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Review Article

Navigating Buprenorphine Therapy: A Closer Look at Microdosing vs. Macrodosing for Pain Management and Opioid Addiction – A Narrative Review

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Abstract

Background: Buprenorphine therapy has emerged as a primary therapy method for both opioid addiction and chronic pain; however, the «one size fits all» approach to buprenorphine administration is no longer tenable. This review analyzes the pharmacology of both dosing approaches and their clinical outcomes, safety profiles, and societal implications, providing valuable insights for healthcare professionals.

Methods: Multiple databases were used in conjunction with a set of inclusion and exclusion criteria to source articles to assess the consensus of best methods for treating opioid use disorder (OUD). This comprehensive review discusses two distinct dosing strategies, microdosing and macrodosing, through a detailed literature search to assess the differences and similarities of each strategy.

Findings: Microdosing entails administering minimal buprenorphine doses, with promise in pain alleviation and addiction management while mitigating the risks of dependence and side effects typically associated with traditional opioids. In contrast, macrodosing employs higher buprenorphine doses, which is well-established for OUD and chronic pain management but raises concerns concerning misuse and overdose.

Conclusion: Tailoring buprenorphine therapy to patients' individual needs is essential in the face of contemporary healthcare challenges related to pain management and opioid addiction.

Keywords: Buprenorphine therapy, Microdosing, Macrodosing, Opioid addiction, Pain management

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Introduction

Opiate use disorder (OUD) poses a persistent challenge in contemporary healthcare, necessitating a comprehensive understanding of its nature and effective treatment strategies.[1,2] This review aimed to provide a straightforward exploration of OUD and the pharmacotherapeutic intervention of buprenorphine, focusing on its mechanisms and clinical variations. OUD is more than a misuse of opiates; it is a complex medical condition characterized by a compelling urge to use opioids despite adverse consequences.[1] OUD spans prescription medications and illicit substances, reflecting a profound dependence that extends beyond the realm of conventional substance abuse.[2] The diagnostic criteria for OUD are outlined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), a standard reference used by physicians and mental health professionals for psychiatric diagnoses. To diagnose OUD, physicians seek to identify the presence of at least two or more of the following criteria over the past 12 months[1,2]:

- Taking larger amounts or using opiates over a longer period than intended[1,2]
- Persistent desire or unsuccessful efforts to cut down on or control opioid use[1,2]
- Significant time spent obtaining, using, or recovering from the effects of opiates[1,2]
- Cravings or a strong desire to use opiates[1,2]
- Recurrent opioid use failing to fulfill major role obligations at work, school, or home[1,2]
- Continued opioid use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opiates[1,2]

- Important social, occupational, or recreational activities are given up or reduced because of opioid use[1,2]
- Recurrent use of opioids in situations where it is physically hazardous[1,2]
- Continued use of opiates despite knowledge of having persistent or recurrent physical or psychological problems that are likely to have been caused or exacerbated by the substance[1,2]
- Tolerance, as defined by either a need for markedly increased amounts of opioids to achieve intoxication or desired effect or a markedly diminished effect with continued use of the same amount[1,2]
- Withdrawal, as manifested by the characteristic withdrawal syndrome for opiates or taking opiates (or a closely related substance) to relieve or avoid withdrawal symptoms[1,2]

The severity of OUD is determined by the number of criteria met: mild (2–3 criteria), moderate (4–5 criteria), or severe (6 or more criteria)[2]. The diagnostic process involves ruling out other potential causes for the symptoms and considering the patient's overall clinical presentation.[2]

As OUD occurs in individuals from all educational and socioeconomic backgrounds, it is found that over 16 million people worldwide and 3 million in the United States meet the criteria for OUD.[3] Consequently, there are over 120 000 OUD-related deaths worldwide, 47 000 of which occur in the United States.[3] Recreational use of opioids was highest in the United States in 2010 and has since gradually decreased before experiencing a slight rise in prevalence over the last decade[4]. The prevalence of OUD from 2010 to 2015 was between 2.36% and 3.13%, increasing to 4.16% by 2019, indicative of 13.6 million individuals in the US meeting the criteria for OUD.[4] In the United States, nearly 6% of the population aged 15–64 reported abusing opioids in 2015, compared to less than 1% for most other countries.[3] Data shows that healthcare providers treat roughly 1000 patients per day for opioid overdoses, and it is estimated that 115 US citizens die daily from opioid overdose, making opioids the cause of more deaths than any other drug in history.[3]

