

CRISM National Guideline

for the Clinical Management of

OPIOID USE DISORDER



CRISM NATIONAL GUIDELINE FOR THE CLINICAL MANAGEMENT OF OPIOID USE DISORDER

About the Canadian Research Initiative in Substance Misuse

Funded by the Canadian Institutes of Health Research (CIHR), the **Canadian Research Initiative on Substance Misuse (CRISM)** is a national research consortium focused on substance use disorder, comprising four large interdisciplinary regional teams (nodes) representing British Columbia, the Prairie Provinces, Ontario, and Quebec/Atlantic. Each CRISM node is an expert network of research scientists, service providers, policy-makers, community leaders, and people with lived experience of substance use disorder. CRISM's mission is to translate the best scientific evidence into clinical practice and policy change. More information about CRISM can be found at <http://www.cihr-irsc.gc.ca/e/44597.html>.

Authors and Contributors

CRISM National Guideline Review Committee*

British Columbia

Evan Wood, MD, PhD, ABIM, FRCPC, Dip. ABAM, FASAM; Nominated Principal Investigator, British Columbia Node of the Canadian Research Initiative in Substance Misuse; Director, British Columbia Centre on Substance Use; Canada Research Chair in Inner City Medicine; Professor of Medicine, University of British Columbia

Keith Ahamad (Clinical Lead), MD, CCFP, CISAM; Division Lead - Addiction, Department of Family and Community Medicine, Providence Health Care; Assistant Professor, University of British Columbia; Clinician Scientist, British Columbia Centre on Substance Use

Nadia Fairbairn, MD, FRCPC, CISAM; Addiction Medicine Physician Lead, St. Paul's Hospital; Assistant Professor, University of British Columbia

Ramm Hering, MD, MSc, CCFP, Dip. PH, Dip. ABAM, FASAM, CCSAM; Physician Lead, Primary Care Substance Use, Island Health; Physician Lead, Victoria Addiction Medicine Consult Service and Rapid Access Addiction Clinic, Island Health; National Board Member, Canadian Society of Addiction Medicine

Leslie Lappalainen, MD, CCFP, Dip. ABAM; Medical Lead for Addiction Medicine, Mental Health and Substance Use Services, Interior Health; Primary Care Physician, Martin Street Outreach Centre (Penticton); Clinical Instructor, University of British Columbia

Zak Matieschyn, NP(Family), MN; Addiction Nurse Practitioner Fellow, British Columbia Centre on Substance Use; Family Nurse Practitioner, Castlegar and Nelson Health Centres

Kenneth W. Tupper, PhD; Director of Implementation and Partnerships, British Columbia Centre on Substance Use; Adjunct Professor, School of Population and Public Health, University of British Columbia

Nader Sharifi, MD, CCFP, Dip. ABAM; Regional Division Head, Addiction Medicine and Addiction Medicine Consultant Physician, Fraser Health; Family Physician, Forensic Psychiatric Hospital; Correctional Physician, Correctional Services Canada; Medical Director, Provincial Health Services Authority Correctional Health Services

Ontario

Benedikt Fischer, PhD; Nominated Principal Investigator, Ontario Node of the Canadian Research Initiative in Substance Misuse; Senior Scientist, Institute for Mental Health Policy Research, Centre for Addiction and Mental Health; Professor, Department and Institute of Medical Science, Faculty of Medicine, University of Toronto

Peter Selby (Clinical Lead), MBBS, MHSc; Clinician Scientist, Addictions, Centre for Addiction and Mental Health; Professor, Family and Community Medicine and Psychiatry and Public Health, University of Toronto

Sharon Cirone, MD; Family Physician in Addiction Medicine and Mental Health

Curtis Handford, MD, CCFP, MHSc; Staff Physician, Department of Family and Community Medicine, St. Michael's Hospital, Toronto; Associate Professor, Department of Family and Community Medicine, University of Toronto

Meldon Kahan, MD, CCFP, FRCPC; Medical Director, Substance Use Service, Women's College Hospital

Alice Ordean MD, CCFP, MHSc, FCFP, Dip. ABAM, FASAM; Medical Director, Toronto Centre for Substance Use in Pregnancy; Medical Consultant, Addiction Medicine Service, St. Joseph's Health Centre; Associate Professor, Department of Family and Community Medicine, University of Toronto

Kathy Pouteau, MD, DTMH; Family Physician, Sioux Lookout

Sheryl M. Spithoff, MD; Physician, Department of Family Medicine, Women's College Hospital; Lecturer, Department of Family and Community Medicine, University of Toronto

Beth A. Sproule, BScPhm, PharmD; Clinician Scientist, Centre for Addiction and Mental Health; Associate Professor, Leslie Dan Faculty of Pharmacy, University of Toronto

Prairie Provinces

T. Cameron Wild, PhD; Nominated Principal Investigator, Prairies Node of the Canadian Research Initiative in Substance Misuse; Professor, School of Public Health, Edmonton Clinic Health Academy, University of Alberta

Ginette Poulin (Clinical Lead), RD, MD, CCFP, CISAM, CMCBT; Medical Director, Addictions Foundation of Manitoba; Assistant Director, International Medical Graduate Program; Director, Mentorship and Clinical Enhancement Program, Postgraduate Medical Education, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba; Lecturer, Department of Family Medicine, University of Manitoba

Marita Athaide, BN, BGS, MD, CCFP, FCFP; Brandon, Manitoba

Kulvir Badesha, MD, FRCPC, ABAM Candidate; Clinical Assistant Professor, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba; Physician and Assistant Professor, Addictions Unit, Health Sciences Centre, Winnipeg, Manitoba; Physician, Addictions Foundation of Manitoba

Peter R. Butt, MD, CCFP, FCFP; Associate Professor, Department of Family Medicine, College of Medicine, University of Saskatchewan

Laura D. Evans, MD, CCFP, Dip. ABAM, CCSAM, CISAM; Clinical Assistant Professor, Department of Family Practice, Cumming School of Medicine, University of Calgary

Morag Fisher, MBChB, CCSAM; Physician, Manitoba Opioid Support and Treatment Program, Addictions Foundation of Manitoba; Lecturer, Department of Family Medicine, Rady Faculty of Health Sciences, University of Manitoba

Michael R. Isaac, MD, MPH, FRCPC; Public Health and Preventive Medicine Physician; Lecturer, Department of Community Health Sciences, Rady College of Medicine, University of Manitoba

Ronald Lim, MD, CCFP, Dip. ABAM, DFASAM, FISAM, CCSAM; Clinical Assistant Professor, Department of Family Practice and Psychiatry, Cumming School of Medicine, University of Calgary

Richard A. Martin, MD, CCFP, FCFP; Clinical Assistant Professor, Department of Family Medicine, Faculty of Medicine and Dentistry, University of Alberta

Matt Rose, MD, CCFP; Medical Director, Boyle McCauley Health Centre; Assistant Clinical Professor, Department of Family Medicine, University of Alberta

Michael Trew, MD, FRCPC; Clinical Associate Professor, Department of Psychiatry, Cumming School of Medicine, University of Calgary

Quebec-Atlantic

Julie Bruneau, MD, MSc; Nominated Principal Investigator, Quebec-Atlantic Node of the Canadian Research Initiative in Substance Misuse; Co-Principal Investigator, Behavioural and Epidemiology Research Lead, Canadian Network on Hepatitis C; Professor, Family Medicine and Emergency Department, School of Medicine, Université de Montréal; Head, Department of General Medicine, Centre Hospitalier de l'Université de Montréal (CHUM)

Marie-Ève Goyer (Clinical Lead), MD, MSc; Physician and Head of Service, Homelessness / Proximity Medicine Stream, Centre de Recherche et d'Aide pour Narcomanes (CRAN), Integrated University Health and Social Services Centres of Centre-Sud-de-l'île-de-Montréal; Clinical Assistant Professor, Family Medicine and Emergency Department, Université de Montréal.

Peter Barnes, MD, MEd, CCFP; Emergency Medicine and Addictions Medicine Physician, Central Health; Clinical Assistant Professor, Discipline of Family Medicine, Discipline of Emergency Medicine, Faculty of Medicine, Memorial University of Newfoundland and Labrador

Patrick Boudreault, BPharm, MSc; Director of External Affairs and Professional Support, Order of Pharmacists of Quebec

Joseph Cox, MD, MSc, FRCPC, FASAM; Associate Professor, Department of Epidemiology, Biostatistics, and Occupational Health, McGill University; Medical Specialist, Public Health and Preventive Medicine, Prevention and Control of Infectious Diseases Service, Regional Public Health Department, Integrated University Health and Social Services Centres of Centre-Sud-de-l'île-de-Montréal; Clinical Director, Chronic Viral Illness Service, McGill University Health Centre – Glen Site

Jacques Dumont, MD, CCFP; General Practitioner; Clinical Professor, Faculty of Medicine, Université Laval

Serge Dupont, MD; Inspector, Collège des médecins du Québec; Practice Enhancement Division, Collège des médecins du Québec

Samuel Hickcox, MD; General Practitioner, Rheumatologist, Psychotherapist, Mental Health and Addictions Hospitalist and Senior Leadership Team Addictions Liaison, Nova Scotia Health Authority

Bruce Hollett, MD; Division Head, Family Medicine, Chronic Pain and Addictions, Geriatric Medicine, Waterford Hospital; Assistant Professor, Family Medicine and Psychiatry, Memorial University of Newfoundland and Labrador

Peter Hooley, MD, CCFP; Medical Director, Queen Street Recovery Clinic, Charlottetown, PEI; Assistant Professor, Department of Family Medicine, Dalhousie University

David Martell, MD, CCFP; Lecturer, Department of Family Medicine, Faculty of Medicine, Dalhousie University; Peer Reviewer, College of Physicians and Surgeons of Nova Scotia (CPSNS) Methadone Maintenance Therapy (MMT) Practice Support Program; Member, CPSNS MMT Handbook Revision Committee; Board Representative for the Maritime Provinces, Canadian Society of Addiction Medicine

Lynn Miller, DNP, NP, FRE; Policy Consultant, College of Registered Nurses of Nova Scotia

Marie-Chantal Pelletier, MD, LLB; Addiction Medicine Service, Centre Hospitalier de l'Université de Montréal (CHUM); Clinical lecturer, Faculty of Medicine, Université de Montréal

Duncan Webster, MD, MA, FRCPC; Division Head, Infectious Diseases, Saint John Regional Hospital; Associate Professor, Faculty of Medicine, Dalhousie University

** NOTE: Committee members participated in guideline development activities in their individual capacity and not as institutional representatives. Patrick Boudreault received authorization from the Order of Pharmacists of Quebec to participate.*

External Reviewers

*Academic Review Panel**

P. Todd Korthuis, MD, MPH; Associate Professor of Medicine and Public Health, Chief, Addiction Medicine Section, Oregon Health and Science University

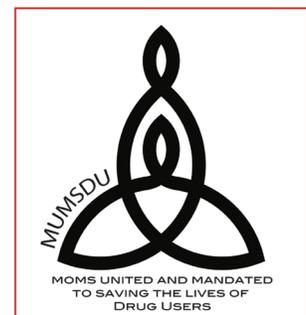
Barbara Broers, MD; Professor, Unit Head, Addictions, Department of Community Medicine and Primary Care, Geneva University Hospitals

** NOTE: Academic reviewers participated in guideline development activities in their individual capacity and not as institutional representatives.*

Stakeholder Review Panel

Canadian Association of People Who Use Drugs

moms united and mandated to saving the lives of Drug Users



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Disclaimer for Healthcare Providers

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 opioid use disorder, 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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This guideline is intended to give an understanding of a clinical problem, and outline one or more preferred approaches to the investigation and management of the problem. This guideline is not intended as a substitute for the advice or professional judgment of a healthcare professional, nor is it intended to be the only approach to the management of a clinical problem. We cannot respond to patients or patient advocates requesting advice on issues related to medical conditions. If you need medical advice, please contact a local healthcare professional.

Table of Contents

EXECUTIVE SUMMARY	12
1.0 INTRODUCTION	14
1.1 Background	14
1.2 Purpose and Scope	16
1.3 Intended Audience	17
1.4 Guideline Development Methodology	17
1.5 Summary of Recommendations	20
2.0 LITERATURE REVIEW	23
2.1 Opioid Agonist Treatments	24
2.1.1 Methadone	24
2.1.2 Buprenorphine/naloxone	26
2.1.3 Transition between methadone and buprenorphine/naloxone	27
2.1.4 Comparison of adverse effects associated with methadone and buprenorphine/naloxone	28
2.1.5 Slow-release oral morphine	33
2.2 Withdrawal Management	36
2.2.1 Important safety notice.....	36
2.2.2 Opioid agonist taper	36
2.2.3 Alpha ₂ -adrenergic agonists	37
2.3 Oral Naltrexone	38
2.4 Psychosocial Treatment and Peer-based Support	39
2.5 Residential Treatment	41
2.5.1 Combining residential treatment with opioid agonist treatment.....	43
2.6 Specific Considerations for Pregnant Women	43
2.6.1 Opioid agonist treatment.....	44
2.6.2 Withdrawal management.....	46
3.0 SUMMARY	47
4.0 GLOSSARY	51
5.0 APPENDICES	56
Appendix 1: Provincial educational and training requirements to prescribe methadone for opioid use disorder.....	57
Appendix 2: Provincial clinical practice guidelines: Dosing recommendations for methadone	62
Appendix 3: Provincial clinical practice guideline recommendations for clinical visits, UDT, and take-home dosing for methadone	65
Appendix 4: Provincial educational and training requirements to prescribe buprenorphine/naloxone	71
Appendix 5: Provincial drug plan coverage and regulations for prescribing buprenorphine/naloxone	76
Appendix 6: Provincial clinical practice guidelines—recommendations for buprenorphine/naloxone.....	78
Table A6.1. Dosing recommendations for buprenorphine/naloxone	78
Table A6.2. Recommendations for clinical visits, UDT, and take-home dosing (carries) for buprenorphine/naloxone.....	80
Appendix 7: Provincial resources for rapid consultation with addiction medicine specialists	82
Appendix 8. DSM-5 Clinical Diagnostic Criteria for Opioid Use Disorder	84
Appendix 9. Guideline methodology and development process	85
REFERENCES	116

EXECUTIVE SUMMARY

Opioid use disorder (OUD) is one of the most challenging forms of addiction affecting Canadian healthcare systems, and a major contributing factor to the recent rise in opioid-related morbidity and mortality across the country. In recent years, the non-medical use of pharmaceutical opioids and the emergence of highly potent illegally manufactured opioids, such as street fentanyl, have increasingly impacted the evolving landscape of opioid use. A national evidence-based guideline articulating the full range of therapeutic options for the optimal treatment of adults and youth with varying presentations of OUD is needed to support the development of a comprehensive and sustainable strategy for addressing this growing challenge to public health.

While recognizing the full scope of possible OUD treatments, this guideline strongly endorses opioid agonist treatment (OAT) with buprenorphine/naloxone as the preferred first-line treatment for OUD when possible. This is in view of buprenorphine/naloxone's considerable advantages, including a safety profile that is superior to that of methadone. However, this guideline recommends the use of methadone as a first-line therapy when buprenorphine/naloxone is contraindicated, and supports the use of methadone as a second-line option when buprenorphine/naloxone treatment proves to have limitations or is ineffective. This guideline also recommends slow-release oral morphine as a potential OAT option in cases where both buprenorphine/naloxone and methadone are ineffective or contraindicated.

This guideline strongly recommends against a treatment 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.

Finally, this guideline supports using a stepped and integrated-care approach where treatment choice or intensity is continually adjusted to accommodate the circumstances and preferences of individual patients over time and recognizes that many individuals may benefit from the

ability to move between evidence-based treatments. This includes intensification (e.g., initiating pharmacotherapy when a non-pharmacotherapy-based strategy is unsuccessful) as well as strategies to de-intensify treatment (e.g., transition from methadone to buprenorphine/naloxone, initiation of opioid agonist taper) for successfully stabilized patients who wish to do so.

1.0 INTRODUCTION

1.1 Background

Opioid use disorder (OUD) is defined as a chronic relapsing illness which, though associated with elevated rates of morbidity and mortality, has the potential to be in sustained remission with appropriate treatment. OUD may involve the use of illicitly manufactured opioids, such as heroin or street fentanyl, or the non-medical use of pharmaceutical opioid medications. In recent years, the landscape of opioid use in Canada has increasingly involved the non-medical use of pharmaceutical opioids and a widening range of highly potent synthetic opioids such as illicitly manufactured fentanyl.¹ Recognized as one of the most challenging forms of addiction facing Canadian healthcare systems, OUD is a major driver of the critical rise in overdose deaths across several Canadian provinces.

