INESSS
LE SAVOIR PREND FORME

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DRUG

OPIOID AGONIST THERAPY

OPIOID USE DISORDER (OUD)

This optimal usage guide is provided for information purposes only and should not replace the professional's judgment. The recommendations in this guide concern individuals with opioid use disorder, whether the opioids are obtained by prescription or illicitly. The recommendations were developed using a systematic process and are supported by the scientific literature and by the knowledge and experience of Québec clinicians and experts. For further details, consult the report **Agonistes opioïdes dans le traitement du trouble lié à l'usage des opioïdes**.

GENERAL INFORMATION

- The illicit use and misuse of opioids increase the risk of developing opioid use disorder (OUD), impair one's well-being and increase the risk of fatal overdose.
- Providing treatment using a harm reduction approach means mitigating the negative consequences of opioid use rather than eliminating the behaviour at all costs, in order to maximize treatment retention.
- Any qualified professional can prescribe opioid agonist therapy (OAT), including specialized nurse practitioners, according to their class of specialization.
  - /The requirement to obtain an exemption from the federal government to prescribe methadone, regardless of the indication, has been removed.
  - Oral OATs are on the regular list for the Québec public prescription drug insurance plan.
- A free OUD treatment training program is offered by the Institut national de santé publique du Québec (INSPQ). It is strongly recommended that this training be taken before initiating OAT in an individual with OUD.
- For further details on the regulatory environment, ethical rules pertaining to the treatment of OUD, and training, see the CMQ-OIIQ-OPQ OUD treatment guidelines.

FACTORS AND BEHAVIOURS INDICATIVE OF OPIOID MISUSE

CATEGORY	EXAMPLES
Change in the route of administration[1]	▸ Administers medications via a route other than the one by which they are intended (e.g., injecting oral medications or taking them intranasally)
Obtaining opioids from other sources[1]	▸ Takes medications belonging to friends or relatives ▸ Buys opioids from a street dealer or via the Internet ▸ Has multiple prescribers or pharmacies (consider the Alerte program)
Unauthorized use	▸ Increases the doses multiple times without permission ▸ Takes several tablets at a time instead of at the scheduled times
Opioid seeking	▸ Misplaces their prescriptions and medications repeatedly ▸ Aggressively insists on the need to increase the dose ▸ Harasses clinic staff to get a prescription or a last-minute appointment ▸ Harasses pharmacy staff to get medications ▸ Claims that nothing else brings relief
Withdrawal symptoms	▸ Pronounced dysphoria, muscle pain, gastrointestinal symptoms, cravings to use
Concurrent illnesses (not an exhaustive list)	▸ Other psychoactive substance use disorder ▸ Underlying mood or anxiety disorder that does not respond to treatment
Opinion about opioid therapy	▸ Sometimes admits to having OUD ▸ Strong resistance to a change or a decrease in opioids ▸ Admits to using them for their effects on mood ▸ Possible recognition of bothersome withdrawal symptoms

1. The behaviours most indicative of OUD.

Québec

CLINICAL PRSENTATION

- A diagnosis of OUD is based on:
  - Problematic use that has led to impaired functioning or significant suffering;
  - The presence of at least 2 of the manifestations listed in the DSM-5 (see Appendix 1) during a 12-month period. Based on their clinical judgment, the qualified professional could conclude that the person has OUD and decide to initiate treatment, even if the criteria for OUD have not been present in the past 12 months;
- The clinical assessment of the person with OUD must include:
  - Reviewing all of their **psychoactive substance use patterns**, including checking with the pharmacist and in the patient's DSQ;
  - Finding out the person's goals (abstinence or a reduction in illicit use);
  - Identifying the presence of comorbidities, concurrent mental health problems, risky behaviours (e.g., sharing drug paraphernalia) or history of overdose;
  - Identifying any complications (e.g., STBBIs or tuberculosis) associated with the use of psychoactive substances (benzodiazepines, alcohol, psychostimulants, etc.), whether prescribed or not (consult the following tool: ITSS à rechercher selon les facteurs de risques décelés).