OUD management is multifaceted as it encompasses behavioral therapies, counseling, and pharmacotherapy, aiming not just for symptom control but also addressing the underlying factors contributing to addiction.[5,6] The goal of treatment is a comprehensive approach that facilitates sustained recovery.[5,6] One medication that can help assist in OUD is buprenorphine, as it is a key player in medication-assisted treatment for OUD and similar disorders.[5,6] It exhibits partial agonism at the mu-opioid receptors, inducing a graded response that reaches a plateau.[6,7] This ceiling effect limits the respiratory depression associated with full agonists, providing a safety advantage that many other medications lack.[6,7] The partial agonist activity contributes to reduced euphoria and sedation, minimizing the reinforcing effects that drive addictive behaviors as well as a reduction in the effects of opioid-induced hyperalgesia.[6] Suboxone and Subutex are two formulations of buprenorphine, where Suboxone combines buprenorphine with naloxone, deterring misuse by inducing withdrawal if injected.[8,9] Subutex, which contains only buprenorphine, is an option when concerns about naloxone use arise.[6-9]

Dosing strategies vary, reflecting the practical nuances of treatment, and both macrodosing and microdosing are methods to consider when treating individuals with these kinds of disorders.[8,10-12] Macrodosing involves standard daily doses for induction and maintenance, whereas microdosing explores lower, less frequent doses and strategies to manage side effects and improve patient compliance.[12] This comprehensive review seeks to navigate the intricacies of the two distinct dosing strategies for buprenorphine, microdosing, and macrodosing, and will examine the effects and appropriateness of each dosing strategy.

Methods

A narrative review approach was chosen for this paper as it was a more suitable method considering the studies found between 2018 and 2023. Some studies examined how buprenorphine was applied, whereas some described the different treatment strategies in certain healthcare settings. Case reports, however, were numerous compared to studies, many of which employed differing strategies from one case to the next, creating a need in the literature for a perspective-based analysis. A narrative review adds the perspectives learned from case reports to strengthen the value of this paper, considering the limited number of found studies.

The research team searched for relevant articles on PubMed and Google Scholar. A set of comprehensive and specific search terms and keywords, such as "macrodosing" and "microdosing" of buprenorphine, were used. The search also included the brand names "Subutex" and "Suboxone" to include a wider range of relevant studies. The final search terms were "buprenorphine," "Subutex," "Suboxone," "macrodosing," and "microdosing." Boolean operators (AND and OR) were used to combine the keywords appropriately for each database to identify relevant articles. Independent searches in this initial phase were carried out on PubMed and Google Scholar to identify all articles containing the specified keywords.

Inclusion criteria

Articles were included if they

- pertained to the topics of "macrodosing" and/or "microdosing" of buprenorphine
- were published in English
- were peer-reviewed and published in academic

journals, books, or conference proceedings
- were published between 2018 and 2023 to ensure the inclusion of recent research

Exclusion criteria

Articles were excluded if
- they were not written in any language other than English
- they were not focused on the topics of interest
- the full text was not accessible for free (i.e., they were paywall-blocked)
- they were not published prior to 2018

Articles between 2018 and 2023 summarized the current research on how buprenorphine can be utilized in different treatment settings. As buprenorphine is used in many healthcare settings, one approach does not apply to all settings. Therefore, only the most recent articles were included to identify these approaches.

Duplicates of articles in both databases were carefully omitted to prevent skew of search results. Data from the selected articles were extracted systematically, and details such as author(s), publication year, study design, key findings, and relevant data related to the research topic were recorded in a structured data extraction form, as seen in Table 1. The extracted data were organized and summarized to identify key themes and trends. This review was conducted following ethical guidelines, including proper citation and referencing of all sources and compliance with copyright and plagiarism policies. The initial search across PubMed and Google Scholar yielded 34 articles. After screening, 17 articles were removed because they did not meet the defined inclusion criteria, met one or more exclusion criteria, or because their relevance to "macrodosing" and "microdosing" of buprenorphine was limited. The final selection for the review comprised 17 articles, which served as the basis for the comprehensive analysis of buprenorphine dosing strategies, including their efficacy and safety in pain management and opioid addiction treatment. All included articles are listed in Table 1 with their main conclusions.

