

Injectable opioid agonist treatment for opioid use disorder: a national clinical guideline

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In 2018, at least 4460 Canadians died from an opioid overdose, of which 94% were determined to be unintentional (accidental) overdoses. This represents a 9% increase in overdose deaths from 2017 and a 48% increase from 2016.¹ The recent emergence of street fentanyl, carfentanil and other highly potent synthetic opioids increasingly cut into heroin and other street drugs is a pressing public health concern that has contributed substantially to the overdose emergency. Contamination of street drugs is ongoing and progressive, with new agents such as benzodiazepine analogs being found in substances sold as opioids.² Fentanyl and other synthetic analogs were implicated in 73% of opioid-related deaths in Canada in 2018, compared with 67% in 2017 and 50% in 2016.¹ Although pan-Canadian opioid-related deaths were not tracked before 2016, at least 655 fentanyl-related deaths occurred between 2009 and 2014,³ compared with an estimated 3256 deaths involving fentanyl or fentanyl analogs in 2018 alone.¹

Opioid agonist treatment has proven to be the most effective approach to reducing all-cause mortality in individuals with opioid use disorder⁴ and harms associated with illicit opioid use, including morbidity and mortality.⁵⁻⁹ However, individuals with severe opioid use disorder who inject opioids may not adequately benefit from oral opioid agonist treatment medications for a variety of reasons, including cravings that persist despite optimal opioid agonist treatment dosing; inability to reach a therapeutic dose; or intolerable adverse effects or contraindications. Individuals who are unable to achieve stabilization or cessation of illicit opioids from first-line medications, or whose circumstances and risks otherwise indicate that they may benefit from injectable opioid agonist treatment, like other individuals using illicit opioids, face substantial risks, including premature death, nonfatal overdose, blood-borne infectious diseases (e.g., HIV and hepatitis C), violence and arrest.^{10,11}

Meta-analyses have shown that, among individuals who are refractory to treatment with methadone, supervised injectable diacetylmorphine is beneficial in terms of reducing illicit opioid

KEY POINTS

- Individuals with severe opioid use disorder who inject opioids and have not adequately benefited from oral opioid agonist treatment face substantial risks, including premature death, nonfatal overdose, blood-borne infectious diseases, violence and arrest.
- Individuals with severe opioid use disorder who inject opioids may not benefit adequately from oral opioid agonist treatment medications, for a variety of reasons.
- This guideline recommends that injectable opioid agonist treatment be considered for individuals with severe, treatment-refractory opioid use disorder and ongoing illicit (nonmedical or illegal or both) injection opioid use.
- For patients who are determined to be likely to benefit from injectable opioid agonist treatment, both diacetylmorphine and hydromorphone are acceptable treatment options.
- Injectable opioid agonist treatment should be provided as an open-ended treatment, with decisions to transition away from injectable opioid agonist treatment made collaboratively with the patient.

use, premature treatment discontinuation (or “treatment drop-out”), criminal activity, incarceration and mortality, as well as improving overall health and social functioning, quality of life and stability.¹²⁻¹⁷ In response to regulatory barriers limiting the provision of diacetylmorphine for the treatment of opioid use disorder in Canada, the Study to Assess Longer-term Opioid Medication Effectiveness (SALOME) trial compared injectable hydromorphone to injectable diacetylmorphine and found that both medications, delivered in identical conditions, showed positive outcomes such as high retention rates and reduction of street opioid use (from daily to a few days per month) and illegal activities.¹⁴ Thus, in jurisdictions where diacetylmorphine is currently not available, or for patients in whom it is contraindicated or unsuccessful, hydromorphone may provide an effective, licensed alternative.¹⁴

This clinical guideline provides 3 key recommendations focused on defining the patient population that should be considered for injectable opioid agonist treatment and outlining considerations for medication selection and length of treatment. Additionally, this document contains expert opinion on clinical care approaches, including eligibility, titration and missed doses.