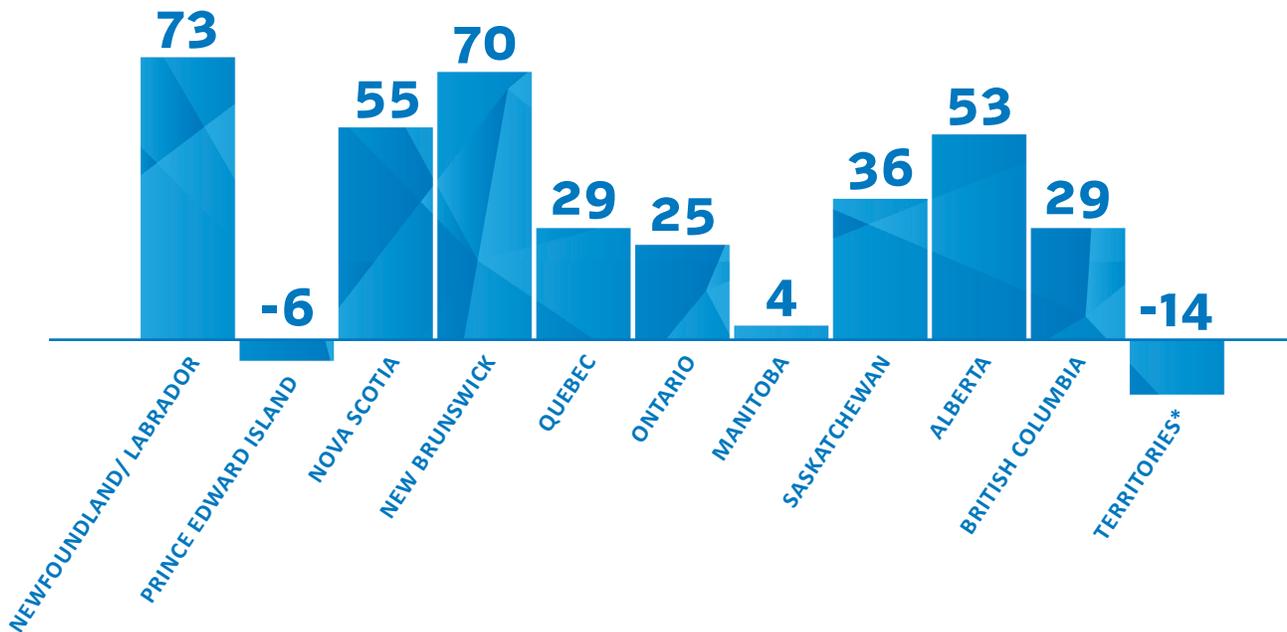
According to recent national data, at least 2,816 Canadians died from opioid overdose in 2016.² While this is the first official national overdose death statistic, provincial overdose death rates over previous years help put the extent of the current opioid emergency into perspective. For example, the number of opioid-related overdose deaths in British Columbia rose by over 87% from 2015 (517) to 2016 (967).³ Alberta also experienced a spike in overdose deaths in 2016 with 363 fentanyl-related deaths; the province's previous fentanyl-related fatal overdose statistics were 66, 117, and 257 in 2013, 2014, and 2015 respectively.^{4, 5} In addition, preliminary reports from Ontario (734 opioid-related deaths in 2015 – a nearly four-fold increase since 1991) also reinforce that untreated OUD is an escalating public health concern.⁶ This unprecedented increase in the number of overdose deaths related to fentanyl and other opioids nationwide underscores the urgency of developing a coordinated evidence-based strategy to address OUD and its associated harms.^{3, 7, 8}

In an analysis of the impact of the opioid emergency on the country's healthcare resources, the Canadian Centre on Substance Use and Addiction (CCSA) and the Canadian Institute for Health Information (CIHI) recently reported that the average number of opioid use-related hospitalizations per province has increased from nine per day in 2007-2008 to 13 per day in 2014-2015.⁸ Figure 1 depicts a province-by-province breakdown of this trend. Importantly, these figures are likely underestimations, as they do not include overdoses that did not involve or require inpatient hospitalization.⁸

Figure 1: Percent increase in significant opioid-poisoning-related[♦] hospitalizations per 100,000 population between 2007-2008 and 2014-2015.

Adapted from: Canadian Institute for Health Information, Canadian Centre on Substance Abuse. Data tables: Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada. Ottawa, ON: CIHI; 2016.

(*Territories include Northwest Territories, Yukon, and Nunavut due to lower volumes.)



♦ “Significant opioid poisonings” are defined as cases in which opioid poisoning was considered influential to the time spent and treatment received by the patient while in hospital [diagnosis types (M), (1), (2), (W), (X), (Y), (6) or (C), according to the ICD-10-CA codes]. Excludes suspected opioid poisoning hospitalizations.

For many years, methadone has been the most commonly prescribed pharmacotherapy for the clinical management of OUD in Canada.⁹ Though more recent literature features a widening range of evidence-based options to address the complex treatment needs of an increasingly diverse patient population, the lack of a comprehensive national guideline has impeded the implementation of these strategies across the country. The development of a cohesive, sustainable, and customizable national OUD care strategy depends on collaboration across multiple domains including public health, clinical care, patients, and peer support groups. The clinical practice recommendations provided in this document are intended to serve as an evidence-based foundation for this collaborative effort.

1.2 Purpose and Scope

The Canadian Research Initiative in Substance Misuse (CRISM) has developed this practice guideline based on current and rigorously reviewed evidence to provide Canadian healthcare professionals with an educational tool and clinical practice recommendations for the treatment of OUD. This guideline is also intended to inform further discussions and collaborations in federal and provincial/territorial policy and program planning. Accordingly, current province-specific training requirements, regulations for prescribing, and dosing schedules for methadone and buprenorphine/naloxone have been provided as appendices.

The guideline presents the scientific and clinical evidence base supporting various OUD treatment approaches, including oral opioid agonist and antagonist pharmacotherapies, as well as withdrawal management strategies, psychosocial interventions, and peer-based support. It is noted that much of the available research evidence in this field involved patients with moderate to severe OUD (as per the DSM-5, see Appendix 8), often with a history of injection heroin use. Thus, this guideline recognizes the need for more studies focused on patients with mild OUD, as well as patients with prescription opioid dependence, who may have fewer comorbidities and may not require intensive pharmacological treatments.

Injectable OAT options, namely diacetylmorphine and hydromorphone, are outside the scope of the present document; however, the guideline review committee acknowledges the body of evidence supporting this treatment approach, which is a standard of care in some international jurisdictions, and emphasizes the need for a dedicated guidance document on injectable opioid treatment options.

While this guideline reviews research evidence regarding the treatment of OUD in the general population, providing pharmacotherapy recommendations that are widely applicable, the committee recognizes the need to develop and implement best practices for treating specific populations, including adolescents and young adults, the elderly, individuals living with concurrent chronic pain, incarcerated individuals, and Indigenous populations (e.g., trauma-informed and culturally optimized care pathways). The evidence presented here is generally extrapolated from studies conducted in adult populations; however, the consensus of the guideline review committee is that the recommendations are equally relevant and applicable to adolescent (aged 12–17 years) and young adult (aged 18–25 years) populations. More specifically—and in line with a recent policy statement from the American Academy of Pediatrics¹⁰—the committee recommends that any clinician providing care to adolescents and young adults with moderate to severe OUD should consider offering first-line pharmacotherapy options where indicated and appropriate. If administration of pharmacotherapy to this patient population is beyond their scope of practice or expertise,

the care provider should refer such patients to a healthcare professional with experience in the treatment of adolescents and young adults with substance use disorders.

Additionally, while this document offers a brief overview of the available evidence specifically related to OUD treatment in pregnant women, it emphasizes the importance of specialist referral and further research and training in this area. Given that specific OUD treatment modalities are governed by provincial regulations, provincial discussions concerning the facilitation of access to OUD treatments for these populations is paramount.

Although harm reduction approaches are outside the scope of the evidence reviewed in this document, the guideline review committee strongly recommends the inclusion of harm reduction services, such as take-home naloxone, sterile needle distribution programs, and supervised consumption or injection services, in the continuum of care for OUD. This recommendation is in line with a well-established and growing body of evidence demonstrating the effectiveness of harm reduction services in reducing HIV and hepatitis C transmission and overdose deaths, while serving as a crucial point of access to further information and care.¹¹⁻²⁰

Finally, detailed treatment procedures and dosing protocols are province-specific and therefore outside the scope of this document. Healthcare professionals should refer to provincial guidelines for this information.

1.3 Intended Audience

This national practice guideline is intended for use by physicians and allied healthcare providers, nurse practitioners, pharmacists, medical educators, or clinical care case managers with or without specialized experience in addiction treatment. Additionally, this guideline may serve as a resource for policymakers and healthcare administrators at the provincial and national levels for the development of evidence-based strategies and programs to address the current gaps in addiction care, addiction medicine training, and treatment access policies across the country.

1.4 Guideline Development Methodology

Please refer to Appendix 9 for a comprehensive description of the guideline development methodology. A brief summary is provided below.

Funding and Committee Membership

Guideline development activities were entirely supported by internal funding from the CIHR Canadian Research Initiative in Substance Misuse (CRISM), without support from the pharmaceutical industry or associated stakeholders.

Between 7-18 individuals were invited to participate from each regional CRISM node; ultimately, an interdisciplinary committee of 43 individuals was assembled. Consistent with best practices for guideline development, CRISM used the AGREE-II instrument²¹ throughout development and revision phases to ensure the guideline met international standards for transparency, high quality, and methodological rigour.

Conflict of Interest Policy

The Guidelines International Network's Principles for Disclosure of Interests and Management of Conflicts²² was used as a framework in the development of this guideline. In brief, committee members were asked to disclose all sources and amounts of direct and indirect remuneration from industry, for-profit enterprises, and other entities (i.e., direct financial conflicts) that could potentially introduce real or perceived risk of bias. In addition, committee members were asked to report indirect conflicts of interest, such as academic advancement, clinical revenue, and professional or public standing that could potentially influence interpretation of evidence and formulation of recommendations.

No committee members were excluded from participation due to direct financial conflicts of interest. Five committee members disclosed direct financial conflicts in the form of paid consulting or advisory board participation ($n = 2$; total remuneration range \$3,000 - \$7,000), and/or paid honoraria for lectures/training ($n = 4$; total remuneration range \$1,000 - \$2,000) for Indivior Inc. in the past five years; none were active at the time of participation. 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 11 clinical recommendations made in the guideline. Additional details regarding the conflict of interest policy can be found in Appendix 9.

Evidence Selection and Review

Guideline content and recommendations are based on a structured review of the literature, and used a traditional hierarchy to identify relevant research evidence, whereby meta-analyses of randomized clinical trials were given the most weight, followed by individual clinical trials, observational reports, and expert opinion.^{23, 24} Independent CRISM medical writers identified and selected studies included in the literature review and compiled evidence summaries for the committee's review and consideration.

Development and Approval of Recommendations

The committee used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool to evaluate the evidence base and clinical recommendations.²³ The GRADE system

takes into account the quality of evidence (based on a range of factors including study design, risk-benefit ratios, potential biases, and scope and consistency of results) to determine the strength of recommendations.^{25, 26} Please refer to Appendix 9 for a more detailed description of the GRADE system and how it was utilized in the development of this guideline.

The consensus of committee members was sought and secured through email communication and tracked document review and revision. The draft guideline and supporting materials were circulated to the committee for two rounds of review in February and March 2017 respectively, and feedback was collated and incorporated into a revised draft for external review.

External Review and Final Approval

Following the two rounds of committee review, the revised guideline was circulated for external review to two international experts and two national stakeholder groups, the Canadian Association of People Who Use Drugs (CAPUD) and moms united and mandated to saving the lives of Drug Users (mumsDU). Final approval and comment was sought from all committee members (excluding individuals with direct conflicts of interest) in August 2017.

Future Updates

The national CRISM consortium will conduct annual reviews of the relevant research literature and update the guideline as required to ensure that advancements in the field reach the intended audience in a timely and effective manner.

1.5 Summary of Recommendations

<i>Recommended first- and second-line treatment options</i>	<i>Quality of evidence</i>	<i>Strength of recommendation</i>	<i>Refer to evidence summary (pp.)</i>
Initiate opioid agonist treatment (OAT) with buprenorphine/naloxone whenever feasible to reduce the risk of toxicity, morbidity and mortality, as well as to facilitate safer take-home dosing.	High	Strong	24-30, Table 2
For individuals responding poorly to buprenorphine/naloxone, consider transition to methadone treatment.	High	Strong	24-27, Table 1
Initiate OAT with methadone when treatment with buprenorphine/naloxone is not the preferred option.	High	Strong	24-29, Table 1
For individuals with a successful and sustained response to methadone who express a desire for treatment simplification, consider transition to buprenorphine/naloxone, since its superior safety profile allows for more routine take-home dosing and less frequent medical appointments.	Moderate	Strong	24-30, Table 1
<i>Alternative or adjunct treatment options</i>	<i>Quality of evidence</i>	<i>Strength of recommendation</i>	<i>Refer to evidence summary (pp.)</i>
In patients for whom first- and second-line treatment options are ineffective or contraindicated, OAT with slow-release oral morphine (ideally prescribed as once-daily witnessed doses) can be considered. Slow-release oral morphine treatment should only be prescribed by physicians with a Section 56 exemption to prescribe methadone, or following consultation with an addiction practitioner experienced in OAT with slow-release oral morphine.	Moderate	Strong	33-35

Offering withdrawal management alone (i.e., detoxification without immediate transition to long-term addiction treatment†) should be avoided, since this approach has been associated with increased rates of relapse, morbidity, and mortality.	Moderate	Strong	36-38
When withdrawal management (without transition to OAT) is pursued, provide supervised slow (>1 month) opioid agonist taper (in an outpatient or residential treatment setting) rather than a rapid (<1 week) 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	36-38
For patients with a successful and sustained response to OAT who wish to discontinue OAT (i.e., desiring medication cessation), consider a slow taper approach (over months to years, depending on the patient). Ongoing addiction care should be considered upon cessation of opioid use.	Moderate	Strong	36-38
Psychosocial treatment interventions and supports should be routinely offered but should not be viewed as a mandatory requirement for accessing OAT.	Moderate	Strong	39-43
Oral naltrexone can also be considered as an adjunct medication if cessation of opioid use is achieved.	Low	Weak	38
<i>Adjunct harm reduction strategies</i>	<i>Quality of evidence</i>	<i>Strength of recommendation</i>	<i>Refer to evidence summary (pp.)</i>
Information and referrals to take-home naloxone programs and other harm reduction services (e.g., sterile injection supplies), as well as other general healthcare services, should be routinely offered as part of standard care for opioid use disorders.	Moderate	Strong	17, 23

Opioid agonist treatment (OAT): Long-term treatment with an opioid agonist medication recognized for use in the treatment of opioid use disorder.

† **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 pharmacological treatment [opioid agonist treatment (OAT) 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”. OAT may be provided in an outpatient or in an inpatient addiction-treatment setting.

2.0 LITERATURE REVIEW

Figure 2. Clinical management of opioid use disorder

Withdrawal Management ¹⁻³	Agonist Therapies		Specialist-Led Alternative Approaches
Tapered methadone, buprenorphine alpha ₂ -adrenergic agonists +/- psychosocial treatment ⁴ +/- residential treatment +/- oral naltrexone ⁵	Buprenorphine/ naloxone ⁶ (preferred)	Methadone ^{7,8}	Slow-release oral morphine ^{9,10} +/- psychosocial treatment ⁴ +/- residential treatment
	+/- psychosocial treatment ⁴ +/- residential treatment		

LOW

TREATMENT INTENSITY

HIGH

If opioid use continues, consider treatment intensification. >>

<<<<<<< Where possible, simplify treatment.

**Harm
Reduction¹¹⁻¹³**

Across the treatment intensity spectrum, evidence-based harm reduction should be offered to all, including:

- Education re: safer use of sterile syringes/needles and other applicable substance use equipment
- Access to sterile syringes, needles, and other supplies
- Access to Take-Home-Naloxone (THN) kits
- Access to Supervised Injection Services (SIS) / Supervised Consumption Services (SCS)

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2.1 Opioid Agonist Treatments

There is substantial research evidence that OAT with either methadone or buprenorphine/naloxone is significantly more effective than non-pharmacological treatments in retaining individuals in treatment and suppressing illicit opioid use.²⁷⁻³¹ In addition, a strong body of evidence demonstrates that OAT is effective in reducing morbidity and mortality,³²⁻⁴³ and reducing risk of HIV and hepatitis C infections among people who inject drugs.⁴⁴⁻⁴⁸

The choice of OAT depends on several patient-specific factors, such as initial presentation, comorbidities (e.g., HIV, hepatitis C, advanced liver disease, prolonged QTc interval), drug-drug interactions, patient preference, treatment history and response to treatment, as well as prescriber experience and appropriate authorizations (i.e., Section 56 exemption to prescribe methadone).

Regardless of the type of treatment, OAT should incorporate provider-led counselling, motivational interviewing, long-term substance use monitoring, 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.

2.1.1 Methadone

Methadone is a long-acting synthetic opioid that acts as a full agonist at the mu (μ) opioid receptor. At a therapeutic dosage, methadone prevents opioid withdrawal, reduces opioid cravings, and blocks the euphoric effects of other opioids.⁴⁹ Methadone has been extensively studied and widely prescribed as a first-line option for OUD treatment since 1964. From the earliest studies conducted on the topic, results have shown that methadone treatment is effective in reducing and/or eliminating heroin use and related mortality and criminality rates.^{50, 51}

However, compared to many other opioids, methadone has an increased risk of toxicity and adverse events due to its long elimination half-life (i.e., ~24–36h on average⁴⁹), narrow therapeutic index, and high potential for interactions with alcohol and other drugs, particularly benzodiazepines.^{52, 53} For example, in the U.S., after controlling for the total number of prescriptions dispensed, methadone-related emergency room visits occur at a rate that is approximately six and 23 times higher than those attributed to oxycodone and hydrocodone, respectively.⁴¹ Moreover, methadone was detected in more than a third of all pharmaceutical opioid-related overdose deaths in the U.S., even though methadone accounts for fewer than 5% of annual opioid prescriptions nationwide.⁴¹ This is consistent with the results of a recent study that reported that approximately 25% of pharmaceutical-opioid-related deaths in British Columbia involved methadone.⁵⁴

The significantly increased risk of overdose death during early stages of methadone treatment (i.e., during initiation, titration, and dose stabilization) and immediately after discontinuing OAT

(i.e., following taper or dropout) has been well described.^{55, 56} Methadone has also been associated with elevated risk of overdose when diverted and used by individuals other than the individual to whom it has been prescribed.^{57, 58} Supervised dosing until patients are stabilized remains one of the more effective methods of preventing methadone-related overdose deaths.^{59, 60}

When dispensed and used as directed, there is considerable evidence demonstrating that methadone is safe and effective for the treatment of OUD and prevention or reduction of related harms.^{27, 29, 37, 49} A 2009 review of 11 randomized controlled trials (RCTs) evaluating methadone in comparison to non-pharmacological treatments demonstrated the superiority of methadone in terms of patient retention and reduction of heroin use, and provided moderate-quality evidence for its comparative effectiveness in reducing criminality and mortality.²⁹ A more recent systematic review, including seven RCTs and 15 reviews or meta-analyses, reached similar conclusions regarding the safety and efficacy of methadone.²⁷

Studies have found that methadone yields optimal treatment outcomes at doses of 80mg/day or higher, and that in some patients, doses above 120mg/day may be required for full opioid blockade and full suppression of withdrawal symptoms.⁶¹⁻⁶⁴ A 2003 systematic review of 21 studies, including 11 RCTs, examined the outcomes for four different dose ranges: low (1–39mg/day), medium (40–59mg/day), high (60–109mg/day), and very high (more than 110mg/day), and found that methadone doses ranging between 60–120mg/day or higher were more effective at retaining individuals in treatment and reducing illicit opioid use compared to lower doses.⁶¹

Higher methadone doses have also been significantly associated with reduced heroin and cocaine use during treatment and fewer and less severe withdrawal symptoms.^{61, 65} In addition, methadone, particularly at higher doses (≥ 100 mg/day), has been independently associated with increased adherence to antiretroviral therapy and improved virologic outcomes (e.g., lower HIV viral loads, higher CD4 counts) in HIV-positive individuals.⁶⁶⁻⁶⁸ The wide range of effective doses for methadone is due to the high level of inter-individual variability in methadone pharmacokinetics and metabolism.⁴⁹ Therefore, after ruling out medical contraindications (e.g., prolonged QTc and contraindicated concurrent medication), determination of optimal methadone dosing necessitates careful individualized dose titration during the induction phase, as opposed to protocol-driven approaches.⁴⁹

Of note, a significantly increased risk of overdose death has been observed at the beginning of methadone treatment (i.e., during initiation, titration, and dose stabilization), and immediately after discontinuing any OAT (i.e., following taper or dropout).^{55, 56} Consequently, particular attention and effort should be directed at retention in treatment and careful patient-specific dose titration until the optimal stable dose is determined (i.e., the minimum dose required to fully alleviate withdrawal symptoms for approximately 24 hours without causing sedation or any other negative side effects).

