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MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.2 Recommendations for Conventional Buprenorphine/naloxone Induction for Opioid Use Disorder

GENERAL CONSIDERATIONS

This chapter will outline recommendations regarding the general approach to a conventional buprenorphine/naloxone induction for the treatment of opioid use disorder (OUD). Buprenorphine is considered first-line therapy for the treatment of OUD, and a conventional induction should be considered for most patients starting buprenorphine/naloxone.

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. This phenomenon of precipitated withdrawal can be very distressing to the patient and may negatively impact treatment retention. Please see The Pharmacology of Buprenorphine, Precipitated Withdrawal & Management of Adverse Effects for further details. **Therefore, the conventional buprenorphine induction takes place after a planned period of abstinence from other opioids and requires clinical evidence of opioid withdrawal**. The initial dose(s) are administered under the direct supervision of a pharmacist, approved prescriber, or nurse.

For select patients who face specific barriers to in-office assessment of withdrawal and witnessed dosing, an unwitnessed ("home") induction may be considered. Alternatively, these patients, and those who are unlikely to tolerate the prerequisite interval of opioid abstinence, may benefit from a micro-dosing induction. Please see the respective chapters, Recommendations for Unwitnessed Induction with Buprenorphine/naloxone and Recommendations for Buprenorphine/naloxone Micro-dosing Induction for details on these approaches.

SPECIFIC CONSIDERATIONS

INITIATING OPIOID AGONIST THERAPY

Urgency of OAT Induction

Following the decision to initiate opioid agonist therapy (OAT), induction should be arranged urgently, ideally the same day or within 2-3 days of presentation. When access to OAT induction within this timeframe is not feasible due to patient, prescriber, geographic, or systemic factors, other interventions should be considered in the interim, including harm reduction strategies (e.g., clean supplies, naloxone), patient safety education, wound care, psychosocial support, and access to primary care and other forms of addiction treatment.

Providers involved in addiction treatment are encouraged to advocate for improved access to OAT in their region of practice.

Initial Assessment & Patient Education

Patients must undergo a comprehensive assessment including history and focused physical examination to establish the diagnosis of OUD before initiating OAT. Please see Initiating OAT: Comprehensive Assessment, Diagnosis, Informed Consent & Investigations for detailed guidance on the assessment process.

Where immediately available, point-of-care urine drug screening should be performed. This is a useful clinical tool in the context of the initial assessment. Relevant lab work, including an STBBI screening, should also be ordered and completed as soon as practically feasible. **While urine drug testing and other investigations are ideal on initial assessment or in early treatment, they should not delay access to timely treatment if OAT is indicated**.

Due to its lower potential for respiratory depression and lethal overdose, buprenorphine is strongly preferred over full agonists (e.g., methadone) for the treatment of OUD among patients with risk factors for opioid toxicity. These include:

- Patients with concurrent use of alcohol, benzodiazepines, and other sedatives. In general, prescribers should avoid prescribing new sedating medications during induction. Patients should be counselled to avoid the use of sedating drugs, including over-the-counter medications, if possible. See Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT for further recommendations.
- Older patients (age > 60).
- Patients with acute or chronic respiratory disease (e.g., COPD, pneumonia).
- Patients with low opioid tolerance (e.g., codeine use only, low-dose or low-potency opioid use, intermittent opioid use, or a recent period of abstinence due to incarceration or residential treatment).

Patients should be educated about the symptoms and signs of opioid toxicity, overdose, and should be offered access to a naloxone kit at the time of induction.

Prescribers should obtain and document informed consent for buprenorphine/naloxone treatment. The use of a written **Treatment Agreement** is strongly recommended. Informed consent and treatment agreements are also discussed in the above-mentioned Comprehensive Assessment chapter.

> IMPORTANT NOTE: PATIENTS WITH SEVERE LIVER IMPAIRMENT
>
> Patients with severe liver impairment may not stabilize on buprenorphine/naloxone as expected. Buprenorphine is absorbed sublingually but naloxone is not. Therefore, during sublingual administration, naloxone in the saliva is eventually swallowed and some of it is absorbed from the gastrointestinal tract. Normally, this naloxone is almost completely inactivated by the liver (i.e., first pass effect) prior to reaching the systemic circulation (about 3% bioavailability). In patients with severe liver dysfunction the first pass effect might be diminished, and a much higher amount of naloxone (approximately ten times as much) can reach the systemic circulation, potentially resulting in ongoing withdrawal symptoms. In such patients, a trial of methadone may be beneficial.

