Transitioning patients with opioid use disorder from methadone to buprenorphine

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Mr. M, age 46, has opioid use disorder (OUD). He is currently stabilized on methadone 80 mg/d but presents to your hospital with uncontrolled atrial fibrillation. After Mr. M is admitted, the care team looks to start amiodarone; however, they receive notice of a drug-drug interaction that may cause QTc prolongation. Mr. M agrees to switch to another medication to treat his OUD because he is tired of the regulated process required to receive methadone. The care team would like to taper him to a different OUD medication but would like Mr. M to avoid cravings, symptoms of withdrawal, and potential relapse.

The opioid epidemic has devastated the United States, causing approximately 130 deaths per day.[1] The economic burden of this epidemic on medical, social welfare, and correctional services is approximately $1 trillion annually.[2] Research supports opioid replacement therapy for treating OUD.[1] Multiple types of opioid replacement therapies are available in multiple dosage forms; all act on the mu-opioid receptor. These include full agonist treatment (eg, methadone) and partial agonist treatment (eg, buprenorphine).[3] Alternatively, opioid antagonist therapies (eg, naltrexone) have also been found to be effective for treating OUD.[1,2,4] This article focuses on partial agonist treatment for OUD, specifically using a buprenorphine microdosing strategy to transition a patient from methadone to buprenorphine.

Buprenorphine for OUD

Buprenorphine binds with high affinity to the mu-opioid receptor, resulting in partial agonism of the receptor.[1,2] Buprenorphine has a higher therapeutic index and lower intrinsic agonist activity than other opioids and a low incidence of adverse effects. Due to the partial agonism at the mu receptor, its analgesic effects plateau at higher doses and exhibit antagonist properties.[1,2] This distinct "ceiling" effect, combined with a lower risk of respiratory depression, makes buprenorphine significantly safer than

Practice Points

- **Buprenorphine microdosing induction protocols should be interpreted with caution** because most available research is case reports.
- Before initiating buprenorphine microdosing, **discuss the risks and benefits with the patient**.
- **Ensure buprenorphine microdosing is completed in an appropriate setting** based on patient preference and safety.
- For patients experiencing inadequate pain control, **consider additional nonopiate treatments for pain** while completing buprenorphine microdosing induction.

Buprenorphine microdosing techniques can help overcome the challenges of transitioning patients from methadone

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Disclosures

The contents of this article do not represent the views of the US Department of Veterans Affairs or the US Government. This material is the result of work supported with resources and the use of facilities at the Chillicothe Veterans Affairs Medical Center in Chillicothe, Ohio. The case presented in this article is fictional and does not represent a specific case or person(s). The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0305

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methadone.[4] Additionally, it has a lower potential for misuse when used with an abuse deterrent such as naloxone.

Common reasons for transitioning a patient from methadone to buprenorphine include intolerable adverse effects of methadone, variable duration of efficacy, drug-drug interactions, or limited access to an opioid treatment program. Traditional buprenorphine induction requires moderate withdrawal before initiating therapy. Due to buprenorphine's high affinity and partial agonism at the mu receptor, it competes with other opioids (eg, heroin, methadone) and will abruptly displace the receptor's full agonist with a lower affinity, resulting in precipitated withdrawal.[1,3,5] To avoid precipitated withdrawal, it is recommended to leave a sufficient amount of time between full opioid agonist treatment and buprenorphine treatment, a process called "opioid washout."[1,5] Depending on the duration, amount, and specific opioid used, the amount of time between ending opioid agonist treatment and initiating buprenorphine treatment may vary. As a result, many patients who attempt to transition from methadone to buprenorphine remain on methadone due to their inability to tolerate withdrawal. Additionally, given the risk of precipitating withdrawal, initiating buprenorphine may negatively impact pain control.[1]

Recently, buprenorphine "microdosing" inductions, which do not require patients to be in opioid withdrawal, have been used to overcome some of the challenges of transitioning patients from methadone to buprenorphine.[2]

Clinical Point

Buprenorphine 'microdosing' induction methods do not require patients to be in opioid withdrawal

Buprenorphine microdosing techniques

Multiple methods of microdosing buprenorphine have been used in both inpatient and outpatient settings.

