Editor's Choice

Low Dose Initiation of Buprenorphine: A Narrative Review and Practical Approach

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Low dose buprenorphine initiation, is an alternative method of initiating buprenorphine in which the starting dose is very low and gradually increased to therapeutic levels over a period of days. This method takes advantage of slow displacement of the full opioid agonist from mu-opioid receptors, avoiding the need for a person with opioid use disorder to experience opioid withdrawal symptoms before initiating buprenorphine, while also minimizing the risk of precipitated opioid withdrawal. With this initiation method, full opioid agonists can be continued as buprenorphine is initiated, expanding the population to which buprenorphine can be offered. To date, the literature on low dose initiation is primarily case-based but rapidly growing. While evidence emerges, guidance for the use of low dose initiation is clearly desired and urgently needed in the context of an increasingly risky and contaminated opioid drug supply, particularly with high potency synthetic opioids, driving overdose deaths. Despite limited evidence, several principles to guide low dose initiation have been identified including: (1) choosing the appropriate clinical situation, (2) initiating at a low buprenorphine dose, (3) titrating the buprenorphine dose gradually, (4) continuing the full opioid agonist even if it is nonmedical, (5) communicating clearly with frequent monitoring, (6) pausing or delaying buprenorphine dose changes if opioid withdrawal symptoms occur, and (7) prioritizing care coordination. We review a practical approach to low dose initiation in hospital-based and outpatient settings guided by the current evidence.

Key Words: Bernese method, buprenorphine, low dose initiation, microdose, opioid-related disorders

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The United States is in the midst of an worsening opioid overdose crisis, the severity and inequality of its impact only exacerbated by the COVID-19 pandemic.[1] Illicitly manufactured high potency synthetic opioids including fentanyl and fentanyl analogs have increasingly entered the drug supply driving the recent and rapid rise in overdoses.[2,3] Medications for opioid use disorder (MOUD), buprenorphine, methadone, and naltrexone, reduce opioid overdoses and mortality; yet access to these lifesaving therapies remain limited.

Buprenorphine, approved by the U.S. Food and Drug Administration in 2002, is available for office-based treatment of opioid use disorder (OUD). For nearly 2 decades, prescribing buprenorphine in outpatient settings required clinicians to obtain an X-waiver from the U.S. Drug Enforcement Agency after completing mandatory training. In April 2021, in an effort to expand the use of buprenorphine, restrictions for buprenorphine prescribing were relaxed to allow all prescribers to treat up to 30 patients after submitting a notice of intent to the U.S. Substance Abuse and Mental Health Services Administration.[4]

In addition to regulatory changes, clinicians are exploring new strategies to address challenges related to initiating and titrating buprenorphine to a therapeutic dose, a process termed induction. One strategy growing in popularity is called low dose initiation, also referred to as microinduction and the Bernese method. Low dose initiation uses low, gradually increasing doses of buprenorphine to avoid the withdrawal symptoms generally required to start buprenorphine, thus facilitating buprenorphine initiation in patients who may otherwise not receive it.

In this narrative review, we describe the mechanism, rationale, and existing methods for performing buprenorphine low dose initiation and provide practical approaches to support outpatient and hospital-based practice, based on the current evidence.

Traditional Induction and Rationale for Low Dose Initiation

Buprenorphine has 3 critical pharmacokinetic and pharmacodynamic properties at the mu opioid receptor that guide its therapeutic action and initiation: (1) partial opioid agonism, (2) high affinity, and (3) slow dissociation. The partial opioid agonism provides a ceiling effect that underpins its safety, allowing for treatment of opioid craving and withdrawal symptoms while reducing risk of respiratory depression and opioid overdose. The high affinity protects individuals from overdose

by preventing full opioid agonists from preferentially binding at mu opioid receptors. The slow dissociation allows for once daily dosing and contributes to stacking of doses if taken in short succession where subsequent dosing builds on prior doses which can be helpful during the initial induction period.