Clinical Stability & Treatment Goals

Prescribers should discuss and document the goals of treatment prior to induction and at regular intervals during follow-up. Both provider and patient-driven goals should be used to inform treatment decisions and support continued buprenorphine/naloxone prescribing.

In most patients, buprenorphine/naloxone allows for rapid dose titration to address opioid withdrawal quickly and effectively. This promotes engagement in further treatment. The patient's dose should be titrated, based on regular clinical assessment, until initial dose stability is reached. A stable dose is achieved when opioid withdrawal is eliminated or adequately suppressed to allow patients to further engage in ongoing medical and psychosocial treatment. **The ultimate goal is to work toward clinical stability**, which is characterized by, but not limited to:

- Absence of opioid withdrawal symptoms and significantly reduced cravings
- Absence or significant reduction in illicit substance use (self-reported and supported by urine drug testing)
- Financial and/or employment stability
- Housing stability
- Improvements in self-care and wellness practices
- Strengthening of supportive relationships (and/or navigating difficult relationships)
- Improvements in mental and physical health

PREPARATION FOR INDUCTION

In most cases, patients should be instructed to abstain from opioid use for 12-24 hours prior to their planned induction or intake appointment, to minimize the risk of precipitated withdrawal. The suggested interval of abstinence may be informed by a thorough clinical history of recent opioid use and knowledge of the pharmacokinetics of various opioids.

Prescribers in community settings may consider scheduling the induction in the morning and on a weekday to facilitate in-person reassessment.

Collaboration with Pharmacy

Collaboration with the pharmacist is strongly encouraged prior to induction and should include:

- **Verify the pharmacy provides OAT**. It is important to note that not all pharmacies in Manitoba dispense OAT, as specialized training is required. Thus, it is important to confirm that a pharmacy does dispense the specific OAT medication selected for treatment (i.e., buprenorphine/naloxone or methadone), prior to faxing a prescription to that pharmacy.
- **Communicate the plan**. Sharing the titration plans and communicating an action plan for any missed doses during the induction phase is helpful for all those involved.
- **Share special instructions**. Specifying any special instructions for the induction schedule is also helpful. Writing the approximate time of day for induction doses on the M3P prescription is very useful to prevent dosing errors and confusion. This is especially true if multiple doses are to be witnessed/dispensed on the same day.
- **Provide comprehensive prescriber contact info.** Supplying the pharmacy with method(s) to contact the prescriber/office outside of regular clinic hours is vital to ensuring that urgent clinical matters can be addressed quickly.

Patients Transitioning from Methadone

For patients using methadone, the methadone dose should ideally be gradually tapered to ≤ 30 mg/day, and the patient should be advised to abstain from methadone for 48-72 hours prior to buprenorphine/naloxone induction. Alternatively, in patients transitioning from methadone to buprenorphine/naloxone, prescribers may consider a micro-dosing induction, or switching from methadone to slow-release oral morphine (SROM/Kadian®, the 24-hour formulation) for five days prior to transitioning to buprenorphine.

Regardless of the clinical approach taken, this can be a challenging process for patients. Patients therefore need to be carefully selected and all appropriate options discussed.

The risk of relapse must be discussed with the patient and the discussion documented. Prescribers who are inexperienced with transitioning patients from methadone to buprenorphine/naloxone are strongly advised to seek expert guidance.

INDUCTION DAY 1

See **Appendix M** for a detailed buprenorphine/naloxone induction flow diagram.

Assess the Severity of Opioid Withdrawal

Prescribers should make use of the Clinical Opiate Withdrawal Scale (COWS) to assess and document the severity of opioid withdrawal prior to administration of the initial buprenorphine dose(s) (see **Appendix N**). Induction typically proceeds when the COWS score is 12 or greater to minimize the risk of precipitated withdrawal.

