Opioid Use Disorder-Related Withdrawal Management

Guidance Document

CRISM-ICRAS
Canadian Research Initiative in Substance Misuse
Initiative Canadienne de Recherche en Abus de Substance

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This document is available in English. A French version will be available on the Canadian Research Initiative in Substance Misuse (CRISM)'s website: https://crism.ca

Land Acknowledgement

We respectfully acknowledge that the work to complete this rapid guidance document was hosted on Treaty 13 territory of many nations including the Mississaugas of the Credit, the Anishnabeg, the Chippewa, the Haudenosaunee and the Wendat people, and is now home to many diverse Indigenous Peoples including First Nations, Inuit, and Metis Peoples.

We recognize that the ongoing criminalization, institutionalization, and discrimination against people who use drugs disproportionately harm Indigenous Peoples, and that continuous efforts are needed to dismantle colonial systems of oppression. We are committed to the process of reconciliation with Indigenous Peoples and recognize that it requires significant and ongoing changes to the health care system.

About the Canadian Research Initiative in Substance Misuse

Funded by the Canadian Institutes of Health Research (CIHR), the Canadian Research Initiative in Substance Misuse (CRISM) is a national research-practice-policy network focused on substance use disorders, comprising five large interdisciplinary regional teams (Nodes) representing British Columbia, the Prairie Provinces, Ontario, Québec, and Atlantic. Each CRISM node includes regional research scientists, service providers, policy makers, community leaders, and people with lived experience of substance use disorders. CRISM's mission is to translate the best scientific evidence into clinical practice, health services, and policy change. More information about CRISM can be found at: https://crism.ca.

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The recommendations in this guideline represent the view of the national guideline review committee, arrived at after careful consideration of the available scientific evidence and external expert peer review. The application of the recommendations in this guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the needs, preferences, and values of an individual patient, in consultation with that patient and their guardian(s) or family members, and, when appropriate, external experts (e.g., specialty consultation). When exercising clinical judgment in the treatment of withdrawal management, healthcare professionals are expected to take this guideline fully into account while upholding their duties to adhere to the fundamental principles and values of the Canadian Medical Association Code of Ethics, especially: compassion, beneficence, non-maleficence, respect for persons, justice and accountability, as well as the required standards for good clinical practice defined by relevant governing bodies within regional or local jurisdictions. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ABBREVIATIONS

CRISM: Canadian Research Initiative in Substance Misuse

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

OAT: Opioid Agonist Therapy

OUD: Opioid Use Disorder

PWUD: People who use drugs

PWLE: People with Lived or Living Experience

WM: Withdrawal Management

1.0 Key points of the guidance document

- **There are a number of approaches to withdrawal management, offered in different settings across Canada, however these are often supported by a limited but evolving evidence-base.**
- **The authors recognize that withdrawal management alone is not an effective nor safe treatment for OUD; offering withdrawal management as a standalone option to patients is not recommended unless it is integrated into ongoing and long-term addiction care.**
- **When discussing treatment options, patients should be clearly informed of the known risks of withdrawal management alone and encouraged to consider other treatment options that suit their individual circumstances.**
- **The current guidance document provides consolidated information based on the best available evidence to offer national recommendations for withdrawal management.**
- **These recommendations are intended for clients who make an informed choice to pursue withdrawal management over Opioid Agonist Therapy (OAT), after being presented with the evidence-based information by their care provider.**
- **For individuals who choose withdrawal management, the clinical team should work with the patient to determine the appropriate taper and taper schedule based on the context of withdrawal, and patient-specific factors and preferences.**
- **In any and all cases, providing linkages to continuing community-based addiction care and other health and social supports is strongly advised.**
- **In order to reduce the risk of fatal overdose among patients who decline long-term OAT, patients and families should be provided with take-home naloxone.**

2.0 Background and Scope

2.1 BACKGROUND

Several different approaches to opioid-related detoxification and withdrawal management exist within the continuum of therapeutic interventions for opioid use disorder (OUD). These practices are provided in a number of institutions, facilities, and community-based organizations across Canada; however, such interventions operate on a highly limited evidence-base and are rather diversified across the country.

