

# Buprenorphine-naloxone microdosing

## Tool for opioid agonist therapy induction

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### Abstract

**Objective** To raise awareness of alternative techniques that can facilitate buprenorphine-naloxone treatment for opioid use disorder.

**Sources of information** PubMed was searched for articles using the terms *buprenorphine*, *buprenorphine/naloxone*, *micro-dosing*, *opioid agonist therapy*, and *induction*. Other relevant guidelines, presentations, and resources were consulted.

**Main message** Buprenorphine-naloxone is the first-line option for opioid agonist therapy owing to its superior safety profile compared with methadone. The uptake of this potentially life-saving drug has been limited by unfamiliarity and prescribing restrictions, but perhaps the biggest barrier is the prerequisite that patients be in moderate to severe withdrawal before initiation. An induction option that does not require withdrawal or immediate cessation of current opioid use, termed *microdosing*, is an appealing choice for patients and a practical approach that can be used by a broader array of practitioners, ultimately increasing access to buprenorphine-naloxone. Family physicians play an important role in the current opioid crisis by helping patients transition to opioid agonist therapy.

**Conclusion** Microdosing is a safe and easy-to-implement regimen that can be used in a variety of practice settings with the help of community pharmacists. This article provides an overview of microdosing and serves as a guide to starting and maintaining treatment.

Opioid use disorder (OUD) is a complex disease and its treatment is evolving in an effort to reach more patients. The first-line approach to OUD is opioid agonist therapy, which provides patients with safe and reliable access to certain long-acting opioids—namely methadone or buprenorphine-naloxone—to prevent withdrawal symptoms and cravings, minimize overdose risk, and provide regular contact with care providers.<sup>1,2</sup> Buprenorphine-naloxone has more recently been recommended over methadone owing to its improved safety profile, fewer prescribing and administration restrictions, and ease of at-home dosing.<sup>1,2</sup> A drawback to traditional initiation of buprenorphine-naloxone is that before induction patients must have abstained from opioids for a minimum of 12 to 36 hours to prevent precipitated withdrawal, which occurs owing to displacement of full opioid agonists from the  $\mu$ -receptor. This abstinence presents a considerable barrier to treatment initiation.<sup>1,3</sup> A novel off-label approach known as *microdosing* or the *Bernese method*<sup>3</sup> might serve as a valuable tool to ease buprenorphine-naloxone induction for both patients and prescribers by circumventing the withdrawal impediment.

### Case description

Ms Z. is a 66-year-old woman with chronic pain as a result of spinal stenosis, back injury, and osteoarthritis of the shoulder. She also has anxiety

### Editor's key points

- ▶ Buprenorphine-naloxone microdosing is a potentially valuable tool to help patients transition from problematic opioid use to opioid agonist therapy. The benefits to this approach include avoiding withdrawal before initiation, making buprenorphine-naloxone induction less daunting, and practicality for everyday practice settings.
- ▶ One of the benefits of microdosing is the potential to mitigate the moderate to severe withdrawal that is required for standard buprenorphine-naloxone induction. Some patients experience mild withdrawal once they cease their opioid. There are many available easy-to-use tools to aid prescribers in quantifying the extent of their patients' withdrawal and therefore assist in providing appropriate management.
- ▶ This approach is not yet supported by guidelines and no standard protocol exists, as the evidence consists mainly of case reports. This technique is driven by patient response and therefore requires frequent contact with the prescriber and other care team members.

and a history of nonadherence that includes altering dosage forms and stockpiling medications. She has no history of illicit substance use. For pain, she is currently using 150- $\mu$ g fentanyl patches applied every 48 hours, 10 mg of oral immediate-release morphine as needed taken up to 5 times daily, 1200 mg of oral gabapentin 3 times daily, 200 mg of oral naproxen twice daily, and as-needed oral acetaminophen and topical diclofenac gel, which are currently dispensed on a monthly basis. Pain Disability Index and Brief Pain Inventory average scores are obtained and the results are 6.3 and 8, respectively, both out of a possible 10. Owing to adverse effects as well as drug interactions increasing her risk of opioid overdose, Ms Z. is interested in decreasing her opioid use, and over 3 months she is able to taper her opioid doses to a 25- $\mu$ g fentanyl patch every 72 hours and to stop morphine; however, she feels she can no longer taper any further and her pain is still unmanaged. Owing to her tendency to use as-needed opioids more often than prescribed, a *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, screen for OUD is conducted, which reveals a score of 5 (moderate). Her history of nonadherence and potential QTc interval interactions with her psychiatric medications mean methadone might not be a reasonable option. Ms Z. balks at undergoing the withdrawal required before standard buprenorphine-naloxone initiation owing to a previous history of severe withdrawal symptoms. How would you manage Ms Z.'s opioid use?