Despite the benefits of buprenorphine's partial opioid agonism and high binding affinity, these 2 properties also come with the potential risk of precipitating opioid withdrawal. Precipitated opioid withdrawal occurs when standard doses of 2–24 mg buprenorphine are taken while full opioid agonists are bound at mu opioid receptors. The full opioid agonist becomes displaced by buprenorphine, causing an abrupt shift from full agonism to partial agonism resulting in the patient experiencing severe opioid withdrawal symptoms. To avoid precipitated withdrawal, traditional induction strategies recommend stopping full opioid agonists and waiting for signs of mild to moderate withdrawal to indicate that full agonists are no longer significantly occupying mu opioid receptors before starting buprenorphine.[5,6] The length of time to wait after stopping full opioid agonists depends on the opioid half-life. Short-acting opioids should be stopped 6–24 hours before initiating buprenorphine and long-acting opioids typically require stopping 24–72 hours before induction. Once mild to moderate withdrawal symptoms are present, buprenorphine is initiated at 2–4 mg, with the dose repeated over hours to days until withdrawal symptoms and opioid cravings are adequately controlled and a therapeutic dose is reached.

This process has become more difficult with an increasingly toxic and contaminated drug supply with high potency synthetic opioids. Specifically, fentanyl and its analogs have a rapid onset, short duration of action, and long half-life partially driven by their lipophilicity.[7] These properties result in more frequent use to avoid withdrawal, a more rapid onset of withdrawal symptoms, and unpredictability regarding when buprenorphine can be safely started; thus complicating traditional induction. Growing data describe the occurrence of precipitated withdrawal following traditional buprenorphine induction in the setting of high potency synthetic opioids.[8,9] In these circumstances, individuals require longer periods than would typically be expected for short-acting opioids between stopping opioid use and initiating buprenorphine, resulting in more severe withdrawal symptoms, often limiting the use of buprenorphine and increasing the risk of precipitated withdrawal.[8,10] This is particularly concerning given data that precipitated withdrawal is associated with decreased treatment retention.[11]

In addition to use of high potency synthetic opioids, there are several other clinical scenarios in which stopping opioids and waiting for withdrawal is risky, challenging, or not possible: current opioid therapy for acute or chronic pain, current methadone treatment for OUD, and previous intolerance to opioid withdrawal. In the first 2 scenarios, discontinuing pain management or current methadone treatment would result in untreated pain and/or OUD increasing the risk of poor outcomes. For example, discontinuing pain management may result in lack of stabilization and premature hospital discharge. Whereas, discontinuing OUD treatment with methadone may result in increased opioid craving, recurrence of opioid use, unintentional opioid overdose, and death. In the third scenario, some patients wishing to start buprenorphine are intolerant to the withdrawal process or have experienced precipitated withdrawal in the past deterring them from starting buprenorphine through traditional induction.

Process of Low Dose Initiation

Low dose initiation is an alternative method of buprenorphine initiation in which full agonists, including non-pharmaceutical opioids, can be continued until a therapeutic dose of buprenorphine is achieved. Although the term microdosing has been used in the literature, we feel it is inaccurate and inappropriate terminology to describe this process for 2 reasons: its established definition in the pharmacologic literature for the use of subtherapeutic doses to study pharmacokinetics/pharmacodynamics[12] and its history with psychedelic use.[13]

The goal of low dose initiation is to minimize opioid withdrawal symptoms and avoid precipitated withdrawal. The most common method, coined the Bernese method when first published in 2010, involves using doses of buprenorphine as low as 0.2 mg per day and gradually increasing the dose over the course of days to weeks while continuing the full opioid agonist.[14] With this method, each sequential dose of buprenorphine displaces only small amounts of a full opioid agonist at mu opioid receptors thus minimizing withdrawal symptoms and the risk of precipitated withdrawal. A helpful analogy to explain this method of low dose initiation is a car speeding down the highway (Fig. 1). Since its original publication, the Bernese method has been adapted for use in both hospital and outpatient settings, over different periods of time, and with different formulations of buprenorphine.