Aiming to improve the guidance on available evidence-based treatment interventions for opioid use disorder, the Canadian Research Initiative on Substance Misuse (CRISM) had developed guidelines for the treatment of OUD, including withdrawal management in 2018.[1] However, as research has evolved, it became clear that a specific focus on recommendation 2.2 on withdrawal management within the National CRISM guideline required updating.

The update of the guidelines specific to withdrawal management was conducted in two phases as part of a specific CRISM EHT project, led by the Ontario Node:[2] The first consisted of a comprehensive environmental scan that identified and described the current organizational practices and context with respect to withdrawal management for individuals with opioid use disorder (OUD) in both private and public Canadian substance use treatment systems.[3] More details and findings on this environmental scan can be found in Rush et al. (in press, 2023).[3,4]

The second phase of the project involved the review and development of a recommendations guideline document on opioid-related detoxification and withdrawal management to address gaps in the evidence-based delivery and practice for therapeutic approaches to opioid disorders. Below, an overview of the methodology for the development of the withdrawal management guidelines are outlined.

2.2 PURPOSE AND INTENDED AUDIENCE

While recognizing the full scope of possible OUD treatments, this guideline strongly endorses OAT as the preferred first-line treatment when possible. OAT with methadone, buprenorphine, is recognized as safe and effective for use in the long-term treatment of OUD.[1]
Slow-release oral morphine (SROM) is an alternative form of OAT, when methadone or buprenorphine cannot be used or is not preferred by the patient.

This guideline strongly recommends against a management strategy involving withdrawal management alone without plans for transition to long-term evidence-based addiction treatment (e.g., OAT), since this approach has been associated with nearly universal relapse and, subsequently, elevated risk of unsafe drug use and/or overdose in comparison to no treatment provision. However, this guideline also acknowledges the importance of strengthening the residential treatment system for the purpose of aiding individuals who expressly wish to cease opioid use without long-term pharmacological treatment and opt for withdrawal management and/or standalone psychosocial treatment and support.

The intent of this document is to provide advice for clients who decline maintenance OAT, and have a desire to discontinue opioid drugs completely via withdrawal management. Therefore, we refer providers to the CRISM National Guideline for the Clinical Management of Opioid Use Disorder for clients who wish to pursue maintenance therapy.

The current guidance document provides consolidated information based on the best available evidence to offer national recommendations for withdrawal management. This set of six withdrawal management recommendations is intended be interpreted as a group, and not in silo.

2.3 METHODOLOGY

2.3.1 Evidence Selection

A comprehensive search of all clinical studies was conducted between June 1st and July 14th 2021, comparing opioid-related detoxification aided by various clinical interventions and dosing regimens against placebo, agonist maintenance therapy, or treatment as usual. The project Working Group, which included a PWLE, clinicians and researchers drafted eight research questions **(see Appendix 1: Research Questions for Grading)** describing withdrawal management treatment approaches and subsequent search strategies were constructed and used to search PubMed, Web of Science and the Cochrane Library databases hierarchically. The committee used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to evaluate the evidence base.[5] Meta-analyses and systematic reviews of randomized controlled trials were prioritized, followed by prospective and retrospective observational cohort studies. Qualitative studies were excluded primarily due to the low number of qualitative studies addressing the relationships of interest, as well as the GRADE methodology's ability to incorporate non-quantitative studies.

All studies included in the review involved opioid dependent participants detoxing from opioids with the aid of a variety of clinical interventions and dosing regimens, measured against placebo, agonist maintenance therapy, or treatment as usual. No distinction was made between the type of opioids used, severity of dependence (e.g. mild, moderate, severe), or route of administration (e.g., injection, inhalation, ingestion). No restrictions were imposed in terms of studies of outpatients, inpatients, those with comorbid states.

Upon assessment for inclusion by an independent reviewer (MR), 63 (10 systematic reviews, 37 clinical trials, and 16 observational studies) of the 8067 identified records satisfied all the inclusion criteria. Three additional independent reviewers assessed the risk of bias for each study included in the review using a modified version of the Cochrane Collaboration ROB 2 Tool.[6] Quality of evidence underlying each outcome of interest was assessed and graded by the same three reviewers using the GRADE tool through an iterative consensus process.