At the prescriber's discretion, a COWS score *less than* 12 may be considered when supported by a thorough history including knowledge of the specific opioids consumed, their potency and duration of action, the time elapsed since last use, and urine drug screen results. For example:

- An experienced prescriber may feel that the COWS assessment underestimates the degree of withdrawal for a particular patient who reliably reports abstinence from opioids for a sufficient interval.
- A patient presenting after a longer period of abstinence (e.g., weeks) may be appropriate for buprenorphine/naloxone induction with a COWS score less than 12, provided the available history is sufficiently reliable and the diagnosis of OUD is certain (e.g., patients previously on OAT, or following discharge from abstinence-based treatment programs).
- An experienced prescriber may determine that the potential for harm in delaying induction to the next available clinic day (e.g., overdose) exceeds the risk of precipitated withdrawal for a particular patient.
- An experienced prescriber may suspect that a patient who uses lower dose opioids, or non-potent opioids only, may never reach a COWS of 12, and therefore elect to proceed with induction after a sufficient amount of time has passed since last reported opioid use.

In other cases, a prescriber may require a *higher* minimum COWS score. For example:

- Some illicit opioids (e.g., "down") contain an unpredictable mixture of short- and long-acting opioids. They may also contain fentanyl analogues which may increase the risk of precipitated withdrawal, due to their high lipophilicity resulting in prolonged clearance among frequent users. A higher COWS score, expert consultation, and/or a micro-dosing induction may be considered in these cases (see Recommendations for Buprenorphine/naloxone Micro-dosing Induction for details).
- Patients may be consuming or withdrawing from other substances that may impact a COWS assessment (e.g., stimulants or benzodiazepines), warranting additional caution to avoid toxicity and/or precipitated withdrawal.

It is strongly encouraged to instruct the pharmacist to communicate any concerns that the patient may have used opioids between the clinic assessment and the induction dose, prior to administering the Day 1 induction dose.

At all times, the prescriber must carefully consider the risk of precipitated withdrawal, as well as the potential harms of delaying the buprenorphine/naloxone induction. In challenging scenarios, a benefit-risk assessment must be documented in the medical record. Prescribers are also encouraged to seek expert guidance in these situations.

Determine the Initial Dose

The initial dose of buprenorphine on Day 1 should be 2-4 mg and should be witnessed by the prescriber, pharmacist, or nurse. In most cases, a 4 mg initial dose is appropriate.

An initial dose of 2 mg may be considered for patients deemed to be at high risk of precipitated withdrawal (e.g., those consuming long-acting opioids) and those with low opioid tolerance (e.g., lower-dose use or recent abstinence).

An initial dose of 6 mg may be considered in *exceptional circumstances* for patients presenting in severe withdrawal (COWS ≥ 25); however, this may increase the risk of toxicity and precipitated withdrawal and may warrant increased monitoring or expert consultation.

Reassess Withdrawal

Reassess the severity of opioid withdrawal 1-2 hours after the initial dose:

- **If withdrawal severity/COWS score has worsened *significantly* after the initial dose**, the prescriber should consider the possibility of precipitated withdrawal (see below, *Management of Precipitated Withdrawal*). If the patient reports feeling better or "a little worse", the induction may proceed. Precipitated withdrawal typically involves the patient feeling *much worse* than before.
- **If withdrawal symptoms have completely resolved after the initial dose**, document the Day 1 total dose, and arrange clinical follow-up on Day 2.
- **If withdrawal symptoms have not completely resolved**, an additional 2-4 mg witnessed dose may be prescribed. Reassessment should occur 1-2 hours after the second dose, at which time a third 2-4 mg witnessed dose may be considered if withdrawal symptoms persist, to a **maximum Day 1 dose of 12 mg**. Where resources permit repeated patient reassessment (e.g., monitored settings), experienced providers may consider a fourth 2-4 mg dose 1-2 hours after the third, for a maximum Day 1 dose of 16 mg.

If withdrawal symptoms persist after reaching the Day 1 maximum dose, consider prescribing non-opioid medications for symptomatic management (see **Appendix O**). Typically, regularly scheduled acetaminophen and ibuprofen is sufficient. Use caution when prescribing symptomatic management medications with sedating properties.

Take-home Dose(s) on Day 1 of Induction

When repeated in-office reassessment after the initial Day 1 dose(s) is not feasible and continued withdrawal is anticipated, prescribers may consider prescribing one or two 2 mg tablets (maximum of 4 mg) for the patient to take home to complete the induction, up to a maximum Day 1 dose of 12 mg. **The patient should be counselled regarding recognition of withdrawal and the appropriate timing of take-home doses** (e.g., "2 mg SL q 2h PRN for withdrawal symptoms"). Please see Recommendations for Unwitnessed Induction with Buprenorphine/naloxone for details.