To date, the literature on low dose initiation spans case reports,[14–27] case series,[28–39] 1 retrospective chart review,[40] and 4 reviews.[41–44] The overwhelming majority focused on successful cases. Methods of low dose initiation and clinical context have varied across these cases. The process has taken as short as 3 days[17,24,30] to as long as 1 month.[29] Various buprenorphine formulations have been used for the initial low doses of the initiation process, including split films/tablets,[15,18–20,24,25,28,33,35,38] transdermal patches,[16,18,22,31,36,37,39,40] intravenous,[23,34] and buccal.[26] Low dose initiations have occurred in the hospital[17,18,20–24,26,27,30,32–34,36,37,39,40] and outpatient[14–16,19,28,29,31,35,36,38] setting. Individuals have transitioned from prescription opioids including oral and injectable opioid agonist therapy[15,17,20,21,24,26–32,34–36,38,40] (the latter only available in certain countries) with morphine milligram equivalents as high as 1944 mg/d,[25] methadone[16,18,21–23,29,33–36,40] with doses up to 180 mg,[29] and nonprescription opioids (eg, heroin, high potency synthetic opioids).[14,19,29,35] In some hospital-based case reports, individuals using nonprescription opioids before hospitalization were initiated on full opioid agonists (eg, short-acting prescription opioids or methadone) for stabilization before starting the low dose initiation protocol.[17,24,30,32–34,40]

There is a clear desire and need for guidance around low dose initiation. Despite the heterogeneity of the existing literature, several key principles have been identified to help guide the use of low dose initiation in outpatient and hospital-based settings.

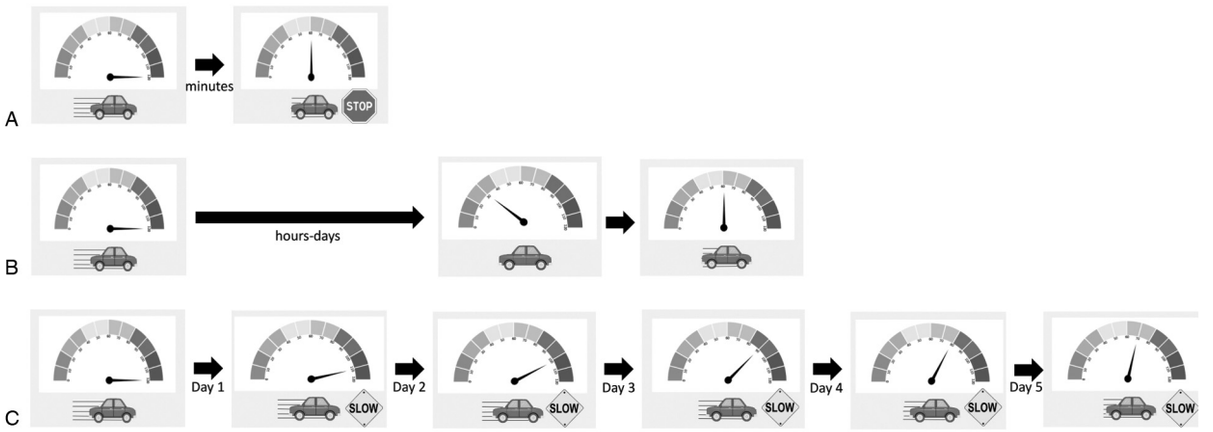


FIGURE 1. Car analogy to describe the process of low dose initiation. In this analogy, full opioid agonism is akin to a car speeding at 120 mph. Buprenorphine, a partial agonist, represents a car going 60 mph. A, Precipitated opioid withdrawal. If full opioid agonists occupy mu opioid receptors when buprenorphine is started at standard doses traditional dosing, the full agonist is rapidly displaced by buprenorphine (the car rapidly slows from 120 mph to 60 mph) – this sensation of sudden stopping is precipitated withdrawal. B, Traditional buprenorphine induction. In traditional induction, the full opioid agonist is stopped until it no longer occupies mu opioid receptors as evidenced by mild to moderate withdrawal (the car has slowed to 30 mph). Buprenorphine is then given to improve withdrawal symptoms (the car speeds up to 60 mph). C, Low Dose Initiation. In low dose initiation, the full opioid agonist is continued and buprenorphine is started at a low dose and increased by an incremental amount each day leading to only small amounts of the full agonist being displaced at mu opioid receptors (the car gradually slows each day until it reaches 60 mph). This gradual slowing rather than sudden stopping avoids the sensation of abruptly stopping (precipitated withdrawal).

