Management of opioid use disorder: 2024 update to the national clinical practice guideline

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Cite as: *CMAJ* 2024 November 12;196:E1280-90. doi: 10.1503/cmaj.241173

Abstract

Background: In an evolving landscape of practices and policies, reviewing and incorporating the latest scientific evidence is necessary to ensure optimal clinical management for people with opioid use disorder. We provide a synopsis of the 2024 update of the 2018 National Guideline for the Clinical Management of Opioid Use Disorder, from the Canadian Research Initiative in Substance Matters.

Methods: For this update, we followed the United States Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines and used the Appraisal of Guidelines Research and Evaluation—Recommendation Excellence tool to ensure guideline quality. We carried out a comprehensive systematic literature review, capturing the relevant literature from Jan. 1, 2017, to Sept. 14, 2023. We drafted and graded recommendations according to the Grading of Recommendations, Assessments, Development and Evaluation approach. A multidisciplinary external national committee, which included people with living or lived experience of opioid use disorder, provided input that was incorporated into the guideline.

Recommendations: From the initial 11 recommendations in the 2018 guideline, 3 remained unchanged, and 8 were updated. Specifically, 4 recommendations were consolidated into a single revised recommendation; 1 recommendation was split into 2; another recommendation was moved to become a special consideration; and 2 recommendations were revised. Key changes have arisen from substantial evidence supporting that methadone and buprenorphine are similarly effective, particularly in reducing opioid use and adverse events, and both are now considered preferred first-line treatment options. Slow-release oral morphine is recommended as a second-line option. Psychosocial interventions can be offered as adjunctive treatment but should not be mandatory. The guideline reaffirms the importance of avoiding withdrawal management as a standalone intervention and of incorporating evidence-based harm reduction services along the continuum of care.

Interpretation: This guideline update presents new recommendations based on the latest literature for standardized management of opioid use disorder. The aim is to establish a robust foundation upon which provincial and territorial bodies can develop guidance for optimal care.

Opioid use disorder is characterized by a problematic pattern of opioid use occurring within a 12-month period, which leads to clinically significant impairment or distress; the disorder is categorized from mild to severe, according to the number of diagnostic criteria met.[1] Between 2013 and 2023, drug use in general has increased globally, but opioid use and opioid use disorder continue to be the leading causes of drug-related deaths worldwide.[2] In Canada, the total number of apparent opioid-related deaths increased from 2831 deaths in 2016 to 8049 deaths in 2023.[3] Despite an expansion of treatment options for opioid use disorder in Canada — notably, the lifting of restrictions on methadone prescribing in 2018[4] — a substantial surge in opioid-related harms has occurred. This increase in harms was exacerbated by the sudden limitations of access to services and the changes in substance supply and toxicity[5–7] after the onset of the COVID-19 pandemic.

Ongoing opioid-related harms, along with new scientific evidence regarding treatment options, changes in accessibility and the need for adequate, evidence-based treatments and interventions, warranted an update to the 2018 National Guideline for the

Clinical Management of Opioid Use Disorder, developed by the Canadian Research Initiative in Substance Matters (CRISM).[8]

Scope

We developed this updated clinical practice guideline to help provide optimal access to evidence-based care for people with opioid use disorder. It is primarily intended for physicians, nurse practitioners, pharmacists, clinical psychologists, social workers, medical educators, clinical care case managers with or without specialized experience in addiction treatment, and other allied health care professionals who provide care for people with opioid use disorder.

Updates to the 2018 recommendations are based on recent scientific evidence regarding treatment approaches and strategies available in Canada for the general adult population who receive a diagnosis of opioid use disorder (aged ≥ 18 yr), regardless of the severity of the disorder.

In accordance with the previous scope of the 2018 guideline,[8] this update focuses solely on oral formulations, including special considerations for pregnant people and for people who use oral naltrexone. Injectable opioid agonist therapy, extended-release agonists, and antagonists are outside the scope of this update. For recommendations on injectable opioid agonist therapy, please refer to the 2019 national guideline.[9]

The nature and the extent of research needed to provide recommendations on extended-release agonists and antagonists, as well as specific treatment protocols (e.g., take-home and medication induction protocols and dosages), warrant evaluation in separate projects.

Not enough evidence was available to address emerging issues requested by health care providers and people with living or lived experience with opioid use disorder (PWLLE) whom we consulted, such as alternative prescribing ("safer supply") recently implemented after COVID-19 risk mitigation strategies. Therefore, we have begun a separate project to identify future steps toward generating the evidence needed to guide recommendations in this area.[10]

Recommendations

Following the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) approach[11] (Box 1), we formulated 8 recommendations (Table 1). Three of the initial 11 recommendations from 2018 did not change; 8 were revised with minor and major changes. Specifically, we consolidated 4 recommendations into 1, split 1 recommendation into 2, moved 1 recommendation to become a special consideration, and changed 2 other recommendations.