2.1.2 Buprenorphine/naloxone

Buprenorphine is a long-acting partial mu (μ) opioid receptor agonist that can relieve opioid withdrawal symptoms and cravings for 24 hours or longer when absorbed sublingually. The average elimination half-life of buprenorphine is 37 hours,⁶⁹ although research shows a wide inter-individual variation in half-life (24 to 69 hours) following sublingual administration.^{70, 71} While its higher affinity for the opioid receptor enables buprenorphine to displace other opioids, its maximal opioidergic agonist effect is lower than full opioid agonists (e.g., methadone, morphine, and heroin) due to its limited activating effect on the mu (μ) receptor.⁷² This “ceiling effect” lowers the risk of respiratory depression, side effects, and non-medical use, and contributes to the superior safety profile of buprenorphine.⁷³ The safety profile of buprenorphine is further augmented through co-formulation with naloxone, an opioid antagonist that reduces the risk of diversion and non-medical use.^{74, 75} The naloxone component exerts no antagonist effect when taken sublingually as directed, but can precipitate withdrawal symptoms in opioid-tolerant individuals if injected.

A 2014 meta-analysis of 31 randomized controlled trials demonstrated the superiority of buprenorphine/naloxone over placebo for treatment retention at doses greater than 2mg/day.³⁰ For suppression of illicit opioid use, moderate-quality evidence showed that higher doses of buprenorphine (≥ 16 mg) were more effective than placebo.³⁰

Early trials comparing buprenorphine/naloxone to methadone have been critiqued for using lower buprenorphine/naloxone doses and slower induction protocols than current practice standards.⁷⁶ A 2014 meta-analysis found that lower doses (≤ 6 mg/day) of buprenorphine were less effective at retaining patients in treatment than the lower methadone doses (≤ 40 mg/day). However, at medium (7–16mg/day) and high (≥ 16 mg/day) doses, buprenorphine was found to be equivalent to medium and high methadone doses of 40–85mg/day and ≥ 85 mg/day, respectively, for both treatment retention and reduction of opioid use.³⁰

In the case of flexible dose studies, where the dose is adjusted to individual needs, rather than participants being randomly assigned to a fixed dose, the same meta-analysis yielded high-quality evidence that buprenorphine/naloxone was less effective than methadone in retaining participants in treatment.³⁰ However, for participants who did remain in treatment, moderate-quality evidence showed that both treatments were equally efficacious at suppressing illicit opioid use, as assessed by urinalysis or self-report.³⁰

A 2016 meta-analysis of six RCTs evaluated methadone and buprenorphine/naloxone for the treatment of pharmaceutical opioid-dependent individuals.⁷⁷ The authors found that buprenorphine/naloxone was superior to withdrawal management or psychological treatment alone in terms of retention in treatment, frequency of adverse events (moderate-quality evidence), and reduction in non-medical opioid use (low-quality evidence from three studies).

In studies comparing buprenorphine/naloxone and methadone, no difference was found for treatment retention (low-quality evidence from three studies), self-reported opioid use or opioid-positive urine drug tests (moderate-quality evidence from two studies), or reported adverse events (moderate-quality evidence from two studies) for this specific population.⁷⁷ While further study is needed, the research currently available comparing methadone and buprenorphine/naloxone suggests that both treatments appear equally efficacious in the treatment of pharmaceutical opioid-dependent individuals.

A 2009 meta-analysis examining the efficacy of treatment among individuals who use both heroin and cocaine found that OAT, particularly methadone-based treatment, reduced cocaine use.⁷⁸ However, review authors caution that the included studies did not account for the possible impact of psychosocial elements or other environmental factors. A more recent meta-analysis found no significant differences between methadone and buprenorphine/naloxone, but that neither treatment was effective in reducing concurrent cocaine use.³⁰

2.1.3 Transition between methadone and buprenorphine/naloxone

Several clinical trials demonstrate the feasibility of transitioning from low to moderate methadone doses (up to 60–70mg/day) to buprenorphine/naloxone.⁷⁹ Although this practice must be individually tailored, it generally involves a gradual methadone dose reduction or switching to a short-acting opioid prior to buprenorphine/naloxone induction. For conversion directly from methadone, buprenorphine/naloxone should be initiated no sooner than 24 hours, preferably 36–72 hours, after the last dose of methadone in order to minimize the risk of precipitated withdrawal.^{80,81} When transitioning from methadone doses greater than 70mg/day, there is an increased risk of significant withdrawal symptoms and consequent relapse; adjunct medications and/or inpatient treatment (e.g., medical withdrawal management programs) may be required for safe conversion in such cases.⁷⁹

Conversely, transition from buprenorphine/naloxone to methadone is relatively uncomplicated since this represents a shift from a partial agonist to a full agonist.^{82,83} Generally, the first dose of methadone can be administered within 24 hours of the last dose of buprenorphine/naloxone, using established standards for methadone induction in opioid-tolerant patients. Given the relative ease of transitioning from buprenorphine/naloxone to methadone, a clinical trial was conducted in 2007 to compare a stepped care strategy—which involved treatment initiation with buprenorphine/naloxone at doses up to 32mg/day and a transition to methadone if necessary—to standard methadone treatment.⁸⁴ This study found that the stepped care approach was equally efficacious compared to optimally delivered methadone treatment, and the authors concluded that these results, in combination with buprenorphine’s superior safety profile, were sufficient to warrant broader implementation of buprenorphine/naloxone as a first-line treatment for OUD.⁸⁴

Clinicians with limited experience in managing transitions between treatments are advised to consult an addiction medicine specialist before initiating the process.

2.1.4 Comparison of adverse effects associated with methadone and buprenorphine/naloxone

The main advantages and disadvantages of methadone and buprenorphine/naloxone are summarized in Table 1.

The “ceiling effect” of buprenorphine/naloxone reduces its overdose potential in comparison to methadone, resulting in a superior safety profile. A recent study conducted in the U.K. of over 19 million prescriptions over a six-year period found that buprenorphine/naloxone was six times safer than methadone in terms of overdose risk.⁸⁵ Similarly, other studies have found that the risk of non-medical use and fatal overdose associated with methadone is four times higher than buprenorphine,⁸⁶⁻⁸⁸ while recent reports and an expert panel have also highlighted the substantial risks of fatal overdose during methadone treatment initiation.^{49, 56} Buprenorphine/naloxone has a lower potential for respiratory depression, and standard OAT doses are well below the opioid-naïve threshold lethal dose.³² In comparison, the standard methadone doses used in OUD treatment often exceed the opioid-naïve threshold lethal dose.⁸⁷

The superior safety profile of buprenorphine/naloxone also permits greater flexibility and patient autonomy, allowing for earlier provision of take-home doses than methadone, and unobserved home inductions where circumstances permit (e.g., stable housing) and when no contraindications are present (e.g., sedative use). Previous research has demonstrated that patient outcomes are not improved when buprenorphine/naloxone is provided via daily witnessed ingestion compared to take-home dosing regimens,⁸⁹⁻⁹¹ and there is some evidence that quick transition to take-home dosing can improve treatment compliance and retention.^{92, 93} Additionally, research has shown that unobserved buprenorphine/naloxone inductions are comparable to office-based inductions in terms of safety, patient retention, and reduction in opioid use.⁹⁴⁻⁹⁷

Importantly, however, buprenorphine/naloxone initiation requires the patient to be in moderate withdrawal prior to induction, in order to avoid precipitated withdrawal. Therefore, buprenorphine/naloxone may not be appropriate for all patients due to individual factors such as intolerable symptoms during treatment initiation.⁹⁸ In these cases, medically supervised buprenorphine/naloxone induction in an inpatient setting (i.e., inpatient withdrawal management or residential treatment) could facilitate more intensive monitoring, support, and symptom management for patients during challenging inductions.

Methadone has a higher potential for drug-drug interactions with many common medications (e.g., antibiotics, antidepressants, antiretrovirals), most notably with benzodiazepines.^{55, 99-101}

For example, a retrospective analysis of buprenorphine/naloxone and methadone poisoning cases reported to the American Association of Poison Control Centers' National Poison Data System (NPDS) between 2002 and 2010 showed that among the 692 methadone-related cases and 72 buprenorphine-related cases identified, the clinical toxic effects associated with concomitant use of benzodiazepines were more severe with methadone than with buprenorphine, particularly concerning the occurrence of coma (22.4% vs. 5.6%), respiratory arrest (4.5% vs. 0), hypotension (11.8% vs. 2.8%) and cardiac arrest (1.9% vs. 0).¹⁰²

Methadone can cause a clinically significant prolongation of the QTc interval, particularly at higher doses over 100mg/day.¹⁰³⁻¹⁰⁵ Due to this QTc-prolonging effect, methadone can increase the risk of Torsade de Pointes, a rare, but potentially fatal, cardiac arrhythmia.⁵² Conversely, buprenorphine/naloxone has not been associated with QTc prolongation,¹⁰⁴ and case series have reported that transitioning methadone-treated patients who develop Torsades de Pointes to buprenorphine/naloxone reverses the condition, with the QTc interval returning to pre-treatment values within a few weeks.¹⁰⁶⁻¹⁰⁸ In view of these findings, buprenorphine/naloxone should be considered the preferred first-line OAT option for patients with cardiac disease or other risk factors for Torsades de Pointes, such as genetically-inherited cardiac repolarization defects, electrolyte imbalances, and concomitant use of other QTc-prolonging agents.^{103, 109, 110}

While opioid use is more prevalent among men, study outcomes are generally not reported in terms of gender. The few studies that have examined the influence of gender and/or sex reported no differences between men and women in risks or outcomes of buprenorphine/naloxone- or methadone-based OAT.^{106, 107} More research is needed to explore gender- and sex-related differences in risks (e.g., Torsade de Pointes incidence) and on various outcomes during OAT.

Long-term opioid use, including OAT, may lead to abnormalities in the endocrine system, mainly affecting the gonadal axis and leading to hypogonadism.^{113, 114} In line with this, low testosterone levels and erectile dysfunction have been associated with long-term opioid use, including OAT.¹¹⁵ A meta-analysis of four studies comparing the effect of buprenorphine/naloxone to methadone on erectile dysfunction in men receiving OAT showed that methadone was associated with a significantly higher frequency of sexual dysfunction than buprenorphine.¹¹¹ Because several factors may influence sexual dysfunction among men receiving OAT, the authors concluded that additional studies are required to identify other clinical factors associated with sexual dysfunction among methadone patients.¹¹⁶ Nonetheless, clinicians should inquire about sexual dysfunction in OAT patients and monitor testosterone levels so that sexual dysfunction and related symptoms may be treated appropriately.

Patient-reported concerns with methadone also include the potential for tooth decay, which has been largely under-studied and possibly under-acknowledged by care providers.¹¹⁷ There are several oral side effects common to all opioid medications, such as suppressed salivary secretion and bruxism.¹¹²⁻¹¹⁵ In addition, the high-sucrose syrup often used to administer methadone could further contribute to development of dental caries.¹¹⁷ Conversely, buprenorphine/naloxone is less frequently associated with oral health issues compared to methadone, with the exception of a small case series (n=11) that reported that sublingual buprenorphine/naloxone can reduce salivary pH and buffering capacity, which could, in turn, potentially increase the risk of dental caries.¹¹⁵ While more research is needed to confirm these findings, clinicians should be aware of these oral health risks and provide referrals to low-cost or free local dental care services when available.

Table 1. Advantages and disadvantages of methadone vs. buprenorphine/naloxone

Methadone	Buprenorphine/Naloxone
Advantages	
<ul style="list-style-type: none"> • Potentially better treatment retention, particularly in patients with higher-intensity OUD (e.g., long history of opioid use, injection heroin use, high tolerance, and frequent use), or at high risk of drop out¹⁻³ • May be more effective for withdrawal-symptom control in chronic, severe OUD^{2, 3} • Treatment initiation may be easier • No maximum dose • Approved in Canada for the indication of pain control 	<ul style="list-style-type: none"> • Health Canada exemption is not required to prescribe buprenorphine/naloxone in most provinces and territories (see Appendices 4 & 5) • Lower risk of overdose due to partial agonist properties and ceiling effect for respiratory depression (in the absence of benzodiazepines or alcohol)⁴⁻⁶ • Lower risk of public safety harms if diverted^{7, 8} • Milder side effect profile^{2, 3} • Easier to transition from buprenorphine/naloxone to methadone if treatment is unsuccessful^{2, 3} • Shorter time to achieve therapeutic dose (1-3 days)⁹⁻¹¹ • Lower risk of toxicity and drug-drug interactions¹² • 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 OUD), and individuals planning to taper off OAT in a relatively short period of time^{2, 3} • Optimal for rural and remote locations where access to care is limited, methadone prescribers are lacking, and/or where daily witnessed ingestion at a pharmacy is not feasible • More flexible dosing schedules, including alternate-day dosing, earlier provision of 1- to 2-week take-home prescriptions, and unobserved home inductions support patient autonomy and can reduce costs¹⁴⁻¹⁷ • Easier to adjust and re-titrate following missed doses, due to its partial agonist properties

Disadvantages

- Health Canada exemption is required to prescribe methadone in all provinces and territories
- Higher risk of overdose⁴⁻⁶
- 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 every ~4 weeks; see Appendix 3), which can be inconvenient or not feasible for some patients
- More severe side-effect profile (e.g., somnolence, erectile dysfunction, cognitive blunting)^{2, 3}
- Longer time to achieve therapeutic dose (several weeks)¹⁷
- Can be more challenging to transition from methadone to buprenorphine/naloxone if treatment is unsuccessful^{2, 3}
- Higher risk of public safety harms if diverted^{7, 8}
- Higher potential for adverse drug-drug interactions (e.g., antibiotics, antidepressants, antiretrovirals)¹²
- Associated with QTc prolongation and increased risk of cardiac arrhythmia in patients prescribed higher doses, with pre-existing risk factors, and/or taking other medication(s) that prolong QTc interval^{2, 3}
- Can be more expensive if prescribed as daily witnessed doses, mainly due to fees associated with dispensing and witnessed ingestion¹⁵⁻¹⁶
- Potentially lower treatment retention, particularly in higher-intensity OUD¹
- May cause precipitated withdrawal if appropriate dose-induction protocols are not followed¹¹
- Withdrawal-symptom suppression may be inadequate for individuals with high opioid tolerance^{2, 3}
- Reversing effects of overdose can be challenging due to pharmacology of buprenorphine (high affinity for opioid receptors, long half-life)¹²
- 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)
- Non-adherence to treatment may require frequent re-inductions

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2.1.5 Slow-release oral morphine

Slow-release oral morphine (24-hour formulation) is widely used for pain management, but there is also a growing evidence base for its use as an OAT medication. Slow-release oral morphine has been approved for clinical use in the treatment of OUD in Austria since 1998, Slovakia and Slovenia since 2005, Bulgaria and Luxembourg since 2006, Switzerland since 2013, and Germany since 2015.¹²¹⁻¹²³ Slow-release oral morphine is also legally available as a treatment for OUD in several other European countries (France, Croatia, Malta, the Netherlands, and Italy)¹²¹, although, in general, access is strictly regulated (i.e., special approval is required to prescribe), and use is restricted to specialized clinics and specific patient populations. In Canada, slow-release oral morphine for treatment of OUD has been eligible for coverage under Health Canada’s Non-Insured Health Benefits (NIHB) program since November 2014,¹²⁴ and as a regular benefit under British Columbia’s provincial drug plan (PharmaCare) since June 2017.¹²⁵

Available clinical trial evidence suggests that slow-release oral morphine may provide similar benefits to methadone-based OAT. A 2013 Cochrane Review including three randomized trials (n=195) comparing slow-release oral morphine to methadone or buprenorphine/naloxone found no significant differences between treatments in retention, medication adherence, or non-medical opioid use.¹²⁶ However, due to the small number of trials that met inclusion criteria, the quality of this evidence was assessed as low (i.e., high likelihood that new evidence could change direction or magnitude of findings) and insufficient to make any conclusions regarding its use in clinical practice.¹²⁶ The authors also noted a higher incidence of adverse events for slow-release oral morphine compared to other opioid agonist treatments.¹²⁶

Since the publication of the Cochrane review, an international multi-site randomized crossover trial has provided additional safety and efficacy evidence for slow-release oral morphine as an alternative to methadone treatment.¹²⁷ In this study, 278 patients were assigned to receive methadone and slow-release oral morphine treatment in two 11-week blocks, with the order of treatment randomly assigned. Results showed no differences in retention rates, heroin use, or adverse events between treatments in either intention-to-treat or per-protocol analyses (n=157). Moreover, subsequent analyses found that slow-release oral morphine was superior to methadone in patient satisfaction and improvements in mental health, with no significant differences in overall physical health,¹²⁸ or alleviation of withdrawal symptoms and reduction of cravings.¹²⁹

