

# Management of opioid use disorders: a national clinical practice guideline

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The full guideline in English and French is available in Appendix 1 at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170958/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170958/-/DC1)

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**O**pioid use disorder is one of the most challenging forms of addiction facing the Canadian health care system, and a major contributor to the marked rises in opioid-related morbidity and death that Canada has been seeing in recent years. The evolving landscape of nonmedical opioid use has become increasingly dominated by prescription opioids diverted from the medical system and, more recently, by highly potent, illicitly manufactured synthetic opioids (e.g., fentanyl and its analogues, including carfentanil).<sup>1</sup>

The mean national rate of hospital admissions related to opioid poisonings increased from 9 hospital admissions per day in 2007/08 to more than 13 admissions per day in 2014/15.<sup>2</sup> A corresponding rise in injection of prescription opioids has been observed among people who inject drugs in Canada,<sup>3,4</sup> and has been associated with an increased risk of hepatitis C and HIV infections.<sup>5-7</sup> For 2016, the mean rate of apparent opioid-related overdose deaths has reached 7.9 per 100 000 population (i.e., corresponding to a total of 2861 fatalities), with the highest death rates reported for western Canada.<sup>8</sup> This upsurge in opioid-related harms, including overdose deaths,<sup>2-6,8,9</sup> underscores the critical need for coordinated, evidence-based approaches to prevention, treatment and harm reduction to address this national public health emergency.

In most Canadian jurisdictions, poor geographic coverage and availability of evidence-based treatments for substance use disorders has limited the therapeutic options for individuals with opioid use disorder.<sup>10</sup> Further, even in settings where multiple treatment options are offered, detailed clinical guidance articulating their optimal use for varying presentations of opioid use disorder is lacking. Therefore, this guideline is intended to promote the use of evidence-based interventions for treatment of opioid use disorder across the addiction care continuum in Canada.

## KEY POINTS

- Opioid use disorder is often a chronic, relapsing condition associated with increased morbidity and death; however, with appropriate treatment and follow-up, individuals can reach sustained long-term remission.
- This guideline strongly recommends opioid agonist treatment with buprenorphine–naloxone as the preferred first-line treatment when possible, because of buprenorphine’s multiple advantages, which include a superior safety profile in terms of overdose risk.
- Withdrawal management alone is not recommended, because this approach has been associated with elevated risks (e.g., syringe sharing) and death from overdose in comparison to providing no treatment, and high rates of relapse when implemented without immediate transition to long-term evidence-based treatment.
- This guideline supports using a stepped and integrated care approach, in which treatment intensity is continually adjusted to accommodate individual patient needs and circumstances over time, and recognizes that many individuals may benefit from the ability to move between treatments.

## Scope

This guideline was developed to provide Canadian health professionals with an educational tool and clinical practice recommendations for the treatment of opioid use disorder. These recommendations are primarily relevant for the clinical management of this disorder in adults, including young adults.

This guideline is intended for use by physicians and nurse practitioners, allied health care providers, pharmacists, medical educators and clinical care case managers, with or without specialized experience in addiction treatment. Such guidelines are the main resources to inform policy-makers and health care administrators

at the provincial, territorial and national levels for the development of evidence-based strategies. This guideline is intended to serve as a tool to address current gaps in care for opioid use disorder, addiction-medicine training for clinicians and other health care professionals, and treatment access policies across the country.

The recommendations in this guideline are based on the clinical evidence base regarding treatment approaches for opioid use disorder currently available in Canada, including oral opioid agonist treatment and antagonist pharmacotherapies, as well as withdrawal management strategies, residential treatment and psychosocial treatment interventions. The evidence base for pharmacotherapies not yet widely available in Canada, including long-acting and extended-release opioid antagonists, as well as injectable opioid agonist treatment (i.e., diacetylmorphine and hydromorphone), was not reviewed in this guideline.

## Methods

The Canadian Research Initiative in Substance Misuse (CRISM), a Canadian Institutes of Health Research (CIHR)-funded research network composed of four regional networks (nodes) distributed across Canada (British Columbia, the Prairies, Ontario and Quebec-Atlantic), developed this national guideline using a structured literature review approach. Relevant search terms and structured search strategies were used to search PubMed, Web of Science, the Cochrane Library databases and reference lists using a hierarchical approach, whereby meta-analyses and systematic reviews were given the most weight, followed by individual randomized controlled trials (RCTs), quasi-experimental studies, observational studies and, lastly, expert opinion. At least two independent CRISM staff members manually reviewed titles, abstracts and full text of identified citations, selected evidence for inclusion, and compiled narrative evidence reviews for the guideline review panel. A detailed description of the methods used to compile evidence summaries for each recommendation can be found in Appendices 1 and 2, available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170958/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170958/-/DC1).

### Composition of guideline review panel

Each of the four CRISM nodes nominated a clinical lead, to whom the coordination of guideline review activities was delegated in each region. In consultation with the node principal investigator, relevant individual experts and stakeholder organizations from their region, each clinical lead invited 7–13 individuals to participate on the review committee. Including the clinical leads and principal investigators, the pan-Canadian review committee consisted of 43 individuals, including primary care physicians, addiction medicine physicians and other specialists, nurse practitioners and registered nurses, social workers, pharmacists, program managers and administrators, and policy-makers.