We considered the balance of benefits and risks, values and preferences, cost, and availability of resources when making recommendations. To weigh these, we relied on scientific evidence and input from health care providers and PWLLE, to understand and incorporate their values and preferences.

This guideline highlights the importance of adhering to the highest standards of care (Box 2). Clinicians and health care professionals are encouraged to apply these to all clinical recommendations.

Box 1: GRADE approach[11]

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to formulate and determine the strength of recommendations involves key factors such as the certainty of evidence, the balance between benefits and harms, values and preferences, and costs and resources.

Certainty of evidence

The GRADE system initially categorizes the evidence according to study design: meta-analyses and randomized controlled trials are considered high-quality evidence, quasi-experimental studies moderate-quality evidence, and observational studies are low quality. This rating permits lowering the confidence level by considering the risk of bias, inconsistency across studies, indirectness, and publication bias. The confidence level can be upgraded given a large effect size or a dose–response effect. The final rating is interpreted as below:

- **High:** The body of evidence has very few limitations and variations. We are very confident that further research will not change the estimated effect.
- **Moderate:** There are only a few studies with no major limitations. Further research may change the estimate.
- **Low:** There are major limitations and variations in the studies' findings. We are uncertain about the estimated effect, and further research is very likely to change the estimate.

Going from evidence to recommendations: other factors

The GRADE process classifies each recommendation as "strong" or "weak." Importantly, a weak recommendation does not necessarily imply low-quality evidence and a strong recommendation does not necessarily suggest high-quality evidence. Other factors are considered in the process and are applied as described below:

- **Balance between benefits and harms:** The greater the net benefit, the more a strong recommendation is expected. The smaller the net benefit and the lower the certainty for that benefit, the more probable a weak recommendation is justified.
- **Values and preferences:** Patients' perspectives, beliefs, expectations, and goals for health and life. The greater the variability in values and preferences, or uncertainty in values and preferences, the more a weak recommendation is relevant.
- **Cost and resources:** The higher the cost of an intervention (the more resources consumed), the less a strong recommendation is assured.

Strength of recommendations: the significance

- **A strong recommendation:**
  - *For clinicians and patients:* Most people should follow the recommended course of action, but only a small number would not. Formal decision-support tools would not be necessary.
  - *For policy-makers:* The recommended course of action can be adopted as a policy, and variability between individuals and regions would be inappropriate.
- **A weak recommendation:**
  - *For clinicians and patients:* Most people should follow the recommended course of action, but a substantial number might not. Different choices may be appropriate for different patients, and formal decision-support tools can help make decisions.
  - *For policy-makers:* Policy-making will require substantial debate and involvement of many key partners.

Table 1: Summary of recommendations

Recommendation	Certainty of evidence	Strength of recommendation
Recommended opioid agonist treatments		
1. Buprenorphine and methadone should both be considered as standard first-line treatment options for opioid agonist therapy. • *For people who initiate opioid agonist therapy with buprenorphine, clinicians should be aware of the higher risk of attrition after the first month of initiation and offer alternative opioid agonist medications in these circumstances (high certainty).* • *When considering methadone, clinicians should be aware of the higher risk of mortality during the first month compared with the remainder of the treatment period (moderate certainty).*	High	Strong
Revision: Methadone becomes an equally recommended first-line treatment option		
2. Opioid agonist therapy with slow-release oral morphine should be available and offered as a second-line treatment option.	Moderate	Strong
Revision: Slow-release oral morphine becomes a second-line treatment option. Section 56 exemption is no longer required.		
Withdrawal management strategies		
3. Patients with opioid use disorder should not be offered withdrawal management alone because of the increased rates of relapse, morbidity, and mortality. Concurrent long-term addiction treatment is recommended.	Moderate	Strong
Revision: No change (minor rewording for clarity)		
4. When withdrawal management alone is pursued, a supervised slow opioid agonist taper (depending on the patient) should be provided, with close follow-up, and opioid agonist therapy should immediately be offered if the risk of relapse emerges.	Moderate	Strong
Revision: No change (minor rewording for clarity)		
5. For patients with a successful and sustained response to opioid agonist therapy who wish to discontinue opioid agonist therapy (i.e., desiring medication cessation), clinicians should consider a slow taper approach (depending on the patient). Ongoing addiction care should be considered upon cessation of opioid use.	Moderate	Strong
Revision: No change		
Adjunct psychosocial interventions and harm reduction strategies		
6. Psychosocial treatments, interventions, and supports can be offered as adjunct treatments to opioid agonist therapy to increase treatment retention.	Moderate	Strong
Revision: Psychosocial intervention to increase retention		
7. Psychosocial treatment should not be a mandatory component of standard treatment for opioid use disorder and should not prevent access to opioid agonist therapy.	Moderate	Strong
Revision: Clarity regarding the optional aspect of psychological interventions		
8. Harm reduction strategies should be offered as part of the continuum of care for patients with opioid use disorder. • *Current evidence supports the use of the following harm reduction programs: provision of sterile consumption equipment, overdose prevention education, and access to take-home naloxone kits.*	Moderate	Strong
Revision: Addition of a list of evidence-based harm reduction programs		
Special considerations		
Alternative option: For patients who decline or are not on standard treatments for opioid use disorder and have withdrawn from opioids, oral naltrexone could be discussed as an adjunct pharmacological option.		
Special populations: Pregnant people with opioid use disorder who are not in treatment should be encouraged to start a first-line treatment as soon as possible during pregnancy.		
Revision: Change from a recommendation to a special consideration for oral naltrexone. Addition of a special consideration for pregnant people based on a systematic review of the literature published since 2018.		