The prescription must have clear instructions as to which doses are to be witnessed or released as take-home doses. Storage of Day 1 take-home doses in a locked box is strongly recommended.

Management of Precipitated Withdrawal

If withdrawal symptoms worsen significantly *shortly* after the initial buprenorphine dose (within 15-60 minutes), the prescriber must decide whether to continue or terminate the induction.

There is currently limited evidence to guide this decision, which should consider the patient's preferences and an informed discussion of the risks and benefits of each approach:

- If the induction is terminated, the patient can be rescheduled for another attempt at induction (e.g., the next clinic day). Non-opioid medications to manage withdrawal symptoms (**Appendix O**) may be considered. In inpatient settings, experienced prescribers may consider administering short-acting opioids to relieve withdrawal symptoms.
- Alternatively, the prescriber may continue the induction with frequent reassessment and administration of 2 mg doses every 1-2 hours until withdrawal symptoms have resolved (to a maximum 12 mg on Day 1).

When discussing the treatment plan and obtaining informed consent it is important to discuss a plan for potential precipitated withdrawal management with the patient *prior* to induction.

INDUCTION DAY 2

Reassess the Severity of Withdrawal

Reassess the severity of opioid withdrawal prior to Day 2 dosing:

- **If no withdrawal symptoms have emerged prior to Day 2 dosing**, prescribe the total Day 1 dose for witnessed administration on Day 2 and subsequent days.
- **If withdrawal symptoms have emerged prior to Day 2 dosing**, increase the Day 2 dose by 2-4 mg. If possible, reassess the patient 2-4 hours after administration, and consider an additional top-up dose of 2-4 mg at that time if withdrawal persists.

STABILIZATION - DAY 3 ONWARDS

Frequent Reassessment In the Beginning

The patient should ideally be reassessed frequently (e.g., daily) until they achieve relief of withdrawal symptoms and cravings, in the absence of sedation or toxicity, for a complete 24-hour period following their dose. During this time, prescribers may titrate the dose in 2-4 mg increments each day to a maximum of 24 mg daily (usual dose 8-24 mg). A more gradual titration should be considered for those at high risk of opioid toxicity, including those concurrently taking other sedative medications.

In exceptional cases, doses greater than 24 mg may be considered (up to 32 mg/day). In such cases, the clinical rationale should be clearly documented, and inexperienced prescribers should consider expert consultation.

Additionally, after the first week of treatment, prescribers should consider allowing 3-7 days between further dose increases, especially if increasing the dose beyond 24 mg to allow the patient to experience the full benefit of each increase.

After an initial stable dose has been achieved (typically 3-7 days), continue to reassess the patient every 1-2 weeks. The frequency of follow-up can be reduced as the patient on a stable dose begins to demonstrate evidence of clinical stability.

MAINTENANCE

Ongoing Follow Up

At each follow-up visit, review and document the patient's dosage, withdrawal symptoms and cravings if present, ongoing substance use, missed doses, adverse effects, and relevant markers of clinical stability. Please see Initiating OAT: Comprehensive Assessment, Diagnosis, Informed Consent & Investigations for a detailed list of items to address upon routine follow up, as applicable.

