10.1016/j.drugalcdep.2014.07.035
28. **Danilewitz M, McLean M.** High-dose buprenorphine for treatment of high potency opioid use disorder. Drug Alcohol Rev 2020; 39(2):135–137. doi:10.1111/dar.13017
29. **Ahmadi J, Jahromi MS, Ghahremani D, London ED.** Single high-dose buprenorphine for opioid craving during withdrawal. Trials 2018; 19(1):675. doi:10.1186/s13063-018-3055-z
30. **Huhn AS, Hobelmann JG, Oyler GA, Strain EC.** Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Depend 2020; 214:108147. doi:10.1016/j.drugalcdep.2020.108147
31. **Quattlebaum THN, Kiyokawa M, Murata KA.** A case of buprenorphine-precipitated withdrawal managed with high-dose buprenorphine. Fam Pract 2022; 39(2):292–294. doi:10.1093/fampra/cmab073
32. **Greenwald MK, Herring AA, Perrone J, Nelson LS, Azar P.** A neuropharmacological model to explain buprenorphine induction challenges. Ann Emerg Med 2022; 80(6):509–524. doi:10.1016/j.annemergmed.2022.05.032
33. **Mendelson J, Jones RT, Welm S, Brown J, Batki SL.** Buprenorphine and naloxone interactions in methadone maintenance patients. Biol Psychiatry 1997; 41(11):1095–1101. doi:10.1016/S0006-3223(96)00266-1
34. **Salapenka I, Konakanchi JS, Sethi R.** Outpatient rapid microinduction of sublingual buprenorphine in 3 days from methadone for opioid use disorder. Prim Care Companion CNS Disord 2022; 24(6):21cr03150. doi:10.4088/PCC.21cr03150
35. **Robbins JL, Englander H, Gregg J.** Buprenorphine microdose induction for the management of prescription opioid dependence. J Am Board Fam Med 2021; 34(suppl):S141–S146. doi:10.3122/jabfm.2021.S1.200236
36. **Penn Medicine Center for Addiction Medicine and Policy.** Low dose/microdose buprenorphine instructions. Buprenorphine cross-tapering using a micro-dosing strategy. https://penncamp.org/clinical/micro-dosing. Accessed August 21, 2023.
37. **De Aquino JP, Parida S, Sofuoglu M.** Buprenorphine microinduction: logistical barriers and the need for convergent evidence. Clin Drug Investig 2021; 41(7):665. doi:10.1007/s40261-021-01049-y
38. **Spadaro A, Sarker A, Hogg-Bremer W, et al.** Reddit discussions about buprenorphine associated precipitated withdrawal in the era of fentanyl. Clin Toxicol (Phila) 2022; 60(6):694–701. doi:10.1080/15563650.2022.2032730
39. **Oakley B, Wilson H, Hayes V, Lintzeris N.** Managing opioid withdrawal precipitated by buprenorphine with buprenorphine. Drug Alcohol Rev 2021; 40(4):567–571. doi:10.1111/dar.13228
40. **Sevarino K.** Medically supervised opioid withdrawal during treatment for addiction. UpToDate. Updated July 26, 2023. https://www.uptodate.com/contents/medically-supervised-opioid-withdrawal-during-treatment-for-addiction. Accessed August 21, 2023.
41. **Herring AA, Vosooghi AA, Luftig J, et al.** High-dose buprenorphine induction in the emergency department for treatment of opioid use disorder. JAMA Netw Open 2021; 4(7):e2117128. doi:10.1001/jamanetworkopen.2021.17128

Address: *Roberto León-Barriera, MD, Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213; ral187@pitt.edu*

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