Recommendations cover oral opioid agonist treatment options, withdrawal management strategies, psychosocial treatments, harm reduction interventions, and special considerations for pregnant people and people who use oral naltrexone.

In this synopsis, we briefly discuss recommendations with key evidence. The full guidance document can be found in Appendix 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.241173/tab-related-content. A visual summary of the guideline is available in Figure 1.

Box 2: Standards of care

The guideline development committee embraces the highest standards of care for opioid use disorder, as recognized by the World Health Organization.[12]

- This guideline strongly endorses a **patient-centred approach** that respects patient rights and dignity. Treatment plans should be based on the patient's goals, preferences, and experience while balancing benefits and risks.
- Patients should have access to an **integrated continuum of care** with sustained harm reduction services, opioid agonist therapy, withdrawal management services, and psychosocial treatments. Health care providers should adopt trauma- and violence-informed approaches and, if necessary, refer patients to complementary services, such as employment or legal assistance.
- **Antiracist and culturally safe practices** should be integrated into treatment programs for opioid use disorder to prevent discrimination and stigmatization.

These principles should be applied to any recommended courses of treatment to ensure the best care.

First- and second-line treatment options

In this update, the term "buprenorphine" refers to both the monoproduct and the combination buprenorphine–naloxone.

Buprenorphine and methadone should both be considered as standard first-line treatment options for opioid agonist therapy (strong recommendation, high certainty of evidence).

- *For people who initiate opioid agonist therapy with buprenorphine, clinicians should be aware of the higher risk of attrition after the first month of initiation and offer alternative opioid agonist medications in these circumstances (high certainty of evidence).*
- *When considering methadone, clinicians should be aware of the higher risk of mortality during the first month compared with the remainder of the treatment period (moderate certainty of evidence).*

The 2018 guideline recommended initiating "opioid agonist therapy with buprenorphine whenever feasible to reduce the risk of toxicity, morbidity, and death, and to facilitate safer take-home dosing."[8] We now recommend offering both methadone and buprenorphine as first-line options, with different precautions for each.

According to a recent meta-analysis of 36 observational studies, being on opioid agonist therapy with buprenorphine or methadone reduces the risk of mortality by half compared with no treatment (risk ratio [RR] 0.47, 95% confidence interval [CI] 0.47–0.53).[13] In a comparison between methadone and buprenorphine, newly published meta-analyses showed similar effectiveness in reducing opioid use and adverse events.[14–16]

Buprenorphine was associated with a lower retention rate in several studies;[14–16] in particular, a recent and largest meta-analysis found a gradual reduction in treatment retention after the first month of treatment (RR at 1 month 0.95, 95% CI 0.90–1.00; RR at 3 months 0.88, 95% CI 0.82–0.95; RR at 6 months 0.76, 95% CI 0.67–0.85).[16]

Overdose-specific mortality rates were higher in patients on methadone than those on buprenorphine (crude mortality rates [overdose deaths] for methadone 6 per 1000 person-years, 95% CI 5–7; buprenorphine 3 per 1000 person-years, 95% CI 3–4).[17] The relative risks of all-cause mortality and drug-related poisoning were higher in the first month of treatment than in the remainder of the treatment period for the methadone group, but not for the buprenorphine group (RR for methadone 2.81, 95% CI 1.55–5.09; buprenorphine 0.58, 95% CI 0.18–1.95).[13]

This finding was consistent with data from cohort studies that also indicated an elevated risk of poisoning at methadone initiation.[18,19] The all-cause mortality risk diminished after initiation of opioid agonist treatment (first 2 weeks of treatment) to the lowest rate in the remaining treatment period (RR in first 2 weeks of treatment 1.44, 95% CI 0.20–2.69; RR in remaining treatment period 0.57, 95% CI 0.52–0.69).[20]

In a comparison of periods in and out of treatment, patients discontinuing methadone had a higher rate of all-cause mortality (crude mortality rate 2.03, 95% CI 1.67–2.39) than those exiting buprenorphine (crude mortality rate 0.80, 95% CI 0.38–1.22).[20]

We formulated the equal recommendation of buprenorphine and methadone as first-line therapy based on strong evidence. Given this recommendation, the patient's preferences and previous experiences are key considerations when choosing the medication. It is important to adapt ongoing monitoring protocols according to the type of opioid agonist therapy, such as focusing on the risk of overdose with methadone. Conversely, as buprenorphine may result in higher attrition rates among patients taking this drug in comparison to methadone, adaptation of ongoing care may need to focus on improving patient engagement.

