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Low-Dose Initiation of Buprenorphine: A Narrative Review

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Abstract

Purpose of Review Opioid use disorder (OUD) is a chronic disorder in which a person loses control over the use of opioids, develops a compulsive behavior, and defends the use despite knowing the negative consequences. There are numerous treatments for OUD, including buprenorphine. Since it is displacing a full agonist opioid, precipitated withdrawal can occur with standard inductions involving buprenorphine.

Recent Findings Case reports have noted success with a low-dose initiation of buprenorphine, which is different from typical protocols, relatively limited by adverse effects when patients were recently administered full agonists. A cohort investigation studied the use of a transdermal patch as part of the protocol, which was fairly well tolerated.

Summary While ongoing research is being conducted on this topic, recent case studies and smaller cohort studies have demonstrated the feasibility of a trial to treat OUD with low-dose initiation of buprenorphine.

Keywords Buprenorphine · Withdrawal · Opioid use disorder · Fentanyl · Lose dose · Addiction treatment

Introduction

Opioid use disorder (OUD) is a chronic disorder in which a person loses control over the use of opioids, develops a compulsive behavior, and defends the use despite knowing the negative consequences. Opioids have a variety of chemical structures and they act by binding to delta, kappa, and mu receptors in the central nervous system (CNS) and throughout the body [1]. In general, opioids alter the reward system in the CNS and enhance the sense of pleasure and euphoria. The growing prevalence of OUD arises from the wide availability and increasing prescription of opioid pain medications and the illicit manufacture of fentanyl, with a higher potency than the majority of other opioids [2].

Buprenorphine is an office-based treatment for OUD that has had a significant positive effect on patients for several reasons. Buprenorphine is a partial opioid agonist and is thought to stop cravings and withdrawal symptoms without causing the same euphoric feelings inherent in full opioid agonists. Since it is a partial agonist, it can cause withdrawal symptoms when it displaces a full agonist from the receptor, called precipitated withdrawal. To try to prevent this from occurring, a standard initiation of buprenorphine usually occurs when the patient is in at least a mild withdrawal state. However, in the era of fentanyl, this type of initiation can be difficult as it is challenging to predict how long fentanyl will linger in a patient's system. In order to combat this issue, another form of scheduling each daily dose has been termed low-dose initiation of buprenorphine. This manuscript, therefore, is a narrative review of buprenorphine and its low-dose initiation in patients.

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Opioid Use Disorder Overview

OUD Pathophysiology

Among the various neurological systems impacted by opioids, the mesocorticolimbic reward system is activated. The nucleus accumbens is an area of the brain that when stimulated produces a sense of pleasure and reward. Actions that repeatedly activate this area are reinforced. In OUD, when opioids attach to one of the opioid receptors, the mu receptors specifically, this triggers a release of dopamine into the nucleus accumbens, providing euphoria and reward the drug use. The body also has a similar system to reward positive, healthy acts such as eating, exercise, and sexual activity through endogenous opioids such as endorphins, enkephalins, and dynorphins, which are synthesized in the body. Exogenous opioids, however, activate these receptors to create a supraphysiologic dopamine release and shut down endogenous opioid production [3]. Frequent use of these exogenous opioids causes the brain to change both neuronal connections and signals, which is thought to cause the diminished effect of opioids over time in these individuals [4]. These changes lead to ordinary things not causing the same pleasurable effects, and it turns the focus and attention of those taking these drugs to obtaining and using opioids [3].

Another pathway is the hypothalamus–pituitary–adrenal axis, a neuroendocrine system that responds to stress. Our body produces cortisol in stressful situations. A stress response includes things we associate with a fight or flight response, which includes increased heart rate, blood pressure, energy metabolism, and suppression of gastrointestinal movement and the immune system. When opioids are introduced into a patient, this system is suppressed. Conversely, when a patient is in withdrawal, this system is heightened. With repeated fluctuation of this response, this system can become overactive and induce significant stress on the individual. In this regard, studies also show that stress can trigger cravings which can lead to relapse of these patients [4, 5].

Opioid Use Disorder Treatment

Related to the chronic nature of OUD, treatments for OUD are primarily pharmaceuticals that are used to help patients satisfy cravings and minimize withdrawal symptoms. Three drugs mainly used in this setting are buprenorphine, methadone, and naltrexone. The efficacy of these treatments, which has shown promise, but that is assuming patient compliance and adherence to the proper treatment regimen provided by physicians. Methadone is a full opioid agonist, and buprenorphine is a partial opioid agonist, while naltrexone is an opioid antagonist. Due to the properties of the two-agonist drugs, these drugs have the potential to be misused in treatment regimens and may cause relapse. Methadone can produce the same dose-dependent sedation, analgesia, feelings of euphoria, and risk of respiratory depression as other illicit opioid full agonists [6, 7]. Although previous studies show methadone as the gold standard of medical treatment of OUD, there is a risk of misuse and partial adherence related to the burdens daily dosing at a clinic.