At the conclusion of the trial, 94% of retained participants (n=198) elected to continue on or transition to slow-release oral morphine for a 25-week extension phase to assess long-term outcomes of treatment.¹³⁰ Over the extension period, there were no signs of adaptation or loss of efficacy among study participants with the continued use of slow-release oral morphine (i.e., no change in mean daily dose, no increase in heroin use, and a gradual decline in heroin craving).¹³⁰ Treatment satisfaction, daily stress, and mental health scores also remained stable, and dysthymic symptoms significantly improved.¹³⁰ Overall, 71.2% (141/198) of patients were retained in treatment at 25 weeks, which involved a minimum of three witnessed doses in pharmacy per week.¹³⁰ Authors also reported a significant decrease in QTc interval following transition from methadone to slow-release oral morphine,¹³⁰ suggesting a potential safety advantage for patients with pre-existing or emergent cardiovascular risks (e.g., congenital long QT syndrome, cardiac arrhythmia, Torsades de Pointes¹³¹) or taking concomitant medications that prolong QTc interval (e.g., antipsychotics, antidepressants, antiemetics, cytochrome P450 inhibitors).¹⁰⁹

Several non-randomized studies have also assessed the safety and efficacy of slow-release oral morphine for the treatment of OUD.¹³² A multi-centre study including patients intolerant to or insufficiently responding to methadone (n=67) found that transitioning from methadone to slow-release oral morphine was relatively simple and well-tolerated by patients, with significant advantages observed over time, including reduced withdrawal symptoms and cravings, and improved physical and psychological health.¹³³ Similarly, a small open-label crossover study (n=18) assessed outcomes of transitioning patients from methadone to six weeks of slow-release oral morphine treatment, after which methadone treatment was resumed.¹³⁴ Compared to methadone, slow-release oral morphine was associated with improved social functioning and reduced heroin craving, with no change in heroin use, depression symptoms, and overall health scores.¹³⁴ The majority of patients (78%) expressed a preference for slow-release oral morphine over methadone, with reasons including fewer and less severe side effects, feeling more “normal”, and improved withdrawal suppression, sleep quality, and energy levels.¹³⁴ Several additional small non-randomized, uncontrolled studies have reported similar improvements in quality of life, withdrawal symptoms, opioid craving, and heroin use compared to baseline or pre-treatment levels.¹³⁵⁻¹³⁷

Despite the above findings, it is acknowledged that these studies have limitations; namely, only a small number of RCTs have compared slow-release oral morphine to first-line OAT, and several of the above-described studies had notable biases (e.g., non-randomized studies, open label clinical trials). Consequently, there is less high-quality evidence regarding the comparative efficacy and safety of slow-release oral morphine. For this reason, it is recommended that slow-release oral morphine should only be considered for use in patients who are intolerant to or have not responded to first-line OAT and who remain at high risk of opioid-related harms, including overdose death. As with any medical treatment, exceptions can be made at the discretion of the treating clinician, after carefully balancing risks and benefits of treatment for a particular patient.

It is the consensus of this committee that healthcare providers who wish to prescribe slow-release oral morphine for the treatment of OUD should hold a valid federal Section 56 exemption from the *Controlled Drugs and Substances Act* to prescribe methadone, or have consulted with an addiction medicine specialist with experience prescribing slow-release oral morphine for treatment of OUD. Regardless of methadone exemption status, any care provider who does not have experience prescribing slow-release oral morphine for treatment of OUD should seek specialist consultation prior to initiating treatment.

As with any OAT, policies to prevent non-medical diversion and ensure patient safety are required. These include regular follow-up and assessment, scheduled and random urine drug tests to confirm adherence (i.e., used for monitoring, not used punitively), and random medication counts if take-home doses are prescribed. It is recommended that, in most cases, slow-release oral morphine be prescribed as daily witnessed doses. Exceptions to daily witnessed dosing may be considered if the patient has shown exceptional and sustained improvements in clinical and social stability, as per the best judgment of the treating clinician.

The use of slow-release oral morphine for treatment of OUD is off-label in Canada, and requires careful consideration, discussion, and documented fully informed consent from the patient. Although it is beyond the scope of this guideline to provide detailed dosing protocols, according to existing literature, the average (mean) slow-release oral morphine dose prescribed ranges from 235–791mg/day.^{126, 130, 132} The full range of slow-release oral morphine doses described in the literature is 60–1200mg/day.^{126, 130, 132}

Finally, it is important to note that only the once-daily, 24-hour formulation of slow-release oral morphine has been studied in clinical trials for the treatment of OUD. 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 treatment of OUD.

2.2 Withdrawal Management

2.2.1 Important safety notice

Withdrawal management alone is not an effective nor safe treatment for OUD, and offering this as a standalone option to patients is neither sufficient nor appropriate. Withdrawal management without linkage to long-term addiction care is associated with elevated rates of relapse and, in turn, HIV and hepatitis C infections and overdose, and should be avoided.¹³⁸⁻¹⁴⁵

Clinical trials report relapse rates ranging from 53.1–66.7% at one month, and 61.1–89.2% at six months following a short-term methadone taper.^{146, 147} Similarly, a randomized controlled trial involving 243 patients reported that receiving withdrawal management without linkage to another treatment modality resulted in a relapse rate of approximately 88% within six months of treatment.¹⁴⁰ A large U.S.-based observational cohort (n=990) reported significantly lower rates of sustained abstinence at six-years follow-up for outpatient withdrawal management (12%) compared to other treatment approaches (18 to 21%).¹⁴⁸ Additionally, individuals who have completed inpatient withdrawal management alone face an increased risk of death from opioid overdose compared to those who receive no treatment.¹⁴⁹ This phenomenon is attributed to a loss of tolerance to opioids, which is also thought to explain the increased risk of fatal opioid overdose observed following release from prison.¹⁵⁰

Due to these increased risks, withdrawal management is not recommended unless it is integrated into ongoing addiction treatment (e.g., long-term OAT, intensive outpatient treatment, residential treatment). 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. For individuals who choose withdrawal management over long-term OAT (including patients with high opioid tolerance), a slow outpatient taper should be considered. Close and ongoing follow-up with an outpatient care provider is advised to ensure longer-term OAT is offered when possible. In order to reduce the risk of fatal overdose among patients who decline long-term OAT, patients and families should receive naloxone kits along with overdose prevention and rescue education.¹²

2.2.2 Opioid agonist taper

Methadone taper

Tapered methadone doses appear to reduce the severity of withdrawal symptoms and drop-out rates compared to placebo, but the majority of patients still relapse to opioid use if a strategy involving only tapering is employed.^{144, 151} Tapered methadone does not appear to differ from other pharmacological agents (e.g., alpha₂-adrenergic agonists or other opioid agonists) in terms of severity of withdrawal symptoms, adverse effects, withdrawal completion, or sustained abstinence.¹⁴⁴

It should be noted that wide variations in the literature represent a major limitation when comparing tapered methadone to other treatments (e.g., different studies assessed different outcomes of withdrawal management using methadone vs. other treatments, restricting comparisons between treatment approaches in certain contexts).¹⁴⁴

Buprenorphine/naloxone taper

Similar to tapering off opioids with methadone, an agonist taper involving buprenorphine/naloxone appears to reduce the severity of withdrawal symptoms, but the majority of patients still relapse to opioid use if a strategy involving only buprenorphine/naloxone taper is employed without linkage to long-term addiction treatment.¹⁵² For instance, the Prescription Opioid Addiction Treatment Study, which included persons with prescription OUD, demonstrated significantly lower sustained abstinence rates eight weeks after tapering off buprenorphine/naloxone (8.6%) compared to abstinence rates during buprenorphine/naloxone treatment (49.2%).¹⁵³ Longer buprenorphine/naloxone tapers (28-56 days) have been associated with improved outcomes at completion (abstinence from non-medical opioid use, retention in treatment) compared to shorter buprenorphine/naloxone tapers (7-28 days).^{93, 154}

Buprenorphine/naloxone tapers may offer some advantages over methadone tapers, such as faster symptom relief and higher rates of withdrawal completion (61.2% versus 51.8%).¹³⁸ There does not appear to be a significant difference in terms of the severity of withdrawal symptoms for individuals managed with buprenorphine/naloxone compared to methadone.¹³⁸

Compared to the α_2 -adrenergic agonists clonidine and lofexidine, buprenorphine/naloxone reduces the severity of withdrawal symptoms more effectively, and results in longer retention in treatment and greater likelihood of completing treatment (66.2% versus 42.8%).¹³⁸ There does not appear to be a significant difference between buprenorphine/naloxone and α_2 -adrenergic agonists in adverse effects, however, clonidine is associated with higher rates of drop-out due to side effects.¹³⁸

2.2.3 Alpha₂-adrenergic agonists

Compared to placebo, α_2 -adrenergic agonists have been found more effective at reducing the severity of opioid withdrawal symptoms and increasing the probability of completing the withdrawal management phase.¹⁵⁵ While the signs and symptoms of withdrawal appear to resolve earlier with α_2 -adrenergic agonists in comparison to tapered methadone doses, significantly more adverse effects have been reported with clonidine than with methadone.¹⁵⁵ Although the overall likelihood of completing withdrawal management appeared similar between α_2 -adrenergic agonists and methadone, α_2 -adrenergic agonists tended to require shorter treatment durations.¹⁵⁵ However, compared to methadone tapers, α_2 -adrenergic agonists

(e.g., clonidine) were somewhat less effective in mitigating the severity of withdrawal symptoms, and were more likely to be associated with adverse effects such as hypotension.¹⁵⁵

2.3 Oral Naltrexone

Naltrexone is an opioid receptor antagonist that blocks the euphoric effects of opioids at adequate doses.¹⁵⁶ Oral naltrexone, currently the only formulation available in Canada, has been shown to have limited benefits in the treatment of OUD, as evidenced by a 2011 meta-analysis that found no statistically significant differences in retention or abstinence rates for oral naltrexone compared with placebo or no treatment.¹⁵⁷ In this 2011 review, the only outcome that favoured naltrexone over placebo was reduced rates of re-incarceration, but this finding was limited to two of the 13 randomized trials included in the analysis.¹⁵⁷ Based on limited data, the review authors concluded that oral naltrexone was not superior to psychotherapy alone (two studies), benzodiazepine-based treatment (one study), or buprenorphine monotherapy (one study) in terms of retention in treatment, abstinence from opioid use, and reported side effects.¹⁵⁷ Across studies, treatment retention rates were also low with oral naltrexone treatment (28%).¹⁵⁷ Of note, a single randomized trial published subsequent to the meta-analysis reported a significantly higher proportion of opioid-negative urine tests among individuals on oral naltrexone (42.7%) compared to placebo (34.1%).¹⁵⁸

Potential benefits of oral naltrexone include ease of administration, lack of induced tolerance during long-term treatment, and lack of potential for dependence or non-medical use.¹⁵⁵ However, as an opioid antagonist, naltrexone fully blocks the effects of all opioid medications, including opioid analgesics prescribed for pain. Additionally, the loss of tolerance to opioids associated with naltrexone-based treatment can increase relative overdose risk in patients who discontinue their medication and subsequently relapse to opioid use, as demonstrated by national surveillance data from Australia that showed that naltrexone-associated mortality rates were three to seven times higher than methadone-related mortality rates.¹⁶⁰

Although research evidence has shown that oral naltrexone has limited benefits compared to other pharmacological treatments for OUD, and in some cases, is no more effective than placebo in reducing opioid use and retaining individuals in treatment, there may be circumstances where oral naltrexone is preferred or requested by a patient. For example, patients may wish to avoid OAT, or may work in a safety-sensitive position that prohibits OAT. In these cases, the lack of evidence for efficacy and known safety risks of oral naltrexone must be carefully reviewed with patients prior to initiating treatment, particularly the high rates of relapse and risk of overdose due to loss of opioid tolerance. In addition, patients prescribed oral naltrexone for the treatment of OUD must be assessed regularly on follow-up and closely monitored for risk or signs of relapse to opioid use.

2.4 Psychosocial Treatment Interventions and Peer-based Support

As is the standard of care for any complex or chronic medical condition, all clinicians providing medical management to patients with OUD should provide general support and unstructured counselling. Medical management, by definition, includes, but is not limited to: providing non-judgmental support and advice; assessing motivation and exploring barriers to change; developing and regularly reviewing a treatment plan with the patient; promoting alternative strategies for managing stress; and providing referrals to health, recovery support, and social services when requested or appropriate.¹⁶¹ Establishing a trusting, respectful and collaborative therapeutic relationship with patients remains a cornerstone of treating substance use disorders in clinical practice.

In addition, due to the higher prevalence of trauma history and comorbid post-traumatic stress disorder among individuals with substance use disorders compared to the general population, clinicians should incorporate the principles of trauma-informed practice (e.g., trauma awareness; safety and trustworthiness; choice, collaboration and connection; strengths-based approaches and skill building) where appropriate.¹⁶² Furthermore, where available, clinicians should consider undertaking cultural safety training to improve their ability to form positive partnerships with Indigenous clients seeking care for substance use and related harms.

A 2011 Cochrane Review of 35 RCTs (n=4319) found that, compared to OAT with standard medical management alone, the addition of structured psychosocial treatment interventions to OAT did not improve retention in treatment, abstinence from opioid use during or after treatment, or adherence.¹⁶³ When analyses were stratified by type of psychosocial treatment intervention [i.e., behavioural (n=24); cognitive behavioural treatment and contingency management; psychoanalytic (n=4); counselling (n=7); and other (n=2)], pooled results remained non-significant for all comparisons and outcomes.¹⁶³ The authors concluded that there was high-quality evidence that the addition of psychosocial treatment interventions to standard OAT does not improve retention or abstinence rates, and moderate-quality evidence that adjunct psychosocial treatment interventions do not improve adherence over standard OAT incorporating clinician-led medical management.¹⁶³

RCTs published subsequent to the 2011 review have yielded mixed results.¹⁶⁴ For example, four RCTs evaluating OAT with adjunct cognitive behavioural therapy (CBT) found no difference in treatment retention and abstinence compared to standard OAT¹⁶⁵⁻¹⁶⁸ — although a subsequent sub-analysis of one trial did report that the addition of CBT to OAT was associated with a significant increase in mean number of opioid-free weeks in individuals with prescription OUD.¹⁶⁹ Of four RCTs assessing OAT with ancillary contingency management (CM), two trials reported

significantly higher attendance and retention rates, longer periods of continuous abstinence, and reductions in non-medical opioid use with prize-based CM;^{170, 171} one trial reported significantly higher 12-month retention rates with contingent take-home doses;¹⁷² and one trial reported no difference in retention, continuous abstinence, or non-medical opioid use for prize-based CM versus standard OAT.¹⁶⁷ Finally, of two RCTs that evaluated OAT with ancillary counselling, one found that ancillary counselling led to significantly higher 12-month retention rates in patients with no previous OAT experience,¹⁷³ while another found no difference in attendance rates, adherence, or non-medical opioid use with ancillary counselling compared to standard OAT.^{153, 174}

Considered together, the 2011 Cochrane Review and more recent studies have not provided consistent evidence that ancillary psychosocial treatment interventions improve patient outcomes over OAT incorporating standard medical management. Ongoing research is needed to better understand the role and effectiveness of psychosocial treatment interventions in the clinical management of OUD. These findings do, however, underscore that a patient's decision not to participate in ancillary psychosocial treatment interventions should never preclude or delay provision of evidence-based pharmacological treatments.¹⁷⁵ In addition, there is sufficient research evidence to challenge the traditional notion that OAT models of care that do not include ancillary psychosocial treatment interventions—such as low-threshold/low-barrier and office-based primary care models without concomitant ancillary psychosocial treatment—are inherently inferior to more comprehensive addiction treatment programs.¹⁷⁶

It is emphasized that the assessment and monitoring of emotional and mental health is an essential component of care for patients with OUD, particularly given the high prevalence of concurrent mental health diagnoses in this population (e.g., post-traumatic stress disorder, depression, anxiety).^{174, 177-179} While the evidence for ancillary psychosocial treatment interventions in the general patient population is equivocal, there may be benefits for some individuals, including more complex patient populations typically excluded from RCTs. There is some evidence that the addition of psychosocial treatment interventions can improve both substance use and mental health outcomes for individuals with concurrent disorders, including alcohol and other substance use disorders, post-traumatic stress disorder, and severe mental illness (e.g., schizophrenia, schizoaffective disorder).¹⁸⁰⁻¹⁸² However, due to the small number of trials, this evidence is considered to be low-quality, with considerable heterogeneity between trials and pooled-effect sizes that are generally small to moderate in scale.

Further research is required to assess the effect of specific types of psychosocial support (e.g., housing, employment, and legal support services) on treatment outcomes. No systematic reviews have examined the impact of providing supports for various social needs, however previous studies have demonstrated that addressing housing and other survival needs can have a significant positive impact on patient outcomes.¹⁸³⁻¹⁸⁵ There is likely a benefit to OUD

treatment being offered in the context of interdisciplinary care teams that are equipped to address these needs when possible.

Peer-based support groups are widely available community resources often recommended as an adjunct to clinical management of substance use disorders, or as a source of additional guidance and support following treatment (e.g., aftercare). A widely recognized example is Narcotics Anonymous (NA), an international fellowship of support groups composed of individuals in recovery, which offers emotional support and a structured “12-step” approach to achieving abstinence. Research and evaluation of peer-based support has primarily focused on 12-step facilitation (TSF) approaches, which refers specifically to 12-step programs led by a trained professional, such as a substance use counsellor. There have been no well-designed, controlled studies of the effectiveness of these groups in supporting treatment goals of individuals with OUD, although a small number of observational studies have reported associations between active participation in 12-step programs and improved treatment outcomes among individuals with substance use disorders.¹⁸⁶⁻¹⁸⁸

It should be noted that the TSF model is not always supportive of the use of opioid agonist medications for the treatment of OUD. Underlying philosophical conflicts, if present, can also negatively affect engagement and disclosure and deter regular attendance.¹⁸⁹ If patients identify incompatibilities between personal beliefs and TSF as barriers to participation, alternative options can be provided when possible. For example, peer support groups with a secular mandate (e.g., SMART Recovery®, LifeRing®), or groups for specific populations (e.g., youth, women, Indigenous peoples, individuals with concurrent mental health issues) may be locally available; however, it is noted that the efficacy of these support groups has not been empirically studied.

