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MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.5 Recommendations for Buprenorphine/naloxone Micro-Dosing Induction for Opioid Use Disorder

GENERAL CONSIDERATIONS

As a partial agonist with high affinity for the *mu*-opioid receptor, buprenorphine has the potential to displace other full agonists at the receptor level, and precipitate clinically significant opioid withdrawal symptoms. This occurs when an initial dose of buprenorphine/naloxone is taken by a patient who has recently consumed other opioids. Therefore, the Conventional Buprenorphine Induction requires 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 waiting period may be intolerable or impractical for some patients for a variety of reasons. Additionally, 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, as well as some flexibility in the patient and prescriber's availability for assessment and dose titration. This may lead to overall lower utilization of buprenorphine/naloxone despite the superior safety profile.

Comparatively, micro-dosing of buprenorphine/naloxone (commonly referred to as the "Bernese method") involves a buprenorphine 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 suggested here as an equally evidence-based* alternative to the Conventional Buprenorphine Induction method described in this manual. The evidence supporting the micro-dosing 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.

Micro-dosing induction may be considered for select patients who are unlikely to tolerate the prerequisite interval of opioid abstinence, and when barriers exist to repeat in-office assessment of withdrawal and witnessed dosing. Some patients may also meet criteria for unwitnessed ("home") induction, as described in Recommendations for Unwitnessed Induction with Buprenorphine/naloxone.

SPECIFIC CONSIDERATIONS

It is the responsibility of the prescriber to educate a patient being considered for micro-dosing induction about 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 providing afterhours contact number(s) for support.

See the Conventional Buprenorphine Induction chapter for guidance on *Management of Precipitated Withdrawal*, and The Pharmacology of Buprenorphine, Precipitated Withdrawal & Management of Adverse Effects for further details.

Patients Appropriate for Micro-Dosing

Micro-dosing induction may be considered in the following patients:

- Patients who fear withdrawal or experience severe withdrawal symptoms during conventional induction (as above, 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 psychosocial instability that makes attending a scheduled clinic appointment for induction challenging (examples may include no access to reliable transport, a lack of financial resources for transport, significant mobility limitations, chaotic lifestyle, lack of social supports, etc.)

Good Candidates for Micro-Dosing

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 transitions, specialist guidance must be sought to ensure appropriate customization of the micro-dosing schedule, including appropriate cross-titration of methadone, or the other high-dose long-acting opioid being discontinued. See Ongoing Care for further guidance on the ROTATION OF OAT MEDICATIONS.
- 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 comorbid physical or mental health condition.
- Pregnant persons 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. See Treatment of OUD in Pregnancy and In-Hospital Care for detailed recommendations.

Witnessed Dosing Requirements & Reassessment

Generally, with conventional induction, buprenorphine/naloxone should be dispensed as daily witnessed doses. Daily witnessed doses are self-administered under the direct supervision of a pharmacist, approved prescriber, or a nurse, until the patient has demonstrated sufficient clinical stability to be considered for take-home (carry) doses.

Comparatively, the following is recommended for micro-dosing inductions:

- In most cases, buprenorphine/naloxone doses should be witnessed at the pharmacy starting **no later than Day 4**, with evening doses being provided as carries.
- Under exceptional circumstances (e.g., geographic isolation from the pharmacy, with phone support and reassessment from prescriber or experienced clinic staff), patients may be given more than a 3-day supply of medication for a micro-dosing induction. The rationale for this approach must be clearly documented and communicated to the pharmacy.
- After initiating a buprenorphine micro-dosing protocol, the patient should be **reassessed no later than Day 7, in person, by the prescriber or experienced clinic staff**. If this is not possible for any reason, a phone assessment should be completed, with in-person follow-up as soon as possible thereafter.

All interactions with clinic staff (by phone or in person) during the micro-dosing induction should be documented in the patient's medical record.

Criteria for the provision of take-home doses are discussed elsewhere in this manual. See Take-home (Carry) Dosing Recommendations and Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT for take-home guidance, and Ongoing Care for a detailed review of other issues often encountered during the maintenance phase of treatment.

Pharmacy Communication

Clear communication with the pharmacy is essential to facilitate a smooth micro-dosing induction process. Even if the 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, as 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 the patient's medication record (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 T** for suggested template):

- A copy of the micro-dosing induction protocol/instructions provided to the patient (see **Appendix U** for an example).
- 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 to commence witnessed dosing.
- Clinic contact 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 induction approaches 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 U**. These induction instructions, or a similar customized protocol, should be provided to the patient and the pharmacy.

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 Conventional Buprenorphine Induction chapter for further induction and titration dosing guidance, and the Ongoing Care chapter for recommendations around overall dosing stability.

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 starter pack from hospital or clinic stock and the medication has not been entered into the DPIN system. The wallet card serves as a notification to EMS/ER staff that the patient was prescribed a micro-dosing induction protocol. See **Appendix V** for a micro-dosing induction wallet card template.

Appendix T

PHARMACY MICRO-DOSING INDUCTION NOTIFICATION

Date:	
Pharmacy:	
Phone:	
Fax:	

Dear Pharmacist,

RE:		
DOB:		
PHIN:		
Clinic Phone:	Fax:	

I have assessed the above-named patient and they are a candidate for micro-dosing induction of buprenorphine/naloxone. I have provided instructions to the patient regarding their micro-dosing induction. A copy of the induction protocol is included. **Please note the following**:

☐ The patient has been provided with a **starter pack of buprenorphine/naloxone from clinic/hospital stock** to start micro-dosing. They 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 3 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 _____ to speak to our on-call prescriber.

Sincerely,

_____

Prescriber Name, signature, & credentials

Appendix U

BUPRENORPHINE/NALOXONE (SUBOXONE®) MICRO-DOSING INSTRUCTIONS

Micro-dosing Suboxone® is one way to start opioid agonist treatment (OAT) when you aren't able to stop your opioid use.

Your pharmacy will give you 3 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 going to your pharmacy daily to continue the micro-dosing process. During this time, you can continue using opioids, but will gradually decrease the amount of opioids you use.

Prescriber Name: _____

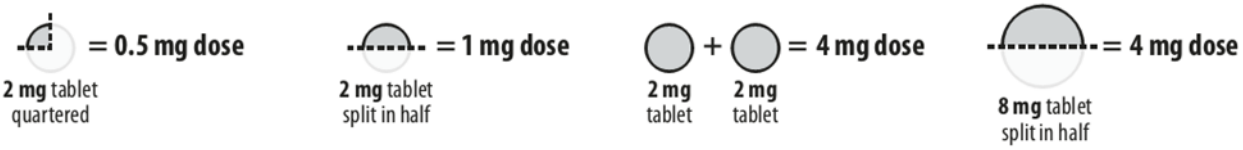
Prescriber Phone: _____

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 & onwards	Your doctor may continue to adjust your medication to relieve withdrawal symptoms until a stable dose is achieved.	



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

Appendix V

SAMPLE WALLET MICRO-DOSING INDUCTION NOTIFICATION CARD

FRONT

MICRO-DOSING INDUCTION NOTIFICATION CARD
For buprenorphine/naloxone (Suboxone®)

I, _____ (NAME)
and _____ (DOB) am undergoing a micro-dosing induction with Suboxone®

Pharmacy Name: _____

Pharmacy Address: _____

Pharmacy Phone: _____

Start date: _____

BACK

PRESCRIBER/HOSPITAL INFORMATION
(**could be copy of business card**)

Suboxone® starter pack provided?

☐ **Yes** ☐ **No**

Provided by: _____

(Prescriber/Hospital Name)

Address: _____

Phone: _____

After Hours Ph: _____