Naltrexone's role in OUD treatment is to bind to but not activate the opioid receptors, and this prevents the high the individual gets with opioids. Buprenorphine provides mild opioid activation and withdrawal relief, while naltrexone blocks opioid receptors, controlling the opioid activation and the subsequent pleasant feelings and euphoria. The proper dosing could prevent the urge to use and possible relapse; however, it should be noted that this is not the preferred method of medical treatment as relapse rates are higher than with methadone or buprenorphine. Naltrexone could be an option for patients who do not wish to be on an opioid medication, for personal or professional reasons. The different aspects of treatment complement each other to provide a more effective treatment for OUD than the short-term taper and is subsequently associated with longer-term adherence to treatment regimens [8].

Buprenorphine

Buprenorphine is a partial agonist at the mu-opioid receptor. It was first discovered in 1966 and was initially approved by the United States Food and Drug Administration (FDA) in the 1980s as a Schedule III parenteral agent (Buprenex) for treating moderate to severe pain in the inpatient setting [1, 9]. Due to its unique properties, the use of buprenorphine in treating OUD was extensively studied. The sublingual formulations (buprenorphine, known as Subutex, and buprenorphine/naloxone, known as Suboxone) were approved by the FDA for treating opioid use disorder or opioid dependence in 2002 [10]. It provides a potent analgesic effect that parallels the effect of opioids with full agonistic properties. Buprenorphine also produced clinical effects similar to other opioids, which include sedation, euphoria, and respiratory depression. Buprenorphine has a relatively high safety profile, with a ceiling effect on respiratory depression, analgesia, and other effects that could prevent those adverse effects [11]. This explains the lower mortality rate associated with buprenorphine treatment compared to methadone despite broader availability and fewer restrictions.

Buprenorphine has a high affinity for and slowly dissociates from the μ receptors. The prolonged fixation to the receptors is associated with an extended duration of action and, in turn, prolonged analgesic properties and less withdrawal effect, all of which favor buprenorphine over other medications in managing OUD and pain control [1].

Standard Induction and Challenges with Standard Initiation

In treating opioid dependence with buprenorphine, various models of induction exist. When determining the appropriate approach, several factors should be considered, including the type and duration of action of the opioid product used, the time of last drug use, and the severity of dependence.

Traditional induction with buprenorphine in patients with short-acting opioid (e.g., heroin, oxycodone) dependence is initiated when the person exhibits signs of mild to moderate withdrawal and at least 6 to 12 h have elapsed after the last use to avoid buprenorphine-precipitated withdrawal. In patients whose last use was with a long-acting opioid (e.g., morphine or oxycodone controlled-release products), induction is initiated at least 24 h after the last use. For fentanyl patch users, buprenorphine is commenced 48–72 h after discontinuation of therapy. For persons who receive maintenance with methadone and wish to transition to buprenorphine, initiation of buprenorphine is delayed until at least 72 h from the last dose of methadone.

Titration of buprenorphine dosage to clinical effectiveness in a timely manner is crucial; gradual titration over several days was associated with a higher rate of dropping out of the treatment. On the 1st day of induction, the initial recommended dose is 2 or 4 mg, after which the patient is monitored for withdrawal symptoms. If the initial dose is well tolerated, additional 2- to 4-mg increments may be administered every 2 h under supervision until the withdrawal signs and symptoms are controlled. A dosage of up to 8 mg is recommended on the first day of induction. On the 2nd day of induction, a single dose of up to 16 mg is recommended.

In the traditional model, frequent assessment of the symptoms of opioid withdrawal with tools such as the Clinical Opiate Withdrawal Scale (COWS) helps guide the titration of therapy. In this model, induction commencement is delayed until patients with OUD start experiencing withdrawal symptoms. Provided the strong binding affinity, early administration of buprenorphine after the last opioid use may lead to the displacement of the full agonistic opioid with less affinity from the μ receptors, culminating in acute precipitated opioid withdrawal, which sometimes may be severe. The fear of experiencing withdrawal symptoms with delayed initiation or precipitated opioid withdrawal with induction poses a significant fear among opioid users and resembles a significant barrier to seeking treatment.