Referrals to psychosocial treatment interventions and community-based supports, including peer-support groups, may be routinely offered to patients in conjunction with pharmacological treatment. All care providers should be aware of local resources including waitlists, costs to patients, and practitioner expertise and approach, in order to provide informed referrals appropriate to individual patient needs.

2.5 Residential Treatment

There is limited evidence on the impacts of residential treatment programs on OUD. To date, no systematic reviews or meta-analyses have been conducted in this area. In addition, there are no large clinical trials comparing residential treatment to other interventions and few rigorous studies identifying specific characteristics of an effective residential treatment program or factors that make a patient a good candidate for this treatment modality.

Observational cohort studies in the U.K. have highlighted the relatively high rate of relapse among patients discharged from residential treatment for OUD. For example, outcomes of a six-week residential treatment program in Ireland that consisted of methadone-based withdrawal management, psychosocial therapy (i.e., group, individual and/or family therapy) and an aftercare component demonstrated that 80% of participants reported relapse within one month, with 59% relapsing within one week of discharge.¹⁹⁰ Several factors that were predictive of early relapse were identified, including younger age, not completing the full six weeks of treatment, higher rates of heroin use prior to treatment, a history of injection use, and opting out of aftercare.¹⁹⁰ Similarly, in the National Treatment Outcome Research Study (NTORS), approximately 57% of clients reported heroin use within 30 days of discharge, with 31% relapsing to regular levels of heroin use at one-year follow-up.¹⁹¹ However, for the full cohort of individuals who attended residential treatment for alcohol or substance use disorders, the NTORS study did find that injecting rates dropped from 61% at intake to 29% at 4–5 years following discharge, while abstinence from heroin use increased from 23.2% to 48.6% across the same period.¹⁹² Individuals in the NTORS study who completed at least one course of residential treatment also demonstrated improvements in terms of safer injection practices, psychological and physical health, and reductions in criminal behaviour at 4–5 years following discharge.¹⁹²

U.S.-based studies also present varied results. One longitudinal study of abstinence-based treatment programs found similar rates of retention, completion and patient satisfaction among individuals in outpatient and residential treatment programs.¹⁹³ A randomized trial found a close correlation between residential treatment duration and positive outcomes: treatment duration of less than seven weeks yielded results comparable to receiving no treatment, whereas patients enrolled in residential treatment for seven weeks or longer were found to have a decreased likelihood of heroin use and criminal activity, and an increased likelihood of employment or enrolment in school.¹⁹⁴ An additional study found that a four-week residential treatment program significantly reduced several maladaptive cognitive and behavioural patterns that may contribute to ongoing substance use problems in adults with OUD.¹⁹⁵ Another randomized clinical trial found that combining community reinforcement, family involvement and training with residential withdrawal management using buprenorphine/naloxone was positively and significantly associated with improved retention in treatment and reductions in opioid and other drug use.¹⁹⁶ The results of this study suggested that patients may benefit from residential treatment that involves fostering family and other social connections.

Although the NTORS study found that residential treatment was associated with lower rates of non-fatal overdose at one-year follow-up (7%) compared to pre-treatment rates (22%),¹⁹⁷ providers should be aware of the risks associated with loss of tolerance for patients who attend residential treatment programs without OAT. For instance, a national cohort study in England found that the risk of fatal overdose was twice as high for patients who completed psychosocial treatment only (outpatient or residential treatment) compared to patients who had recently discontinued OAT.³⁸

2.5.1 Combining residential treatment with opioid agonist treatment

Traditionally, OAT has been viewed as philosophically incompatible with the abstinence-oriented approach of some residential treatment programs, often causing the two treatment models to develop and operate separately from one another.¹⁹⁸ In recent years, the proven benefits of OAT (e.g., reduction in non-medical drug use and related harms; and improvements in mental health, social functioning, and quality of life) have prompted efforts to integrate these approaches. Some residential treatment programs have revised admission policies and service provision to accommodate evidence-based treatment and patient preference.¹⁹⁸⁻²⁰⁰ This trend of integration may, in part, reflect a growing recognition that excluding individuals stabilized on OAT from residential treatment may create barriers to access among those most in need of a higher intensity of care. In the context of the national opioid emergency and the known challenges in accessing addiction treatment, it is important to explore inclusive strategies and strengthen both OAT and residential treatment programs through the integration of evidence-based treatment and care.

For individuals engaged in polysubstance use (e.g., cocaine and heroin), combining residential treatment with opioid agonist or antagonist treatment may be beneficial. For example, the residential setting can facilitate ongoing provision of psychosocial supports (e.g., counselling, contingency management) for reducing cocaine use while agonist or antagonist treatment mitigates non-medical opioid use. This may be particularly valuable given the evidence suggesting that a change of environment can be beneficial for individuals seeking treatment for severe concurrent opioid and cocaine dependence.^{201, 202}

2.6 Specific Considerations for Pregnant Women

Untreated maternal OUD during pregnancy is associated with numerous adverse outcomes, including fetal growth restriction, fetal demise, and neonatal abstinence syndrome (NAS).¹⁹⁹ Pregnancy is also associated with increased access to healthcare services and motivation for recovery, presenting an important opportunity to engage patients in treatment for substance use.²⁰³ Yet stigma against women who use substances in pregnancy and lack of knowledge regarding treatment options for this population are frequently cited as barriers to appropriate treatment.^{204, 205} Pregnant women who do seek treatment are often prescribed pharmacological interventions that are insufficient in dose and/or duration.²⁰⁴ In addition to describing available treatment options for pregnant women, this guideline underscores the essential role of respectful and specialized care for this patient population. It is beyond the scope of this text to provide specific dosing recommendations. Care providers who are not experienced in treating OUD in pregnancy should consult an addiction medicine specialist.

2.6.1 Opioid agonist treatment

OAT has long been the standard treatment for OUD in pregnant women as it has been shown to eliminate or substantially reduce illicit opioid use with minimal adverse effects on the fetus in comparison to rapid withdrawal management and untreated OUD.²⁰¹⁻²⁰³ Abundant supporting evidence has rendered methadone the most frequently prescribed opioid agonist in pregnancy; however, more recent research suggests that buprenorphine (monoproduct) may be similarly effective for the treatment of OUD in pregnancy.²⁰⁷⁻²⁰⁹ Although more research is needed, a recent meta-analysis found no overall difference between the two treatment options for all maternal, neonatal or treatment outcomes under study, but some evidence that methadone may be superior in terms of retention in treatment, while buprenorphine may be associated with less severe NAS.²⁰⁷ It is recommended that care providers seek specialist consultation as needed to determine, on a case-by-case basis, the appropriate OAT agent for treatment of a pregnant patient.

Methadone

Compared to untreated OUD and medically supervised withdrawal management, methadone treatment is associated with positive maternal and neonatal outcomes, including longer gestation, higher live-birth rate, greater birth weight, and earlier hospital discharge of infants.²¹⁰ In addition to preventing relapse, methadone has been shown to minimize the sharp fluctuations in maternal serum opioid levels that occur with short-acting opioids (e.g., heroin).²⁰⁴ Thus, at an appropriate therapeutic dose, methadone can eliminate fetal stress associated with cyclical intoxication and withdrawal of continued illicit or non-medical opioid use.²⁰⁴

Like other opioids, methadone can cause NAS, a treatable cluster of neonatal withdrawal symptoms that may require hospitalization and pharmacologic treatment. Neonatal methadone withdrawal lasts longer than withdrawal symptoms attributed to heroin.²¹⁰⁻²¹³ Nevertheless, the symptoms of NAS are treatable, and the risks of methadone treatment are proven to be far fewer and less severe than those associated with untreated OUD and acute withdrawal during pregnancy.^{214, 215}

Buprenorphine

While the rates of some neonatal outcomes associated with buprenorphine and methadone exposure in pregnancy are similar, research shows that the NAS symptoms resulting from buprenorphine may be less severe due to its partial agonist characteristics, requiring a shorter treatment period.^{214, 215} A recent systematic review (three RCTs, n=223; 15 observational cohort studies, n=1923) comparing the maternal and neonatal outcomes of buprenorphine and methadone found that buprenorphine treatment resulted in lower risk of preterm labour, larger head circumference, and greater birth weight in comparison to methadone.²⁰⁸

The authors noted no significant differences between the two treatments in terms of spontaneous fetal loss (i.e., spontaneous miscarriage) and congenital abnormalities.²⁰⁸ Moreover, a systematic review of OAT options for pregnant women in rural areas found that, due to its superior safety profile, buprenorphine may be advantageous compared to methadone in locations where access to specialized care is limited.²¹⁶ In view of these findings, buprenorphine may be considered as a first-line option in certain cases.

It should be noted that the buprenorphine-only formulation is currently only available via authorization through Health Canada's [Special Access Programme](#).

Buprenorphine/naloxone

Only a few studies have investigated the efficacy and safety of buprenorphine/naloxone during pregnancy; most likely due to the theoretical risk that naloxone may pose to the fetus through elevation of maternofetal cortisol levels. Recent retrospective studies have found no statistically significant differences between buprenorphine/naloxone and buprenorphine or methadone related to pregnancy and treatment outcomes.^{208, 217-219} For example, a 2013 study compared the maternal and neonatal outcomes of 10 women treated with buprenorphine/naloxone to the corresponding summary statistics of seven previously published studies examining methadone and buprenorphine treatment in pregnancy.²¹⁹ While the authors emphasized the need for more research to fully characterize the impact of buprenorphine/naloxone on the fetus, they reported similar results for maternal outcomes, gestation period, and the incidence and severity of NAS.²¹⁹ Another study that compared 31 pregnant women treated with buprenorphine/naloxone to 31 pregnant women treated with methadone reported that infants exposed to buprenorphine/naloxone had a lower incidence of NAS and shorter overall hospital stays than those exposed to methadone.²¹⁸ Similarly, a study that compared 30 pregnant women treated with buprenorphine/naloxone to 134 pregnant women exposed to other opioids found no significant differences in maternal and neonatal outcomes between groups, except for a significantly higher birth weight among infants exposed to buprenorphine/naloxone than infants exposed to other opioids.²¹⁷

More research is needed, but based on this limited evidence, buprenorphine/naloxone appears to be safe for use in pregnancy,²¹⁷⁻²¹⁹ and it is noted that pregnancy was recently removed as a contraindication in the Health Canada-approved buprenorphine/naloxone product monograph.⁶⁹ Thus, for patients with established clinical stability on buprenorphine/naloxone prior to pregnancy, continuation of buprenorphine/naloxone treatment may be considered on a case-by-case basis as per the best judgment and experience of the treating clinician, and with appropriate monitoring, follow-up, and specialist consultation as needed. In these cases, risks and benefits of transitioning from buprenorphine/naloxone to another OAT agent should be carefully considered under the guidance of a specialist and discussed with the patient and their family (if appropriate).

Dose adjustments in pregnancy

For pregnant patients on methadone, the acceleration of maternal metabolism in the course of pregnancy may require an increase in daily dose to address emergent withdrawal symptoms and prevent fetal stress, particularly in the second or third trimesters.²¹⁶ Since higher doses given at once may cause fluctuations in serum opioid levels and, in turn, fetal stress, split doses may also be required.²¹⁶ Buprenorphine is somewhat less likely to require significant dose changes, since its extended half-life renders changes in maternal blood volume less concerning. Adequate doses of buprenorphine (e.g., individually titrated dose that sufficiently reduces or prevents withdrawal symptoms for a 24-hour period, with minimal side effects) can help address the risk of attrition associated with this medication.²⁰⁵

2.6.2 Withdrawal management (not advisable due to high risk of relapse)

Many clinicians prescribe short-term withdrawal management, rather than OAT, for pregnant women with substance use disorder in an effort to minimize the risks of fetal exposure to opioid medication.²⁰⁴ This is likely based on some evidence suggesting that successfully managed withdrawal can diminish the symptoms of NAS.²⁰³ However, withdrawal management is not recommended during pregnancy primarily due to the high rates of relapse, which are similar to those in the general population of patients with OUD, and can lead to increased risk of morbidity (e.g., infections) and mortality (e.g., fatal overdose).^{210, 221} Moreover, numerous studies demonstrate that the sharp physiological fluctuations associated with rapid withdrawal from opioid use and subsequent relapse can lead to adverse outcomes that are more severe and longer-lasting than NAS, such as maternal and fetal distress, fetal demise, fetal hypoxia, preterm labor, and long-term developmental issues.²⁰⁴

If a patient expressly wishes to discontinue opioid use after being informed of the risks, gradual withdrawal management should take place between 14 and 32 weeks gestation, when the risk of miscarriage is minimized, followed by intensive long-term monitoring and support.^{203, 222}

3.0 SUMMARY

Opioid use disorder, recognized as one of the most challenging forms of addiction facing Canadian healthcare systems, is a major driver of the critical rise in overdose deaths across several Canadian provinces. In recent years, the non-medical use of pharmaceutical opioids and the emergence of highly potent illegally manufactured synthetic opioids, such as street fentanyl, have significantly altered the opioid use landscape, leading to an unprecedented increase in the number of overdose deaths nationwide. This national crisis has revealed significant gaps in knowledge, access, and use of evidence-based treatment options currently available for OUD in Canada, and highlighted a profound need to improve the overall OUD system of care.

In the context of the current public health crisis, there is an urgent need for a national evidence-based guideline articulating the full range of therapeutic options for the optimal treatment of adults with varying presentations of OUD. This lack of a comprehensive guideline has resulted in gaps and inconsistencies in the knowledge base of care providers and in the utilization of available psychosocial and medical interventions for OUD, creating challenges for national and provincial/territorial health systems. To address these gaps, CRISM convened a pan-Canadian guideline committee comprising representatives from each of regional CRISM nodes (British Columbia, the Prairies, Ontario, and Quebec/Atlantic), to develop this expert guideline.

OUD is often a chronic, relapsing disease that is associated with significantly elevated rates of morbidity and mortality. With appropriate treatment and follow-up, individuals with OUD can reach sustained long-term remission. To that end, it is important that all patients are offered evidence-based treatment for their illness. Individuals with OUD can be offered a range of pharmacological and/or psychosocial treatments and supports based on their clinical presentation, addiction severity, comorbidities, current psychosocial circumstances (e.g., homelessness), and personal preferences. While this guideline supports the diversity of possible treatments available for individuals with OUD, it strongly recommends against strategies involving withdrawal management alone, since this approach has been associated with elevated risks of HIV and hepatitis C infection and overdose deaths in comparison to providing no treatment.

As a preferred first-line treatment approach for individuals with OUD, the committee recommends OAT with buprenorphine/naloxone when induction is feasible and there are no contraindications to its use. Research has shown that treatment outcomes (i.e., retention, reduction in illicit opioid use) with buprenorphine/naloxone are similar to methadone, but that buprenorphine/naloxone has fewer side effects and important safety advantages. These advantages include a significantly lower risk of fatal overdose due to its lower potential for respiratory depression, a lower risk of adverse events including cardiac arrhythmias, and a

lower likelihood of drug–drug interactions (e.g., with antibiotics, antidepressants, and HIV medications). The safety profile of buprenorphine/naloxone also permits greater flexibility and patient autonomy, allowing for earlier take-home dosing and unobserved home inductions where appropriate. This may be particularly advantageous in circumstances where long-term daily witnessed ingestion at a pharmacy is a substantial barrier or deterrent to retention in treatment, and/or in remote locations where daily witnessed pharmacy dispensation is not practical.

Methadone can be considered an alternative first-line option in cases where buprenorphine/naloxone induction would be challenging, or where loss to follow-up could be highly problematic from the perspective of individual or public health (e.g., risk of HIV transmission). For example, methadone may be preferred for individuals with severe OUD who primarily inject heroin and/or those with significant social instability.

For individuals not benefiting from adequately-dosed buprenorphine/naloxone or methadone, transitioning to the alternative first-line agent may be considered. The transition from buprenorphine/naloxone to methadone is relatively uncomplicated clinically, and is another reason that buprenorphine/naloxone is recommended as the preferred first-line treatment for OUD. For patients desiring treatment simplification or wishing to discontinue methadone treatment due to dissatisfaction with daily witnessed ingestion requirements, difficulty obtaining take-home doses, or other concerns, transitioning from methadone to buprenorphine/naloxone may be advantageous. The transition from the full opioid agonist methadone to the partial opioid agonist buprenorphine/naloxone can be more challenging due to the need to slowly taper the methadone dose to a lower dose before induction onto buprenorphine/naloxone, and the need for patients to be in moderate withdrawal prior to initiation. Specialist consultation is recommended for challenging transitions from methadone to buprenorphine/naloxone.

In patients for whom first- and second-line treatment options are ineffective or contraindicated, OAT with slow-release oral morphine (initially prescribed as once-daily witnessed doses) may be considered. Slow-release oral morphine as OAT has been less well-studied than other oral OAT options, however, recent studies have demonstrated that safety and effectiveness outcomes are comparable to methadone, with potentially greater reductions in heroin craving. For safety reasons, care providers who wish to prescribe slow-release oral morphine as an OAT should hold a valid federal Section 56 exemption from the *Controlled Drugs and Substances Act* to prescribe methadone, or have formally consulted with a skilled addiction medicine practitioner prior to initiating treatment. Regardless of Section 56 exemption status, any practitioner who lacks experience prescribing slow-release oral morphine for treatment of OUD should consult with an experienced prescriber prior to initiating treatment.

This guideline strongly recommends against a treatment strategy involving withdrawal management alone, as this approach has been associated with elevated risk behaviours and overdose death in comparison to providing no treatment, as well as high rates of relapse when implemented without immediate transition to long-term evidence-based addiction treatment. Although this guideline strongly recommends against withdrawal management alone, it is recognized that some patients may express a preference for an opioid agonist taper over long-term agonist treatment when initially seeking treatment. In these scenarios, the higher relative risk of relapse and overdose associated with standalone withdrawal management should be carefully explained, and the benefits of OAT should be discussed. If patients continue to express a preference for opioid taper over OAT, a supervised slow (>1 month) taper in a residential or outpatient setting should be pursued rather than a rapid (<1 week) inpatient taper. During the slow taper, patients should be transitioned to long-term addiction treatment in order to prevent relapse and other associated health risks. Patients who have had a successful and sustained response to OAT who wish to discontinue OAT should similarly use a slow taper (over months to years) alongside ongoing addiction care, with continued addiction care considered at cessation of opioid use.