Bernese method. In 1997, Mendelson et al[6] completed a trial with 5 patients maintained on methadone. They found that IV buprenorphine 0.2 mg every 24 hours did not produce a withdrawal effect and was comparable to placebo.[6] Haamig et al[5] hypothesized that repetitive administration of buprenorphine at minute doses in adequate dosing intervals would not cause withdrawal. Additionally, because of its high receptor binding affinity, buprenorphine will accumulate over time at the mu receptor. Thus, eventually the full mu agonist (eg, methadone) will be replaced by buprenorphine at the mu receptor as the receptor becomes saturated.[4,5]

The goal is to taper the opioid agonist therapy while titrating buprenorphine. This taper method is not described in current treatment guidelines, and as a result, there are differences in doses used in each taper because the amount of opioid agonist and type of opioid agonist therapy can vary. In most cases, buprenorphine is initiated at 0.25 mg/d to 0.5 mg/d and increased by 0.25 mg/d to 1 mg/d as tolerated.[4,5] The dose of the full opioid agonist is slowly decreased as the buprenorphine dose increases. The Bernese method does not require frequent dosing, so it is a favorable option for outpatient therapy.[4] One limitation to this method is that it is necessary to divide tablets into small doses.[4] Additionally, adherence issues may disrupt the tapering method; therefore, some patients may not be appropriate candidates.[4]

Transdermal patch method. This method aims to provide a consistent amount of buprenorphine—similar to dividing tablets into smaller doses as seen in the Bernese method—but with the goal of avoiding inconsistencies in dosing. Hess et al[7] examined 22 patients with OUD who were maintained on methadone 60 mg/d to 100 mg/d. In the buprenorphine transdermal patch method, a 35 mcg/h buprenorphine patch was applied 12 hours after the patient's final methadone dose.[1,7] This was intended to provide continuous delivery over 96 hours.[1] Additionally, small, incremental doses of sublingual buprenorphine (SL-BUP) were administered throughout the course of 5 days.[1] A potential strength of this method is that like the Bernese method, it may be completed in outpatient therapy.[4] Potential limitations include time to initiation, off-label use, and related costs.

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- Van Hale C, Gluck R, Tang Y. Laboratory monitoring for patients on buprenorphine: 10 questions. Current Psychiatry. 2022;21(9):12-15,20-21,26.
- Moreno JL, Johnson JL, Peckham AM. Sublingual buprenorphine plus buprenorphine XR for opioid use disorder. Current Psychiatry. 2022;21(6):39-42,49.

Drug Brand Names

Amiodarone • Cordarone
Buprenorphine • Subutex, Sublocade
Buprenorphine/naloxone • Suboxone, Zubsolv
Methadone • Dolophine, Methadose
Naltrexone • ReVia, Vivitrol

Clinical Point

Unlike the rapid method, the Bernese and transdermal patch methods can be completed in outpatient settings

Rapid microdosing induction method. Contrary to typical microdosing, rapid microdosing induction requires buprenorphine to be administered every 3 to 4 hours.[4] As with most buprenorphine microinduction protocols, this does not require a period of withdrawal prior to initiation and may be performed because of the 1-hour time to peak effect of buprenorphine.[4] Due to the frequent dosing schedule, it is recommended to use this method in an inpatient setting.[4] With rapid microdosing, an individual may receive SL-BUP 0.5 mg every 3 hours on Day 1, then 1 mg SL-BUP every 3 hours on Day 2. On Day 3, the individual may receive 12 mg SL-BUP with 2 mg as needed. A limitation of this method is that it must be performed in an inpatient setting.[4]

CASE CONTINUED

To ensure patient-inclusive care, clinicians should conduct a risk-benefit discussion with the patient regarding microdosing buprenorphine. Because Mr. M would like to be managed as an outpatient, rapid microdosing is not an option. Mr. M works with his care team to design a microdosing approach with the Bernese method. They initiate buprenorphine 0.5 mg/d and increase the dose by 0.5 mg to 1 mg from Day 2 to Day 8. The variance in buprenorphine titration occurs due to Mr. M's tolerance and symptoms of withdrawal. The team decreases the methadone dose by 5 mg to 10 mg each day, depending on symptoms of withdrawal, and discontinues therapy on Day 8. Throughout the microdosing induction, Mr. M does not experience withdrawal symptoms and is now managed on buprenorphine 12 mg/d.

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