Where possible, recommendations were based on the highest level of evidence (systematic review/meta-analyses of randomized controlled trials). However, it is important to note that even where systematic reviews were available, the certainty of the evidence was often low. This highlights the need for additional research to inform best practice guidelines in the future.

2.3.2 Development of Recommendations

The Working Group drafted seven recommendations along with their rationale based on the available evidence, as the quality of evidence for the eighth research question (see Appendix I) was very low, making conclusions difficult to draw. A group of potential Canadian reviewers were then identified by the Working Group and a call for participation in a formal review panel was sent out via email to a total of 18 nominated experts from across Canada. Upon expressing their interest and disclosing any conflict of interests, a final panel was convened consisting of nine clinicians representing different academic and clinical institutions from across the country. Each panel member individually reviewed the seven drafted recommendations and graded the quality of evidence as either "strong", "moderate" or "weak" based on a specific set of grading criteria. Quality of evidence was scored using the GRADE tool by the same reviewers for each clinical recommendation. [5]

After the initial round of grading, an online meeting was held between the review panel to discuss discrepancies that had emerged for the grading of five of the seven recommendations. Revisions to the recommendations were made based on the feedback received and consensus reached among the review panel members. Revised recommendations were re-circulated to the panel for a second round of review. Feedback from review panel members, which mainly focused on wording, was collated and a revised set of recommendations were recirculated to the panel for a third round of review. Suggestions were forthcoming from several members regarding the inclusion of a preamble to the recommendations, and this was subsequently incorporated. The review panel was then invited to provide final comments for the fourth round of review on the structure, language, and content of the recommendations, which included suggestions to combine two of the recommendations to avoid repetition. The review panel then met to finalize the recommendations and address additional comments suggested by two of the panel members, arriving at a set of six opioid-specific withdrawal management recommendations, identified below. These recommendations were reviewed by people with lived and living experience and addressed by all members of the panel, whereby the strength of each recommendation was included.

2.3.3 Grading of Recommendations

The withdrawal management guideline recommendations were assessed on the quality of evidence and the strength of recommendations using the GRADE framework. The GRADE ratings are defined in the following tables **(Tables 1 and 2)**. **Table 3** describes the scoring system used to arrive at the final assigned grades. Further details about the search strategy including a list of keywords used are presented in **Appendix 2: Search Strategy.**

Table 1. Definitions in grading for quality of evidence (Adapted from GRADE Working Group, 2004).[7]

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

Table 2. Definitions in grading for strength of recommendations.[8]

Weak	The panel concludes that the desirable effects of the recommendation likely outweigh the undesirable consequences, however, is less certain. In such cases, they recognize that different choices may be appropriate for individual patients.
Strong	The panel is confident that the desirable effects of the recommendation outweigh the undesirable consequences

Table 3. Rating process used to determine final grading.[1]

1. Initial Score

Study Design	Initial Confidence
Meta analyses, RCTs	High (4)
Quasi-experimental	Moderate (3)
Observational studies	Low (2)
Expert opinion	Very low (1)

2. Evaluate + Assess

Lower score if:	Lower score by:
Risk of Bias	Serious (-1)
	Very serious (-2)
Inconsistency between study results	Serious (-1)
	Very serious (-2)
Uncertainty about directness	Some (-1)
	Major (-2)
Imprecision of the estimated effect	Serious (-1)
	Very serious (-2)
Publication bias	Strongly suspected (-1)

3. Final Decision

Confidence in estimated effect (in context of limitations):	
High	●●●●
Moderate	●●●○
Low	●●○○
Very low	●○○○

3.0 Guidelines for Withdrawal Management

The results presented below offer recommendations based on the best available evidence. This set of six withdrawal management recommendations is intended be interpreted as a group, and not in silo. Each recommendation has been assigned a grading on the quality of evidence and one for the strength of the recommendation itself.

3.1 RECOMMENDATION 1

In any circumstance, offer take-home naloxone. As part of collaborative care planning, the clinical team should share information with the patient regarding the evidence for maintenance opioid agonist therapy compared with withdrawal management alone, in order for the patient to make an informed choice.