Discussion

After reviewing the 17 selected articles, the authors found that both macrodosing and microdosing can be useful in different scenarios. Macrodosing is primarily useful for quick agonist effects or up-titration in withdrawal symptoms from a full opioid agonist, achieving a full receptor occupancy with higher initial doses (16–32 mg).[12,14] This approach finds its primary application in emergency departments (EDs) where rapid stabilization is paramount due to overdose risk or limited follow-up options.[12,14] In contrast, microdosing begins with low buprenorphine doses (2–4 mg), gradually increasing them based on individual needs and withdrawal severity.[19] Patients receiving this approach will need access to regular follow-up care.[6]

The process of initiating buprenorphine microdosing does not have a standard protocol, and some of the articles vary in the initiation of the therapy.[8] However, various papers follow or are derived from the Bernese protocol or method.[8,10,11,19] The Bernese protocol involves repetitive, low-dose exposure to buprenorphine over several days, which can start with ongoing use of the full μ-agonist, decreasing the probability of withdrawal.[10,11,19] Once buprenorphine has reached a sufficient dose, the full opioid agonist is discontinued without tapering.[8,10] When patients experience withdrawal symptoms upon discontinuing complete opioid agonist treatment, especially when they are at lower doses of buprenorphine (12 mg), Marwah et al suggest providing them with as-needed doses of 2 mg and 0.5 mg buprenorphine-naloxone to help alleviate minor withdrawal symptoms.[8]

One article showed that microdosing resulted in complete abstinence of withdrawal symptoms while macrodosing did not.[27] Microdosing reduces the chance of precipitated withdrawal through its slow titration, empowers patients through personalized titration, and reduces the potential for misuse due to its lower doses.[19,25,26] This method is efficient even for patients who transition from macrodosing or OUD to buprenorphine/naloxone maintenance.[15,19,25] Microdosing is most effective for patients with mild to moderate OUD who have good medical stability and access to regular follow-up care.[6] The initiation of buprenorphine microdosing treatment in a patient with OUD is usually started and completed in a hospital setting. However, there have been patients who have done the transition in an outpatient setting.[30] However, more research is needed on the retention and abstinence rates to fully understand the utility of microdosing versus macrodosing in patients with chronic OUD.[22] Additionally, it was found that microdosing can be beneficial to patients with chronic pain who cannot tolerate opioid-free periods, with success rates similar to standard initiation treatment for pain.[13,28] Microdosing of at least 7 mg per day has proven to be as effective as methadone in treatment retention and decreasing opioid use.[24]

However, the gradual nature of the microdosing means slower symptom relief, necessitating frequent clinic visits and potentially posing challenges for those with limited resources or unstable environments.[25,26] In contrast, macrodosing excels in the treatment of individuals experiencing severe withdrawal, recent overdoses, or those at high risk of continued opioid use if treatment is delayed.[12] This macrodosing strategy offers fast symptom relief, potentially decreases re-hospitalization risk, and may improve treatment engagement by quickly addressing their immediate needs.[12] However, there are concerns regarding the increased risk of precipitated withdrawal, the potential for misuse, and the limited scope

Table 1. A summary of articles relevant to screening for "macrodosing" vs. "microdosing" for buprenorphine