Opioid agonist therapy with slow-release oral morphine should be available and offered as a second-line treatment option (strong recommendation, moderate certainty of evidence).

Slow-release oral morphine has been used off label in Canada to treat opioid use disorder since the 2010s, resulting in the need for guidance regarding its use. The 2018 guideline recommended slow-release oral morphine as a third-line option when buprenorphine (first-line) and methadone (second-line) could not be used or were not effective. The 2018 recommendation also suggested that only physicians with a Section 56 exemption to administer methadone should prescribe slow-release oral morphine.[8] With Health Canada no longer requiring the Section 56 exemption for practitioners, we now recommend slow-release oral morphine as the second-line treatment without prescribing restrictions.[4] Because the availability of slow-release oral morphine may vary across Canada, we also recommend that this medication should be made widely available to ensure better equity.

Since 2018, 2 meta-analyses have been published, in 2019[21] and 2022,[22] with data coming from the same 4 randomized controlled trials (RCTs) published before 2014. These meta-analyses did not find significant differences between slow-release oral morphine and methadone for treatment retention (RR for 2019 meta-analysis 0.98, 95% CI 0.94–1.02;[21] RR for 2022 meta-analysis

Opioid use disorder (OUD) management in adults aged ≥ 18 years

APPLY THE STANDARDS OF CARE
- Patient-centred approach
- Continuum of care
- Antiracist and culturally safe practices

HARM REDUCTION
"Do you have or need access to harm reduction services?"

PATIENT GOALS AND PREFERENCES
Ask the patient:
"What are your goals?" Discuss goals and potential treatment plan options

YES
Offer harm reduction services
- Provision of sterile consumption equipment
- Overdose prevention education
- Access to take-home naloxone kits

CLINICAL MANAGEMENT
"Are you interested in evidence-based OUD treatment (i.e., long-term opioid agonist therapy [OAT])?"

If appropriate, suggest psycho-social interventions and treatments
- Ensure suitable to the patient's needs
- Not mandatory in order to receive OAT treatment

YES

FIRST-LINE OAT: BUPRENORPHINE OR METHADONE

Monitoring depends on specific OAT:
- High attrition during the first month of buprenorphine initiation
- Higher risk of mortality during the first month of methadone initiation

SECOND-LINE OAT: SLOW-RELEASE ORAL MORPHINE

NO

WITHDRAWAL MANAGEMENT

Inform about risks of withdrawal alone
- Avoid because of high risk of return to use, morbidity and mortality

Suggest a slow OAT taper approach that is:
- Individualized
- Based on the patient's goals, needs and experience
- Supervised with close follow-up

When appropriate, discuss available treatment options (i.e., long-term OAT) again

Consider slow taper for OAT discontinuation if:
- Patient wishes to discontinue OAT
- Successful and sustained response to OAT

Figure 1: Clinical considerations for opioid use disorder management in adults aged 18 years and older.

1.04, 95% CI 0.71–1.52[22]) and heroin use (RR 0.96, 95% CI 0.61–1.52).[21] Treatment retention between buprenorphine and slow-release oral morphine was also equivalent (RR 0.86, 95% CI 0.57–1.28).[22]

Conversely, data from recent cohort studies showed more adverse events with slow-release oral morphine.[23,24] The findings from cohort studies should be interpreted with caution, however, given their observational design and potential selection bias.

The confidence level in the 2018 body of evidence was moderate, and new evidence was evaluated as low in quantity and quality. Consequently, the certainty of evidence remains moderate, and we reaffirm the use of slow-release oral morphine as an alternative option to buprenorphine and methadone. We still strongly suggest that only experienced physicians prescribe slow-release oral morphine for opioid use disorder. In cases where an experienced prescriber is unavailable on site, alternative means such as mentoring or teleconsultation should be employed.

Withdrawal management

There were no major changes to the 2018 recommendations on withdrawal management (Table 1).

Since 2018, very few studies have compared long-term treatment with opioid agonists to opioid withdrawal management alone.[25–28] However, they all highlighted the need to link people with opioid use disorder to long-term support after withdrawal management. If people with opioid use disorder wish to pursue withdrawal management, the new evidence shows that methadone or buprenorphine could be offered[29] as part of a slow taper strategy,[30] in conjunction with close long-term support. A longer taper approach should also be suggested in case of discontinuation of opioid agonist therapy.[31,32] As the evidence does not allow us to specify a taper duration, the duration should be individualized according to the patient's experiences and goals.

Given the low certainty of new evidence, we maintain the existing recommendations that opioid withdrawal management as a stand-alone treatment should be avoided and that appropriate long-term management beyond the initial phase is critical to ensure the safety and well-being of people with opioid use disorder.