Scope

This guideline was created to provide Canadian health professionals with clinical recommendations and guidance for the treatment of severe opioid use disorder with injectable opioid agonist treatment. These recommendations are relevant for the clinical management of severe opioid use disorder in adults who inject opioids and have continued to experience substantial health or social consequences related to their opioid use disorder, despite past experience with oral opioid agonist treatment at appropriate dosages, previous attempts on opioid agonist treatment without being able to achieve a therapeutic dose, or other circumstances and risks that indicate the patient may benefit from injectable opioid agonist treatment. Individuals who are not appropriate candidates for injectable opioid agonist treatment should be treated according to *Management of Opioid Use Disorders: A National Clinical Practice Guideline*¹⁸ developed by the Canadian Research Initiative in Substance Misuse (CRISM).

Methods

Composition of the guideline committee

The CRISM National Injectable Opioid Agonist Treatment Steering Committee, funded by CRISM, a research network funded by the Canadian Institutes of Health Research, was assembled to coordinate activities to prepare the guideline, which included recruiting the guideline review committee. Representation was sought from each of the 4 CRISM nodes (British Columbia, Prairies, Ontario and Quebec–Atlantic) for the steering committee. The steering committee (N.F., B.L.F., M-E.G., M.T., J.T., K. M., M.P.) included representation from British Columbia, Alberta, Ontario and Quebec; each member had relevant expertise, including in prescribing, research and service planning of injectable opioid agonist treatment.

The steering committee decided to create 2 complementary documents: a clinical guideline and an operational guidance document. To that end, the steering committee assembled the National Injectable Opioid Agonist Treatment Clinical Guideline Review Committee and the National Injectable Opioid Agonist Treatment Operational Guidance Review Committee for the operational guidance document.

Each member of the steering committee was invited to nominate relevant experts from their own province and across the country. As guideline review committee members accepted the invitation to join, they were encouraged to nominate additional members to ensure a diverse guideline review committee that represented a range of experience and expertise. Final committee composition was determined by consensus of the guideline review committee co-chairs (N.F. and C.S.). The guideline review

committee was composed of 30 individuals, including the 2 co-chairs, and physicians, nurses and nurse practitioners, pharmacists, people with lived experience, researchers, treatment providers and front-line staff. A full list of the guideline review committee is available in Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190344/-/DC1.

Guideline development

The guideline review committee co-chairs (N.F. and C.S.) and medical writer (J.R.), on behalf of CRISM, used a structured literature review approach to develop the recommendations. We used relevant search terms and structured search strategies to search PubMed, the Cochrane Library databases, and reference lists (up to Aug. 1, 2018) using a hierarchical approach (J.R.), 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.

The medical writer manually reviewed titles, abstracts and full text of identified citations; selected evidence for inclusion; and compiled narrative evidence reviews, including cost-effectiveness data, for the co-chairs and the guideline review panel. The medical writer also conducted grey literature searches for any other existing guidelines on injectable opioid agonist treatment, and engaged international researchers and other experts in the field to determine whether injectable opioid agonist treatment guidelines exist anywhere in the world. Although some individual clinics have various protocols and manuals, this process helped us to ascertain that the British Columbia Centre on Substance Use's 2017 provincial guidance document for injectable opioid agonist treatment¹⁹ is the only clinical guidance document in existence, to date. The medical writer brought any questions or uncertainties in the literature search, evidence review and synthesis processes to the co-chairs for clarity and consensus. A detailed description of the methods used to compile evidence summaries for each recommendation, including search terms, can be found in Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190344/-/DC1.

Development of recommendations

The guideline review committee co-chairs in conjunction with the medical writer developed key questions and developed and graded draft recommendations (Box 1), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool²⁰⁻²³ through an iterative consensus process. This guideline also contains clinical guidance that is distinct from the recommendations, which were formally categorized using the GRADE system. The rest of the guidance in this guideline can be understood as clinical guidance informed by the existing literature, expert opinion and clinical expertise, and reached by consensus of the experts on the guideline review committee.

Review of recommendations

The review process consisted of 2 rounds of revisions of the draft guideline recommendations and evidence review by the guideline review committee. The medical writer and committee co-chairs

Box 1: GRADE approach and interpretation of grading

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach²⁰⁻²³ to rating quality of evidence starts with a simplified categorization of study types (meta-analyses and randomized controlled trials (RCTs), quasi-experimental studies, observational studies and expert opinion), accompanied by initial estimated levels of confidence (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 either strong or weak — also known as “conditional.” For this guideline, “conditional” was used rather than “weak.” It is important to note that, although quality of evidence is an important factor when classifying strength of recommendations, “strong” or “conditional” 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 conditional recommendation is warranted.