### Development of recommendations

Recommendations were developed and graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool<sup>11–14</sup> (Box 1) through an iterative consensus process. The node principal investigators developed draft recommenda-

tions and assigned initial GRADE scores, which were then revised by the full committee in two consecutive rounds of review, as described below. Following each round of review, two guideline authors (E.W. and J.B.) edited and approved the final version of recommendations, which incorporated all input received from committee members, for subsequent committee review (Appendices 1 and 2 provide a more detailed explanation of the evidence underlying each recommendation and score).

### Review of recommendations

The review process consisted of two rounds of revisions of the draft guideline recommendations and evidence review by the pan-Canadian review committee. CRISM staff consolidated guideline revisions and conducted additional structured literature searches as needed to address committee feedback. Differences in opinion or interpretation with regard to the guideline recommendations or the evidence review were resolved through facilitated discussions in regional committee teleconferences or direct communication. A final decision was reached for all cases without the need for arbitration. Following the two rounds of committee review, two international experts and two organizations representing people affected by opioid use disorders reviewed and provided input on the final draft.

### Management of competing interests

This guideline was entirely funded through the CIHR-funded CRISM network and without pharmaceutical industry support. Competing interests were assessed using the Guidelines International Network's Principles for Disclosure of Interests and Management of Conflicts in Guidelines.<sup>15</sup> No current or ongoing direct competing interests were disclosed by the 43 members of the review committee or the four CRISM principal investigators on screening for participation in the review committee. Among the 43 committee members, five individuals reported past direct competing interests in the five years before committee participation in the form of paid consulting, services as a technical advisor, or fees to participate in a speaker panel or training seminar. To mitigate potential, perceived or real risk of bias, these five individuals were asked to recuse themselves from the final review and approval process, which included formal endorsement of the guideline recommendations.

## Recommendations

The complete guideline is available in Appendix 1 and includes a detailed discussion of the evidence pertaining to the 11 recommendations presented in Table 1. In this synopsis, we briefly review the evidence base supporting selected key recommendations.

### First- and second-line treatment options

*Initiate opioid agonist treatment (with buprenorphine-naloxone whenever feasible), to reduce the risk of toxicity, morbidity and death, and to facilitate safer take-home dosing (strong recommendation; high-quality evidence).*

*For individuals responding poorly to buprenorphine-naloxone, consider transition to methadone treatment (strong recommendation; high-quality evidence).*

*Initiate opioid agonist treatment with methadone when treatment with buprenorphine–naloxone is not the preferred option (strong recommendation; high-quality evidence).*

Given the superior safety profile of buprenorphine–naloxone and its potential for flexible take-home dosing in comparison to other opioid agonist medications,<sup>16–20</sup> we strongly recommend initiating opioid agonist treatment with buprenorphine–naloxone as the preferred first-line treatment when possible. Alternatively, methadone should be considered for individuals poorly responding to buprenorphine–naloxone, or when buprenorphine–naloxone is not the preferred option.<sup>18,21</sup> The main advantages and disadvantages of methadone and buprenorphine–naloxone are summarized in Table 2.

Compared with use of  $\alpha_2$ -adrenergic agonists or psychosocial treatment alone, opioid agonist treatment with buprenorphine–naloxone or methadone has proven superior in terms of reten-

tion in treatment, sustained abstinence from illicit opioid use, and reduced risk of morbidity and death.<sup>21,25,37–40</sup> Recent meta-analyses have found that buprenorphine–naloxone and methadone were essentially equally efficacious across these traditional metrics when sufficient (i.e., medium- or high-dose, but not low-dose) buprenorphine–naloxone or methadone were used.<sup>18,21,38</sup>

### Risk of death

While shown to be essentially as efficacious as methadone in clinical trials,<sup>18,21,38</sup> the partial opioid agonist buprenorphine–naloxone has several safety advantages over methadone (a full opioid agonist), including a reduced risk of fatal overdose because of its lower potential for respiratory depression.<sup>16,17,19,25</sup> According to a large retrospective study conducted in the United Kingdom, which included more than 19 million prescriptions over a six-year period

### Box 1: GRADE approach and interpretation of grading

The GRADE approach<sup>11–14</sup> to rating quality of evidence starts with a simplified categorization of study types (i.e., meta-analyses and RCTs, quasi-experimental studies, observational studies and expert opinion), accompanied by initial estimated levels of confidence (i.e., high, moderate, low or very low) in the estimate of a treatment effect. The rating scheme allows for factors that would raise or lower a level of confidence. Factors that would lower confidence in evidence include risk of bias, inconsistency across the RCTs, indirectness and publication bias; factors that would increase confidence include large effect size and an observed dose–response effect. The final quality ratings are reflective of the confidence in the estimated effect in context of bias and limitations that have been identified, as described below:

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The GRADE approach uses a binary system to classify strength of recommendations as strong or weak. It is important to note that although quality of evidence is an important factor when classifying strength of recommendations, “strong” or “weak” in this case does not refer exclusively to the quality of evidence underlying a given recommendation. Except for cost and resource allocation, the recommended GRADE factors to classify strength of recommendations were considered:

- Balance between desirable and undesirable effects: The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.
- Quality of evidence: The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
- Values and preferences: The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.