Guiding Principles for Low Dose Initiation

1. Choosing the Appropriate Clinical Situation

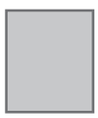
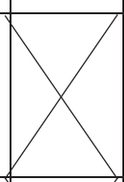
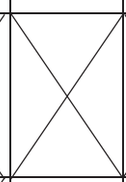
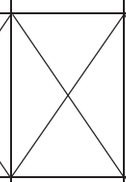
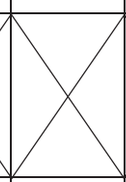
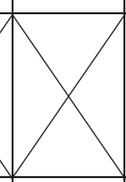
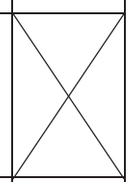
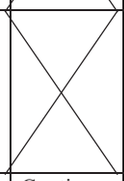
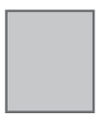
   Traditional buprenorphine induction remains the standard of care in most clinical situations due to the wealth of evidence supporting its use. As described in detail above, there are 4 broad situations in which traditional induction is more challenging or not feasible but low dose initiation can allow for the initiation of buprenorphine. They are (1) current opioid therapy for acute or chronic pain, (2) current treatment with methadone, (3) intolerance to withdrawal, and (4) regular use of high potency synthetic opioids. As with all treatment decisions, patient centeredness, and shared decision-making is integral to care engagement and successful outcomes. Consequently, low dose initiation may be considered based on a patient's preference to avoid withdrawal symptoms using this approach over traditional induction.
2. Initiating at a Low Buprenorphine Dose

   Starting doses of buprenorphine on day 1 of the transition generally range from 0.2 to 0.5 mg per dose. These starting doses can be achieved using several formulations of buprenorphine depending on institutional availability, regulations for use of buprenorphine, and treatment setting.
3. Titrating the Buprenorphine Dose Gradually

   Although the range of protocol length is wide, in general, the most common regimens are 3–7 days. If there is no time constraint, slow upward titration is theoretically less likely to cause precipitated withdrawal. In the hospital setting, more rapid protocols using frequent dosing (every 3–4 hours) and frequent monitoring have been used and are being further evaluated in an upcoming randomized controlled trial.[45] It is reasonable to use a rapid protocol in the setting of time constraints or patient safety concerns. In the case of transitioning from methadone to buprenorphine, protocols are often more gradual with slower increases in buprenorphine doses.[16,29,40] It is reasonable to start with a 7-day protocol (Fig. 2A) and extend the protocol by several days to allow for more gradual dose increases in response to any signs of withdrawal.
4. Continuing the Full Opioid Agonist, Even if Nonmedical

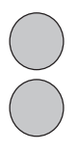
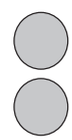
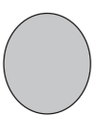
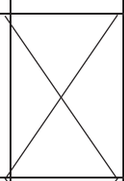
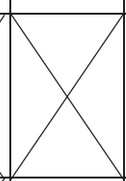
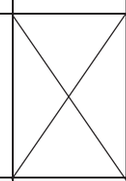
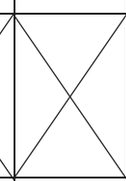
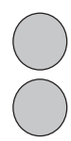
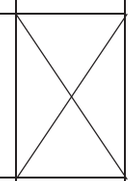
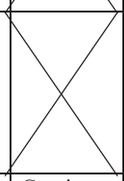
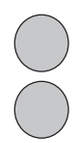
   Low dose initiation works through slow replacement of the full opioid agonist with buprenorphine at mu opioid receptors. Stopping the full opioid agonist early in the process can lead to withdrawal symptoms that can cloud the clinical picture when monitoring for withdrawal symptoms related to buprenorphine initiation. The full opioid agonist should be tapered or stopped only after a therapeutic dose of buprenorphine is reached. It is worth noting that one of the few published case reports of severe precipitated withdrawal while undergoing low dose initiation occurred in the setting of stopping methadone >24 hours before beginning buprenorphine transdermal patch.[22]