Interpretation of strength of recommendations

Examples of how a strong versus conditional 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 conditional 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.

consolidated guideline revisions 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 by the guideline review committee through teleconference or direct communication. A final decision was reached for all cases, without the need for arbitration.

All 30 guideline review committee members participated in multiple rounds of review and revision of the draft and granted final approval of the guideline contents and clinical recommendations.

External review process

This guideline was reviewed by the National Injectable Opioid Agonist Treatment Operational Guidance Review Committee, which was responsible for the development of its partner document. After this review, 10 international experts, individuals

with lived experience of opioid use disorder, and 1 family member affected by opioid use disorder reviewed and provided input on the final draft. These external reviewers provided input on the clinical guidance, not on the 3 key recommendations.

After external review, the guideline review committee reviewed the entire guideline a final time and signed off on it, after which the guideline review committee co-chairs did the same (a more detailed explanation of the development of recommendations is available in Appendix 2).

Schedule and process for updates

In line with Appraisal of Guidelines for Research & Evaluation (AGREE) II criteria,²⁴ every 2 years, a structured literature search from the last date update will be conducted, and the guideline review committee will be reconvened to determine which updates from research evidence and expert consensus should be added.

Management of competing interests

This guideline was entirely funded through the CRISM network, which in turn is funded by the Canadian Institutes of Health Research, 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.²⁵ No current or ongoing direct competing interests were disclosed by the 30 members of the clinical subcommittee on screening for participation in the review committee. Twenty-one individuals disclosed special interests in relation to the guideline content, pertaining to specific expertise or clinical experience or both, involvement with provincial programs and committees for opioid agonist treatment or injectable opioid agonist treatment, or research interests and publications. No individual reported that their clinical revenue would be influenced by the guideline recommendations. Upon review by the committee co-chairs, none of the potential direct or indirect conflicts of interest or bias disclosed by committee members were deemed to be of sufficient relevance or weight to warrant the members' exclusion from the committee.

Recommendations

The 3 key recommendations are based on the existing literature on injectable opioid agonist treatment, including 2 systematic reviews and meta-analyses. The rest of the guidance in this guideline can be understood as clinical guidance informed by the existing literature and reached by consensus of the experts on the guideline review committee. A list of the recommendations is shown in Table 1, and a summary of the clinical guidance is shown in Table 2. The complete guideline is available in Appendix 1 and includes additional commentary on each of the 3 key clinical recommendations, as well as clinical guidance.

Injectable opioid agonist treatment

Injectable opioid agonist treatment should be considered for individuals with severe, treatment-refractory opioid use disorder and ongoing illicit injection opioid use (quality of evidence: moderate; strength of recommendation: conditional).

The accompanying full guideline in Appendix 1 provides additional guidance and tools for providing injectable opioid agonist treatment, including eligibility considerations, the pre- and postinjection evaluation tool (the Pasero Opioid Sedation Scale²⁶), titration protocols and missed-dose protocols.

Evidence summary

Meta-analyses and systematic reviews of clinical trials involving patients with long-term, refractory heroin addiction have shown the efficacy of diacetylmorphine in comparison with methadone in terms of reducing illicit heroin use, criminal activity and involvement in sex work, as well as improving overall health and social functioning.^{12,13} These meta-analyses include a 2011 Cochrane Review that found that supervised injection of diacetylmorphine, paired with flexible doses of methadone, was superior to oral methadone alone in retaining treatment-

refractory patients in treatment (4 RCTs; $n = 1388$, relative risk [RR] 1.44, 95% confidence interval [CI] 1.19 to 1.75)¹² and a 2015 systematic review and meta-analysis that found supervised injectable heroin treatment to be superior to methadone in treating treatment-refractory opioid use disorder (4 RCTs; $n = 1377$, RR 1.37, 95% CI 1.03 to 1.83).¹³ Both systematic reviews also reported greater reductions in illicit drug use (both heroin and other illicit substances), but owing to heterogeneity in reporting, these were reported narratively rather than included in the meta-analyses.