Author	Title	Study design	Main conclusions
Raheemullah et al[13]	Buprenorphine microdosing cross tapers: A time for change	Review	Microdosing bypasses the precipitated withdrawal period[13]. It is valuable in situations where opioid-free periods cannot be tolerated, such as in chronic pain patients.[13]
Spadaro et al[14]	Buprenorphine precipitated opioid withdrawal: Prevention and management in the ED setting	Narrative review	Microdosing has been shown to prevent initial withdrawal, whereas macrodosing has been used as an alternative to gradual uptitration in the context of withdrawal from a full opioid agonist.[14]
Antoine et al[15]	Method for successfully inducting individuals who use illicit fentanyl onto buprenorphine/naloxone	Narrative review	Using microdoses of buprenorphine following full opioid agonist use helps patients transition from OUD to buprenorphine/naloxone maintenance.[15]
Rudolf[16]	Buprenorphine in the treatment of chronic pain	Narrative review	Micro-induction of buprenorphine may be introduced earlier in withdrawal but is better for hospitalized patients in whom titration can be conducted under close monitoring.[16]
Herring et al[17]	High-dose buprenorphine induction in the emergency department for treatment of opioid use disorder	Retrospective cross-sectional study	High-dose buprenorphine treatment was a safe and effective method of induction and did not increase rates of precipitated withdrawal, oversedation, or other adverse events attributable to buprenorphine.[17]
De Aquino et al[18]	The pharmacology of buprenorphine microinduction for opioid use disorder	Narrative review	Micro-induction is a novel approach that may allow circumventing the need for prolonged opioid tapers and reduce the risk of precipitated withdrawal.[18]
Robbins et al[19]	Buprenorphine microdose induction for the management of prescription opioid dependence	Protocol study	The authors transitioned eight patients on high-dose prescribed opioids for pain to sublingual buprenorphine-naloxone using a microdose protocol without any precipitated withdrawal.[19]
Adams et al[20]	Initiating buprenorphine to treat opioid use disorder without prerequisite withdrawal: A systematic review	Systematic review	Alternative buprenorphine initiation strategies can be used in patients who cannot tolerate traditional prerequisite withdrawal found with buprenorphine.[20] Buprenorphine microdosing and buprenorphine patch bridging were the most common strategies.[20] The impact of omitting prerequisite withdrawal on long-term outcomes is unknown.[20]
Greenwald et al[21]	A neuropharmacological model to explain buprenorphine induction challenges	Article review	Proposes a neuropharmacological working model of alternative buprenorphine induction strategies, such as quickly maximizing buprenorphine agonist effects (e.g., macrodosing) or, conversely, giving smaller initial doses and slowing the rate of buprenorphine dosing to avoid antagonist/withdrawal effects (e.g., microdosing).[21]
Shulman et al[22]	Buprenorphine treatment for opioid use disorder: An overview	Review article	With chronic opioid use disorder, buprenorphine, compared to placebo, improves retention in treatment at low, medium, and high doses.[22] Higher doses of buprenorphine increase retention and abstinence rates.[22]
Weimer et al[23]	Low- and very low-dose buprenorphine induction: New(ish) uses for an old(ish) medication?	Editorial	The case demonstrated a transition to buprenorphine over 7 days using a low-dose buprenorphine induction to avoid precipitated withdrawal and severe pain.[23]
Zoorob et al[24]	Buprenorphine therapy for opioid use disorder	Review article	Medication-assisted treatment with buprenorphine is as effective as methadone in terms of treatment retention and decreased opioid use when prescribed at fixed dosages of at least 7 mg per day. The dose of 16 mg per day is superior to placebo.[24]
Brar et al[25]	Use of a novel prescribing approach for the treatment of opioid use disorder: Buprenorphine/naloxone micro-dosing – A case series	Brief report	Seven participants completed a 7-day sublingual buprenorphine/naloxone micro-dosing protocol (Day 1, 0.5mg OD to Day 7, 12 mg OD)[25]. After day 7, buprenorphine/naloxone was subsequently titrated to a daily dose of between 12 and 32 mg.[25] All patients reported success with buprenorphine/naloxone induction with no precipitated withdrawal.[25]
Ahmed et al[26]	Microinduction of buprenorphine/naloxone: A review of the literature	Systematic review	From the available data, patients, primarily in the inpatient setting, were transitioned from opioids without significant withdrawal, and initial doses ranged most frequently from 0.2 to 0.5 mg.[26] Most transitioned over 4–8 days and most participants completed the cross-titration at 8–16 mg.[26]
Racha et al[27]	Pharmacotherapy of opioid use disorder: Update and current challenges	Review	The review demonstrates that "macrodosing" or initiating high-dose buprenorphine (>12 mg) in the emergency department was not associated with significant precipitated withdrawal symptoms.[27] While "microdosing" circumvents complete abstinence from full opioid agonists.[27]
Weimer et al[28]	ASAM clinical considerations: Buprenorphine treatment of opioid use disorder for individuals using high-potency synthetic opioids	Narrative review	Studies of ED patients reported precipitated opioid withdrawal in<1% after receiving initial buprenorphine doses of 8 mg or greater and reported no increased adverse events compared with standard initiation[28]. Since opioids may be legally prescribed to patients with OUD to treat pain, outpatient low-dose buprenorphine-opioid continuation (LDB-OC) use has been demonstrated in such chronic pain patients.[28] Reviews described similar success rates with standard initiation and LDB-OC, with most cases of LDB-OC occurring in the hospital.[28]
Button et al[29]	Low-dose buprenorphine initiation in hospitalized adults with opioid use disorder: A retrospective cohort analysis	Retrospective cohort study	The hospital-based addiction medicine consult service consulted 68 individuals who underwent 72 low-dose buprenorphine initiations between July 2019 and July 2020.[29] Of the 72 low-dose buprenorphine initiations, 50 (69.4%) were completed in the hospital, 9 (12.5%) were completed as outpatient treatment, and 13 (18.1%) were terminated early.[29]