### Interpretation of strength of recommendations

Examples of how a strong versus weak recommendation could be interpreted by selected audience or user groups are listed below.

A strong recommendation indicates the following:

- **For patients:** Most people in your situation would want the recommended course of action, and only a small proportion would not; you should request discussion with your care provider if the intervention is not offered.
- **For clinicians:** Most patients should receive the recommended course of action. As an example, in this scenario, an algorithm or decision-making tool would not be necessary — the benefits of the recommended course of action would clearly outweigh any advantages of alternative interventions.
- **For health care administrators:** The recommendation can be adopted as a policy in most situations.

A weak recommendation indicates the following:

- **For patients:** Most people in your situation would want the recommended course of action, but many would not.
- **For clinicians:** You should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences. In this scenario, an algorithm or decision-making tool would be advantageous to determine the best course of action.
- **For health care administrators:** Policy-making will require substantial debate and involvement of many stakeholders.

Note: GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial.

(2007–2012), buprenorphine–naloxone was six times safer than methadone in terms of overdose risk.<sup>19</sup> In a similar study conducted in France between 1994 and 1998, the annual estimated death rate related to methadone was at least three times greater

than that for buprenorphine.<sup>16</sup> More recently, a systematic review and meta-analysis of observational cohort studies confirmed that pooled death rates were lower for buprenorphine–naloxone compared with methadone, both during treatment and in the period

**Table 1: Summary of recommendations for the clinical management of opioid use disorder\***

Recommendation	Quality of evidence	Strength of recommendation
<b>First- and second-line treatment options</b>		
1. Initiate opioid agonist treatment with buprenorphine–naloxone whenever feasible, to reduce the risk of toxicity, morbidity and death, and to facilitate safer take-home dosing.	High	Strong
2. For individuals responding poorly to buprenorphine–naloxone, consider transition to methadone treatment.	High	Strong
3. Initiate opioid agonist treatment with methadone when treatment with buprenorphine–naloxone is not the preferred option.	High	Strong
4. For individuals with a successful and sustained response to methadone who express a desire for treatment simplification, consider transition to buprenorphine–naloxone, because its superior safety profile allows for more routine take-home dosing and less frequent medical appointments.	Moderate	Strong
<b>Alternative or adjunct treatment options</b>		
5. In patients for whom first- and second-line treatment options are ineffective or contraindicated, opioid agonist treatment with slow-release oral morphine (initially prescribed as once-daily witnessed doses) can be considered. Slow-release oral morphine treatment should be prescribed only by physicians with a Section 56 exemption to prescribe methadone, or following consultation with an addiction practitioner experienced in opioid agonist treatment with slow-release oral morphine.	Moderate	Strong
6. Offering withdrawal management alone (i.e., detoxification without immediate transition to long-term addiction treatment†) should be avoided, because this approach has been associated with increased rates of relapse, morbidity and death.	Moderate	Strong
7. When withdrawal management (without transition to opioid agonist treatment) is pursued, provide supervised slow (> 1 mo) opioid agonist taper (in an outpatient or residential treatment setting) rather than a rapid (< 1 wk) taper. During opioid-assisted withdrawal management, patients should be transitioned to long-term addiction treatment† to help prevent relapse and associated health risks.	Moderate	Strong
8. For patients with a successful and sustained response to opioid agonist treatment who wish to discontinue treatment (i.e., desiring medication cessation), consider a slow taper approach (over months to years, depending on the patient). Ongoing addiction care should be considered on cessation of opioid use.	Moderate	Strong
9. Psychosocial treatment interventions and supports should be routinely offered but should not be viewed as a mandatory requirement for accessing opioid agonist treatment.	Moderate	Strong
10. Oral naltrexone can also be considered as an adjunct medication if cessation of opioid use is achieved.	Low	Weak
<b>Adjunct harm-reduction strategies</b>		
11. Information and referrals to take-home naloxone programs and other harm reduction services (e.g., provision of clean drug paraphernalia), as well as other general health care services, should be routinely offered as part of standard care for opioid use disorders.	Moderate	Strong

\*The evidence supporting these recommendations is discussed in detail in Appendix 1.

†Long-term addiction treatment: In this context, “addiction treatment” refers to continued care for opioid use disorder delivered by an experienced care provider, which could include pharmacologic treatment (opioid agonist treatment or antagonist treatment), evidence-based psychosocial treatment, residential treatment or combinations of these treatment options. In isolation, withdrawal management, harm reduction services, low-barrier housing and unstructured peer-based support would not be considered “addiction treatment.” Opioid agonist treatment may be provided in an outpatient or in an inpatient addiction-treatment setting.

after completing treatment.<sup>41</sup> A retrospective analysis of administrative mortality data in British Columbia showed that among the 1674 deaths associated with prescription opioids reported between 2004 and 2013, 25% involved methadone without another prescription opioid, 5% involved methadone and another prescription opioid, and the remaining 70% involved all other non-methadone prescription opioids and heroin (no specific data on buprenorphine–naloxone).<sup>42</sup> Overall, the safety advantages of

buprenorphine–naloxone are also relevant from a public health perspective; if diverted to an individual other than to whom it was prescribed, it is far less likely than methadone to cause overdose-related harms, including death.

