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The College of Physicians & Surgeons of Manitoba
Buprenorphine/naloxone Recommended Practice Manual

Recommendations for buprenorphine/naloxone induction using the micro-dosing method.

Introduction:

Conventional buprenorphine/naloxone induction recommendations require a patient to be in moderate opioid withdrawal before initiating buprenorphine/naloxone. This can take 8 – 24 hours for short-acting and slow-release opioids and 48 – 72 hours for long-acting opioids such as methadone. The opioid withdrawal symptoms experienced during this wait time may be intolerable or impractical for some patients due to a variety of reasons.

Furthermore, the logistics involved with planning a conventional buprenorphine/naloxone induction may be challenging for both patients and providers. Presenting for induction in moderate withdrawal requires careful planning and some flexibility in the patient and prescriber's availability for assessment and dose titration. This may lead to lower overall utilization of buprenorphine/naloxone even though it has a superior safety profile.

Micro-dosing of buprenorphine/naloxone (also commonly referred to as the "Bernese method") involves a buprenorphine/naloxone induction overlapping with the continued use of a full opioid agonist by the patient and does not require a patient to reach moderate withdrawal. It is based on the hypothesis that small, repetitive dosing of buprenorphine with adequate dosing intervals should not precipitate withdrawal. Due to its high receptor affinity and long binding time, buprenorphine will gradually replace the full opioid agonist at the mu receptor as it slowly accumulates at the receptor sites.

It is important to note that micro-dosing is **not** being proposed as an equally evidence-based alternative to the conventional induction method described in the "Induction with buprenorphine/naloxone" section of this manual. In fact, the evidence supporting this approach is lacking and consists mainly of case descriptions. However, there is a substantial amount of practical experience with this method in Canada and it has gained acceptance as a viable alternative when the conventional induction method is not practical or possible.

General Recommendations:

It is the responsibility of the prescriber to educate a patient being considered for a micro-dosing induction regarding the risks of this approach, including but not limited to precipitated withdrawal. The prescriber must ensure that the patient can adequately understand these risks and that they know where to seek help if concerns arise. This includes an afterhours contact phone/pager number.

Patients for whom you may consider a micro-dosing induction onto buprenorphine/ naloxone:

- Patients who fear withdrawal or experience severe withdrawal symptoms during conventional induction (moderate withdrawal is required to begin a conventional induction).
- Patients who have failed a conventional induction due to inability to tolerate moderate withdrawal.
- Patients with significant social instability that makes attending a scheduled clinic appointment for induction challenging (examples may include no access to reliable transport or a lack of financial resources for transport, chaotic lifestyle, lack of social supports etc.)

Patients who may be particularly good candidates for micro-dosing include:

- Patients who are being switched from methadone, or other high dose long-acting opioids, to buprenorphine/naloxone. Due to the complexity and case-by-case variability of these medication switches, specialist guidance must be sought to ensure appropriate customization of the micro-dosing schedule, including appropriate cross-titration of methadone, or other high dose long-acting opioids being discontinued.
- Patients who are using illicit fentanyl and/or fentanyl analogues (due to the uncertain risk of precipitated withdrawal).
- Patients who may be unable to tolerate moderate withdrawal due to a medical or mental health condition.
- Pregnant women who are not currently in withdrawal and for whom methadone is contraindicated, who refuse treatment with methadone, or who do not have access to methadone treatment in their home community. An inpatient admission for induction may also be reasonable under these circumstances.
- Individuals who present to the emergency department or other episodic care facilities with serious complications of opioid use disorder such as overdose, infectious complications or a mental health crisis. These patients may not be in enough withdrawal to facilitate a buprenorphine/naloxone induction in the emergency department and may not be appropriate for a traditional home induction. Discharging

these individuals with a limited medication supply and micro-dosing instructions may be an effective way to engage this high-risk population in care, if infrastructure for follow-up care exists. Patients being offered a micro-dosing induction in the emergency department must be provided with written information on where they can reasonably access follow-up care as part of the induction plan.

Witnessed dosing requirements and reassessment:

- In most cases, buprenorphine/naloxone doses should be witnessed at the pharmacy starting no later than day 4, with evening doses being provided to take home.
- Under exceptional circumstances (e.g. geographic isolation from pharmacy, with phone support and reassessment from prescriber or experienced clinic staff) patients may be given more than a three-day supply of medication for a micro-dosing induction. The rationale for this approach must be clearly documented and communicated to the pharmacy.
- The patient should be reassessed by the prescriber or experienced clinic staff, in person, no later than day 7 after initiating a buprenorphine/naloxone micro-dosing protocol. If this is not possible for any reason, a phone assessment should be completed with in-person follow-up as soon as possible after that.
- All interactions with clinic staff (by phone or in person) during the micro-dosing induction should be documented in the patient's medical record.

Pharmacy Communication:

- Clear communication with the pharmacy is essential to facilitate a smooth micro-dosing induction process. Even if a patient is provided with a medication starter pack from clinic or hospital stock, the community pharmacy that the patient attends for continued treatment must be contacted and made aware of the plan since the patient may seek support from the pharmacy at any time during the micro-dosing induction process.
- If possible, the induction doses should be dispensed by the pharmacy and not given as a starter pack from clinic or hospital stock to ensure that the medication is entered into DPIN.
- If the patient is given a medication starter pack from clinic or hospital stock, the community pharmacy that receives the follow-up M3P prescription must also be provided with the following information (see appendix E for suggested template):
    - A copy of the micro-dosing induction protocol/schedule provided to the patient
    - The micro-dosing induction start date

    - Advice to be given to the patient if one or more doses are missed. This is at the prescriber's discretion – no clear evidence exists to guide approach.
    - When the patient is expected to attend the pharmacy for witnessed dosing
    - Clinic information
    - After-hours prescriber contact information
- Due to the small starting doses, tablets need to be split. Pharmacists should dispense or administer split buprenorphine/naloxone tablets to the same patient in consecutive doses since splitting tablets can result in uneven doses and may hasten the degradation of the tablet.
- As micro-dosing inductions are still under development and not entirely evidence-based, prescribers must ask pharmacists to share treatment outcomes for data collection and quality improvement purposes.