Offering withdrawal management alone (i.e., detoxification without immediate transition to longer-term opioid agonist therapy; OAT) should be avoided, since this approach has been associated with increased rates of relapse, lower rates of retention in treatment, and higher rates of mortality, morbidity, and other adverse events.

Quality of Evidence: High
Strength of Recommendation: Strong

3.2 RECOMMENDATION 2

In any circumstance, offer take-home naloxone. As part of collaborative care planning, if a patient declines maintenance OAT after being presented with the evidence-based information by the clinical team to inform their choices, and wishes to pursue withdrawal management alone, **and declines Recommendation 1**:

Provide buprenorphine, methadone or slow-release oral morphine for the opioid agonist taper as needed, depending on the patient's informed choice as well as other contextual factors. This approach is associated with improved retention and abstinence from opioids during the withdrawal period, and reduced withdrawal symptom severity at the end of the withdrawal taper.

Quality of Evidence: Low
Strength of Recommendation: Weak

3.3 RECOMMENDATION 3

In any circumstance, offer take-home naloxone. As part of collaborative care planning, if a patient declines maintenance OAT after being presented with the evidence-based information by the clinical team to inform their choices, and wishes to pursue withdrawal management alone, **after declining Recommendation 1**:

Offer an appropriate taper schedule based on the context of withdrawal, and patient specific factors and preferences, rather than non-opioid therapy or symptomatic management. Buprenorphine, methadone or slow-release oral morphine may be used, but in all cases, slower and longer tapers are preferred.

Quality of Evidence: Low
Strength of Recommendation: Weak

3.4 RECOMMENDATION 4

In any circumstance, offer take-home naloxone. As part of collaborative care planning, if a patient declines maintenance OAT after being presented with the evidence-based information by the clinical team to inform their choices, and wishes to pursue withdrawal management alone without the use of opioids, **after declining both Recommendations 2 and 3**:

Provide withdrawal management using an alpha2-adrenergic agonist, as this approach is associated with fewer withdrawal symptoms and increased likelihood of treatment completion, compared to no treatment whatsoever.

Quality of Evidence: Moderate
Strength of Recommendation: Weak

3.5 RECOMMENDATION 5

In any circumstance, offer take-home naloxone. As part of collaborative care planning, if a patient declines maintenance OAT after being presented with the evidence-based information by the clinical team to inform their choices, and wishes to pursue withdrawal management alone*:*

Offer treatment either in an outpatient or inpatient setting.

Quality of Evidence: Low
Strength of Recommendation: Weak

3.6 RECOMMENDATION 6

In all cases, provide linkages to continuing community-based addiction care, as well as other health, mental health and social supports (as appropriate), as this approach has been found to be associated with higher rates of treatment completion and abstinence from opioids, as well as lower mortality rates and adverse events following treatment.

Quality of Evidence: Moderate
Strength of Recommendation: Strong

4.0 Conclusion

This document offers recommendations based on the available evidence. These recommendations address withdrawal management practices for individuals who choose withdrawal management over maintenance OAT, whilst recognizing that withdrawal management alone is not an effective nor safe treatment for OUD and is not recommended as the standard of care in Canada.

The current guidance document outlines six recommendations for providing withdrawal management as part of a collaborative care planning process between the clinical team and the client. It is important to note that the available evidence for withdrawal management is limited and the strength of the evidence was often weak. As such, it is imperative that care plans, services and supports are responsive and tailored to the unique needs of the individual client, and close and ongoing follow-up with a care provider is advised. In order to reduce the risk of fatal overdose among patients who decline long-term OAT, patients and families should receive take-home naloxone along with overdose prevention and rescue education.