#### Drug–drug interactions and adverse events

Methadone is associated with a higher frequency of clinically important adverse reactions and drug–drug interactions (e.g.,

**Table 2: Advantages and disadvantages of methadone versus buprenorphine–naloxone**

Methadone	Buprenorphine–naloxone
<b>Advantages</b>	
<ul style="list-style-type: none"> <li>• Potentially better treatment retention, particularly in patients with higher-intensity opioid use disorder (e.g., long history of opioid use, injection heroin use, high tolerance and frequent use), or at high risk of dropping out<sup>18,22,23</sup></li> <li>• May be more effective for withdrawal-symptom control in chronic, severe opioid use disorder<sup>22,23</sup></li> <li>• Treatment initiation may be easier</li> <li>• No maximum dose</li> <li>• Approved in Canada for the indication of pain control</li> </ul>	<ul style="list-style-type: none"> <li>• Health Canada exemption is not required to prescribe buprenorphine–naloxone in most provinces and territories (Appendix 1)</li> <li>• Lower risk of overdose due to partial agonist properties and ceiling effect for respiratory depression (in the absence of benzodiazepines or alcohol)<sup>19,24,25</sup></li> <li>• Lower risk of public safety harms if diverted<sup>26,27</sup></li> <li>• Milder adverse effect profile<sup>22,23</sup></li> <li>• Easier to transition from buprenorphine–naloxone to methadone if treatment is unsuccessful<sup>22,23</sup></li> <li>• Shorter time to achieve therapeutic dose (1–3 d)<sup>28–30</sup></li> <li>• Lower risk of toxicity and drug–drug interactions<sup>31</sup></li> <li>• Milder withdrawal symptoms when discontinuing treatment; may be a better option for individuals with lower-intensity opioid dependence (e.g., oral opioid dependence, infrequent or no injection use, short history of opioid use disorder), and individuals planning to taper off opioid agonist treatment in a relatively short period<sup>22,23</sup></li> <li>• Optimal for rural and remote locations where access to care is limited, methadone prescribers are lacking, or daily witnessed ingestion at a pharmacy is not feasible</li> <li>• More flexible dosing schedules (e.g., alternate-day dosing, earlier provision of 1- to 2-week take-home prescriptions, and unobserved home inductions) support patient autonomy and can reduce costs<sup>32–35</sup></li> <li>• Easier to adjust and retitrate following missed doses, owing to its partial agonist properties</li> </ul>
<b>Disadvantages</b>	
<ul style="list-style-type: none"> <li>• Health Canada exemption is required to prescribe methadone in all provinces and territories</li> <li>• Higher risk of overdose<sup>19,24,25,36</sup></li> <li>• More often prescribed as witnessed doses; prescription of take-home doses typically use slow graduated schedule (e.g., increase of 1 take-home dose per week about every 4 weeks), which can be inconvenient or not feasible for some patients</li> <li>• More severe adverse effect profile (e.g., somnolence, erectile dysfunction, cognitive blunting)<sup>22,23</sup></li> <li>• Longer time to achieve therapeutic dose (several weeks)<sup>36</sup></li> <li>• Can be more challenging to transition from methadone to buprenorphine–naloxone if treatment is unsuccessful<sup>22,23</sup></li> <li>• Higher risk of public safety harms if diverted<sup>26,27</sup></li> <li>• Higher potential for adverse drug–drug interactions (e.g., antibiotics, antidepressants, antiretrovirals)<sup>31</sup></li> <li>• Associated with QTc prolongation and increased risk of cardiac arrhythmia in patients prescribed higher doses, with pre-existing risk factors or taking other medication(s) that prolong QTc interval<sup>22,23</sup></li> <li>• Can be more expensive if prescribed as daily witnessed doses, mainly owing to fees associated with dispensing and witnessed ingestion<sup>34,35</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Potentially lower treatment retention, particularly in higher-intensity opioid use disorder with low-dose buprenorphine–naloxone<sup>18</sup></li> <li>• May cause precipitated withdrawal if appropriate dose-induction protocols are not followed<sup>30</sup></li> <li>• Suppression of withdrawal symptoms may be inadequate for individuals with high opioid tolerance<sup>22,23</sup></li> <li>• Reversing effects of overdose can be challenging because of the pharmacology of buprenorphine (i.e., high affinity for opioid receptors and long half-life)<sup>31</sup></li> <li>• Patients require education on how to take sublingual doses correctly (i.e., hold under tongue until dissolved — up to 10 minutes; do not drink or smoke, and minimize swallowing)</li> <li>• Nonadherence to treatment may require frequent reinductions</li> </ul>
Note: QTc = corrected QT.	

with antiretrovirals, antibiotics and some antidepressants) than buprenorphine–naloxone.<sup>43–45</sup>