   In the hospital setting, patients using nonprescribed opioids before admission may be transitioned to a full opioid agonist, such as hydromorphone or methadone, to prevent withdrawal during the low dose initiation process.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine dose	0.5mg daily	0.5mg BID	1mg BID	2mg BID	4mg BID	4mg TID	8mg BID
Film size	2mg	2mg	2mg	2mg	2mg	2mg	8mg
Morning dose							
Afternoon Dose							
Night dose							
Full agonist	Continue	Continue	Continue	Continue	Continue	Continue	STOP

BID=twice per day
TID=Three times per day

A Dosing Guide for an example low dose initiation regimen

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine dose	0.5mg daily	0.5mg BID	1mg BID, 0.5mg in afternoon	2mg BID	4mg BID	4mg TID	8mg BID
Pill size	2mg	2mg	2mg	2mg	2mg	2mg	8mg
Morning dose							
Afternoon Dose							
Night dose							
Full agonist	Continue	Continue	Continue	Continue	Continue	Continue	STOP

BID=twice per day
TID=Three times per day

B Dosing Guide for an example blister pack regimen

FIGURE 2. Dosing guides for outpatient low dose initiation.

In the outpatient setting, patients using nonprescription opioids should continue to use the non-prescribed opioids throughout the low dose initiation process. To maximize safety of continued nonprescription opioid use, patients should receive harm reduction education around safer use practices, overdose prevention, and access to naloxone.

In the case of transitioning from methadone to buprenorphine, the literature describes various approaches. Some taper methadone to a prespecified dose during the transition,[40] others cross taper the methadone,[34] and some continue the full methadone dose until stopping at the end of the transition.[21,29,33,35] To avoid withdrawal symptoms related to tapering the methadone that can confuse the low dose initiation process, it is reasonable to maintain the patient's current methadone dose throughout the transition.

5. Communicating Clearly With Frequent Monitoring

   Patients should receive clear instructions and expectations about the low dose initiation process. Clinicians should recognize that taking buprenorphine in conjunction with a full opioid agonist may provoke anxiety, especially among patients who have previously experienced precipitated withdrawal or have undergone traditional buprenorphine inductions. To monitor symptoms and make necessary dose adjustments, close follow-up is critical throughout the process. In the hospital setting, close monitoring is guaranteed but clear communication with the patient and nursing staff is vital given the differences in the low dose initiation process and expectations compared to traditional induction. In the outpatient setting, patient check-ins to assess symptoms and progress can be as frequent as daily, especially for patients with more severe OUD, or up to every 2–3 days.[19] Checking in before stopping the full opioid agonist is absolutely necessary. With all check-in sessions, telehealth can be used to facilitate and decrease barriers when available.
6. Pausing or Delaying Buprenorphine Dose Changes if Opioid Withdrawal Symptoms Occur

   In the setting of withdrawal symptoms, pausing dose increases until symptom resolution is a reasonable approach. As dose increases are gradual, withdrawal symptoms are likely related to increasing the dose too quickly. Pausing to allow equilibration at that dose is likely the safest option. As with any initiation of MOUD, adjunctive medications, such as clonidine, to treat withdrawal symptoms should be prescribed.
7. Prioritizing Care Coordination