SIGNS AND SYMPTOMS OF OPIOID WITHDRAWAL		
▸ Agitation, anxiety, irritability	▸ Craving	▸ Piloerection
▸ Yawning	▸ Shedding tears, nasal discharge	▸ Tachycardia
▸ Diarrhea, abdominal cramps	▸ Mydriasis	▸ Sweating
▸ Pain (e.g., joint, muscle or bone)	▸ Nausea, vomiting	▸ Tremors

LABORATORY TESTS

- Paraclinical tests could be suggested, depending on the person's risk factors and health status. However, a refusal to undergo such tests should not preclude starting treatment.
- Urine testing is a clinical tool that can be useful to show evidence of opioid consumption as a supplement to history-taking during initial assessment and the follow-up period. It can also facilitate discussion. Consult the CMQ-OIIQ-OPQ guidelines for further details.
- A b-HCG test should be carried out for females of child-bearing potential.

TREATMENT PRINCIPLES

- An OAT should be routinely proposed to all persons with OUD. Buprenorphine-naloxone and methadone are the two OATs[1] recommended for the management of OUD, even in pregnant women.
  - Preference should be given to buprenorphine-naloxone because of its better profile of adverse effects and interactions and its lower risk of overdose, and to facilitate safer unsupervised dosing.
  - During pregnancy, it is best to maintain clinical stability by avoiding changing OATs because of the associated risk of withdrawal episodes.[2]
  - The advantages and drawbacks of OAT should be communicated to the person. Consult the Aide-mémoire : discussion avec l'usager (user discussion checklist) to facilitate this discussion.

1. Once-daily slow-release morphine is not approved by Health Canada for the treatment of OUD. Based on the advisory committee members' clinical expertise, it can be considered a treatment option following failure, intolerance or contraindication to buprenorphine-naloxone and methadone. If need be, consult an experienced colleague.
2. Switching to buprenorphine monotherapy is not necessary during pregnancy for women receiving buprenorphine-naloxone. However, some pregnant women may wish to receive monotherapy after being informed of the risks and benefits of each option.

- The treatment should be accompanied by:
  - A proposal for psychosocial and support interventions, without them being perceived as conditional or mandatory for access to OAT (consult your regional addiction rehabilitation centre, CRD);
  - Explanations on how to start the medication and on its adverse effects, to maximize the success of switching to OAT.
- Diagnosed comorbidities should be managed or the person referred to the appropriate resource at the time of initial assessment or later during the follow-up period.
- Information and a referral to the program for free, universal access to community naloxone, harm reduction services (e.g., the distribution of sterile drug paraphernalia) and other available health care and services should be routinely proposed, as part of basic OUD care.

WITHDRAWAL MANAGEMENT

- Withdrawal without OAT should be avoided as a proposal for managing OUD, as this method is associated with a high relapse rate (up to 89%), increased risk of overdose, and a higher rate of STBBI transmission.
- If the person insists on pursuing withdrawal management, OAT should first be initiated (if this has not already been done). They would then be gradually weaned over a period of at least 1 to 2 months and monitored during and after withdrawal, with OAT reintroduced, if necessary, in the event of an imminent or confirmed relapse.
- **Withdrawal management should not be offered to pregnant woman.**

CHRONIC PAIN SYNDROMES

- **In persons with chronic pain syndromes and concurrent OUD:**
  - OAT should be considered on a first-line basis if the OUD is not already being treated;
  - The usual non-opioid treatments, including nonpharmacologic measures, must be attempted when indicated (e.g., acetaminophen, NSAIDs, infiltration, gabapentinoids).

CONSIDER CONSULTING AN EXPERIENCED COLLEAGUE

- Consideration should be given to consulting an experienced colleague for any situation in which the professional feels less comfortable, such as the following:
  - OAT induction and managing switching between two OATs;
  - Supporting gradual opioid cessation, with or without OAT;
  - Managing patients under 18 years of age or pregnant women;
  - When extended-release forms of buprenorphine (by injection or implant) are being considered for persons treated with sublingual buprenorphine-naloxone at a stabilized dose.

TREATMENT

- Given the risk of death from opioid overdose, a naloxone kit must be offered to anyone taking opioids.
  - Whenever possible, families and loved ones should be encouraged to obtain a naloxone kit and to participate in training sessions on its use.
- During induction, buprenorphine-naloxone can cause precipitated withdrawal within 30 to 90 minutes of the first dose, because of its higher affinity for opioid receptors and lower intrinsic activity than the pure opioid agonists present in the user. The use of microdosing methods1 may however help limit the onset of signs and symptoms of withdrawal.
- Methadone titration must be gradual because of the higher risk of intoxication in the first days or even weeks of treatment.