### Main message

Patients with OUD have diverse backgrounds and histories that lead to their disease. Patients might present with OUD secondary to use of legally prescribed opioids, while others might use illicitly sourced "street drugs" to prevent withdrawal, provide euphoric effects, and numb physical and emotional pain. Regardless of history, control of their addiction and management of comorbid pain conditions are reasonable and achievable goals of therapy. Patients and their care teams need to establish a trusting relationship where frequent and open communication is key to monitoring for withdrawal and preventing relapse.

Buprenorphine-naloxone has an increased safety profile relative to methadone, and initiation can start in the clinic, at home as an outpatient, or as an inpatient. Furthermore, using the aforementioned microdosing technique as an initiation tool negates the need for patients to be in withdrawal and fully abstinent from their opioid. This potentially alleviates patient apprehension for those who were previously unable to achieve buprenorphine-naloxone induction and are fearful of trying again, or those who are anxious about withdrawal.<sup>3</sup> It is potentially associated with fewer and less severe withdrawal symptoms, and might be easier to implement than the standard induction procedure.<sup>3</sup>

It is important to note that the microdosing technique is not currently recommended or supported by any major clinical guidelines. The evidence for this practice mainly exists as case reports, born out of a need for treatment to reach more patients with OUD and simplify the induction process for both patients and practitioners. Therefore, it is critical that informed patient consent be obtained before initiation.<sup>4</sup>

**Pharmacology.** It is hypothesized that microdosing does not precipitate withdrawal, as small repetitive doses allow for gradual accumulation and occupation of buprenorphine at opioid receptors owing to the drug's high  $\mu$ -receptor affinity and slow dissociation. This receptor occupation slowly displaces other opioids, and once doses of approximately 4 mg and 1 mg<sup>4,5</sup> of buprenorphine-naloxone are reached, the receptors should be sufficiently occupied by buprenorphine to allow for rapid discontinuation of short-acting opioids without severe withdrawal.<sup>5</sup> Higher doses of buprenorphine might be required for longer-acting opioids (**Table 1**).<sup>4-8</sup>

The role of naloxone in buprenorphine-naloxone is to discourage injection or snorting of the drug, as the naloxone would become an active compound and precipitate withdrawal.<sup>9</sup> When taken orally or sublingually, naloxone has minimal absorption and does not antagonize buprenorphine or other opioids in the central nervous system.<sup>9</sup>

**Starting treatment.** There is no standard microdosing initiation protocol that exists at the time of this publication. **Table 1** demonstrates potential approaches to microdosing initiation.<sup>4-8</sup> Once-daily dosing (option 1) offers the benefit of convenience and can eliminate the need for carries (ie, take-home doses) in situations where prescribers feel uncomfortable providing them to patients; however, owing to a shorter half-life at lower doses of buprenorphine, twice-daily dosing (options 2 and 3) might alleviate the risk of a "wearing-off" effect and potential risk of subsequent precipitated withdrawal. Patients who are using short-acting opioids, such as morphine, oxycodone, hydromorphone, or heroin, might attempt to cease their opioid once a dose of 4 mg and 1 mg to 12 mg and 4 mg is achieved. For those using longer-acting formulations, such as fentanyl patches or methadone, it is advisable to discontinue or quickly taper down the long-acting medication when the buprenorphine dose is higher and occupying more receptors. Patients are more likely to experience withdrawal symptoms when their full opioid agonist is discontinued at lower doses of buprenorphine-naloxone (ie, less than 12 mg and 4 mg).<sup>4</sup> It might be advisable to provide patients with as-needed doses in the form of 2 mg and 0.5 mg buprenorphine-naloxone to combat minor withdrawal symptoms, should they occur, once the opioid has been stopped (**Table 1**).<sup>4-8</sup> Other medications,