Psychosocial treatment interventions and supports should be routinely offered in conjunction with pharmacological treatment but should not be viewed as a mandatory requirement for accessing OAT. Research evidence suggests that in uncomplicated patient populations, the addition of structured psychosocial treatment interventions to OAT does not improve treatment outcomes compared to standard OAT with clinician-led medical management (i.e., general support and unstructured clinician-led counselling), which is traditionally provided as standard of care for treatment of OUD. However, this does not suggest that pharmacotherapy should be offered in isolation, but rather that medical management include ongoing assessment, monitoring, and support for all aspects of physical, emotional, mental, and spiritual health, as these remain equally important components of treating OUD; addressing these needs should be considered the standard of care. Evidence-based psychosocial supports focused on individual circumstances (e.g., housing, employment) and other survival needs (e.g., social assistance) may also be helpful in supporting recovery from OUD.

Patients with OUD may benefit from harm reduction interventions, including education about sterile syringe use and safer injection practices to reduce the risk of blood-borne (HIV, hepatitis C) and soft tissue infections, as well as access to take-home naloxone, syringe distribution programs, and supervised consumption services to reduce the risk of blood-borne infection and fatal overdose among high-risk patients or patients with ongoing opioid use.

OAT has long been the standard treatment for OUD in pregnant women, as it has been shown to eliminate or substantially reduce illicit opioid use and minimize adverse effects on the fetus. While methadone is the most frequently prescribed opioid agonist in pregnancy, recent evidence

supports the equal efficacy and safety of buprenorphine (monoproduct) for OUD treatment in pregnancy, with some findings that buprenorphine may have benefits over methadone, such as less severe NAS. There have been very few research studies on the use of buprenorphine/naloxone in pregnancy. The limited evidence available appears to suggest that the efficacy and safety of buprenorphine/naloxone is similar to that of buprenorphine and methadone; however, additional research is needed to formulate strong evidence-based recommendations regarding its use in pregnancy. The selection of the appropriate OAT agent during pregnancy should be considered on a case-by-case basis with the guidance of a specialist and in collaboration with the patient, with appropriate monitoring and follow-up.

To address gaps within the OUD system of care nationally, major emphasis among policymakers is required to better understand and address barriers to accessing evidence-based treatments as reviewed in this guideline. It is also crucial to establish healthcare implementation science mechanisms to promote action on OUD on several fronts and monitor the progression and/or regression of the opioid emergency across the country in the short- and long-term. To this end, development of a multidisciplinary and actionable roadmap to improve clinical care strategies (e.g., address wait times for treatment, linkages to care) and strengthen the integration of care and research across the public health and clinical domains is critical.

Additionally, urgent action is required at multiple levels to reduce barriers to accessing specialist-led treatment interventions that are not reviewed here, such as injectable OAT with diacetylmorphine and hydromorphone. The guideline review committee acknowledges the body of evidence supporting this treatment approach, which is a standard of care in some international jurisdictions, and emphasizes the need for a national, dedicated guidance document on injectable opioid treatment options.

4.0 GLOSSARY

Addiction treatment: In this document, addiction treatment refers to ongoing or continued care for substance use disorder delivered by a trained care provider. For opioid use disorder, this could include evidence-based pharmacological treatment (opioid agonist or antagonist treatment), evidence-based psychosocial treatments, residential treatment, or combinations of these treatment options. Addiction treatment may be provided in outpatient or inpatient settings. In isolation, withdrawal management, harm-reduction services, low-barrier housing and unstructured peer-based support would not be considered “addiction treatment”.

Alpha₂-adrenergic agonist: Non-opioid medication that acts centrally in the brain to moderate some symptoms and signs of noradrenergic hyperactivity. Clonidine is commonly used to treat withdrawal symptoms and is available in Canada as oral tablets.

Diversion: Any non-intended or non-medical use of a prescribed opioid (including prescribed opioid agonist medication), or use by any individual other than the individual for whom it was prescribed.

Harm reduction: Policies and programs that aim to minimize immediate health, social, and economic harms (e.g., transmission of infectious disease, overdose mortality, criminal activity) associated with the use of psychoactive substances, without necessarily requiring a decrease in substance use or a goal of abstinence. Examples include needle and syringe exchange programs, take-home naloxone programs, supervised injection or consumption services, and outreach and education programs for high-risk populations.

Illegally manufactured opioid: Illegally manufactured opioids are not subject to quality-control measures and are typically mixed (or “cut”) with potentially harmful substances and contaminants to increase volume and profit in the illegal drug market. Common examples of illegally manufactured opioids are street heroin, fentanyl, carfentanil, morphine, and oxycodone. Illegal opioids may also be found in the form of counterfeit tablets pressed to look like pharmaceutical opioids.

Medical management: Medical management for opioid use disorder is medically focused, unstructured, informal counselling provided by the treating clinician in conjunction with pharmacological treatment. Medical management includes, but is not limited to: health and wellness checks, support and advice, assessing motivation and identifying barriers to change, creating a treatment plan, fostering medication adherence, optimizing dosing, supporting treatment adherence and relapse prevention, and providing referrals to appropriate health and social services.

Medically assisted withdrawal management: The use of pharmacological treatment (e.g., opioid agonist tapers, alpha₂-adrenergic agonists) to mitigate withdrawal symptoms and withdrawal-related adverse events when an individual stops using opioids in pursuit of abstinence. This terminology represents a deliberate shift away from the use of “detox” or “detoxification” to refer to medically supervised withdrawal from substances.

Slow taper: Gradual dose reduction of opioid agonist medication, typically in an outpatient or residential setting over a month (or longer) period.

Rapid taper: Rapid dose reduction of opioid agonist medication, typically in a hospital or dedicated inpatient withdrawal management facility over a period of one week or less.

Mutual-support/peer-support programs: Support that is provided through a network of peers through meetings, open discussions of personal experiences and barriers to asking for help, sponsorship, 12-step programs, and other tools of recovery. Examples include Narcotics Anonymous, SMART Recovery®, and LifeRing® Secular Recovery.

Opioids: Substances commonly prescribed for pain management that bind and activate opioid receptors in the brain, suppressing the ability to feel pain. At high doses, opioids can cause euphoria, dysphoria, and respiratory depression. Opioids may be prescribed or obtained illegally, and include synthetic (e.g., fentanyl, methadone, buprenorphine), semi-synthetic (e.g., heroin, hydromorphone, oxycodone), and naturally derived (e.g., opium, morphine, codeine) classes. The term “opiate” refers to compounds naturally derived from the opium poppy. Depending on the opioid type, formulation and individual preference, opioids are consumed via ingestion, inhalation, transdermal delivery, or subcutaneous, intramuscular or intravenous injection.

Opioid agonist: Any substance that binds to and activates mu (μ) opioid receptors, providing relief from withdrawal symptoms and cravings in people with opioid use disorder, and pain relief if used for chronic pain management. Oral opioid agonists used for treating opioid use disorder include methadone, buprenorphine, and slow-release oral morphine.

Methadone: A long-acting synthetic opioid that acts as a full mu (μ) opioid receptor agonist. It has a half-life of approximately 24 to 36 hours and is well absorbed. In Canada, it is most frequently administered as an oral solution, generally given as a single daily dose. Methadone tablets are also available in a limited context (e.g., for travel). Currently, methadone is classified as a controlled drug in accordance with Section 56 of the *Controlled Drugs and Substances Act*, requiring clinicians to hold an exemption from Health Canada in order to prescribe it for the treatment of opioid use disorder or pain.

Buprenorphine: A long-acting synthetic opioid that acts as a partial mu (μ) opioid receptor agonist with a half-life of approximately 24 to 42 hours. Buprenorphine has a high affinity for the opioid receptor, but as a partial agonist has a lower intrinsic activity or effect at the opioid receptor compared to full agonist opioids. These pharmacological properties create a "ceiling" on opioidergic effects—including respiratory depression—at higher doses. Buprenorphine's high affinity for the opioid receptor also confers an antagonistic effect on other opioids; it preferentially binds to the receptor and displaces other opioids if they are present, which can cause precipitated withdrawal (see below). In Canada, buprenorphine is available in a combined formulation with naloxone (see below). Buprenorphine monoproduct is only available through Health Canada's Special Access Programme and for specific clinical indications (e.g., pregnancy).

Buprenorphine/naloxone: A 4:1 combined formulation of buprenorphine and naloxone, available as a sublingual tablet in Canada. Naloxone is an opioid antagonist with poor oral bioavailability when swallowed or administered sublingually, and is included to deter non-medical injection and diversion. When buprenorphine/naloxone is taken as directed sublingually, the naloxone component has negligible effects and the therapeutic effect of buprenorphine predominates. However, if diverted for injection use via subcutaneous, intramuscular, or intravenous routes, sufficient naloxone is absorbed to induce some withdrawal symptoms in physically dependent active opioid users. Buprenorphine/naloxone is generally taken once daily, but due to its favourable safety profile and pharmacological properties, it can also be prescribed at higher doses on alternate-day schedules. Most provinces in Canada do not require prescribers to hold a Section 56 exemption for methadone in order to prescribe buprenorphine/naloxone, though many recommend education and training prior to prescribing buprenorphine/naloxone for opioid use disorder (see Appendices 4 & 5).

Slow-release oral morphine: A 24-hour slow-release formulation of morphine, a full agonist at the mu (μ) opioid receptor, that is taken orally once per day. In Canada, slow-release oral morphine is available as a capsule containing polymer-coated pellets (to slow absorption and release) of morphine sulfate. Its elimination half-life is approximately 11 to 13 hours. It is currently approved for pain management in Canada, and its use for treatment of opioid use disorder would be considered off-label.

Opioid agonist treatment (OAT): Opioid agonist medications prescribed for the treatment of opioid use disorder. OAT is typically provided in conjunction with provider-led counselling; long-term substance-use monitoring (e.g., regular assessment, follow-up, and urine drug tests); comprehensive preventive and primary care; and referrals to psychosocial treatment interventions, psychosocial supports, and specialist care as required. In this document, OAT refers to long-term (>6 months) treatment with an opioid agonist medication that has an evidence base for use in the treatment of opioid use disorder. "Opioid agonist treatment (OAT)" is the preferred terminology, representing an intentional shift from the use of "opioid substitution treatment (OST)", "opioid maintenance treatment (OMT)", and "opioid replacement therapy (ORT)".

Opioid antagonist: Medication that works by blocking opioid receptors, preventing the body from responding to opioids. Opioid antagonist medications may be used to rapidly displace opioid agonist molecules from receptors in an overdose situation (e.g., naloxone), or to facilitate continued abstinence from using opioid drugs (e.g., naltrexone). In Canada, naloxone is available in the form of an intramuscular injection preparation (an intranasal formulation is available to a limited extent), while naltrexone is available as an oral tablet taken once per day.

Opioid use disorder (OUD): A problematic pattern of opioid use leading to clinically significant impairment or distress that meets the DSM-5 Diagnostic Criteria for Opioid Use Disorder (see Appendix 8). OUD includes the use of synthetic and/or naturally derived opioids, whether prescribed or illegally obtained. The DSM-5 terminology represents a deliberate shift away from DSM-IV terminology of "opioid abuse" or "opioid dependence", which may be considered pejorative and/or stigmatizing, to describe this condition.

Pharmaceutical opioid: An opioid that is manufactured by licensed and regulated pharmaceutical companies, either domestically or imported through legal channels, to be dispensed at hospital or community pharmacies.

Precipitated withdrawal: A withdrawal syndrome that can occur when an opioid antagonist or partial agonist, such as buprenorphine, is administered to a patient who is physically dependent and has recently used a full opioid agonist. Due to buprenorphine's high affinity but low intrinsic activity at the mu (μ) receptor, the partial agonist displaces full agonist opioids from the mu (μ) receptors, without activating the receptor to an equivalent degree, resulting in a net decrease in effect. Precipitated withdrawal is more intense and has a much faster onset than typical withdrawal from opioids.

Prescription opioid: A pharmaceutical opioid that has been medically prescribed to an individual by a licensed health professional (e.g., physician, nurse practitioner, dentist) within their scope of practice.

Psychosocial supports: Non-therapeutic social support services that aim to improve overall individual and/or family stability and quality of life, which may include community services, social and family services, temporary and supported housing, income-assistance programs, vocational training, life-skills education, and legal services.

Psychosocial treatment interventions: Structured and/or manualized treatments delivered by a trained care provider that incorporate principles of cognitive behavioural therapy, interpersonal therapy, motivational interviewing, dialectical behaviour therapy, contingency management, structured relapse prevention, biofeedback, family and/or group counselling. Psychosocial interventions may include culturally specific approaches such as traditional healers, elder involvement, and Indigenous healing ceremonies.

Residential treatment: Treatment for substance use disorder provided in a structured live-in, therapeutic setting. The duration of residential treatment programs ranges from several weeks to months, depending on the individual, approach and the setting. Residential treatment programs potentially include some, or all, of the following elements: withdrawal management, pharmacological treatment, psychosocial treatment interventions, medical management, individual and group counselling, peer support, education, and harm reduction. This terminology represents a deliberate shift away from the use of “rehab” or “rehabilitation” to describe these programs.

5.0 APPENDICES

- Appendix 1:** Provincial educational and training requirements to prescribe methadone for opioid use disorder
- Appendix 2:** Provincial dosing recommendations for methadone
- Appendix 3:** Provincial recommendations for clinical visits, urine drug testing (UDT), and take-home dosing for methadone
- Appendix 4:** Provincial educational and training requirements to prescribe buprenorphine/naloxone
- Appendix 5:** Provincial drug plan coverage and regulations for buprenorphine/naloxone prescribing
- Appendix 6:** Provincial clinical practice guidelines—recommendations for buprenorphine/naloxone
- Appendix 7:** Provincial resources for rapid consultation with addiction-medicine specialists
- Appendix 8:** DSM-5 Clinical Diagnostic Criteria for Opioid Use Disorder
- Appendix 9:** Guideline methodology and development process

Appendix 1: Provincial educational and training requirements to prescribe methadone for opioid use disorder

For **all provinces**, the requirements to obtain and maintain authorization to prescribe methadone for opioid use disorder are:

- Licensed to practice medicine and in good standing with the provincial regulatory college
- Where applicable, licensed as nurse practitioner and in good standing with the provincial regulatory college
- Obtained a Section 56 methadone exemption from Health Canada, and have the exemption endorsed by the provincial regulatory college
 - In Quebec, British Columbia, Alberta, Manitoba, and Ontario, practitioners may obtain a methadone exemption by contacting their provincial licensing authority directly
 - The initial exemption is issued for one year, with subsequent exemptions issued every three years

Province*	Education and Practice Requirements
British Columbia	<ul style="list-style-type: none"> • Completion of an eight-hour online course (includes both Mainpro+ and MOC CME credits) through the Provincial Opioid Addiction Treatment Support Program, hosted by the BC Centre on Substance Use (BCCSU) • Two half-days of preceptorship, or additional learning as needed (with BCCSU-approved preceptor) • If Methadone 101 has been previously completed through the College of Physicians and Surgeons of B.C., but physician has not yet completed a preceptorship, or has completed educational requirements in another province or jurisdiction, they may contact the BCCSU for guidance • A temporary methadone exemption (valid for 60 days, non-renewable) may be obtained through completion of specific modules of the online course and PharmaNet review

Alberta

- Completion of Methadone Maintenance Treatment (MMT) workshop or course recognized by the CPSA
 - Experience in an Opioid Dependency Program (ODP) setting or evidence of appropriate post-graduate training
 - Standards for initiating physicians:
 - Complete a period of direct training, supervision and mentorship with an experienced, CPSA-approved Initiating Physician until approved as competent in MMT
 - Show documentation of clinical competence
 - Document ongoing education relevant to MMT that is acceptable to the CPSA, e.g.:
 - Completion of a recognized course on the fundamentals of addiction medicine within two years of acquiring methadone exemption
 - Minimum of 40 hours of formal Continuing Medical Education (CME) in some aspect of addiction medicine every five years (time spent at a recognized MMT workshop/course qualifies)
 - Equivalent education acceptable to the Council of the CPSA
 - Must have access to laboratory services and a pharmacy
 - Must collaborate with maintaining physicians of former patients and pharmacists dispensing to current patients
 - Make reasonable efforts to provide non-pharmacological support to patients (e.g., pharmacy, addiction services, counselling)
 - To maintain methadone treatment for a patient stabilized by a specialist, must submit a letter of support from the initiating physician with application for a methadone exemption
 - Standards for maintaining physicians:
 - Maintain an ongoing association with an experienced initiating physician
 - Have an understanding of methadone pharmacology and, in addition to the MMT workshop/course, attend the original MMT workshop/course or another approved educational course relevant to addiction medicine, within five years of acquiring a methadone exemption
 - Must collaborate with initiating physician and other healthcare providers (e.g., pharmacist, counsellor, laboratory)
 - Standards for both initiating and maintaining physicians:
 - An interview with the registrar of the CPSA or his/her designate may be required
 - If going away or suspending their practice, must ensure the patient receives continued care from another physician trained in MMT
 - Must access prescribing databases, including the Triplicate Prescription Program (TPP) and/or Netcare
 - Requirements for temporary prescribing physicians in hospitals and corrections:
Please see *Alberta MMT Standards and Guidelines*
-