Supporting Documents:

- An example of a micro-dosing induction protocol for patients with moderate to high-dose opioid use is included as Appendix F. For patients with low-dose opioid use or other risk factors for over-sedation or toxicity, lower overall induction doses will need to be used (see the section on dosing during the induction phase). This induction protocol, or a similar customized protocol, should be provided to the patient and the pharmacy.
- The patient must also be provided with a micro-dosing induction wallet card. This is especially important when a patient is given a micro-dosing induction medication starter pack from the hospital or clinic stock if it has not been entered into the DPIN system. The wallet card thus serves as a notification to EMS/ER staff that the patient was prescribed a micro-dosing induction protocol. See Appendix G for a template of what such a wallet card may look like.

Appendix E

Name of Clinic and Address (IF NOT ON CLINIC LETTERHEAD) Date

Pharmacy Name
Address

RE: MICRO-DOSING INDUCTION NOTIFICATION

Dear Pharmacist,

This letter is regarding patient _____NAME_____ DOB: _____

I have assessed _____PATIENT NAME_____ and they are a candidate for a buprenorphine/ naloxone micro-dosing induction.

I have provided instructions to the patient regarding their micro-dosing induction. A copy of the induction protocol is included.

Note the following:

☐ Patient has been provided with a starter pack of buprenorphine/naloxone from clinic stock to start micro-dosing and will present to pharmacy on _____(DATE)_____ to commence witnessed dosing. An M3P prescription is included.

OR

☐ An M3P prescription is included and the patient will present to pharmacy on _____(DATE)____ to obtain the micro-dosing induction medication supply. Please supply the first 3 days of medication in blister packaging with tablets already split as required by the dosing regimen. Unless otherwise indicated, these first three days do not require witnessed dosing.

The Patient will present to pharmacy again on _____ (DATE)_____ to commence witnessed dosing.

Please notify my clinic at _____ (phone number) of any missed doses, in case the induction schedule needs to be adjusted. I have advised my patient as follows regarding missed doses at home:

_____

After hours I can be reached at _____Phone Number_____ or call _____Phone Number_____ to speak to our on-call prescriber.

Sincerely

Prescriber Name

Buprenorphine/naloxone (Suboxone®) microdosing

Microdosing buprenorphine/naloxone is one way to start opioid agonist treatment (OAT) when you aren't able to stop your opioid use.

Your pharmacy will provide you with three days of medication to take at home in gradually increasing doses, reducing the risk of experiencing sudden severe withdrawal symptoms ("precipitated withdrawal"). On Day 4, you'll start attending your pharmacy daily to continue the microdosing process. During this time, you are able to continue using opioids, but will gradually decrease the amount of opioids you use.

Prescriber Name: _____

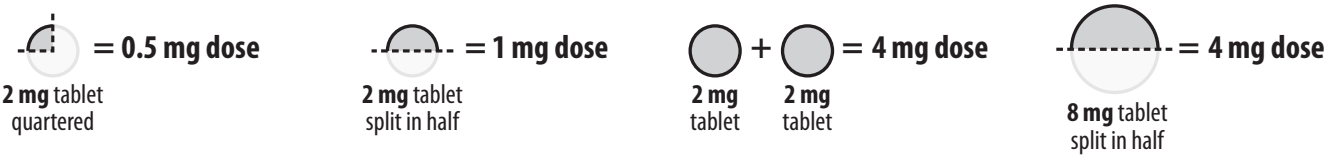
Prescriber Phone: _____

Next Appointment: _____

Pharmacy Name: _____

Pharmacy Phone: _____

	BUPRENORPHINE/NALOXONE	OTHER OPIOIDS
Day 1	0.5 mg, twice per day	
Day 2	1 mg, twice per day	Start gradually reducing your opioid use
Day 3	2 mg, twice per day	
Day 4	3 mg, twice per day	
Day 5	4 mg, twice per day	
Day 6	4 mg, three times per day	Last day of other opioids
Day 7	12 mg, once per day	No other opioids
Day 8 and onwards	Your doctor may continue to adjust your medication to relieve withdrawal symptoms until a stable dose is achieved.	



This induction protocol is provided as an example only. Prescribers should adjust dosages to reflect factors such as low opioid tolerance.

Appendix G

Sample Wallet Induction Notification Card

FRONT

MICRO-DOSING INDUCTION NOTIFICATION CARD
(buprenorphine/naloxone)

I, _____NAME_____
____DOB_____ am undergoing a micro-dosing induction with buprenorphine/naloxone.

Pharmacy Name _____

Pharmacy Address _____

Pharmacy Phone No _____

Start date _____

BACK

PRESCRIBER/HOSPITAL INFORMATION
(Could be copy of business card)

Starter pack provided? Yes ☐ No ☐

By who? ____ (Prescriber/Hospital Name) _____

_____

Address _____

Phone No. _____

After Hours Contact No._____