Late-precipitated opioid withdrawal complicates induction with buprenorphine in persons with long-term use of illicit fentanyl [12, 13]. Fentanyl has lipophilic properties; its excretion is delayed after long-term use and remains in the body's peripheral tissues. Early low-dose initiation of buprenorphine rather than full induction doses has been introduced to overcome this challenge; in other words, it reduces the risk of precipitated withdrawal and may improve the patient's experience during induction [12].

Clinical Studies

Case Reports

A case report in Switzerland in 2016 explored the use and effectiveness of the Bernese method [14]. The Bernese method is the repetitively administering small buprenorphine doses at intervals of around 12 h [14]. This allows sufficient buprenorphine to gather at the mu receptor and, with a large enough accumulation, will be able to replace the full agonist at the receptor site [14]. This process makes for the "overlapping induction of buprenorphine with ongoing use of street heroin or in patients on high doses of full mu agonist maintenance therapy" [14]. Case 1 investigated conventional induction in a 30-year-old female with a history of crack-cocaine and heroin use. When she was most recently admitted to outpatient treatment, she used "3 g of street heroin daily." This patient was first started on conventional induction treatment in which she was given four separate sublingual doses of 0.4 mg buprenorphine over 2 h. After each dose, she reported experiencing increasing withdrawal symptoms including diarrhea, flashbacks, and severe anxiety. The patient participated in 2 weeks of this treatment and then proceeded to stop taking buprenorphine, returning to street heroin use. Still, she presented a week later with a desire to restart treatment. This time, the Bernese method was used. The patient was offered to begin buprenorphine at a 0.2 mg while continuing illicit opioids. The suggestion was then to proceed with small daily dose increases until a sufficient buprenorphine dose is reached, in which the patient should abruptly cease heroin use. At first, the patient was not adherent or cooperative to treatment, though, after a few instances of non-cooperativity, the patient began increasing buprenorphine doses more rapidly. She then stabilized and was free of heroin use for 2.5 years. The patient demonstrated individual success from using the Bernese method of overlap using a low dose for the initiation of buprenorphine [14].

A similar case report in 2021 detailed the strategy of a low-dose initiation of buprenorphine with concurrent very high-dose full opioid agonist use [15]. The patient was a female between 30 and 40 years old. She initially presented in acute pain due to injection drug use-induced osteomyelitis. She expressed desires to start buprenorphine for OUD. Still, she concurrently required treatment to manage her acute pain due to the infection, which ruled out the possibility to use standard dosing and protocol for buprenorphine. Therefore, the patient was administered an alternative treatment regimen which was defined by a low-dose initiation of buprenorphine with gradual cross-tapering of her full

agonists. She started at "1 mg transdermal drug delivery (TDD) on day 1, 3 mg TDD on day 2, and 8 mg TDD on day 3" while having full agonist overlap and tapering down the full agonist on day three and again on day 8. Beyond day 8, the patient's buprenorphine was titrated to 8 mg three times daily. This patient reported no discomfort or worsening withdrawal symptoms due to the low-dose initiation and agonist overlap. The results of this individual case demonstrate that a cross-taper of buprenorphine paired with full agonists can achieve maintained tolerability and lead to a successful induction [15].

A different case report explores the concept of low-dose initiation previously discussed in both case reports [16]. However, this case report includes a focus on assertive outreach in combination with a low-dose initiation schedule. This assertive outreach involved using an interdisciplinary team, which included primary care, psychiatry, peer support, and other services. It is directed towards patients with needs that may not be able to be met in a traditional office setting. For example, high-risk youth living with mental illness would be candidates for this assertive outreach. Using this method, patients between 18 and 25 years old with OUD were identified and offered buprenorphine/naloxone in a low-dose initiation protocol. Within 6 months, 8 out of 14 patients demonstrated successful inductions with no withdrawal symptoms caused by the initiation. Due to the potential benefits conveyed, a parent of one of the youth outreach patients was then specifically chosen for a case presentation of this concept. This patient was a 55-year-old man who used heroin daily and crystal meth weekly. He was prescribed a buprenorphine/naloxone dosing regimen. He was supported by an outreach team, who provided reminders to pick up his medications and offers to help with pick up. Though this patient was not cooperative with continuous treatment for a long period, he did not report withdrawal symptoms. This result communicates the possible benefits of low-dose initiation in relation to avoidance of the discomfort of withdrawal symptoms, as those symptoms could potentially lead to relapse [16].