Regarding adverse events, only a minor effect on corrected QT (QTc) interval duration has been reported with therapeutic doses of buprenorphine–naloxone, without proarrhythmic effects.<sup>46,47</sup> Conversely, methadone can increase the risk of a rare but fatal ventricular arrhythmia (torsades de pointes) because of its substantial QT-prolonging effects, especially at higher doses.<sup>47</sup> Case series have reported that transitioning patients taking methadone who were experiencing torsades de pointes to buprenorphine corrected the condition.<sup>48,49</sup>

Long-term opioid use, including opioid agonist treatment, may lead to abnormalities in the endocrine system, mainly affecting the gonadal axis and leading to hypogonadism.<sup>50,51</sup> A meta-analysis including four studies showed that methadone was associated with a significantly higher frequency of male sexual dysfunction than buprenorphine–naloxone.<sup>52</sup>

### Treatment flexibility

For methadone, to optimize patient and public safety and prevent diversion, provincial and territorial clinical practice guidelines generally recommend a slow increase in dosing and a mandatory period of daily witnessed ingestion at pharmacies following treatment initiation (range 2–3 mo), which should be continued indefinitely in patients with ongoing substance use or other measures of clinical and social instability. Daily pharmacy attendance can cause substantial lifestyle (e.g., employment) disruption to patients. In contrast, because of comparative safety advantages, buprenorphine–naloxone can safely be provided for take-home dosing as soon as clinical stability is achieved (e.g., often within 7–10 days of treatment initiation), which has the potential to improve patients' quality of life and reduce the burden of requiring daily pharmacy attendance without compromising retention in care.<sup>32,53,54</sup> Further, the partial agonist effect allows more rapid titration to a therapeutic dose (< 1 wk).<sup>22</sup>

There is also potential for cost savings and greater patient autonomy with home induction of buprenorphine–naloxone,<sup>34,35</sup> which under appropriate circumstances, yields similar outcomes as office-based induction in terms of patient safety, retention and reductions in nonmedical opioid use.<sup>33</sup> However, buprenorphine–naloxone requires an individual to be in moderate withdrawal before induction to avoid precipitated withdrawal, which can present greater challenges than methadone inductions, making buprenorphine–naloxone less attractive in certain cases.<sup>55</sup>

The relative ease of transition from buprenorphine–naloxone to methadone further supports the use of buprenorphine–naloxone as the preferred first-line treatment when appropriate. A stepped care strategy involving initial treatment with buprenorphine–naloxone and transition to methadone if necessary was shown to be equally efficacious as an optimally delivered methadone treatment.<sup>56</sup> In contrast, although transitioning to buprenorphine–naloxone from methadone is achievable,<sup>57</sup> this practice must be individually tailored and can be highly challenging for some patients.<sup>58</sup> Indeed, when transitioning from higher daily doses of methadone, there is an increased risk of substantial withdrawal symptoms and consequent relapse;

adjunct medications or inpatient treatment (e.g., medically supervised withdrawal management programs) may be required for safe conversion in such cases.<sup>57</sup>

### Alternative specialist-led approach

*In patients for whom first- and second-line treatment options are ineffective or contraindicated, opioid agonist treatment with slow-release oral morphine (initially prescribed as once-daily witnessed doses) can be considered. Slow-release oral morphine treatment should be prescribed only by physicians with a Section 56 exemption to prescribe methadone, or after consultation with an addiction practitioner with experience in opioid agonist treatment with slow-release oral morphine (strong recommendation; moderate-quality evidence).*

We recommend the 24-hour formulation of slow-release oral morphine as a potential option for opioid agonist treatment in cases where both buprenorphine–naloxone and methadone are ineffective or contraindicated. Other formulations of oral morphine, such as twice-daily, 12-hour sustained- or extended-release formulations — or any other long-acting synthetic opioid — have not been empirically studied in this context and are not recommended by this committee for the treatment of opioid use disorder.

A 2013 Cochrane review including three RCTs comparing slow-release oral morphine to methadone (two studies) or buprenorphine–naloxone (one study) reported no significant difference between treatments for retention in treatment, medication adherence or nonmedical opioid use.<sup>59</sup> Since this review, an international multisite randomized cross-over trial found that slow-release oral morphine was as effective as methadone in reducing illicit opioid use and retaining individuals in treatment,<sup>60</sup> and superior to methadone for overall patient satisfaction, and reducing cravings and symptoms of dysthymia.<sup>61–63</sup> However, because of the small number of trials comparing slow-release oral morphine to other opioid agonist treatments, slow-release oral morphine should generally be considered only for use in patients who are intolerant to or have not responded to first- and second-line opioid agonist treatment, and who remain at high risk of opioid-related harms, including overdose death.

Widely used for opioid agonist treatment in Europe, slow-release oral morphine has been eligible for coverage under Health Canada's Non-Insured Health Benefits program for the treatment of opioid use disorder since November 2014,<sup>64</sup> although this indication is considered off-label in Canada. It is the consensus of this committee that health care providers who wish to prescribe opioid agonist treatment based on slow-release oral morphine should hold a valid federal exemption under Section 56 of the Controlled Drugs and Substances Act to prescribe methadone as an indication of experience with opioid use disorder treatment, or consult with an addiction medicine specialist experienced in prescribing slow-release oral morphine for this indication.