Adjunct psychosocial interventions

Psychosocial treatments, interventions, and supports can be offered as adjunct treatments to opioid agonist therapy to increase treatment retention (strong recommendation, moderate certainty of evidence).

Psychosocial treatment should not be a mandatory component of standard treatment for opioid use disorder and should not prevent access to opioid agonist therapy (strong recommendation, moderate certainty of evidence).

Recent studies examining the added value of psychosocial interventions to opioid agonist therapy have reported mixed results depending on the outcome. For treatment retention, most individual RCTs reviewed did not report a difference between the combination of psychosocial interventions plus opioid agonist therapy and opioid agonist therapy offered with basic medical management (Appendix 1). However, a recent meta-analysis of 48 RCTs showed that treatment retention was significantly greater when people with opioid use disorder received psychosocial interventions in combination with opioid agonist therapy, regardless of the follow-up duration.[33]

Studies included in the meta-analysis reported conflicting results regarding unregulated or nonprescribed opioid use. Some reported greater opioid use reduction from a combination of opioid agonist therapy and psychosocial intervention versus opioid agonist therapy alone (RR 0.6, 95% CI 0.5–0.8; $Z = 3.9$, $p < 0.001$),[34] whereas others reported no difference.[35]

The effect of combined psychosocial intervention and opioid agonist therapy is at least equivalent to the impact of opioid agonist therapy offered with basic medical management. Psychosocial interventions can and should, when desired or clinically indicated, be offered in addition to long-term opioid agonist therapy. However, given the limited new evidence published since 2018 for the benefit of adding psychosocial interventions to opioid agonist therapy, a new recommendation highlights that psychosocial treatments should not be mandatory and should not be a barrier to accessing opioid agonist therapy.

Harm reduction strategies

Harm reduction strategies should be offered as part of the continuum of care for patients with opioid use disorder (strong recommendation, moderate certainty of evidence).

- *Current evidence supports the use of the following harm reduction programs: provision of sterile consumption equipment, overdose prevention education, and access to take-home naloxone kits.*

In studies published since 2018, needle and syringe programs, overdose prevention education, and access to take-home naloxone kits have been shown to be effective and valuable in the care of people with opioid use disorder. The provision of sterile injecting equipment reduces the incidence of injecting risk behaviours (adjusted odds ratio 0.52, 95% CI 0.32–0.83) and HIV (RR 0.42, 95% CI 0.22–0.81).[36] Another meta-analysis reported that high-coverage needle and syringe programs (i.e., regular attendance in needle and syringe programs or obtaining 100% of sterile needles and syringes from a safe source), combined with opioid agonist therapy, could reduce the risk of hepatitis C virus infection by 74% (RR 0.26, 95% CI 0.07–0.89).[37] Overdose education programs decrease risky behaviours[38] and the use of opioids alone[39] as well as reduce the percentage of visits or admissions to the emergency department.[40] Providing take-home naloxone kits and overdose education may be relevant strategies to help reduce opioid-related deaths.[41]

This evidence supports the importance of offering evidence-based harm reduction strategies. Providing information and education about the potential adverse effects of opioid use and being responsive to goals and needs is an essential part of the continuum of care for people with opioid use disorder, regardless of their addiction treatment plan.

Special considerations

Alternative option: oral naltrexone

Limited new evidence since 2018 has shown no clear benefits of oral naltrexone over other treatments or placebo,[14] and a higher risk of treatment discontinuation compared with opioid agonist therapy.[42] Given this evidence and scarcity of requests for this medication, we changed the previous recommendation to a special consideration (for further details, see Appendix 1).

Special population: pregnant people

Although the results from recent evidence are mixed, most studies tend to favour buprenorphine for the treatment of opioid use disorder in pregnant people (for the complete list of studies, please refer to the full guideline in Appendix 1). However, the lack of precision on neonatal exposure to opioid agonist therapy does not allow for the formulation of a formal recommendation for 1 medication over another. As such, pregnant people could be offered buprenorphine or methadone as treatment options for opioid use disorder.

Methods

This practice guideline is an update of the 2018 national guideline, developed under the direction of CRISM and supported by grant funding from Health Canada's Substance Use and Addictions Program (2223-HQ-000151). We followed the US Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines,[43] the GRADE approach,[11] and the Appraisal of Guidelines Research and Evaluation—Recommendation Excellence tool (AGREE-REX).[44] The full description of the methodology is available in Appendix 1.

Composition of participating groups

Three separate working committees were formed: a guideline steering committee, a guideline development committee, and an external review committee. The guideline steering committee comprised 5 principal investigators (i.e., node leads) from CRISM (J.B., E.W., D.H., J.R., S.S.).

The guideline development committee consisted of 20 members, including a 6-member scientific team (J.B. [clinical lead], I.Y. [scientific lead], Y.M., K.G., J.B., R.F.) with knowledge of systematic reviews and methodology, 1 guideline development manager, 2 guideline coordinators, and 5 addiction medicine experts (T.D.B., P.B., M-E.G., P.S., G.P.).