The SALOME trial compared diacetylmorphine to injectable hydromorphone in a population of patients ($n = 202$) with long-term, treatment-refractory opioid use disorder. Both per-protocol (PP) and intention-to-treat (ITT) analyses found that injectable hydromorphone was not inferior to injectable diacetylmorphine for long-term injection street opioid users not currently benefiting from oral opioid agonist treatment, in terms of retention rates ($\geq 92\%$ PP; $\geq 77\%$ ITT) and reduction of any street opioid use (-0.15 , 90% CI -2.09 to 1.76) PP; -0.85 , 90% CI -2.97 to 1.25 , ITT) and illegal activities (-1.06 , 95% CI -3.46 to 1.14 , PP; -0.98 , 95% CI -3.11 to 1.04 , ITT).¹⁴ Per-protocol analysis also found noninferiority for reduction in street heroin use (-1.44 , 90% CI -3.22 to 0.27). Thus, in jurisdictions in which diacetylmorphine is currently not available, or for patients in whom it is contraindicated or unsuccessful, hydromorphone provides an effective, licensed alternative.¹⁴

The quality of evidence is rated moderate to reflect a moderate confidence in the effect estimate. This is owing to the low number of trials and the possibility (although low) that a single study with results strongly in favour of oral opioid agonist treatment could substantially alter the effect size in the direction of no effect. This recommendation is rated as conditional given that although there are many patients who would choose injectable opioid agonist treatment, there will be some who would find the attendance requirements onerous or otherwise not have their needs met by injectable opioid agonist treatment.

Medication selection

For patients who are determined to be likely to benefit from injectable opioid agonist treatment, both diacetylmorphine and hydromorphone are acceptable treatment options (quality of evidence: low; strength of recommendation: strong).

The accompanying full guideline in Appendix 1 provides additional guidance on medication selection, preparation and dispensation.

Evidence summary

As outlined above, 2 systematic reviews support the recommendation of diacetylmorphine for the treatment of severe opioid use disorder.^{12,13} Both PP and ITT analysis in the SALOME trial found that injectable hydromorphone was not inferior to injectable diacetylmorphine for long-term injection street opioid users not currently benefiting from oral opioid agonist treatment, in terms of retention rates ($\geq 92\%$ PP; $\geq 77\%$ ITT) and reduction of any street opioid use (-0.15 , 90% CI

Table 1: Recommendations summary*

Category	Recommendation	Quality of evidence	Strength of recommendation
Injectable opioid agonist treatment	Injectable opioid agonist treatment should be considered for individuals with severe, treatment-refractory opioid use disorder and ongoing illicit injection opioid use.	Moderate	Conditional
Medication selection	For patients who are determined to be likely to benefit from injectable opioid agonist treatment, both diacetylmorphine and hydromorphone are acceptable treatment options.	Low	Strong
Treatment end date	Injectable opioid agonist treatment should be provided as an open-ended treatment, with decisions to transition to oral opioid agonist treatment made collaboratively with the patient.	Low	Strong

*Protocols and other clinical guidance can be found in the full guideline in Appendix 1. The 3 key recommendations were formulated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and are based on the existing literature on injectable opioid agonist treatment, including 2 systematic reviews and meta-analyses.

Table 2: Clinical guidance summary*

Category	Clinical guidance
Eligibility	Guideline recommendations for eligibility should be considered in concert with clinical judgment and precautions.
Titration process	The titration protocol should be followed.
Pre-intake assessment	This must be performed by a qualified health professional or other trained staff member supervised by a health professional to ensure the patient is not intoxicated or in any other contraindicated acute clinical condition.
Administration of injectable medications	<ul style="list-style-type: none"> • Generally, up to 3 visits per day are recommended. • Individuals should self-administer under supervision of a qualified health professional. • Patients may inject intravenously, intramuscularly or subcutaneously. • Intravenous injection is recommended in upper extremities only. Lower extremity injection should be discussed and risks identified for those who cannot find an appropriate site in their upper extremities or who otherwise prefer intravenous injection in their legs or feet. • Intramuscular sites should be identified by a qualified health professional and rotated according to established practice standards.
Postintake assessment	This must be performed by a qualified health professional or other trained staff member supervised by a health professional to ensure safety and attend to dose intolerance or other adverse event.
Co-prescription of oral opioid agonist treatment	Co-prescription of slow-release oral morphine or methadone should be considered, to prevent withdrawal and cravings between injectable opioid agonist treatment doses, particularly overnight.
Missed doses	The missed-doses protocol should be consulted.
Ongoing substance use	Ongoing substance use while on injectable opioid agonist treatment may be an indication to intensify treatment, which may include increasing dosage, transferring to a more intensive model of care, or increasing psychosocial and other supports. The substance-specific guidance should be consulted.
Stabilization	<p>Stabilization will be patient specific, depending on each patient's circumstances and needs and how these change over time. Patients' DSM-5 diagnoses, physical and mental health comorbidities, and social determinants of health (e.g., poverty, homelessness) should be identified at baseline and tracked over time. Stabilization includes:</p> <ul style="list-style-type: none"> • Clinical stabilization, which includes <ul style="list-style-type: none"> • Lack of cravings • Improved sleep quality and duration • Overall well-being • Psychosocial stabilization, which may include <ul style="list-style-type: none"> • Integrating new activities • Reconnecting with family • Attaining safe housing