Considering the wide range of doses described in the literature,<sup>65</sup> we suggest that practitioners holding a federal exemption with no prior experience in prescribing slow-release oral morphine for opioid agonist treatment also consult with a specialist. As is the case with methadone, because of patient and public safety risks associated with slow-release oral morphine diversion,

the committee suggests that the standard should be to prescribe slow-release oral morphine as daily witnessed doses.

As in the case of methadone, take-home doses of slow-release oral morphine should be prescribed only to individuals who meet recommended criteria (Appendix 1). If take-home doses of slow-release oral morphine are prescribed, individuals should be closely monitored and appropriate strategies should be employed to reduce the risk of diversion (e.g., random urine drug testing, unannounced pill counts).

### Approach to avoid

*Offering withdrawal management alone (i.e., detoxification without immediate transition to long-term addiction treatment) should be avoided, because this approach has been associated with increased rates of relapse, morbidity and death (strong recommendation; moderate-quality evidence).*

This guideline strongly recommends against a treatment strategy involving withdrawal management alone. Moderate-quality evidence indicates that this approach, when administered without linkage to long-term addiction treatment and care, is associated with elevated risk of relapse, HIV and hepatitis C transmission, and death from drug overdose.<sup>66–68</sup> Patients should be clearly informed of the known risks of withdrawal management alone and engaged in discussion about other treatment options corresponding to their individual needs and circumstances.

Studies have found no significant difference among buprenorphine–naloxone, methadone and  $\alpha_2$ -adrenergic agonists in terms of severity of withdrawal symptoms, adverse effects, withdrawal completion and, importantly, of the poor sustained abstinence rates in the absence of linkage to long-term addiction treatment.<sup>69–71</sup> If withdrawal management is offered as part of an immediate transition to psychosocial or residential treatment, then, among available pharmacologic approaches used for withdrawal management, a buprenorphine–naloxone taper may offer advantages such as faster symptom relief and higher rates of withdrawal completion over methadone tapers.<sup>71</sup> If cessation of opioid use is achieved, oral naltrexone can be considered as an adjunct medication to support abstinence (low-quality evidence).<sup>72</sup>

### Adjunct psychosocial treatment interventions

*Psychosocial treatment interventions and supports should be routinely offered in conjunction with pharmacologic treatment, but should not be viewed as a mandatory requirement for accessing opioid agonist treatment (strong recommendation; moderate-quality evidence).*

In 2011, a Cochrane review of 35 RCTs compared the effect of adding psychosocial treatment interventions to standard opioid agonist treatment programs that included clinician-led medical management and counselling.<sup>73</sup> The authors found, based on moderate- and high-quality evidence, that ancillary psychosocial treatment did not confer additional benefits in terms of retaining individuals in treatment, supporting abstinence or preventing relapse. Clinical trials published after this review have yielded mixed results (Appendix 1). Collectively, these findings suggest that while information and referrals to psychosocial treatment interventions and supports should be routinely offered, a

patient's decision not to participate in psychosocial treatment interventions should never preclude or delay provision of evidence-based pharmacologic treatments.<sup>73</sup> Considering the apparent gaps in knowledge existing in this area, and also that psychosocial treatment interventions and peer-based support systems without associated opioid agonist treatment are widely used throughout Canada's addiction treatment services, the CRISM network is currently undertaking a comprehensive review of the role of psychosocial treatment interventions and other supports in the care of people with opioid use disorder.

### Values and preferences

Inclusion of values and preferences for balancing the magnitude of desirable and undesirable outcomes in management of opioid use disorder was based on relevant published literature, including studies of patient values and preferences, on the expertise of our review panel, and on consultations with groups of experienced clinicians and two community groups of people affected by opioid use disorders. Based on this global assessment, this guideline recommends using a stepped and integrated care approach, in which treatment intensity is continually adjusted to accommodate individual patient needs and circumstances over time, and recognizes that many individuals may benefit from the ability to move between treatments (Figure 1).<sup>74</sup> The choice of treatment should also take into account several patient-specific factors such as initial presentation, comorbidities (e.g., advanced liver disease, prolonged QTc interval), drug–drug interactions, treatment preference and response to treatment, and the prescriber's experience. Details of value- and preference-specific assessments according to recommendations can be found in Appendices 1 and 2.