Cohort Study

A retrospective observational cohort study was conducted at Washington University School of Medicine in 2022 to consider the effectiveness of the use of a transdermal buprenorphine as an efficacious option to bridge the transition from full agonist opioids to sublingual buprenorphine in patients with OUD as part of a low-dose initiation protocol [17]. This strategy was developed due to observed discomfort in many OUD patients when transitioning from full agonists to sublingual buprenorphine because of opioid withdrawal symptoms. Forty-one patient cases were included in the study and fit the criteria of being hospitalized between January 2019 and December 2020 at the hospital in which the study was conducted. On each patient, the median milligram morphine equivalent (MME) level was 63.8 on the day before receiving transdermal buprenorphine and 34.5 the day of transdermal application. The median initial dose of sublingual buprenorphine first-day dose was 8 mg, and the last-day median dose was 16 mg. Out of 41 patients, 38 patients completed the transition from opioids to sublingual buprenorphine with the use of transdermal patch as a bridge. Around 59% of those patients reported that the transition protocol they experienced was "well tolerated," and around 32% reported tolerating the transition "fairly." This study identifies that it would be advantageous to continue to explore and improve treatment protocols for OUD [17].

Feasibility and Continuing Studies

The feasibility of performing a clinical trial using microdosing of take-home buprenorphine was explored in a study conducted at Vancouver General Hospital [18]. There were 68 participants, comprised of patients of 18 years or older diagnosed with OUD that presented to the Vancouver General Hospital emergency department. Patients were randomized into two groups: a group receiving 3-day standard dosing or a group receiving 6-day low-dose initiation. Of the 21 patients on standard dosing, 23.8% remained on the opioid agonist therapy for 30 days [18]. Of the 25 patients on a low-dose initiation protocol, 32% remained on agonist therapy for 30 days. Moreover, this study demonstrates that it would be feasible to conduct ED-initiated take-home standard dosing and low-dose buprenorphine programs. In addition, its results promote the potential for a future controlled trial, which likely leads into the controlled trial conducted around a year later at the same hospital [18].

A randomized controlled trial in 2021 aimed to examine and compare the safety and efficacy of using rapid low-dose initiation on subjects with OUD against the use of a standard induction method of buprenorphine [19]. The open-label study was conducted at Vancouver General Hospital in Canada with participants that were eligible patients with OUD. Participant eligibility inclusion criteria stated that participants must have a diagnosis of OUD fitting the DSM-5 criteria, be individuals seeking opioid agonist treatment (OAT), be of age of 19 or older, be willing to comply, give written consent, and be in agreeance to use effective birth control through the study if the childbearing potential is present. Prospective participants were excluded if testing positive on a urine drug screen for methadone. There were 50 participants total ($n = 50$), and each was assigned randomly to one of two groups: "the rapid micro-induction arm" ($n = 25$) or the group receiving standard, first-line OUD treatment ($n = 25$) [19]. The "rapid micro-induction arm" received hydromorphone and buprenorphine, while

the standard treatment group received only the latter [19]. Hydromorphone is an opioid used in this study for managing pain, craving, and withdrawal [19]. The "rapid micro-induction arm" received 48 h of this protocol, starting on day 1, which was completed after receiving a total daily dose of ≥ 8 mg of Suboxone [19]. Before being administered buprenorphine, the standard treatment group must score 11 or higher on the COWs and abstain from long-acting opioids for 24–72 h; this group's induction is completed after receiving a total daily dose of ≥ 8 mg of buprenorphine [19]. Though the study is not yet complete, it is hypothesized that the "rapid micro-induction arm" participants who are successfully induced will experience much lower levels of withdrawal compared to participants in the standard treatment group [19]. The results of this study will be very important and applicable to the current social and clinical setting, especially with a surge of "fentanyl-detected overdose deaths" [19]. Moreover, after the completion of the currently ongoing clinical trial, the authors propose that the results will generate the first major body of clinical evidence on the effectiveness and safety of rapid micro-induction [19].