**Table 1. Select microdosing strategies from the literature**

DAY	BUPRENORPHINE-NALOXONE DOSAGES			ADJUNCTIVE THERAPIES FOR MANAGING WITHDRAWAL SYMPTOMS
	OPTION 1	OPTION 2	OPTION 3	
1	0.5 mg and 0.125 mg SL daily	0.5 mg and 0.125 mg SL once daily	0.25 mg and 0.0625 mg SL once daily	<ul style="list-style-type: none"> <li>• 0.1 mg of clonidine twice daily as needed for agitation</li> <li>• 400-600 mg of ibuprofen 4 times daily as needed and 650-1000 mg acetaminophen every 6 h as needed for myalgia</li> <li>• 50 mg of dimenhydrinate every 6 h as needed for nausea or vomiting</li> <li>• 2 mg of loperamide after loose bowel movement as needed for diarrhea</li> <li>• Can consider providing 2 doses of 2 mg and 0.5 mg of SL buprenorphine-naloxone every h as needed for withdrawal</li> </ul>
2	0.5 mg and 0.125 mg SL daily	0.5 mg and 0.125 mg SL twice daily	0.25 mg and 0.0625 mg SL twice daily	
3	1 mg and 0.25 mg SL daily	1 mg and 0.25 mg SL twice daily	0.5 mg and 0.125 mg SL twice daily	
4	1.5 mg and 0.375 mg SL daily	2 mg and 0.5 mg SL twice daily (can stop short-acting or begin tapering long-acting opioids)	1 mg and 0.25 mg SL twice daily	
5	2 mg and 0.5 mg SL daily	3 mg and 0.75 mg SL twice daily	2 mg and 0.5 mg SL twice daily (can stop short-acting or begin tapering long-acting opioids)	
6	3 mg and 0.75 mg SL daily	4 mg and 1 mg SL twice daily	4 mg and 1 mg SL twice daily	
7	4 mg and 1 mg SL daily (can stop short-acting or begin tapering long-acting opioids)	12 mg and 4 mg SL once daily (stop all opioids)	12 mg and 4 mg SL once daily (stop all opioids)	
8	5 mg and 1.25 mg SL daily	Adjust further dosing based on patient symptoms	Adjust further dosing based on patient symptoms	
9	6 mg and 1.5 mg SL daily			
10	7 mg and 1.75 mg SL daily			
11	8 mg and 2 mg SL daily			
12	10 mg and 3 mg SL daily			
13	12 mg and 4 mg SL daily (stop all opioids)			
14	Adjust further dosing based on patient symptoms			

SL—sublingual.  
Data from Patel et al,<sup>4</sup> Lee,<sup>5</sup> Crawley et al,<sup>6</sup> Sandhu et al,<sup>7</sup> and Cho and Lu.<sup>8</sup>

such as clonidine, dimenhydrinate, ibuprofen, acetaminophen, and loperamide, might be prescribed along with buprenorphine-naloxone to manage withdrawal symptoms, should they occur.<sup>6</sup> Starting with lower doses (option 3) might be possible in a patient who has had exceptionally bad withdrawal experiences in the past, is at a higher risk of precipitated withdrawal, or is being rotated from methadone to buprenorphine-naloxone. Given the (albeit low) risk of precipitated withdrawal, it might be prudent for someone (eg, prescriber, clinic nurse, pharmacist) to witness patients taking doses to identify and treat distressing symptoms quickly.

Pharmacists can aid patients in this process by ensuring the accuracy of titration and minimizing confusion by witnessing patients taking doses. If choosing option 2 or 3, one dose might be witnessed and the other given as a carry. Doses might also be prepared and packaged in a blister pack for patients for whom daily witnessing might not be viable. Currently, the lowest available dose in Canada of buprenorphine-naloxone is 2 mg and 0.5 mg. To achieve the doses required for microdosing

regimens, tablets must be split. This results in potentially inconsistent dosing in the beginning, but it is important to remember that these doses serve to gradually build the receptor blockade, and as long as the doses are similar (eg, quartered vs halved tablets), microdosing is still effective. If a patient misses a dose during induction, the patient can repeat the previous day's dose and then proceed with the induction. If 2 or more doses are missed, consider restarting the initiation process.<sup>4</sup>