The external review committee comprised 63 members, recruited from all Canadian regions by CRISM node managers. It included physicians, PWLLE, nurses, pharmacists, clinical psychologists, policy-makers, and social workers. We specially invited 11 PWLLE to give feedback on the recommendations and the language used throughout the guideline. The prefinal version of the guideline was reviewed by 3 international experts in addiction medicine. The detailed composition of the external review committee is available in Appendix 1.

Selection of priority topics

This update was developed based on the original 11 clinical questions of the 2018 guideline (Appendix 1).[8] The guideline topics were approved by consensus during a video conference in July 2022, with the scientific and clinical members of the guideline development committee. In addition to the original 2018 topics, we decided to include a systematic search of the literature on pregnant people.

Between June 2022 and March 2023, we held a focus group with 4 PWLLE from the CRISM network and surveyed 98 health care providers (i.e., addiction care physicians, primary care physicians, nurses, pharmacists, and psychiatrists) across Canada, to be informed about emerging substance use issues. The survey was disseminated by different communities of practice and networks, including Communauté de Pratique Médicale en Dépendance in Quebec, META:PHI in Ontario, BC ECHO in British Columbia, the Canadian Society of Addiction Medicine, and the National Safer Supply Community of Practice. One issue raised was safer supply, which we are considering separately from the guideline. A summary of the results of the focus group and survey is available in Appendix 1.

Literature review and quality assessment

We gathered literature supporting the updated guideline's recommendations via systematic reviews, focusing on peer-reviewed research only and adhering to the Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness Research[45] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[46] The protocol for the study was preregistered with PROSPERO (CRD42023398663).

An expert librarian carried out 2 separate searches for literature on pharmacotherapeutic and psychosocial treatments and harm reduction interventions (Appendix 1). Studies had to be in English, report on human participants only, and be conducted between January 2017 and September 2023. We searched the MEDLINE, Embase, PsycINFO, ISI Web of Science, Cochrane Central Register of Controlled Trials, and CINAHL databases for meta-analyses, RCTs, quasi-experimental studies, and observational cohort studies. We reviewed the reference lists of all included studies.

We implemented a 2-stage data screening protocol, with inter-rater reliability evaluation occurring at each stage. Stage 1 involved title and abstract screening, with any studies that potentially met inclusion criteria included in a stage 2 full-text review (Y.M., K.G., J.B., R.F.). Studies that passed the full-text review stage were moved to data extraction and synthesis performed (Y.M., K.G., J.B., R.F.) (Appendix 1).

We (Y.M., K.G.) used study design–matched tools to evaluate the quality of each study and assess potential bias (e.g., A Measurement Tool to Assess Systematic Reviews, version 2 for meta-analyses,[47] the Cochrane RoB-2 tool for RCTs,[48] the Cochrane ROBINS-I for non-RCTs,[49] and the Newcastle–Ottawa Scale [NOS] for cohort studies[50]). We (Y.M., K.G.) judged the overall certainty of evidence for key outcomes according to the GRADE approach.[11] GRADE tables are available in Appendix 1.

Development of recommendations

In the first round, held virtually in December 2023, 4 scientific members of the guideline development committee (J.B., I.Y., Y.M., K.G.) drafted recommendation statements based on the

GRADE framework (Box 1). In the second round, held virtually in January 2024, the 5 addiction medicine experts from the guideline development committee revised the draft recommendations, drawing from their clinical judgment and experience. These scientists and clinical experts agreed on the wording and which recommendations should be updated, removed, or unchanged. In the third round, held virtually in February 2024, the steering committee and the clinical lead (J.B.) discussed and approved by consensus the draft recommendations.

We used the GRADE rating process to determine the strength of the recommendations.[11] Four members of the scientific team (J.B., I.Y., Y.M., K.G.) determined the initial rating, followed by consensus through discussion with the addiction medicine experts, and approval by the steering committee.

External review

The national external review began on Apr. 19, 2024, and finished on May 21, 2024. The international review began on Sept. 24, 2024, and finished on Oct. 15, 2024. We used a structured, systematic approach to get feedback from our external review committee, including an online survey with specific questions from validated sources (AGREE-REX[44] and the Institute of Medicine[51]). We used scales and scores to assess the appropriateness of the recommendations, clinical applicability, evidence validity, and clarity of the guideline document. We provided space in the survey for qualitative comments. Nearly all external reviewers (98% of the national and 100% of the international reviewers) found the guideline clear and comprehensible. However, 2% of external reviewers had concerns about the wording of recommendations, and most PWLLE reported encountering some stigmatizing language; we revised the draft guideline document to address this feedback. A summary of the survey results is available in Appendix 1.