Saskatchewan	<p><i>Similar to education and practice requirements for Alberta, with the following distinctions:</i></p> <ul style="list-style-type: none"> • Initiating physicians must complete two days of direct training • Initiating physicians must have mentorship and support from an established methadone prescriber during the first two years of practice • Initiating physicians must document a minimum of 30 hours of formal CME in addiction medicine every five years • New methadone prescribers will be limited to a maximum of 50 patients until the first audit • Must access the Pharmaceutical Information Program (PIP) Viewer prescribing database • Requirements for temporary prescribing physicians in hospitals and corrections: Please see <i>Opioid Substitution Therapy Guidelines and Standards for the Treatment of Opioid Addiction/Dependence</i>, available from the CPSS.
Manitoba	<ul style="list-style-type: none"> • Completion of provincial Opioid Replacement Therapy 101 course, two-day addiction and methadone training course in Ontario, or online CAMH Opioid Dependence Treatment Core Course • Alternative training programs, such as a six- to eight-hour review of assessment and guidelines with an experienced methadone provider certified in addiction medicine, may be considered with prior approval from the CPSM • Completion of several supervised shifts in a methadone/buprenorphine clinic (minimum of four half days) • Alternatively, extensive experience in methadone/buprenorphine addiction practice in another province may fulfill requirements, if discussed with the CPSM registrar <p><i>Note: in Manitoba, nurse practitioners may also obtain an exemption to prescribe methadone if they fulfill the requirements below:</i></p> <ul style="list-style-type: none"> • Must maintain prescribing authority for controlled drugs and substances • Attend Opioid Replacement Therapy 101 course • Complete minimum of four half-days training with experienced methadone provider • Must apply for and receive a methadone exemption from Health Canada <p>Before the Section 56 exemption period expires, practitioners must submit a renewal application specifying education and practice completed to maintain methadone prescribing competency</p>
Ontario	<ul style="list-style-type: none"> • Must complete an application form and agree to practice in accordance with the CPSO's expectation document (available from the CPSO) • Complete the CAMH Opioid Dependence Treatment Core Course • Complete two days of clinical training with a MMT physician approved by the CPSO <p><i>Nurse practitioners must complete approved education for controlled substances and may only prescribe methadone on a continuation basis, only in hospital settings</i></p>
Quebec	<ul style="list-style-type: none"> • Must complete and submit an application form for methadone exemption to the Collège des médecins du Québec (CMQ) • Must attend a one-day education session provided by L'Institut national de santé publique du Québec • In the application to the CMQ, must name a mentor willing to support the physician if necessary

<p>New Brunswick</p>	<ul style="list-style-type: none"> • Participation in a formal in-person training program deemed appropriate by the CPSNB • Alternative training programs or a mentorship from an experienced prescriber may be considered with prior approval • Must demonstrate completion of additional training in addiction medicine every five years <p><i>Nurse practitioners:</i> Must maintain prescribing authority for controlled drugs and substances</p>
<p>Nova Scotia</p>	<ul style="list-style-type: none"> • Complete an application form and agree to practice in accordance with the <i>CPSNS Methadone Maintenance Treatment Handbook</i> • Successfully complete the CAMH Opioid Dependence Treatment Core Course or equivalent approved course • Complete eight hours of clinical training with a MMT physician approved by the CPSNS • Within each three-year renewal cycle, must have a practice review conducted by an experienced MMT prescriber • Within 3 years of receiving exemption, complete the Opioid Dependence Treatment Certificate Program • Must access the PMP prescribing database <p><i>Nurse practitioners:</i></p> <ul style="list-style-type: none"> • Must meet CRNNS requirements and standards to prescribe controlled drugs and substances • Follow requirements above for practicing according to guidelines, initial coursework, and clinical training • Must apply for and receive a methadone exemption from Health Canada
<p>Prince Edward Island</p>	<ul style="list-style-type: none"> • Agree to participate in practice review(s) if required by the CPSPEI • Complete a Methadone Maintenance Treatment workshop/course recognized by the CPSPEI • Complete the CPSPEI Commitment Form • Maintain an ongoing association with an experienced physician who has been prescribing MMT for at least two years • Complete ongoing education relevant to MMT, including: <ul style="list-style-type: none"> - A recognized course on the fundamentals of addiction medicine within two years of acquiring a methadone exemption - Minimum 20 hours of formal CME in some aspect of addiction medicine every five years (MMT workshop or course qualifies) or equivalent acceptable to the CPSPEI • Review the CPSO Methadone Maintenance Guidelines
<p>Newfoundland and Labrador</p>	<ul style="list-style-type: none"> • Complete an application form and agree to practice in accordance with the CPNSL's expectation document • Successfully complete the CAMH Opioid Dependence Treatment Core Course • Complete two days of clinical training with a MMT physician approved by the CPSNL • Within 3 years of receiving exemption, complete the Opioid Dependence Treatment Certificate Program

**Note: Information was not available for Yukon, Northwest Territories, or Nunavut*

For further information and standards for prescribing methadone for the treatment of OUD, practitioners may refer to their provincial college's guidelines.

Sources:

British Columbia: [Provincial Opioid Addiction Treatment Support Program](#)

Alberta: [Alberta Methadone Maintenance Treatment Standards and Guidelines for Dependence](#)

Saskatchewan: [Opioid Substitution Therapy Guidelines and Standards for the Treatment of Opioid Addiction/Dependence](#)

Manitoba: [Manitoba Methadone & Buprenorphine Maintenance Recommended Practice](#)

Ontario: [Methadone Maintenance Treatment Program Standards and Clinical Guidelines](#); [CNO Q&A on controlled substances](#)

Quebec: [A Cross-Canada Scan of Methadone Maintenance Treatment Policy Developments](#); [CMQ Questionnaire pour une demande d'exemption](#)

New Brunswick: [CPSNB Treatment of Opioid Addictions](#); Personal Correspondence, Laurie Janes, Executive Director, NANB

Nova Scotia: [CPSNS Methadone Maintenance Treatment Handbook](#); [Nurse Practitioner Standards of Practice](#)

Prince Edward Island: [CPSPEI Prescribing Methadone Maintenance Treatment for Opioid Dependency Policy](#)

Newfoundland and Labrador: [CPSNL Methadone Maintenance Treatment Standards and Guidelines](#)

Appendix 2: Provincial clinical practice guidelines: Dosing recommendations for methadone

The following standards represent the upper range¹ of the recommended dose for a typical patient; doses may be administered in smaller amounts or increased over a greater number of days than those specified.

	Initiation (starting dose)	Titration/ induction ² (dose increase)	Stabilization (dose increase) ³	Typical stabilization dose range
British Columbia	LR: 20–30mg	5–10mg / 5+ days	10mg / 5–7 days	60–120mg; additional ECG advised if dose >150mg
	MR: 10–20mg			
	HR: 5–10mg			
Alberta	LR: 30mg	10mg / 3 days	10mg / 5–7 days	60–120mg; additional ECG advised if dose >100 mg and at any dose that meets or exceeds a multiple of 20mg above 100 (i.e., 120mg, 140mg, 160mg)
	MR: 20mg	10mg / 4 days		
	HR: 10mg	5mg / 5 days		
Saskatchewan	LR: 30mg	10mg / 3 days	at 60mg (Day 10) hold dose for at least 1 week (up to Day 17) 10mg / 5–7 days	60–120mg; additional ECG advised if dose >100 mg and at any dose that meets or exceeds a multiple of 20mg above 100 (i.e., 120mg, 140mg, 160mg)
	MR: 20mg	10mg / 4 days		
	HR: 10mg	5mg / 5 days		
Manitoba*	LR: 10–30mg	5–10mg / 3–4 days	During maintenance or if dose ≥ 80mg, 5–10mg / 5–14 days	50–120mg, est. within 2–8 weeks of initiation Caution and additional ECG advised if dose >120 mg; consultation advised if dose >150mg
	MR: 10–20mg			
	HR: 10–20mg			
Ontario	LR: 30mg	10–15mg / 3–5 days	During maintenance or if dose ≥80mg, 5–10mg / 5–7 days	60–120mg; ECG required if dose >150mg. Caution and additional ECG advised if dose >120mg in patients with risk factors for Torsades de Pointes
	MR: 20mg	5–10mg / 3–5 days		
	HR: 10mg	5mg / 5 days		
Quebec	Individualized dosing/schedule approach determined by care provider. 20–30mg typical; 40mg max	5–20mg / 4–6 days	Individualized dosing/schedule approach determined by care provider	Average 80–90mg Justification required if >120mg Post-dose medical assessment required if >200mg

	Initiation (starting dose)	Titration/ induction ² (dose increase)	Stabilization (dose increase) ³	Typical stabilization dose range
Newfoundland and Labrador	LR: 30mg	10–15mg / 3–5 days	Maintenance or if dose is ≥80mg, 10mg / 5–7 days	60–120mg Additional ECG advised if dose >150mg
	MR: 20mg	5–10mg / 3–5 days		
	HR: 10mg	5mg / 5+ days		
New Brunswick	10–30mg	Stabilization phase (up to 60mg): 5–15mg / 3–4 days	Transition phase or above 60–80mg: 5–10mg / 3–4 days	Established within 2–6 weeks of initiation; >100mg= in the high range; Max 120–150mg
Nova Scotia	LR: 30mg	10mg / 3 days or 15mg / 5 days	When dose ≥60mg: 10mg / 5–7 days	60–120mg ECG required if dose ≥150mg and at every 30- 50mg dose increase
	MR: 20mg	5mg / 3 days or 10mg / 5 days	If dose >100mg: 10mg / 7–14 days	
	HR: 10mg	5 mg / 3–5 days		
Prince Edward Island	<i>See dosing standards for Ontario</i>			

LR = **low risk** of toxicity; high tolerance, no risk factors or recent abstinence

MR = **moderate risk** of toxicity; unknown tolerance; higher risk for toxicity

HR = **high risk** of toxicity; low tolerance, opioid naïve, or recent abstinence from opioids
(or abstinent for >7 days)

*Manitoba defines high risk as recent abstinence with negative initial urine drug screen and/or meeting one of the following circumstances: patients recently using benzodiazepines, patients using other sedating drugs, patients with problematic alcohol use, patients who are older (>60 years) and have a respiratory illness, patients who are on drugs that inhibit or promote methadone metabolism, and patients with low opioid tolerance.

- 1 There is no “maximum” dose that can be prescribed, and certain cases may require doses above those given in this table.
- 2 In Alberta, Manitoba, and Ontario, this phase is divided into ‘early stabilization’ (0-2 weeks) and ‘late stabilization’ (2-6 weeks). In Saskatchewan, this phase is considered to be within the initiation phase. In New Brunswick, it is called stabilization.
- 3 In New Brunswick, this phase corresponds to the ‘transition’ and ‘community’ phases.

Sources:

British Columbia: [A Guideline for the Clinical Management of Opioid Use Disorder](#)

Alberta: [Alberta Methadone Maintenance Treatment Standards and Guidelines for Dependence](#)

Saskatchewan: [Opioid Substitution Therapy Guidelines and Standards for the Treatment of Opioid Addiction/Dependence](#)

Manitoba: [Manitoba Methadone & Buprenorphine Maintenance Recommended Practice](#)

Ontario: [Methadone Maintenance Treatment Program Standards and Clinical Guidelines](#)

Quebec: [Utilisation de la méthadone dans le traitement de la toxicomanie aux opiacés](#)

New Brunswick: [Methadone Maintenance Treatment Policies and Procedures](#)

Nova Scotia: [CPSNS Methadone Maintenance Treatment Handbook](#)

Prince Edward Island: [CPSPEI Prescribing Methadone Maintenance Treatment for Opioid Dependency Policy](#)

Newfoundland and Labrador: [CPSNL Methadone Maintenance Treatment Standards and Guidelines](#)

Appendix 3: Provincial clinical practice guideline recommendations for clinical visits, urine drug testing (UDT), and take-home dosing for methadone

Note: Clinical stability and ability to safely store methadone are required prior to take-home dosing in every province.

Province	Treatment stage	Schedule of clinical visits	Schedule of UDTs	Take home/Carries
British Columbia	Titration	1–2 times per week	1–2 per week	<p>≥4 weeks on stable dose and 12 weeks negative UDT (Approx. 3 mo. on MMT)</p> <p>Begin with one take-home dose per week. Subsequent increases in take-home doses: 1 additional carry per week every 1–2 mo. Most are established on 2 witnessed doses per week with remaining doses as carries.</p>
	Stabilization/maintenance	Weekly with progression to schedule as determined by care provider	Monthly	
Alberta	Initiation	At least weekly	At least 1 UDT before initiation	<p>≥3 mo. on MMT and 3 consecutive negative UDT</p> <p>Begin with one take-home dose per week. Subsequent increases in take-home doses: 1 additional carry per week every 4 weeks, to a maximum of 6 per week. 14 carries can only be given after 2 years of stability and negative urine tests.</p>
	Stabilization	Weekly	Monthly	
	<3 mo.	At least every 2 weeks	Every 3 mo.	
	3–6 mo.	At least monthly	Every 3 mo.	
	6–12 mo.	At least every 2 mo.	Every 3 mo.	
	>12 mo.	At least every 3 mo.	Every 3 mo.	

Province	Treatment stage	Schedule of clinical visits	Schedule of UDTs	Take home/Carries
Saskatchewan	Initiation	At least weekly	At least 1 UDT before initiation	Negative UDT for 3 months Must increase number of take-home doses at a rate of 1–2 per week, to a maximum of 6 take-home doses per week.
	Stabilization	Every 1–4 weeks until dose is stable	At every visit	
	<6 mo.	At least monthly	At least every 3 mo.	
	6-12 mo.	At least every 2 mo		
	>12 mo.	At least every 3 mo.		
Manitoba	Early stabilization phase (0–2 weeks)	2 per week	At least 1 UDT before patient is initiated	≥ 2 mo. on MMT First 2 mo. on MMT: only one carry per week (Sunday). After at least 2 mo.: one additional carry per mo. each month to a maximum of 6 per week, i.e., 5 plus Sunday.
	Late stabilization phase (2–6 weeks)	At least weekly		
	Maintenance phase (6+ weeks)	Every 1–3 mo.	For stable patients and those receiving carries, every 3 mo. minimum (however, some clinics order ongoing frequent UDT, e.g., 1–2 per week)	

Province	Treatment stage	Schedule of clinical visits	Schedule of UDTs	Take home/Carries
Ontario	Early stabilization (0-2 weeks)	1–2 times/week	Before initiation; 1–2 per week	<p>≥2 mo. on MMT and at least 1 week without problematic substance use, shown by history and UDT</p> <p>Begin with 1 carry dose per week.</p> <p>Subsequent increases in take-home doses: 1 additional carry per week every 4 weeks, to a maximum of 6 per week.</p> <p>13 carries can be given if: ≥5 years of stability and take-home doses, have been abstinent and stable for most of their time on MMT, dose is 120mg or less.</p> <p>Sunday carries permissible after 4 weeks in limited situations.</p>
	Late stabilization (2-6 weeks)	Weekly	≥4 per month	
	Maintenance (6+ weeks)	Reduce visit frequency as required	Progress from weekly to monthly	
Quebec	Initiation and stabilization	Weekly	Before initiation; Weekly	<p>>3 mo. on MMT</p> <p>Begin with 1 take-home dose per week in the 4th mo. of treatment, with increases as per the following schedule, to a maximum of 6 carries per week:</p> <p>5th mo.: 2 carries per week 6th–8th mo.: 3–4 carries per week >8th mo.: 5–6 carries per week</p>
	Maintenance	Reduce frequency to every 6–8 weeks over time	<p>At least twice per mo. for first 3 mo.</p> <p>From 4th to 12th mo.: <1 per mo. if previous results are negative; 2 per mo. if positive results.</p> <p>As needed after 12th mo.</p>	

Province	Treatment stage	Schedule of clinical visits	Schedule of UDTs	Take home/Carries
Newfoundland and Labrador	Early stabilization (0–2 weeks)	At least weekly; twice-weekly recommended	Prior to initiation	<p>≥3 mo. on MMT, 4 consecutive weeks of negative random UDT, and ≥2 mo. without substance use</p> <p>Maximum of 6 carries/week.</p> <p>Schedule A: Begin with 1 carry per week; increase by ≤1 carry every 4 weeks without substance use, to a maximum of 6 per week.</p> <p>Schedule B: Begin with 2 carries on consecutive weekend days; after 8 weeks without drug use, increase to 1 carry of 3 consecutive days and 1 carry of 2 consecutive days. After an additional 12 weeks free of substance use, increase to 6 per week.</p> <p>Accelerated take-home schedule can be considered after 2 mo. in extraordinary situations. See CPSNL MMT Standards.</p>
	Late stabilization (2–6 weeks)	At least weekly	1–4 times per mo. Before take-home doses: Weekly for 4 weeks	
	Maintenance (6+ weeks)	Every 1–2 weeks; patients with carries: weekly; patients with carries and abstinence ≥6 mo.; patients with long-term clinical stability: <1 per mo.	After take-home doses: Weekly for 4 weeks, every 2 weeks for 2 mo., then monthly random collection schedule preferred	
New Brunswick	Stabilization (min. 6 weeks)	Weekly	Before initiation;	≥3 mo. on MMT (with exceptions)
	Transition (min. 6 weeks)	Every 2 weeks	0–6 mo.: weekly	Suggested schedule:
	Community (maintenance)	Every 3–4 weeks	6–12 mo.: 2 per mo. (if stable) >12 months: 1 per mo.	3–6 mo. (depending on drug use): 1–3 carries 6–12 mo. (depending on drug use): 3–5 carries 12+ mo. (drug free): 6 carries

Province	Treatment stage	Schedule of clinical visits	Schedule of UDTs	Take home/Carries
Nova Scotia	Induction, stabilization, maintenance	At least once weekly during induction and with dose changes during stabilization; twice-weekly during the first 2 weeks of treatment recommended	Prior to initiation; At least monthly during induction and stabilization Every 2 mo. when 1 year of negative UDTs Every 3 mo. when >1 year of negative UDTs Before take-home doses: Weekly for 4 weeks After take-home doses: Weekly for 4 weeks, every 2 weeks for 2 mo., then monthly random collection schedule preferred	≥3 mo. on MMT, 4 consecutive weeks of negative random UDT, and ≥2 mo. without substance use Maximum of 6 carries/week. Schedule A: Begin with 1 carry per week; increase by ≤1 carry every 4 weeks without substance use, to a maximum of 6 per week. Schedule B: Begin with 2 carries on consecutive weekend days; after 8 weeks without drug use, increase to 1 carry of 3 consecutive days and 1 carry of 2 consecutive days. After an additional 12 weeks free of substance use, increase to 6 per week. Accelerated take-home schedule can be considered after 2 mo. in extraordinary situations. Obtain UDT weekly. See CPSNS MMT Handbook.
Prince Edward Island	See Ontario guidelines			

Additional Notes:

The Yukon Medical Council has adopted the Alberta MMT standards and guidelines.