   Both in the hospital and outpatient settings, coordination with other healthcare professionals is of paramount importance with specific areas of attention based on the clinical situation and setting.
   a) Opioid Treatment Program Staff: For individuals transitioning from methadone treatment in the U.S., this would likely result in taking 2 forms of MOUD simultaneously for a short period of time potentially from 2 different clinicians (1 at the Opioid Treatment Program coordinating methadone and 1 prescribing buprenorphine). Therefore, coordination and proper education between clinicians regarding expectations (ie, positive buprenorphine on drug screen or buprenorphine on prescription monitoring program) and clinical management (ie, avoidance of abrupt methadone dosing changes) is essential.
   b) Outpatient Pharmacy: It is equally important to discuss the low dose initiation process with the outpatient pharmacy where the prescription is sent to ensure the instructions are clear and the prescription will be filled appropriately. If barriers arise to filling the prescription due to instructions around film splitting, the prescription can be written as ''Take 1 film daily as directed on titration schedule'' with additional written instructions provided to the patient during the clinic visit (Fig. 2A).
   c) Primary Care: Communicating with the patient's primary care provider with the patient's consent or encouraging the patient to communicate with their primary care provider is also important to discuss medication changes and answer any questions about the process.
   d) Hospital Setting: Multidisciplinary discussions with the primary team, nursing, pharmacy, and case managers concerning the length of low dose initiation and its impact on transitions of care are important to ensuring a smooth process during admission and at time of discharge.

Special Considerations for Outpatient Low Dose Initiation

In general, protocols for low dose initiation in the outpatient setting often rely on slower upward titration over 1 week or longer. The protocol used should be dependent on clinician and patient comfort. For the low doses required during the first days of the low dose initiation process, different protocols have described the use of a buprenorphine transdermal patch[31,36] and buprenorphine-naloxone film/tablet splitting,[19,28,35,38] or both.[16] As the buprenorphine transdermal patch is not Food and Drug Administration-approved for OUD and thus not legal to use for OUD in the outpatient setting, film/tablet splitting is generally the most accessible and cost-effective method. Although product labeling warns against splitting films, it is a common practice and a recent study found that films split in half remained stable for at least 7 days.[46]

Low dose initiation in the outpatient setting requires patients or caregivers to manage daily dose changes, often requiring splitting films or tablets, which may be confusing. Clear instructions and preparation can help ease this process alongside close follow-up of daily or near daily check-ins with a member of the healthcare team. A patient dosing guide (Fig. 2A) can also be a useful resource. Partnership with a pharmacy to create blister packs with scheduled dosing for the entire process is possible with advanced planning and discussion.[47] In our experience, splitting films is often the easiest approach for patients, but pharmacists may be resistant to this practice due to packaging instructions stating not to split films. If tablets must be used, generic buprenorphine-naloxone tablets are larger and easier to split for inclusion in blister packs as opposed to brand name buprenorphine-naloxone. If using a blister pack, dosing may need to be adjusted to ensure

the prescription is written to dispense a whole number of tablets to avoid product waste. For example, in Figure 2B representing a blister pack regimen, the afternoon dose on Day 3 was added so that a whole number of tablets could be dispensed. Without this dose, the pharmacy would have to waste and properly dispose of one-fourth of a tablet per Drug Enforcement Agency regulations.

Special Considerations for Hospital-Based Low Dose Initiation

Low dose initiation can be a particularly useful tool for treating patients with OUD who are hospitalized. Starting MOUD in the hospital setting has been shown to help patients complete treatment of substance use-related complications and facilitate connection to outpatient addiction care while reducing likelihood of premature discharge and readmissions.[48] Initiation of buprenorphine through traditional induction is often limited by use of opioids in the setting of acute pain or intolerance to withdrawal during acute illness/injury.