for individual titration, which requires close monitoring and education of the patient.[31] Suppose full agonist opioids are still present in the patient's system. In that case, macrodosing can trigger an intense and potentially dangerous withdrawal reaction, and thus, careful assessment and potential use of comfort medications are

crucial.[12,32] Limited scope for individual titration refers to the time-sensitive nature of ED settings that may limit personalized dose adjustments, potentially adding additional challenges in proper dosing management.[31]

For individuals struggling with OUD, buprenorphine offers a lifeline, easing withdrawal symptoms and preventing relapse.[6] However, initiating treatment poses a delicate challenge: achieving rapid symptom relief while minimizing potential harm, particularly the dreaded precipitated withdrawal, or initiating a treatment that will take time to achieve a slow titration but will decrease side effects and withdrawal symptoms.[6] The withdrawal reaction is triggered when buprenorphine displaces full opioid agonists from receptor sites.[6,33]

The optimal approach hinges on a complex interplay of factors, with precipitated withdrawal being a major consideration. Withdrawal severity, clinical settings, patient risk factors, and individual preferences all contribute to making the right decision for each patient. For severe withdrawal, macrodosing's rapid symptom relief may outweigh the risk of precipitated withdrawal if carefully managed. However, in a clinical setting, microdosing takes priority in controlled settings, such as hospitals, allowing for close monitoring and adjustments to manage potential precipitated withdrawal, while macrodosing suits the time-sensitive nature of EDs. Patient risk factors are another critical component to consider, as macrodosing could be crucial for individuals at high risk of continued opioid use or overdose if treatment is delayed. However, the potential for precipitated withdrawal must be carefully evaluated. Lastly, individual preference should contribute to a clinician's decision as both approaches should respect patient comfort and treatment goals, considering their understanding and tolerance for potential precipitated withdrawal.

Safety considerations in emergency and non-emergency settings

The use of buprenorphine and Suboxone in the emergency room (ER) setting requires careful attention to timing and conditions to minimize the risk of adverse effects. A primary concern is precipitated withdrawal, which can occur if buprenorphine is administered too soon after opioid use.[6] To prevent this, healthcare providers should ensure patients have entered a moderate state of withdrawal before initiating treatment.[6] Starting with lower doses and gradually increasing them can also help reduce the risk of withdrawal.[6] Respiratory depression is another potential complication, although it is less common with buprenorphine than with full opioid agonists.[6,7] Patients with compromised respiratory function or those using other CNS depressants should be closely monitored.[6,7]

In non-ER settings, where buprenorphine and Suboxone are used for long-term management of OUD, additional safety considerations arise.[20] Regular monitoring for signs of misuse or diversion is essential, as is periodic assessment of liver function.[2,31] Cardiovascular risks, such as QT interval prolongation, should also be considered, especially in patients with a history of cardiac arrhythmias or those taking other QT-prolonging medications.[2,31] Mental health is another important factor, as buprenorphine can exacerbate anxiety or depression, particularly in patients with co-occurring mental health disorders.[2,10] A multidisciplinary approach involving mental health support can be beneficial.[2,10] Finally, patient education is crucial as patients should understand the importance of adhering to the prescribed dosing regimen, avoiding concurrent substance use, and attending regular follow-up appointments.[6,12,14] By carefully considering these factors, healthcare professionals can optimize the benefits of buprenorphine and Suboxone while minimizing the risks, ensuring safer and more effective treatment outcomes for patients with OUD.