1. Microdosing involves starting buprenorphine-naloxone at a small dose and gradually increasing the dose over 7 to 13 days. Opioids (prescribed or illicit) are continued until the therapeutic buprenorphine-naloxone dose is reached, after which the opioids can be discontinued. Consult the "USEFUL LINKS" section as needed.

SUBLINGUAL BUPRENORPHINE-NALOXONE[1]

Starting dose (Day 1)[2]
(in the presence of withdrawal symptoms)

Typical initial dose: 2 to 4 mg

- Start if the person's COWS[3] score is between 8 and 12[4]
  - Usually done after there has been no opioid use for ≥ 12 h in the case of short-acting opioids and for ≥ 24 h (ideally 30 to 72 hours) for long-acting opioids
- 1 h after the administration of the 1st dose, check for precipitated withdrawal
- Reassess every 2 to 4 hours and, if necessary, increase the dose by 2 to 4 mg (aim for a COWS score < 5)
- **Maximum dose: 16 mg**

Titration during induction and stabilization
(starting on Day 2)

Initial dose: total dose administered the previous day

- If necessary, increase the dose by 2 to 4 mg every 2 to 4 h (aim for a COWS score < 5)

Maximum dose: 24 mg on Day 2, 32 mg/day[5] thereafter

For well-stabilized persons, the drug can be taken:

- Daily
- Every other day (double dose)
- 3 times a week (double dose on Mondays and Wednesdays and triple dose on Fridays)

Management of precipitated withdrawal[2]

Option 1: Continue induction (preferable)

- Administer 2 to 4 mg/hour of buprenorphine-naloxone until withdrawal symptoms are relieved or the maximum starting dose is reached
- If symptoms are not relieved, prescribe the withdrawal kit up to Day 2
- Continue induction on Day 2 (as per the table above)
- Point out that using opioids can impede induction and stabilization

Option 2 : Suspendre l'induction

- Stop administering buprenorphine- naloxone
- Prescribe the withdrawal kit or short-acting opioids

! Schedule an appointment for the next induction.

If the person's situation is very precarious (e.g., ASCAD) and the withdrawal is severe, consider hospitalization to reverse the state of withdrawal and hydrate the person (rarely necessary)

1. There is a risk of under- or overdose when switching between the tablet and film formulations. When switching, adjust the dose if necessary, according to the symptoms of under- or overdose. The film formulation is not covered by the public prescription drug insurance plan (RPAM).
2. A non-opioid symptomatic treatment may be necessary in the short term (see the "TREATMENT OF WITHDRAWAL SYMPTOMS" section).
3. The Clinical Opiate Withdrawal Scale (COWS) (see Appendix 2) is a useful tool for assessing withdrawal symptoms. The person should also be asked questions to check how they are feeling. The Subjective Opiate Withdrawal Scale (SOWS) is also available and can be used for buprenorphine-naloxone induction at home. Consult an experienced colleague for induction and for the SOWS values to be used for home induction.
4. Some persons do not reach these COWS values but can still start treatment if they have stopped all opioid use and state that they are «not feeling well.»
5. The maximum dose approved by Health Canada is 24 mg/day. According to the advisory committee members, a dose of 32 mg/day is commonly used and is safe in this context.

ORAL METHADONE SOLUTION[6]

Starting dose
(Individualized according to opioid use)

- **Typical initial dose: 20 to 30 mg**
- **Maximum dose: 40 mg**
- Dosage individualized according to several factors (e.g., amount of opioids or other psychoactive substances used, comorbidities)

Titration during induction and stabilization

- If necessary, increase the dose by 5 to 20 mg every 5 to 7 days
- Dosage and schedule individualized according to symptoms and use
- **Dose > 120[7] mg:** Consult an experienced colleague. A post-dose medical assessment may be required.

6. Dilute with a liquid unsuitable for injection to limit diversion. A low-sugar drink, such as Crystal Light®, can be used for persons with diabetes (see product monograph for further details).
7. There is no "maximum" dose that can be prescribed, and some cases may require doses higher than those indicated above.