Appendix 1: Research Questions for Grading

1. Should individuals with opioid use disorder be offered the option of withdrawal management as a stand-alone treatment?
2. Should individuals with opioid use disorder who wish to pursue withdrawal management be offered an opioid agonist taper as a first line treatment?
3. Should individuals with opioid use disorder who wish to pursue withdrawal management be offered the option of a taper using a full (methadone) or partial (buprenorphine) opioid agonist?
4. Should individuals with opioid use disorder who wish to pursue withdrawal management be offered either an extended, or rapid opioid agonist taper?
5. Should individuals with opioid use disorder who wish to pursue withdrawal management be offered the option of a taper using an alpha2-adrenergic agonist?
6. Should individuals with opioid use disorder who wish to pursue withdrawal management be offered the option to do so in an outpatient, or residential setting?
7. Should individuals with opioid use disorder be offered the option of withdrawal management in conjunction with psychosocial treatment/linkage to ongoing or continuing addiction care?
8. Should individuals with opioid use disorder who wish to pursue withdrawal management be offered a combination of an alpha2-adrenergic agonist and opioid agonist in tapered doses?

Appendix 2: Search Strategy

Completed Searches:

1. ((opioid* or narco* or heroin or opiate*) AND (detox* OR withdrawal))
    a. Pubmed
    b. Cochrane Database of Systematic Reviews
    c. Cochrane Central Register of Controlled Trials
2. ((opioid* or narco* or heroin or opiate*) AND (detox* OR withdrawal) AND (taper* or dosage or dosing or dose* or duration or regimen*))
    a. Pubmed
    b. Cochrane Database of Systematic Reviews
    c. Cochrane Central Register of Controlled Trials
3. ((“opioid”) AND (detox* OR withdrawal))
    a. Pubmed
    b. Cochrane Database of Systematic Reviews
    c. Cochrane Central Register of Controlled Trials
4. “opioid use disorder” (detox* OR withdrawal)
    a. Pubmed
    b. Cochrane Database of Systematic Reviews
    c. Cochrane Central Register of Controlled Trials
5. opiate (detox* OR withdrawal)
    a. Pubmed
    b. Cochrane Database of Systematic Reviews
    c. Cochrane Central Register of Controlled Trials
6. ((opioid* OR narco* OR heroin OR opiate* OR oxyco* OR fentanyl OR methadone) AND (dependen* OR addict* OR abus* OR disorder OR misuse) AND (detox* OR withdrawal OR “cold turkey”))
    a. Pubmed
    b. Cochrane Database of Systematic Reviews
    c. Cochrane Central Register of Controlled Trials

7. ((methadone OR buprenorphine OR "buprenorphine/naloxone") OR (opioid agonist OR cessation OR clonidine OR lofexidine OR “cold turkey”) AND (taper* OR dose* OR duration OR regimen*))
    a. Pubmed since 2018
    b. Cochrane Database of Systematic Reviews
    c. Cochrane Central Register of Controlled Trials
8. ((opioid* OR narco* OR heroin OR opiate* OR oxyco* OR fentanyl OR methadone OR morphine) AND (dependen* OR addict* OR abus* OR disorder OR misuse) AND (detox* OR withdrawal OR “cold turkey”) AND (methadone OR buprenorphine* OR "buprenorphine/naloxone") OR (opioid agonist* OR oat OR cessation OR clonidine OR lofexidine OR cess* OR “cold turkey”))
    a. Pubmed since 2018
    b. Cochrane Database of Systematic Reviews
    c. Cochrane Central Register of Controlled Trials
9. ((opioid* OR narco* OR heroin OR opiate* OR oxyco* OR fentanyl OR methadone OR morphine) AND (detox* OR withdrawal OR cold turkey) AND (RCT OR random* OR meta-analysis OR experimental OR clinical trial OR cohort))
    a. Cochrane Database of Clinical Trials
    b. Cochrane Database of Systematic Reviews
    c. Web of Science
10. ((opioid* OR narco* OR heroin OR opiate* OR oxyco* OR fentanyl OR methadone OR morphine) AND (dependen* OR addict* OR abus* OR disorder OR misuse) AND (detox* OR withdrawal OR cold turkey))
    a. Cochrane Database of Clinical Trials
    b. Cochrane Database of Systematic Reviews
    c. Web of Science
11. ((opioid* OR narco* OR heroin OR opiate* OR oxyco* OR fentanyl OR methadone OR morphine) AND (dependen* OR addict* OR abus* OR disorder OR misuse) AND (taper* OR dosage OR dosing OR dose* OR duration OR regimen*))
    a. Pubmed since 2018
    b. Web of Science

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