Note: DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*.

*Protocols and other clinical guidance can be found in the full guideline in Appendix 1.

–2.09 to 1.76, PP; –0.85, 90% CI –2.97 to 1.25, ITT) and illegal activities (–1.06, 95% CI –3.46 to 1.14, PP; –0.98, 95% CI –3.11 to 1.04, ITT).¹⁴ Per-protocol analysis also found noninferiority for reduction in street heroin use (–1.44, 90% CI –3.22 to 0.27).¹⁴

Although diacetylmorphine has substantially more evidence supporting its efficacy in treating opioid use disorder, it may pose an increased risk of adverse events (e.g., histamine reactions, seizures and overdose) compared with injectable hydromorphone.^{14,27} Hydromorphone was associated with a significantly lower risk of both adverse events (0.60, 95% CI 0.39 to 0.90) and serious adverse events (0.21, 95% CI 0.06 to 0.69) compared with diacetylmorphine.¹⁴ For these reasons, either medication can be considered a reasonable choice, based on availability, patient choice and prescriber judgment.

The quality of evidence is rated low owing to the discrepancy in evidence supporting each medication, with 2 systematic reviews supporting the use of diacetylmorphine, and only a single study supporting the use of hydromorphone. The recommendation is rated as strong based on expert consensus, substantial clinical experience in British Columbia, reduced risk of adverse events for hydromorphone compared with diacetylmorphine, and the lack of regulatory and supply barriers affecting access to hydromorphone.

Treatment end date

Injectable opioid agonist treatment should be provided as an open-ended treatment, with decisions to transition to oral opioid agonist treatment made collaboratively with the patient (quality of evidence: low; strength of recommendation: strong).

The accompanying full guideline in Appendix 1 provides additional guidance on continuing care and treatment transitions, including considerations for transitioning off injectable opioid agonist treatment, short-term transition to oral treatment for travel and continuity of care.

Evidence summary

A loss of treatment benefit when prescription diacetylmorphine treatment was discontinued at a predetermined end date has been found in 2 post-RCT observational cohorts.^{28,29} Both of these studies found an increase in street heroin use after end of treatment, to levels comparable with that of the control group. One study found a rapid deterioration in 82% (94/115) of responders in the diacetylmorphine group 2 months after treatment discontinuation, with mean scores on the constituent scales of the multidomain outcome index returning to pretreatment levels,²⁹ while the other showed a significant increase of street heroin use in the diacetylmorphine group 3 months after treatment discontinuation ($p = 0.005$, mean number of days of heroin use in past month = 8 days at 12 months, mean = 14 days at 15 months).²⁸ Another study compared individuals who voluntarily transitioned from injectable diacetylmorphine to oral methadone before the completion of an RCT against those who were involuntarily transitioned at the end of the 12-month trial, and found that the mean prior 30 days of illicit heroin use was higher in the involuntary group than in the voluntary group at 24 months

(adjusted mean difference –5.58, 95% CI –11.62 to 0.47) and treatment retention was significantly lower (adjusted odds ratio 5.55, 95% CI 1.11 to 27.81).³⁰

The quality of evidence is rated low owing to the low number of studies evaluating the impact of predetermined treatment end dates. This recommendation was rated strong despite the low quality of evidence, owing to the risk associated with fentanyl-contaminated illicit opioid use and its alignment with a recommendation from the World Health Organization that opioid agonist treatment be provided as an open-ended treatment.³¹