Methods of low dose initiation in the hospital setting vary in length and formulation of buprenorphine used in the protocol. Before considering low dose initiation, consultation with the hospital pharmacy is required to determine if dose splitting of films/tablets is possible and, if not, which buprenorphine formulations are available on the hospital formulary. Availability can guide which dosing protocol is chosen (Fig. 3). It is also important to consult with hospital nursing staff as low dose initiation requires different monitoring than traditional induction. Standardized hospital protocol order sets may be helpful to reduce errors and ensure consistency. As most data describes the use of film/tablet splitting, if available, it is the method of choice in dosing strategies, similar to low dose initiation in the outpatient setting. Although use of a transdermal buprenorphine patch has been described, methods of its use are particularly variable in the

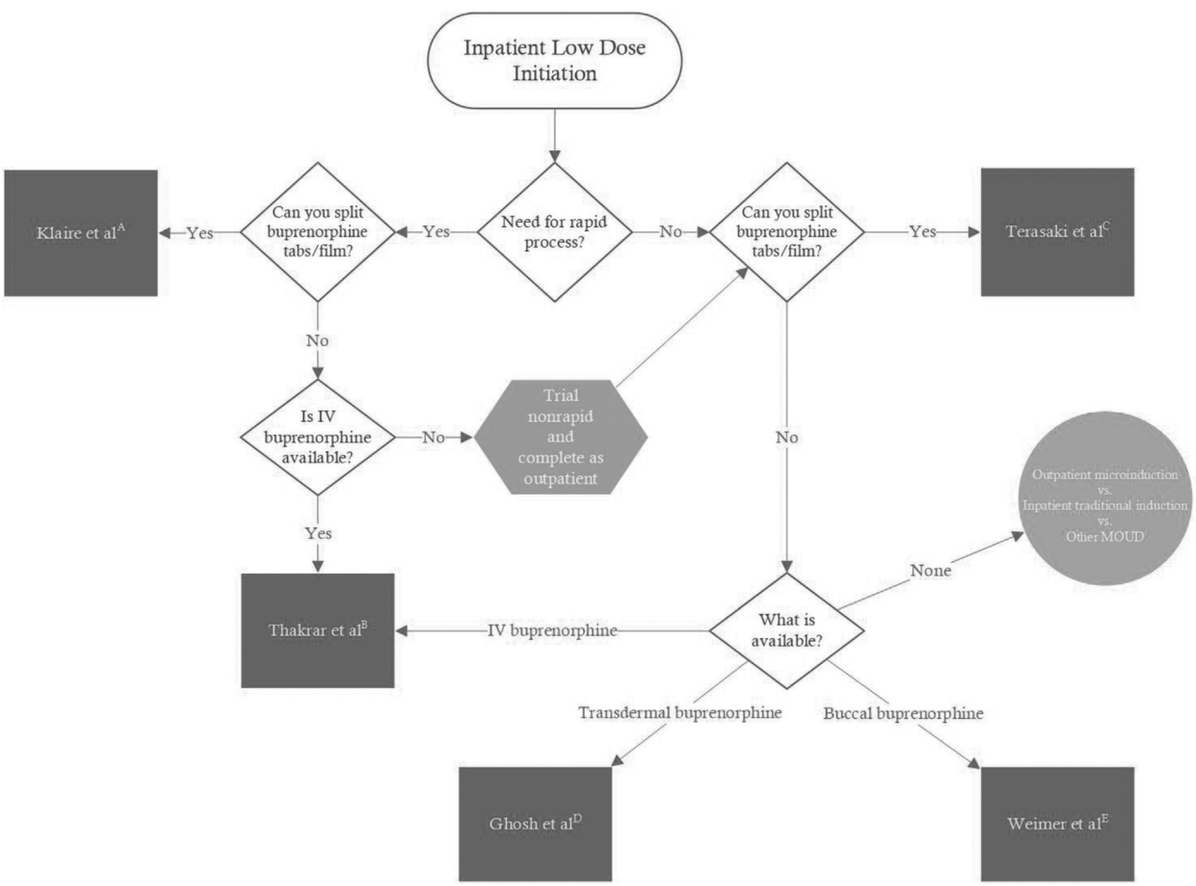


FIGURE 3. Flowchart of hospital-based low dose initiation protocols. A, Rapid method (Klaire et al[30,45]): Day 1 - 0.5 mg SL q3h, Day 2 – 1 mg SL q3h, Day 3 - 8–16 mg SL and additional PRN. B, Intravenous method (Thakrar et al[34]): Day 1 - 0.15 mg IV q6h, Day 2 - 0.3 mg q6h, Day 3 - 0.6 mg IV q6h, Day 4 - 4 mg SL q6h, Day 5 - discharge dose. C, Splitting method (Terasaki et al[33]): Day 1 - 0.5 mg SL daily, Day 2 - 0.5 mg SL q12h, Day 3 - 1 mg SL q12h, Day 4 - 2 mg SL q12h, Day 5 - 4 mg SL q12h, Day 6 - 8 mg SL qd, Day 7 - 8 mg SL QAM and 4 mg SL QPM, Day 8 - 12 mg SL daily. D, Patch method (Ghosh et al[43]): Variable doses and strategies. E, Buccal method (Weimer et al[26]): Day 1 - 225 mcg buccal daily, Day 2 - 225 mcg buccal q12h, Day 3 - 450 mcg buccal q12h, Day 4 - 2 mg SL q12, Day 5 - 4 mg SL q12, Day 6 - 4 mg SL q8, Day 7 - 8 mg SL q12h. IV indicates intravenous; SL, sublingual.

literature and it is very costly. Although the patch does not reach peak effect for 72 hours, some protocols report applying the patch for less than 72 hours making the equivalent sublingual dose hard to discern. Additionally, the patch has often been used in conjunction with film/tablet splitting that may complicate the process and raise questions about its utility.[16,18,40] Although few case reports exist for using intravenous[23,34] or buccal buprenorphine,[26] dosing strategies are based on existing sublingual film/tablet low dose initiation dosing protocols substituting the equivalent intravenous or buccal dose for a sublingual dose. Therefore, protocols using intravenous or buccal buprenorphine for low dose initiation in the hospital setting may be particularly useful if these formulations are available, as they reach peak effect rapidly.