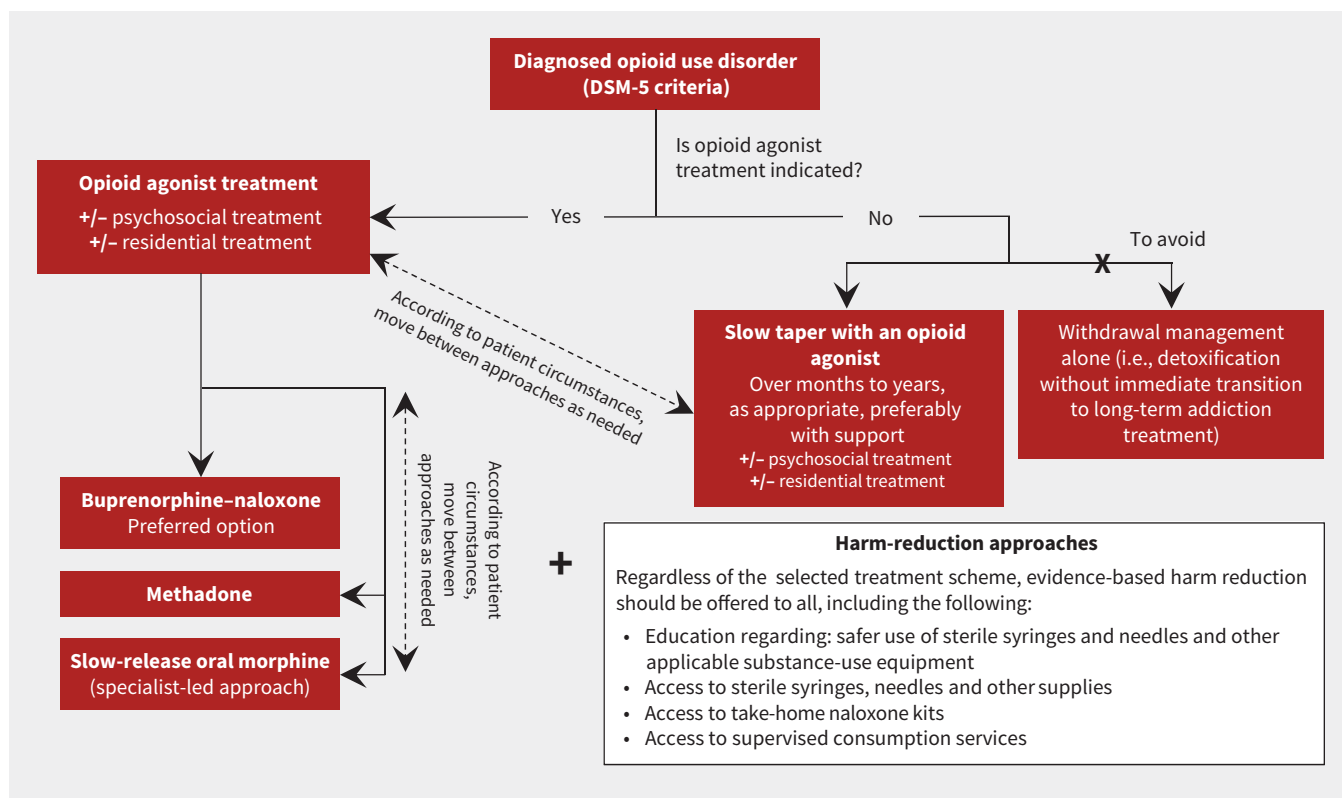
### Special considerations

#### Pregnant women

Opioid agonist treatment has long been the standard therapy for opioid use disorder in pregnant women.<sup>75,76</sup> Abundant supporting evidence has rendered methadone the most frequently prescribed opioid agonist during pregnancy; however, more recent research suggests that buprenorphine (monoproduct) may be similarly safe and effective for the treatment of opioid use disorder in pregnant women.<sup>75,77–79</sup> We suggest that care providers seek specialist consultation as needed to determine, on a case-by-case basis, the appropriate agent for opioid agonist treatment of a pregnant patient. Withdrawal management is not suggested during pregnancy, primarily because of the high rates of relapse and the adverse outcomes associated with rapid withdrawal and subsequent relapse, such as maternal and fetal distress, fetal death, fetal hypoxia, preterm labour and long-term developmental issues.<sup>80</sup>

#### Residential treatment

There are no well-controlled clinical trials or meta-analyses comparing the efficacy of residential treatment to other treatment interventions for opioid use disorder. Observational cohort studies have found that relapse to nonmedical opioid use is relatively common following residential treatment provided without concomitant opioid agonist treatment, with reported relapse rates



**Figure 1:** Treatment algorithm for opioid use disorder. Note: A particular medication may not be indicated for a variety of reasons, including ineffectiveness or medical contraindication, comorbidities, drug–drug interactions, patient preference and specific circumstances, and prescriber’s experience. Any treatment for opioid use disorder, but particularly slow agonist tapers, should incorporate evidence-based psychosocial interventions with qualified professionals, motivational interviewing, long-term monitoring of substance use, provision of comprehensive primary care, and referrals to psychosocial treatment interventions and psychosocial supports as appropriate, with specialist care as required, to optimize physical and mental wellness as the patient progresses in recovery. Withdrawal management (formerly “detoxification”) without linkage to long-term addiction treatment is to be avoided, and patients desiring such approach should be informed of risks and encouraged toward other treatment options that would suit their circumstances. DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, fifth edition*.<sup>74</sup>

ranging from 60% to 90%, potentially increasing the risk of morbidity and death.<sup>20,81,82</sup>

In some residential treatment settings, provision of opioid agonist treatment has been viewed as incompatible with an abstinence-oriented approach, causing the two treatment models to develop and operate separately from one another.<sup>83</sup> Over time, the proven benefits of opioid agonist treatment have prompted efforts to integrate these approaches, and some residential treatment programs have revised admission policies and service provision to accommodate evidence-based treatment and patients’ preference.<sup>83–85</sup> Given the known benefits of opioid agonist treatment, priority should be given to programs and initiatives aimed at strengthening both the opioid agonist and residential treatment systems of care through an integration of evidence-based treatment approaches to opioid use disorder.