Author/date	Focus	Groups/individual studied	Results and findings	Conclusions
Hammig et al., 2016 [14]	To execute the Bernese method to successfully transition a patient to buprenorphine management by low-dose initiation and initially overlapping it with full opioid agonist use	Case report 30-year-old female with a history of heroin and crack-cocaine use, presenting to outpatient treatment with opioid use disorder (OUD)	Using the Bernese method, the patient increased small daily doses of buprenorphine with concurrent heroin use until, at a sufficient buprenorphine dose. She stabilized for 2.5	The patient has been abstinent for an ongoing total of 3 years and 3 months, demonstrating an individual success from using the Bernese method
DeWeese et al., 2021 [15]	To determine if low-dose initiation is effective and tolerable	Case report Female between 30 and 40 years old diagnosed with severe OUD who presented with acute pain due to osteomyelitis	The patient experienced induction using transdermal buprenorphine with overlapping opioid agonist use with a downward taper for 8 days Denied any discomfort or worsening withdrawal symptoms	The results of this individual case demonstrate that of a low-dose initiation protocol could lead to a successful induction even full agonist use
Rozylo et al., 2020 [16]	To explore if assertive outreach and a low-dose initiation schedule contributes to a successful induction of buprenorphine	Case report 55-year-old male diagnosed with OUD, history of daily heroin use and weekly crystal meth use	Patient provided with a low-dose initiation of buprenorphine +transition from opioid use to treatment with low-dose initiation Explicitly denied withdrawal symptoms entirely	A major potential benefit of low-dose initiation is avoidance of the discomfort of withdrawal symptoms as those symptoms could potentially lead to relapse
Baumgartner et al., 2022 [17]	To determine if transdermal buprenorphine provides a successful bridge from full agonist opioids to sublingual buprenorphine	Retrospective observational cohort study 41 patient cases included Participants were hospitalized at some point between January 2019 and December 2020 and administered transdermal buprenorphine before receiving sublingual buprenorphine All diagnosed with OUD	Out of 41 patients, 38 completed the transition from opioid use to sublingual buprenorphine with transdermal as a bridge	Most patients had a well to fair toleration of transitioning to buprenorphine using a low-dose initiation protocol
Moe et al., 2020 [18]	To determine the feasibility of providing ED-initiated take home buprenorphine low-dose initiating programs that could provide these services; in addition, to foresee a possible benefit for a future clinical trial analyzing low-dose initiations in the clinical setting	Feasibility study 68 participants comprised of individuals 18 years old and above with a diagnosis of OUD ($n=68$) Presented to the ED of Vancouver General Hospital [18] Participants randomized into two groups: Group receiving 3-day standard dosing of take home buprenorphine ($n=34$) A group receiving 6-day micro-dosing of take-home buprenorphine ($n=34$)	Of the 21 patients on standard dosing, 23.8% remained on the opioid agonist therapy for 30 days Of the 25 patients on low-dose initiation, 32% remained on agonist therapy for 30 days	Could be feasible to conduct ED-initiated take-home standard-dosing and low-dose initiation buprenorphine programs In addition, its results promote the potential for a future controlled trial, which likely leads into the controlled trial conducted around a year later at the same hospital

Author/date	Focus	Groups/individual studied	Results and findings	Conclusions
Wong et al., 2021 [19]	To test and compare the effectiveness of low-dose initiation protocols of buprenorphine to standard initiation	Continuing randomized clinical trial Participants are 19 years old or older and diagnosed with OUD, seeking treatment with opioid agonists Participants randomized into two groups: - Group receiving "rapid micro-dosing," includes administration of hydromorphone - Group receiving standard treatment, no administration of hydromorphone	To be determined study is still ongoing	Though the study is incomplete, it is hypothesized that the "rapid micro-induction arm" participants who are successfully induced will experience much lower levels of withdrawal compared to participants in the standard treatment group

Conclusion

Low-dose initiation of buprenorphine for OUD continues to be a promising therapeutic target. Due to the more attractive safety protocol compared methadone and its ability to minimize withdrawal symptoms, it poses as a potentially attractive drug for physicians. Related to dramatic increases in opioid-related deaths to illicit opioids, this treatment could serve a major role in helping patients seeking opioid addiction treatment avoid overdose and improve or even restore overall quality of life. The ability of buprenorphine to allow patients to slowly get off opioids while preventing withdrawal symptoms is one of the more appealing characteristics of this treatment. Additionally, some may say the safety profile of buprenorphine, instead of the full opioid agonist methadone, is the key feature to further investigation. An important consideration to make in treatment is the social support of these patients, as it has been shown this improves compliance and prevents relapse. While ongoing research is being conducted on this topic, the current case studies and smaller cohort studies show the feasibility of a trial to treat OUD with low-dose initiation of buprenorphine. In these studies, there seems to be significant efficacy in transitioning OUD patients from opioids to buprenorphine while limiting withdrawal. This serves the potential to restore affected individuals' lives and prevent relapse and even accidental overdose. With more research on this treatment, the ability to successfully treat substance use disorder will improve both patient lives and the economy.

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Data Availability All data presented in this review is available on PubMed.

Compliance with Ethical Standards

Ethics Statement This narrative review did not require consent from subjects or review by an institutional review board.

Conflict of Interest The authors declare no competing interests.

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