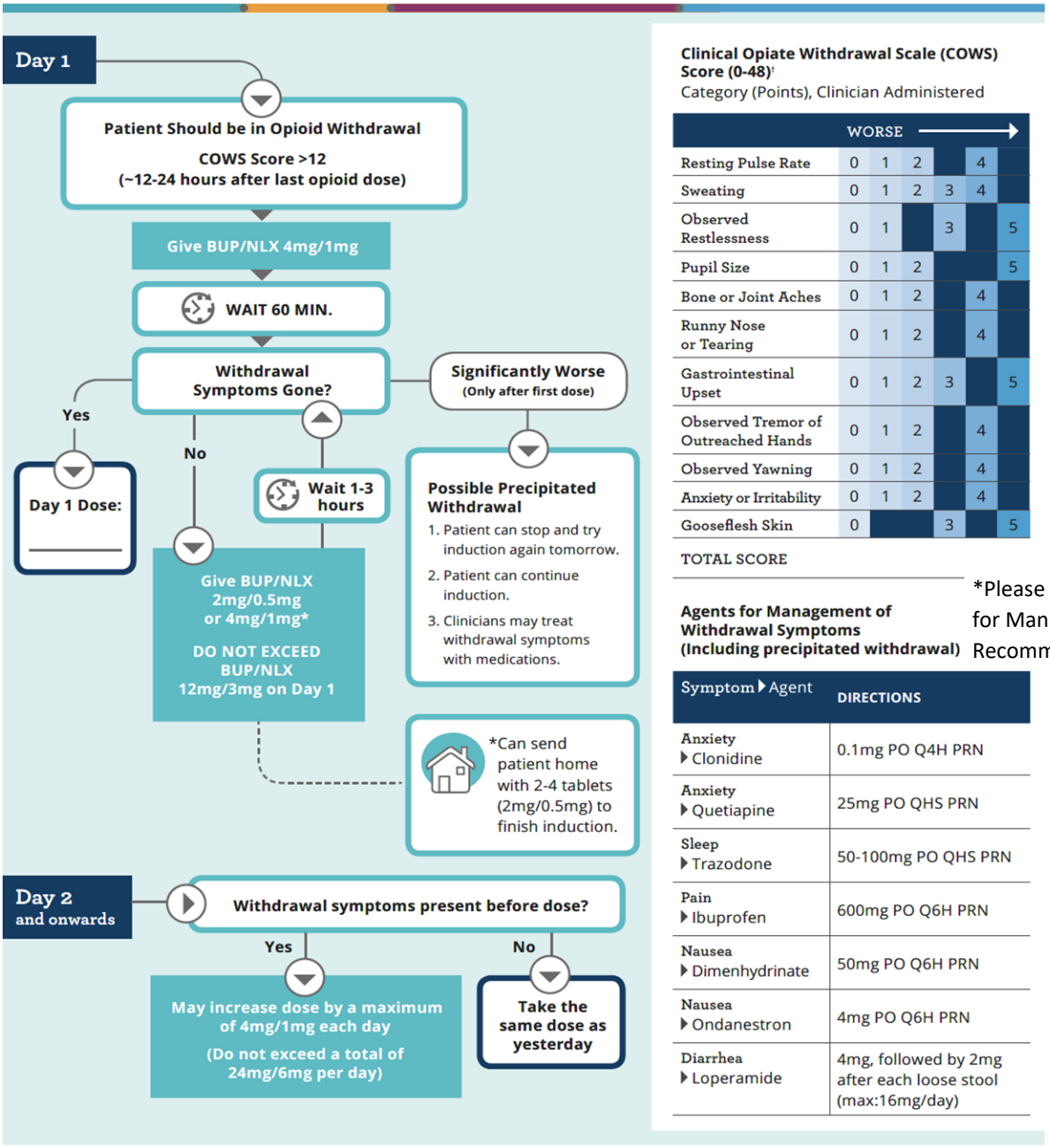
Periodically discuss the patient- and prescriber-driven goals of treatment and discuss adjuncts such as harm reduction strategies and psychosocial supports.

When indicators of clinical stability do not improve as expected during OAT treatment, consider whether continued prescribing is appropriate and aligns with the patient's and prescriber's goals (see other manual sections for guidance on extremely unstable patients).

Criteria for 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 details), along with a detailed review of other issues often encountered during the maintenance phase of treatment.

Appendix M[1]

Buprenorphine/Naloxone (BUP/NLX) Induction Flow Diagram



Clinical Opiate Withdrawal Scale (COWS) Score (0-48)†
Category (Points), Clinician Administered

	WORSE →					
Resting Pulse Rate	0	1	2		4	
Sweating	0	1	2	3	4	
Observed Restlessness	0	1		3		5
Pupil Size	0	1	2			5
Bone or Joint Aches	0	1	2		4	
Runny Nose or Tearing	0	1	2		4	
Gastrointestinal Upset	0	1	2	3		5
Observed Tremor of Outreached Hands	0	1	2		4	
Observed Yawning	0	1	2		4	
Anxiety or Irritability	0	1	2		4	
Gooseflesh Skin	0			3		5
TOTAL SCORE						

Agents for Management of Withdrawal Symptoms (Including precipitated withdrawal)