Implementation

Policy-makers and program planners in each province will have to determine the model or models of care most appropriate for each setting. Considerations will include the number of patients who would benefit from injectable opioid agonist treatment, the infrastructure and services already in place, available funding and staffing requirements. The National Injectable Opioid Agonist Treatment for Opioid Use Disorder — Operational Guidance document provides (available at <https://crism.ca/projects/ioat-guideline/>) in-depth guidance on planning, implementation, operation and evaluation of injectable opioid agonist treatment programs and is intended to guide the development of new injectable opioid agonist treatment programs across the country. With the release and dissemination of a national clinical guideline and operational guidance document, the primary barrier to treatment will be funding. Thus, jurisdictions will need to ensure adequate funding in order to expand access to injectable opioid agonist treatment across the country.

As with the clinical guideline, every 2 years a structured literature search from the last update will be conducted to inform the operational guidance document and the guidance committee will be reconvened to determine which updates from research evidence and expert consensus should be added.

Other guidelines

Three main guidelines on the treatment of opioid use disorder were published in the past decade, 1 by the American Society of Addiction Medicine,³² 1 by the World Health Organization,³³ and 1 by CRISM (the same group funding and leading this guideline).¹⁸ In 2017, the BC Centre on Substance Use released a provincial guidance document for injectable opioid agonist treatment.¹⁹ However, this guideline — a clinical guideline for injectable opioid agonist treatment for opioid use disorder — is the first of its kind in the world, to our knowledge. Although earlier guidelines present evidence and guidance on the use of (oral) opioid agonist treatment, the 2017 BC provincial guidance document and this clinical guideline are the first to provide clinical guidance for injectable opioid agonist treatment for severe opioid use disorder. This guideline also provides more in-depth guidance, including 3 key clinical recommendations using the GRADE approach, on managing ongoing substance use, comprehensive guidance on patient-centred care and guidance on treatment transitions

for patients in hospital or correctional facilities. Additionally, this guideline is national in scope.

Gaps in knowledge

Although treatment with diacetylmorphine is a standard of care in several countries,³⁴ some gaps in knowledge remain. Because of restrictions on accessing diacetylmorphine in Canada, hydromorphone has been used to expand access to injectable opioid agonist treatment, based on a 2016 noninferiority study.¹⁴ Additional research is required to identify whether certain patients benefit more from hydromorphone or diacetylmorphine, and expanded access to diacetylmorphine across Canada is needed.

To date, published evidence on injectable opioid agonist treatment in special populations is limited. Published evidence on the feasibility and safety of injectable opioid agonist treatment during pregnancy is limited to 2 European case reports, both of which attribute positive pregnancy outcomes to the continuation of treatment with diacetylmorphine in the case of women with severe opioid use disorder and multiple comorbidities.^{35,36} In addition, no research has been conducted that specifically looks at injectable opioid agonist treatment in youth.

Most clinical trials evaluating injectable opioid agonist treatment have restricted participation to individuals who have previously undergone oral opioid agonist treatment; thus, the evidence base can be understood as being supportive of injectable opioid agonist treatment for the treatment of patients who have not benefited from oral opioid agonist treatment. However, clinical practice in British Columbia has shifted to broader eligibility considerations, which are aligned with the expanded eligibility considerations presented in the full guideline (Appendix 1). These expanded eligibility considerations should be evaluated.

Finally, for individuals who have stabilized on injectable opioid agonist treatment and wish to transition to a less intensive approach, more research is needed to determine optimal approaches to transitioning to other treatments.

Conclusion

Individuals with severe opioid use disorder who inject opioids may not adequately benefit from oral opioid agonist treatment medications, for a variety of reasons. This guideline provides a framework for how to build a clinical practice of injectable opioid agonist treatment and recommends that this treatment should be considered for individuals with severe, treatment-refractory opioid use disorder and ongoing illicit injection opioid use. For those individuals determined likely to benefit from injectable opioid agonist treatment, both diacetylmorphine and hydromorphone should be considered appropriate treatments. Finally, injectable opioid agonist treatment should be provided as an open-ended treatment, with decisions to transition to oral opioid agonist treatment made collaboratively with the patient.

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