TREATMENT OF WITHDRAWAL SYMPTOMS

- A withdrawal kit containing a day's supply can be considered and adapted for all persons starting OAT.

WITHDRAWAL KIT	SYMPTOM	EXAMPLE OF MEDICATION	Quantity per day
	Nausea	Antiemetic (e.g., dimenhydrinate 25 mg every 6-8 h)	10 tabs
	Diarrhea	Antidiarrheal (e.g., loperamide 4 mg stat, then 2 mg after each liquid stool; max. 12 mg/24 h)	6 tabs
	Anxiety, irritability, sweating	Clonidine 0.1 mg BID-TID as needed during the first 12 h	3 tabs
	Insomnia	Diphenhydramine 25-50 mg HS **or**	2 tabs
		Trazodone 50 mg HS **or**	1 tab
		Quetiapine 25-50 mg HS	2 tabs
	Pain	NSAID (e.g., ibuprofen 200-400 mg every 6-8 h) **or**	6 tabs
		Acetaminophen 500 mg every 4-6 h; max. 4 g/24 h	8 tabs

ADVERSE EFFECTS

METHADONE	BUPRENORPHINE-NALOXONE
▸ Increased sweating ▸ Constipation ▸ Hypogonadism and decreased libido ▸ Weight gain ▸ Nausea ▸ Drowsiness ▸ QT interval prolongation	Similar to methadone but less frequent. Mainly headaches, which usually resolve in 2 to 3 days **Risk of precipitated withdrawal during induction** ▸ in the 30 to 90 minutes after the first dose ▸ Varies considerably in terms of severity (risk is greater in users of long-acting opioids) ▸ **Common withdrawal symptoms:** excessive sweating, abdominal cramps, diarrhea, nausea, cravings and anxiety ▸ Symptoms improve after the 2nd or 3rd dose: steady state achieved

INTERACTIONS

- A pharmacist or up-to-date interaction references should be consulted to ensure that there are no significant pharmacological interactions with the person's other medications, particularly for methadone because of its many interactions with CYP450 and the risk of QT interval prolongation.

! The person must be advised that taking different psychoactive substances (such as alcohol, benzodiazepines, GHB or other opioids) concomitantly can lead to an overdose, respiratory depression, excessive sedation, coma and death.

- If the person has symptoms of CNS depression, the pharmacist can refuse to give them their dose of methadone or buprenorphine.

FOLLOW-UP

- At each visit, assess the person's overall condition and check how they are feeling:
  - Compliance with the treatment and the effectiveness of the dosage, i.e., the effects lasting for at least 24 hours, must be assessed by checking that they are not experiencing any cravings or withdrawal symptoms;
  - The use of other psychoactive substances and diligence in taking the OAT must be checked, being careful to pose questions in a manner that does not appear to be punitive and being on the lookout for a shift in dependence;
    - If the person remains unable to achieve their goals or continues to be uncomfortable despite optimally adjusted treatment, or if the adverse effects are too severe, it may be advisable to consult an experienced colleague to discuss what options should be considered;

- The presence of symptoms or signs of opioid intoxication must be assessed, and the person's use of methadone or buprenorphine-naloxone must be verified (in the DSQ or with the pharmacist);
  - The person must be checked for other signs of intoxication: the smell of alcohol and symptoms of psychoactive substance use (drowsiness, difficulty speaking, dry mouth, confusion);
  - An ECG for QT interval monitoring should be performed when possible and when the OAT is methadone, without making this a barrier to treatment;
- Psychosocial follow-up should be offered, if applicable;
- The following measures should be proposed, if applicable, without making any of them mandatory for continuing the OAT: management of comorbidities, STBBI screening and treatment, contraception and pregnancy tests, vaccination, education and distribution of essential harm reduction materials, polydrug management, and mental health assessment and management;

CONTINUITY OF TREATMENT

The continuity of OAT dosing is paramount for preventing withdrawal and relapse. At each visit, and especially during transition periods (e.g., discharge from hospital, and entering or leaving prison), the clinician should check that the person:

- Has a valid prescription and a follow-up appointment;
- Will be able to obtain their medication (prescription invalid after being 3 days late, access to the pharmacy, validation of the prescription possible with the prescriber if necessary, communication between the treatment teams possible, insurance coverage).