Symptom ▸ Agent	DIRECTIONS
Anxiety ▸ Clonidine	0.1mg PO Q4H PRN
Anxiety ▸ Quetiapine	25mg PO QHS PRN
Sleep ▸ Trazodone	50-100mg PO QHS PRN
Pain ▸ Ibuprofen	600mg PO Q6H PRN
Nausea ▸ Dimenhydrinate	50mg PO Q6H PRN
Nausea ▸ Ondanestron	4mg PO Q6H PRN
Diarrhea ▸ Loperamide	4mg, followed by 2mg after each loose stool (max:16mg/day)

*Please see **Appendix O** for Manitoba Medication Recommendations

† Full COWS Scoring Available at: https://www.drugabuse.gov/sites/default/files/files/ClinicalOpiateWithdrawalScale.pdf
For home induction, use patient administered Subjective Opiate Withdrawal Scale (SOWS) scoring available at: http://www.bccsu.ca/wp-content/uploads/2017/08/SOWS.pdf

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1. From Korownyk C, Perry D, Ton J, et al. Managing opioid use disorder in primary care: PEER simplified guideline. *Canadian Family Physician*. 2019; 65(5): 321-330. Available at https://acfp.ca/tools-resources/tools-resources-opioid-response/simplified-guideline-for-opioid-use-disorder-in-primary-care/

Appendix N[2]

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CLINICAL OPIATE WITHDRAWAL SCALE[1]

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient's name: _____ Date and Time: _____/_____/____:____

Reason for assessment: _____

Resting Pulse Rate _____ beats/minute
Measured after patient is sitting or lying for one minute
0 pulse rate 80 or below
1 pulse rate 81–100
2 pulse rate 101–120
4 pulse rate greater than 120

GI Upset *over last ½ hour*
0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhea
5 multiple episodes of diarrhea or vomiting

Sweating *over past ½ hour not accounted for by room temperature or patient activity*
0 no report of chills or flushing
1 subjective report of chills or flushing
2 flushed or observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face

Tremor *observation of outstretched hands*
0 no tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching

Restlessness *observation during assessment*
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 unable to sit still for more than a few seconds

Yawning *observation during assessment*
0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment
4 yawning several times/minute

Pupil Size
0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
2 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Anxiety or Irritability
0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Bone or Joint Aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

Gooseflesh Skin
0 skin is smooth
3 piloerrection of skin can be felt or hairs standing up on arms
5 prominent piloerrection

Runny Nose or Tearing
Not accounted for by cold symptoms or allergies
0 not present
1 nasal stuffiness or unusually moist eyes
2 nose running or tearing
4 nose constantly running or tears streaming down cheeks

Total Score _____
The total score is the sum of all 11 items.

Initials of person completing assessment: _____

Score: 5–12 = mild; 13–24: moderate; 25–36 = moderately severe; more than 36 = severe withdrawal

Reference:
1. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003;35(2):253–259.

More information:
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[2] From https://www.bccsu.ca/wp-content/uploads/2017/08/Clinical-Opiate-Withdrawal-Scale.pdf

Appendix O

NON-OPIOID MEDICATION FOR SYMPTOMATIC MANAGEMENT OF OPIOID WITHDRAWAL

The following non-opioid medications may be useful to treat symptoms of opioid withdrawal.

Prescribers should exercise caution with all sedating medications during OAT induction, as they may interfere with the assessment of withdrawal severity and increase the risk of fatal overdose. In the absence of precipitated withdrawal, many prescribers prefer to avoid these medications entirely during induction.

- Acetaminophen 500-1000 mg PO Q4-6h PRN for muscle pain (to a maximum dose of 4000 mg in 24 hours, or as appropriate based on known liver function/impairment).
- Ibuprofen 400 mg PO Q6-8H PRN for muscle pain.
- Ondansetron 4 mg PO Q6H PRN for nausea.
- Loperamide 4 mg PO PRN for diarrhea, then 2 mg PO after each loose stool, up to a maximum of 16 mg in 24 hrs.
- Trazodone 50-100 mg PO QHS PRN for insomnia.
- Quetiapine 25-50 mg PO QHS PRN for anxiety/insomnia.
- Clonidine 0.1 mg PO QHS PRN for opioid withdrawal symptoms and insomnia. Clonidine can be titrated up to 0.2 mg PO BID for severe withdrawal, but caution is advised due to the potential risks of sedation, hypotension, and diversion.