Management of competing interests

We followed standards for disclosing competing interests using the Guidelines International Network (GIN)'s principles for disclosure of interests and management of conflicts.[52] All the guideline development committee members and external reviewers were required to complete a standardized form[52] at different time points: at the beginning of the guideline development process and before the external review process. Applying the GIN principles, we excluded people who received remuneration above CAN$1000 for employment or CAN$5000 for a research program from any commercial entity or organization with interests related to our guideline topic within the past 5 years. The project manager of CRISM's Quebec node had the final approval for exclusion of a member.

In total, 22 external reviewers and committee members disclosed receiving remuneration as employees from a commercial entity or as consultants. Of these, 17 received one-time honoraria for delivering or attending an industry-sponsored training seminar, with funds ranging from CAN$200 to $2500. None of these commercial entities were currently involved in the development of recommended pharmaceutical products. None of the disclosed conflicts of interest were judged significant enough to warrant exclusion from the external review or guideline development committee.

Implementation

The purpose of this national guideline is to provide standardization for the clinical management of opioid use disorder across Canada, with the ultimate goal being to translate the recommendations into practice. We will use various strategies to ensure the dissemination and uptake of the guideline. These include social media, press releases, podcasts, and webinars. We will organize training sessions for professionals and patients and distribute printed and digital infographics. People with living or lived experience with opioid use disorder will be involved in the development of all knowledge translation products for patients. We are planning for timely updated recommendations as new evidence emerges, building on a living guideline approach.[53]

Other guidelines

One key national and peer-reviewed guideline on the treatment of opioid use disorder, produced by the American Society of Addiction Medicine,[54] has been updated in the past 6 years, and our recommendations are consistent with that guideline (Table 2).

Gaps in knowledge

Recent, high-certainty evidence regarding the effectiveness of slow-release oral morphine is lacking, as no RCT comparing slow-release oral morphine to another opioid agonist therapy has been published in the last decade. The generation of new evidence is hampered by the limited access to this therapy in most settings. In Canada it is currently used off label, and we recommend its use as a second-line option, but further studies are needed to confirm its comparative safety and efficacy.

Limitations

Values and preferences are part of the GRADE approach to formulating recommendations. Although many studies compared the effectiveness of the medications, very few quantitative studies evaluated patient preferences or satisfaction with the medication they were assigned to, which limited the assessment of this outcome. Patient-centred care and preferences should be considered and included in all treatment plans. We acknowledge the exclusion of qualitative studies from our search strategies as a limitation in our capacity to assess the body of knowledge on patients' preferences to inform recommendations.

Conclusion

This guideline strongly recommends evidence-based treatments and harm reduction strategies for adults with opioid use disorder, regardless of severity. Buprenorphine and methadone are recommended as the first-line treatment options, and slow-release oral morphine is recommended as a second-line option. As per the 2018 guideline, management that comprises withdrawal alone is not recommended. Additionally, psychosocial treatments can be offered but should not be mandatory and,

Table 2: Other national peer-reviewed guidelines on the clinical management of opioid use disorder published since 2018

Guideline title and organization	Year and country	Summary	Key differences from our 2024 guideline update
2020 National Practice Guideline for the Treatment of Opioid Use Disorder: Focused Update,[54] American Society of Addiction Medicine	2020 United States	This guideline updates the one from 2015, replacing it with new recommendations on the clinical management of opioid use disorder. • It gives a thorough description of each medication approved by the Federal Drug Agency (i.e., buprenorphine and its new formulations, methadone and naltrexone). • It provides recommendations based on evidence for each medication, with no distinction such as "first-" or "second-line" treatment options.	Our 2024 update presents and recommends medications in a hierarchical order, based on the latest evidence regarding their safety and efficacy. • Although there are other formulations of medications approved by Health Canada for the treatment of opioid use disorder (e.g., extended-release opioid agonist therapy), this guideline focuses on oral medication and adjunct treatments. • Our guideline proposes slow-release oral morphine as a second-line treatment, as it has been used as an off-label medication for many years in Canada but it is not offered in the United States as a treatment option for opioid use disorder. • No recommendation is formulated regarding extended-release naltrexone, as this medication is currently not available in Canada.

therefore, should not prevent access to evidence-based pharmacologic therapies.

This national guideline provides a strong foundation on which provincial and territorial bodies can build to develop the clinical algorithms and guidance needed to ensure optimal care for people with opioid use disorder.