SPECIAL CASES

- The following situations are special cases for which the professional can refer to the CMQ-OIIQ-OPQ OUD treatment guidelines:
  - Unsupervised doses and reassessment criteria for stopping these doses
  - Missed or vomited doses (the usual dose can cause an overdose after a 3-day hiatus)
  - Pharmacy opening hours (timely access)
  - Pre-trial detention
  - Prison setting
  - Hospital stay
  - Concurrent mental health problem
  - Exceptional use of methadone tablets
  - Foreign travel (the authorized quantity will always be for a maximum of 30 days according to Health Canada rules)

USEFUL LINKS

- For a valid prescription template and other clinical tools:
  - Équipe de soutien clinique et organisationnel en dépendance et itinérance (Homelessness and addiction organizational and clinical support team)
- Support or mentoring from experts:
  - Addiction medicine - CHUM
  - Centre de recherche et d'aide pour narcomanes (CRAN) (Narcotic addiction help and research centre)
  - Regional addiction rehabilitation centres (CRDs)
  - Communauté de pratique médicale en dépendance (Community of medical practice in addiction)
- For a better understanding of microdosing
  - Induction de buprénorphine/naloxone par microdosage (CRDQ)
  - Buprenorphine–naloxone "microdosing": an alternative induction approach… (CMAJ)
  - Buprenorphine/Naloxone Microdosing: The Bernese Method (CHMA)

REFERENCES

To consult the references, see the report supporting the OUG and the systematic review report.

MANIFESTATIONS OF OUD (ACCORDING TO THE DSM-5)

(The severity of OUD is assessed according to the presence of manifestations and is based on the following scale: MILD: 2 or 3 symptoms; MODERATE: 4 or 5 symptoms; SEVERE: 6 or more symptoms).

▸ Opioids are often taken in larger amounts or over a longer period of time than intended.
▸ There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
▸ A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
▸ Craving, or a strong desire to use opioids.
▸ Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
▸ Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
▸ Important social, occupational or recreational activities are given up or reduced because of opioid use.
▸ Recurrent opioid use in situations in which it is physically hazardous.
▸ Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
▸ Tolerance*, as defined by either of the following: • a need for markedly increased amounts of opioids to achieve intoxication or desired effect • markedly diminished effect with continued use of the same amount of an opioid.
▸ Withdrawa*l, as manifested by either of the following: • the characteristic opioid withdrawal syndrome • the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms.

*This criterion does not apply to persons taking opioids solely under appropriate medical supervision.

CLINICAL OPIATE WITHDRAWAL SCALE (COWS)

For each criterion, document the number that best describes the patient's signs or symptoms at the time of each assessment. Ensure scoring is based only on an apparent relationship to opiate withdrawal; e.g. if the heart rate is increased because the person was running just before the assessment, the increased heart rate should not be added to the total score.

1. Resting heart rate: _____/min measured after patient has been sitting or lying for 1 minute

0. heart rate 80 or below
1. heart rate 81 to 100
2. heart rate 101 to 120
4. heart rate greater than 120

2. Sweating: assessed over the last 30 minutes, 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

3. Restlessness: observed during assessment

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

4. 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 iris visible

5. Bone or joint aches: If patient was in pain previously, only the additional component attributed to opiate withdrawal is scored

0. not present
1. mild diffuse discomfort
2. reports severe diffuse aching of joints/muscles
4. patient is rubbing joints or muscles and is unable to sit still because of discomfort

6. 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/tears streaming down cheeks

7. Gastrointestinal upset: over last 30 minutes

0. no gastrointestinal symptoms
1. stomach cramps
2. nausea or loose stool
3. vomiting or diarrhoea
5. multiple episodes of diarrhoea or vomiting

8. 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

9. Yawning: during observation:

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

10. Anxiety or irritability:

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

11. Goosebumps (piloerection):

0. skin is smooth
3. piloerection can be felt or hairs standing up on arms
5. prominent piloerection

Score total : _____

(Le score total est la somme de tous les items)

Withdrawal score: 5-12 = Mild; 13-24 = Moderate; 25-36 = Moderately severe; > 36 = Severe