In the setting of a time constraint or expected short admission, rapid protocols over 2–3 days with frequent small doses of buprenorphine have been used successfully.[17,30] They rely on frequent dosing (every 3 hours) and frequent monitoring to take advantage of peak plasma concentration that occurs in 1 hour.[49]

Future Work

Future research is needed to standardize the method of low dose initiation, compare its efficacy with traditional inductions, and ensure these studies are conducted in varied clinical settings and patient populations. An upcoming randomized controlled trial will compare a rapid protocol to traditional induction in the hospital setting.[45] It will be imperative to also conduct this research in the outpatient setting. A particular population in which low dose initiation has yet to be studied but could have significant impact is pregnant patients given the goals are to treat OUD in the patient and to minimize opioid withdrawal symptoms to reduce risk to the fetus. Although outcomes for pregnant patients and neonates are improved with either methadone or buprenorphine compared to ongoing parental use of opioids, data seems to support slightly improved outcomes with buprenorphine over methadone reinforcing the need to expand buprenorphine availability.[50]

Further efforts to simplify the process of low dose initiation in the outpatient setting are critical. Although it is possible to make blister packs of a low dose initiation protocol, as described above, at this time they require coordination with pharmacists. Future efforts may focus on partnership with the pharmaceutical industry to create a standardized starting pack, such as the one used for varenicline. If this becomes available, it will be important to advocate for broad insurance coverage to ensure equitable availability.

CONCLUSIONS

Low dose initiation of buprenorphine is an alternative method of buprenorphine initiation that minimizes risk of precipitated withdrawal and reduces or avoids opioid withdrawal symptoms. Low dose initiation has a clear role in expanding buprenorphine induction to populations in which it is difficult or impossible to use traditional induction approaches. As the opioid overdose crisis continues to worsen, novel approaches such as low dose initiation are vital to engage and retain patients in care. Based on the current literature, clear principles to guide its use have been identified to help aid clinicians treating OUD in hospital and outpatient settings.

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