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Competing interests: Igor Yakovenko reports receiving research assistant payments from the Canadian Research Initiative in Substance Matters (CRISM), in support of the present manuscript. Dr. Yakovenko also received payment from CRISM to cover travel expenses to a CRISM annual meeting in 2022 to present the proposed project, outside the submitted work. Paxton Bach reports receiving a salary from the British Columbia Centre on Substance Use for leadership work as a co–medical director (which includes the development of clinical guidance and contribution to educational activities in this area), outside the submitted work. Ginette Poulin reports receiving honoraria for presentations from the Master Clinician Alliance and Indivior, outside the submitted work. Peter Selby reports holding the role of Past Chair of the Medical Education Committee, American Society of Addiction Medicine (unpaid), outside the submitted work. Marie-Ève Goyer reports receiving public funding from the Québec Ministry of Health to the Clinical and Organizational Support Team, which produces

tools and guidelines, including on opioid agonist therapy (OAT); Dr. Goyer is also under contract with a public entity, Institut National de Santé Publique du Québec, to guide training on OAT to health care professionals, and has received consulting fees from Médecins du Monde France for serving as an expert in Burundi to develop OAT guidelines, and in Tanzania on the clinical aspects of a research project on long-acting buprenorphine (all outside the submitted work). Jürgen Rehm reports receiving a grant from the Canadian Institutes of Health Research (CIHR), paid to the Centre for Addiction and Mental Health, for the Ontario Canadian Research Initiative Node Team CRISM Phase II Application, outside the submitted work. Evan Wood is a physician who works for Vancouver Coastal Health in the area of withdrawal management and undertakes work in the area of occupational addiction medicine. Dr. Wood is also a professor of medicine based at the University of British Columbia (UBC), a position supported by a CIHR Tier 1 Canada Research Chair, and has received salary support from an R01 from the US National Institute on Drug Abuse, paid to UBC. Dr. Wood's research laboratory is further supported by CIHR grants to CRISM. Dr. Wood has also undertaken consulting work in legal matters related to substance use disorders and for a mental health company called Numinus Wellness, where Dr. Wood is former chief medical officer; Dr. Wood has also received compensation in the form of equity in Numinus. Dr. Wood reports receiving honoraria for non-industry-related lectures and presentations (e.g., at academic or educational conferences), including a talk at the Canadian Society of Addiction Medicine (CSAM) paid by the CSAM conference; a Rounds Presentation at Dalhousie University (paid by the university); and an educational talk for the allied health educational platform, Executive Links (all outside the submitted work; none involved funding from the pharmaceutical industry). Dr. Wood has also received payment for expert reports and expert testimony in legal matters pertaining to substance use disorder, including from the Canadian Medical Protective Association and from trade unions representing workers with possible substance use disorder. Dr. Wood has received travel support from the CIHR. Julie Bruneau reports receiving a CIHR research grant and a grant from Health Canada's Substance Use and Addictions Program research program (in support of the present manuscript; both grants were paid to CRISM). Outside the submitted work, Dr. Bruneau has received a National Institutes of Health (NIH) Research Grant and an NIH Grant from Simon Fraser University (paid to Dr. Bruneau directly). Dr. Bruneau has received consulting fees as a member of advisory boards for Gilead Sciences and AbbVie, payment from Simon Fraser (NIH Grant) as a research clinical advisor (paid to Dr. Bruneau directly), an honorarium for a presentation to Gilead Sciences, and support for attending meetings from a CIHR Research Grant, paid to CRISM. Dr. Bruneau has also served as an expert in a brief for court in Alberta (to clarify the rationale for the Grading of Recommendations, Assessments, Development and Evaluation of 1 recommendation of the injectable opioid agonist therapy guidelines [in 2021; affidavit]); Dr. Bruneau has been conducting research for the past 30 years on topics related to prevention and care for people who use drugs. No other competing interests were declared.

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Contributors: Igor Yakovenko, Jacob Belliveau, and Julie Bruneau contributed to the conception and design of the work. Yvette Mukaneza, Katuschia Germé, Jacob Belliveau, and Ross Fraleigh contributed to the acquisition and analysis of the data. Igor Yakovenko, Yvette Mukaneza, Katuschia Germé, and Julie Bruneau contributed to the interpretation of the data. Igor Yakovenko, Yvette Mukaneza, Katuschia Germé, Paxton Bach, Ginette Poulin, Peter Selby, Marie-Ève Goyer, Thomas D. Brothers, Jürgen Rehm, David C. Hodgins, Sherry H. Stewart, Evan Wood, and Julie Bruneau drafted the manuscript. All of the authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. Yvette Mukaneza and Katuschia Germé contributed equally as second authors.

Funding: This guideline was supported by Health Canada (Substance Use and Addiction Program 2223-HQ-000151) and the Canadian Institutes of Health Research, via the Canadian Research Initiative in Substance Matters (CRISM) Phase II: CRISM—Quebec Node (FRN 181678; Bruneau).

Acknowledgements: The authors thank the other guideline development committee members: Pacifique Bugingo, Marin Coignard, Khadidjatou Dia, Grace O'Connor, and Truman Wood-Lockyer, for their expertise in screening the literature, and Aïssata Sako, Noémie Harriet, and Manuela Mbacfou for coordinating the project. The authors are also thankful for the involvement of the external reviewers and the Canadian Research Initiative in Substance Matters staff involved in the production of this guideline, with a particular mention to Karine Laroche for her review of the full guideline, Robin Parker for her expertise in search strategies, and Jill Fikowski for her contribution to the funding process. Committee details are available in the full guideline (Appendix 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.241173/tab-related-content).

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