**Identifying withdrawal.** One of the benefits of microdosing is the potential to mitigate the moderate to severe withdrawal that is required for standard buprenorphine-naloxone induction. It is expected that some patients might experience mild withdrawal once they cease their opioid. There are many available easy-to-use tools to aid prescribers in quantifying the extent of their patients' withdrawal and therefore assist in providing appropriate management. The Clinical Opiate Withdrawal Scale is a validated 11-point scale based on objective information such as heart rate, myalgia, rhinorrhea, gastrointestinal

upset, and other symptoms,<sup>10</sup> and the Subjective Opiate Withdrawal Scale can be readily completed by patients themselves to categorize their withdrawal symptoms. Both scales are available at **CFPlus**.\*

**Maintaining treatment.** A maintenance dose of buprenorphine-naloxone is one that adequately manages withdrawal symptoms and cravings without causing bothersome adverse effects (nausea, constipation, sedation, abdominal cramps).<sup>11</sup> Many patients might be stable at 12 mg and 3 mg daily; however, others will still experience withdrawal symptoms and frequently take 2-mg and 0.5-mg as-needed doses. These patients might benefit from titrating the dose up to a maximum of 24 mg and 6 mg daily.<sup>12</sup> To aid patients in finding the optimal maintenance dose, frequent follow-up, either in person or over the telephone, might be necessary. Community pharmacists can also play a vital role in communication with patients to evaluate their response to therapy and potential withdrawal symptoms.

### Case resolution

You initiate sublingual buprenorphine-naloxone once daily at a dose of 0.5 mg and 0.125 mg for 2 days (**Table 2**) owing to lack of comfort with providing carries, then increase the dose by 0.5 mg and 0.125 mg daily thereafter, as outlined in option 1 (**Table 1**).<sup>4-8</sup> After 7 days, Ms Z. experiences withdrawal symptoms, so induction is sped up and the dose is increased by 2 mg and 0.5 mg each subsequent day until a dosage of 12 mg and 3 mg is reached, with a 2-mg and 0.5-mg as-needed dose also provided. After approximately 2 more weeks, Ms Z.'s withdrawal symptoms stabilize at 20 mg and 5 mg daily; however, she feels the dose "wears off," prompting a final increase to 24 mg and 6 mg. Three weeks later, you see Ms Z. and she reports her mood and functioning have improved, allowing her to spend more time outdoors, contribute to yard work, and see her friends.

### Conclusion

Buprenorphine-naloxone microdosing is a potentially valuable tool to help patients transition from problematic opioid use to opioid agonist therapy. The benefits to this approach include avoiding withdrawal before initiation, making buprenorphine-naloxone induction less daunting, and practicality for everyday practice settings. This approach is not yet supported by guidelines and no standard protocol exists, as the evidence consists mainly of case reports. This technique is driven by patient response and therefore requires frequent contact with the prescriber and other care team members. 🌿

\*The **Clinical Opiate Withdrawal Scale** and the **Subjective Opiate Withdrawal Scale** are available at [www.cfp.ca](http://www.cfp.ca). Go to the full text of the article online and click on the **CFPlus** tab.

**Table 2. Microdosing regimen used with Ms Z.**

DAY	ADMINISTERED REGIMEN OF BUPRENORPHINE-NALOXONE
1	0.5 mg and 0.125 mg SL once daily
2	0.5 mg and 0.125 mg SL once daily
3	1 mg and 0.25 mg SL once daily
4	1.5 mg and 0.375 mg SL once daily
5	2 mg and 0.5 mg SL once daily
6	2 mg and 0.5 mg SL once daily
7	3 mg and 0.75 mg SL once daily plus 2 mg and 0.5 mg SL as needed twice daily Discontinue fentanyl patch
8	8 mg and 2 mg SL once daily plus 2 mg and 0.5 mg SL as needed twice daily
9	12 mg and 3 mg SL once daily*

SL—sublingual.

\*Over the next 2 weeks, Ms Z.'s dosage was titrated to a total of 24 mg and 6 mg, based on her symptoms.

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All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

#### Competing interests

None declared

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