Limitations

Due to limitations in identifying peer-reviewed published works on buprenorphine dosing that met the inclusion criteria, only 17 articles of the original 34 found could be used in this review. This may narrow the breadth of understanding on the topic, so this may not be the most comprehensive review of best practices on the subject. Though this may be the case, this paper does not seek to be a comprehensive overview of guidelines but rather to work in conjunction with current guidelines to identify key themes and trends in dosing strategies. The limited number of articles found further exemplifies the need for additional research on best practices for buprenorphine microdosing and macrodosing for acute management of OUD.

It is also important to emphasize the absence of a standard microdosing protocol, which may lead to discrepancies when analyzing the protocols implemented in the articles. Conversely, several reviewed articles used the term "chronic pain" without providing a clear definition. This makes it difficult to determine if the management of chronic pain was adequate or not.

The predominance of review articles included in this paper was intentional, as few high-quality original studies or primary research articles were found. Undeniably, including these types of articles, if widely available, would have strengthened this review; however, the available research in the initial search provides enough background and context for a review of this level. This further exemplifies the need for more research to understand better dosing approaches, clinical outcomes, safety profiles, and societal impacts in different settings.

Summary

- Microdosing: In managing brain abscesses,

Table 2. Summary table on microdosing vs. macrodosing

Aspect	Microdosing	Macrodosing
Definition	• Administering smaller, more frequent doses over time	• Administering a larger dose all at once
Pros	• Reduced risk of side effects • Allows for fine-tuning of dosage	• Faster therapeutic effect • Effective in acute management, e.g., managing intracranial pressure or infection
Cons	• It may require more frequent monitoring • Slower response time	• Higher risk of side effects • Potential for overdose or complications, especially in sensitive cases
Preferred clinical scenarios	• Chronic management of conditions requiring gradual intervention (e.g., prolonged antibiotic therapy post-drainage)	• Acute situations needing rapid intervention (e.g., initial control of intracranial pressure or infection in brain abscess)
Condition	• Chronic	• Acute
Patient sensitivity	• High sensitivity	• Low sensitivity
Required onset speed	• Gradual onset acceptable	• Rapid onset needed
Risk of Side Effects	• High risk	• Low risk

microdosing could be relevant for long-term antibiotic therapy, such as the 6–8 weeks of IV antibiotics.
- This approach reduces the risk of adverse effects over prolonged treatment.
- It is applicable in the conditions in treatment centers/hospitals

- Macrodosing:
- Macrodosing aligns with the acute management of intracranial hypertension using hypertonic saline or initial broad-spectrum antibiotic therapy (e.g., cefepime, flagyl, and vancomycin) to rapidly control infection before targeting the specific pathogen (e.g., *Streptococcus intermedius*).

- ERs, acute management

A summary of the different aspects of microdosing and macrodosing can be found below in Table 2.

Conclusion

Buprenorphine continues to emerge as a primary therapy method for both opioid addiction and chronic pain, where microdosing, specifically, has the potential to become the new standardized treatment for chronic pain and OUD. Microdosing has proven to be effective in chronic pain management with fewer side effects and withdrawal symptoms than with higher dosages and can be a bridge from full opioid use to buprenorphine/naloxone maintenance in OUD patients. Being able to tailor buprenorphine therapy to the individual patient's needs is essential to combat many of the healthcare challenges related to pain management and opioid addiction. By better understanding both dosing approaches, their clinical outcomes, safety profiles, and societal implications, healthcare professionals can make more informed decisions on which dosing strategy is best for each patient.

Authors' Contribution

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Competing Interests

The authors have no conflicts of interest to report.

Ethical Approval

This work has not been previously submitted to other publications or presented at any conference or meeting and does not require ethical approval.

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