## Implementation

Considering that research evidence for treatment of opioid use disorder is limited for youth, older adults and other populations (e.g., individuals living with concurrent chronic pain, pregnant women, incarcerated individuals and Indigenous populations), care provision for these populations may require adjustments in terms of

models of care, service delivery and intensity, or coverage policies at the provincial and territorial level. It is also noted that much of the available research evidence in this area involved patients with moderate to severe opioid use disorder as per the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition*.<sup>74</sup>

In most Canadian jurisdictions, the lack of resources dedicated to health care provider education and to overall addiction care, as well as the absence of comprehensive provincial and territorial or national guidelines, have delayed the implementation of evidence-based treatment strategies for opioid use disorder across the addiction care continuum. In the future, updates to this guideline and, where appropriate, modifications to guideline recommendations, will follow the publication of novel research evidence. The CRISM network is developing a systematic knowledge transfer process to support the implementation and uptake of this national guideline in collaboration with key provincial regulatory agencies and front-line clinicians.

## Other guidelines

Two main guidelines on treatment of opioid use disorder were published in the past decade, one by the American Society of Addiction Medicine<sup>86</sup> and the other by the World Health Organization.<sup>87</sup> A key



structural feature that distinguishes the current guideline from these previous guidelines is its presentation of treatment options as components of a continuum of care, providing one comprehensive set of recommendations to facilitate individualized treatment selection. Whereas earlier guidelines present the evidence and recommendations pertaining to each intervention separately, this guideline stratifies available interventions in relation to each other in terms of comparative safety, effectiveness and intensity, as well as discussing interventions to avoid and considerations for moving between and combining treatments.

Although this guideline's endorsement of opioid agonist treatment is in line with other recent international guidelines, its recommendation of buprenorphine–naloxone as a preferred first-line medication is novel. This guideline is also distinct in its explicit classification of standalone withdrawal management as an approach to avoid. However, like other contemporary guidelines, this guideline emphasizes the importance of collaborative patient-centred care that accommodates patient preferences.

In terms of Canadian guidance for the clinical management of opioid use disorder, existing provincial guidelines for opioid agonist treatment are generally focused on specific dosing recommendations, medical visit schedules and treatment plans, but do not recommend approaches across the spectrum of addiction care, nor first- versus second-line treatments or strategies to avoid (e.g., withdrawal management alone). Therefore, unlike available provincial guidelines, this national guideline proposes a set of high-level recommendations for the clinical management of opioid use disorders to inform physicians about a broad range of available treatment options.

## Gaps in knowledge

Whereas there is a need for further research substantiating the evidence base specific to individuals with prescription opioid use disorder, current evidence comparing methadone and buprenorphine–naloxone suggests that both treatments appear equally efficacious, with the above-mentioned advantages of buprenorphine–naloxone also relevant in the prescription opioid context.<sup>88</sup> In addition, as with patients who primarily inject illicit opioids (e.g., heroin), existing research shows that most patients with a prescription opioid use disorder will relapse to nonmedical opioid use when opioid agonist treatment is used for short periods or tapered.<sup>89,90</sup> Additional research is required to identify the ideal length of treatment with opioid agonists and optimal tapering strategies for individuals who have achieved long-term remission and wish to discontinue opioid agonist treatment, as well as to assess the efficacy of nonpharmacotherapy treatment or intervention options, including residential treatment.

Finally, given the substantial need to expand treatment options nationally, major emphasis among policy-makers is required to gain a better understanding and address barriers to evidence-based treatments, as reviewed in this guideline. Urgent action is required at multiple levels to reduce barriers to accessing specialist-led treatment interventions not reviewed here, such as injectable opioid agonist treatment with diacetylmorphine or hydromorphone.

Individuals with opioid use disorder have many comorbid medical and mental health conditions, and face a range of structural and social difficulties. As such, it is crucial to establish health care implementation science mechanisms to promote action on opioid use disorder on several fronts and monitor the progression of the opioid emergency response across the country in the short- and long-term. To this end, it is paramount to develop a multidisciplinary and actionable care roadmap to improve clinical care strategies (i.e., address wait times for treatment and linkage to care), and strengthen the integration of care and research across the public health and clinical domains.

## Conclusion

Opioid use disorder is a public health emergency nationwide. This guideline recommends strongly against offering withdrawal management in isolation; the resulting loss of tolerance coupled with high rates of relapse associated with this practice increases the risk of overdose death. Instead, this guideline recommends a stepped care approach involving opioid agonist treatment with buprenorphine–naloxone as a first-line treatment, progressing toward methadone as second-line if required; then, if needed and appropriate, toward slow-release oral morphine with the support of a specialist. Furthermore, although out of scope of this guideline, evidence-based harm-reduction approaches such as naloxone programs and novel treatments not yet widely available in Canada must be urgently expanded.

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revisions of the manuscript, and contributed substantially to the interpretation of the findings. All of the authors gave final approval of the version to be published and agreed to act as guarantors of the work.

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