Dosing standards for the Northwest Territories and Nunavut are not available at this time.

Carry schedules and frequency of UDT/clinical visits are affected by geographical location (e.g., patients

who reside in rural locations with no pharmacy access on Sundays will receive a default carry).

Sources:

British Columbia: [A Guideline for the Clinical Management of Opioid Use Disorder](#)

Alberta: [Alberta Methadone Maintenance Treatment Standards and Guidelines for Dependence](#)

Saskatchewan: [Opioid Substitution Therapy Guidelines and Standards for the Treatment of Opioid Addiction/Dependence](#)

Manitoba: [Manitoba Methadone & Buprenorphine Maintenance Recommended Practice](#)

Ontario: [Methadone Maintenance Treatment Program Standards and Clinical Guidelines](#)

Quebec: [Utilisation de la méthadone dans le traitement de la toxicomanie aux opiaces; Modifications aux lignes directrice](#)

New Brunswick: [Methadone Maintenance Treatment Policies and Procedures](#)

Nova Scotia: [CPSNS Methadone Maintenance Treatment Handbook](#)

Prince Edward Island: [CPSPEI Prescribing Methadone Maintenance Treatment for Opioid Dependency Policy](#)

Newfoundland and Labrador: [CPSNL Methadone Maintenance Treatment Standards and Guidelines](#)

Appendix 4: Provincial educational and training requirements to prescribe buprenorphine/naloxone

Province	Education + Practice Requirements
<p>British Columbia</p>	<ul style="list-style-type: none"> • The practitioner does not need to hold a methadone exemption to prescribe buprenorphine/naloxone for opioid use disorder, but completion of the buprenorphine/naloxone training modules of the BCCSU Provincial Opioid Addiction Treatment Support Program course are strongly recommended, in addition to consultation via the RACE line for additional expert support <p><i>Nurse practitioners:</i></p> <ul style="list-style-type: none"> • NPs are currently limited to continuation prescribing only (subject to change in fall 2017) • NPs must complete additional education and a preceptorship of a minimum of two half-days' length, under the guidance of a practitioner with expertise in the prescribing of buprenorphine/naloxone and treatment of clients with substance use disorders, and with a license to prescribe methadone • The preceptorship needs to cover the competencies associated with initiation, dosing, writing prescriptions, urine drug testing, carry policy, counselling and documentation
<p>Alberta</p>	<ul style="list-style-type: none"> • The practitioner does not need to hold a methadone exemption to prescribe buprenorphine/naloxone for opioid use disorder • Current recommendations for <i>physician</i> prescribing of buprenorphine/naloxone for opioid use disorder: <ul style="list-style-type: none"> - Completion of accredited buprenorphine course (www.suboxonetrainingprogram.ca [formerly known as www.suboxonecme.ca], CAMH Opioid Dependence Treatment Core Course, or other equivalent course approved by CPSA); must submit proof of course completion to the CPSA - Must be registered to prescribe TPP drugs - Initiating physicians must have experience in treating opioid use disorder (postgraduate training, ODT experience, professional certification with CSAM/ASAM, or equivalent approved by CPSA) - Physicians providing maintenance treatment must have a relationship with a physician experienced in treating opioid use disorder (i.e., a qualified initiating physician) - Temporary buprenorphine-prescribing physicians (i.e., in hospital or incarceration environments) will be permitted to maintain a buprenorphine dose without completion of a buprenorphine prescribing course. A temporary prescribing physician must have a relationship with a physician experienced in treatment of OUD and consult with an experienced physician regarding any dose changes <p><i>Continued on next page...</i></p>

<p>Alberta Continued</p>	<p><i>Nurse practitioners:</i></p> <ul style="list-style-type: none"> • Must complete requirements for prescribing controlled drugs and substances (CDS) <ul style="list-style-type: none"> - Must complete a CDS educational module recognized by CARNA OR have graduated after September 2015, and complete the CARNA CDS jurisprudence module • Prescribe using the TPP • Complete an approved buprenorphine/naloxone prescribing course • Initiating nurses must complete four half-days of preceptorship with a physician or nurse practitioner experienced in treatment of OUD • Maintaining nurses must complete two half-days of preceptorship with a physician or nurse practitioner experienced in treatment of OUD • Temporary prescribing is permitted for maintaining the same dose without completion of a buprenorphine/naloxone prescribing course. Temporary prescribers must have a relationship with a physician or nurse practitioner experienced in treatment of OUD and consult with them for any dose changes • Prescribing methadone or buprenorphine for opioid use disorder requires special authorization and has further requirements
<p>Saskatchewan</p>	<ul style="list-style-type: none"> • The physician must hold a methadone exemption to prescribe buprenorphine/naloxone for opioid use disorder or have spent a minimum of one day with another physician who has received an exemption from Health Canada to prescribe methadone and is experienced in prescribing buprenorphine • Additional requirements for prescribing buprenorphine/naloxone for opioid use disorder: <ul style="list-style-type: none"> - Completion of an approved educational buprenorphine prescribing program - Completion of a CME program which includes a minimum of six hours of training in addiction medicine every two years - Must have a relationship with one or more addictions counsellors and one or more pharmacists, and regularly test patients for non-medical or illegal drug use - Must have access to the PIP to monitor other prescriptions - Must prescribe using the physician’s personalized prescription pad or CPSS-approved electronic prescribing - Must agree to and cooperate with audits by the College - Requirements for temporary prescribing physicians in hospitals and corrections: Please see <i>Opioid Substitution Therapy Guidelines and Standards for the Treatment of Opioid Addiction/Dependence</i>, available from the CPSS
<p>Manitoba</p>	<ul style="list-style-type: none"> • The physician must hold a methadone exemption to prescribe buprenorphine/naloxone for opioid use disorder • Additional requirements for prescribing buprenorphine/naloxone for opioid use disorder include: <ul style="list-style-type: none"> - Completion of online buprenorphine/naloxone education program (i.e., www.suboxonetrainingprogram.ca) <p><i>Nurse practitioners:</i></p> <ul style="list-style-type: none"> • Must maintain prescribing authority for controlled drugs and substances • Complete the online www.suboxonetrainingprogram.ca program

<p>Ontario</p>	<ul style="list-style-type: none"> • The physician does not need to hold a methadone exemption to prescribe buprenorphine/naloxone for opioid use disorder • Current recommendations for prescribing buprenorphine/naloxone for opioid use disorder: <ul style="list-style-type: none"> - Completion of CAMH Opioid Dependence Treatment Core Course - Completion of CAMH Buprenorphine-Assisted Treatment of Opioid Dependence: An Online Course for Front-Line Clinicians - Ongoing continuing education (e.g., online buprenorphine/naloxone education program: www.suboxonetrainingprogram.ca) - A one-day clinical observership of an opioid-dependency practice <p><i>Nurse practitioners:</i></p> <ul style="list-style-type: none"> • Must complete approved education for controlled drugs and substances
<p>Quebec</p>	<ul style="list-style-type: none"> • The physician does not need to hold a methadone exemption to prescribe buprenorphine/naloxone for opioid use disorder • Current requirements for prescribing buprenorphine/naloxone for opioid use disorder: <ul style="list-style-type: none"> - For physicians licensed to prescribe methadone with sufficient experience monitoring opioid dependence (at least 10 patients), completion of online buprenorphine/naloxone education program [e.g., www.suboxonetrainingprogram.ca or Institut national de santé publique du Québec (INSPQ) one-day course] - For physicians new to treating opioid use disorder, completion of a one-day professional development program accredited by the continuing education department of the University of Montreal
<p>New Brunswick</p>	<ul style="list-style-type: none"> • The practitioner does not need to hold a methadone exemption to prescribe buprenorphine/naloxone for opioid use disorder • Current recommendations for prescribing buprenorphine/naloxone for opioid use disorder: <ul style="list-style-type: none"> - Completion of training deemed appropriate by the CPSNB - Evidence of buprenorphine/naloxone training may be requested by the CPSNB <p><i>Nurse practitioners:</i> Must maintain prescribing authority for controlled drugs and substances</p>

<p>Nova Scotia</p>	<ul style="list-style-type: none"> • The practitioner does not need to hold a methadone exemption to prescribe buprenorphine/naloxone for opioid use disorder • Current recommendations for <i>physician</i> prescribing of buprenorphine/naloxone for opioid use disorder: <ul style="list-style-type: none"> - Completion of CAMH Opioid Dependence Treatment Core Course - Completion of CAMH course: CAMH Buprenorphine-Assisted Treatment of Opioid Dependence: An Online Course for Front-Line Clinicians - Familiarity with the individual patient factors to be taken into consideration in the choice of buprenorphine for opioid dependence as an OAT - Familiarity with the CAMH buprenorphine/naloxone practice guidelines <p><i>Nurse practitioners:</i></p> <ul style="list-style-type: none"> • Must meet CRNNS requirements and standards to prescribe controlled drugs and substances • Must possess the knowledge, skill and ability to prescribe buprenorphine/naloxone (i.e., seeking and completing a buprenorphine/ naloxone education course) • The medication must be required for the client population treated by the nurse practitioner • Recommended completion of the CAMH course: Buprenorphine-Assisted Treatment of Opioid Dependence: An Online Course for Front-Line Clinicians • Formal or informal consultation with a prescriber experienced in the use of buprenorphine/ naloxone is strongly recommended. • No provincial exemption is required to prescribe buprenorphine/naloxone, however, individual districts' health authorities may set and enforce policies for prescribing
<p>Prince Edward Island</p>	<ul style="list-style-type: none"> • The physician does not need to hold a methadone exemption to prescribe buprenorphine/naloxone for opioid use disorder • Current requirements for prescribing buprenorphine/naloxone for OUD: <ul style="list-style-type: none"> - Completion of online buprenorphine/naloxone education program: (i.e., www.suboxonetrainingprogram.ca) - Completion of a recognized course on the fundamentals of addiction medicine within first two years of commencing prescribing - Completion of a minimum of 20 hours of formal CME in some aspect of addiction medicine every five years or equivalent training approved by the CPSPEI • Completion of "Commitment by Physicians who Undertake Buprenorphine Treatment for Opioid Dependency" form

**Newfoundland
and Labrador**

- **The physician does not need to hold a methadone exemption** to prescribe buprenorphine/naloxone for opioid use disorder
- **Current requirements** for prescribing buprenorphine/naloxone for opioid use disorder:
 - Completion of [CAMH Opioid Dependence Treatment Core Course](#) or equivalent program approved by the CPSNL
 - Completion of an educational program on prescribing buprenorphine (i.e., www.suboxonetrainingprogram.ca)
 - Establishment of a program for the regular testing of patients receiving buprenorphine for drugs of possible abuse
 - Participation in ongoing continuing medical education (CME) in opioid-dependence treatment and/or addiction medicine

Note: Information was not available for Yukon, Northwest Territories, or Nunavut

Sources:

British Columbia: [CPSBC Important Notice Regarding Suboxone](#); [Scope of Practice for Nurse Practitioners](#)

Alberta: [CPSA Suboxone Prescribing](#); [Prescribing Changes for Buprenorphine/Naloxone \(Suboxone\); Medication-Assisted Treatment for Opioid Dependence: Guidelines for Pharmacists and Pharmacy Technicians](#); [Prescribing Standards for Nurse Practitioners \(NPs\)](#)

Saskatchewan: [Opioid Substitution Therapy Guidelines and Standards for the Treatment of Opioid Addiction/Dependence](#)

Manitoba: [Suboxone \(buprenorphine/naloxone\)—Important practice notes for pharmacists; CRNM Prescribing Controlled Drugs and Substances](#)

Ontario: [CPSO Frequently Asked Questions about Prescribing Buprenorphine](#); [CNO Q&A on controlled substances](#)

Quebec: [La buprénorphine dans le traitement de la dépendance aux opioïdes](#)

New Brunswick: [CPSNB Treatment of Opioid Addiction](#); Personal Correspondence, Dawn Torpe, RN, MN/II, M.Sc.inf, Nursing Practice Consultant, NANB

Nova Scotia: [Opioid Treatment Disorder](#); [CPSNS Methadone Maintenance Treatment Handbook](#); Personal Correspondence, Lynn Miller, DNP, NP, Policy Consultant, CRNNS

Prince Edward Island: [Prescribing Buprenorphine Treatment for Opioid Dependency](#)

Newfoundland and Labrador: [CPSNL Methadone Maintenance Treatment Standards and Guidelines](#); [Practice Guideline: Suboxone® for Opioid Dependence](#)

Appendix 5: Provincial drug plan coverage and regulations for prescribing buprenorphine/naloxone

Province	Coverage	Criteria for Coverage	Section 56 Exemption	Professional Roles
British Columbia	Regular Benefit	Open coverage for treatment of opioid dependency in adults	No exemption required	Physicians Nurse Practitioners
Alberta	Regular Benefit	Open coverage for treatment of opioid dependency in adults	No exemption required	Physicians Nurse Practitioners
Saskatchewan*	Exceptional Status	Covered if methadone is contraindicated, not available or inappropriate	Prescribers must have a methadone exemption OR have spent a minimum of one day with another physician who has received an exemption from Health Canada to prescribe methadone	Physicians
Manitoba	Regular Benefit (Part 1 Drug Product)	Open coverage for treatment of opioid dependency in adults	Physicians must have a methadone exemption No exemption required for Nurse Practitioners	Physicians Nurse Practitioners
Ontario	General Benefit	Open coverage for treatment of opioid dependency in adults	No exemption required	Physicians Nurse Practitioners
Quebec*	Codified Exceptional Medication	Covered if methadone is contraindicated, not available or inappropriate	No exemption required	Physicians
New Brunswick	Special Authorization	Covered if methadone is contraindicated, not available or inappropriate	No exemption required	Physicians Nurse Practitioners
Nova Scotia	Exception Status (Criteria Code for Immediate Coverage)	Adults aged 18–24: covered for treatment of opioid addiction Adults over 24: covered if methadone is contraindicated, not available or inappropriate	No exemption required	Physicians Nurse Practitioners

Province	Coverage	Criteria for Coverage	Section 56 Exemption	Professional Roles
Prince Edward Island*	Special Authorization	Adults aged 18–24: covered for treatment of opioid addiction Adults over 24: Covered if methadone is contraindicated, not available or inappropriate	No exemption required	Physicians
Newfoundland and Labrador*	Open Benefit	Open coverage for treatment of opioid dependency in adults	No exemption required	Physicians

**Nurse practitioners in these provinces are not currently authorized to prescribe buprenorphine/naloxone for opioid use disorder; however, these policies are undergoing revision and upcoming regulatory changes are anticipated.*

Sources (coverage):

British Columbia: [BC PharmaCare Formulary Search](#)

Alberta: [Alberta Drug Benefit List](#)

Saskatchewan: [Saskatchewan Drug Plan Formulary](#)

Manitoba: [Manitoba Pharmacare Formulary Drug Lookup](#)

Ontario: [Ontario Drug Benefit Formulary/Comparative Drug Index Edition 42](#)

Quebec: [Public Health Plan - List of Medications](#)

New Brunswick: [New Brunswick Drug Plan Formulary](#)

Nova Scotia: [Nova Scotia Drug Formulary](#)

Prince Edward Island [P.E.I. Pharmacare Formulary](#)

Newfoundland and Labrador: [NLPDP Drug Product Database](#)

Appendix 6: Provincial clinical practice guidelines—recommendations for buprenorphine/naloxone

Table A6.1. Dosing recommendations for buprenorphine/naloxone

*Note (1): The table below summarizes currently available national and provincial guidelines on induction and stabilization protocols for buprenorphine/naloxone. **Please also refer to the Suboxone® product monograph for dosing standards approved by Health Canada.***

Note (2): For simplicity, dose strength of the buprenorphine component only (in milligrams) of the combined buprenorphine/naloxone formulation is reported (e.g., 2mg indicates 2mg buprenorphine and 0.5mg naloxone).

	Induction (Day 1)	Induction/titration (Day 2 onward)	Stabilization dose
CAMH Buprenorphine/ Naloxone for Opioid Dependence: Clinical Practice Guideline	<p>2–4mg (up to 6mg)</p> <p>Reassess in 1–3 hours; consider prescribing additional dose up to max. 8mg total on Day 1.</p> <p>This may include 1–2 2mg tablets to take home in case of withdrawal symptoms.</p>	<p>Reassess within 1–3 days of Day 1.</p> <p>If follow-up is in 3 days, write prescription for same total amount as on Day 1 for the next 1–2 days.</p> <p>If significant withdrawal symptoms continue on reassessment, increase dose to max. additional 8mg (on average a 2–4mg increase is required) as early as the 2nd induction day.</p>	<p>Avg. 8–12mg/day</p> <p>Max. 24mg/day</p> <p>Once at a stable dose, consideration can be given to alternate-day dosing (i.e., double the dose on M/W/F and a single dose on Sunday).</p>

<p>British Columbia</p>	<p>Most common starting dose: 2 x 2mg (4mg total)</p> <p>If high risk of precipitated withdrawal or currently abstinent: 1 x 2mg OR use buprenorphine patch (e.g. BuTrans®) as adjunct.</p> <p>If severe withdrawal at time of induction: 3 x 2mg (6mg total)</p> <p>If withdrawal symptoms not adequately relieved after 1–3 hours, administer additional dose(s) up to max. total 12mg on Day 1. This may include 1–2 2mg tablets to take home in case of withdrawal symptoms.</p>	<p>Day 2: Same total dose as Day 1, plus one or two additional 4mg doses every 2–3 hours if needed to relieve persistent withdrawal symptoms.</p> <p>Max total dose on Day 2 should not exceed 16 mg.</p> <p>Day 3 onward: Same total dose as previous day. If needed (i.e., persistent withdrawal symptoms), repeat induction schedule of 4mg increase with reassessment every 2–3 hours.</p> <p>Otherwise, titrate as needed (by an increase or decrease of 2–4mg at a time) to an optimal dose*. Target dose is generally 12–16mg/day by the end of the first week.</p>	<p>Max. 24mg/day; clear documentation and justification required to exceed 24mg. Of note, U.S. guidelines state that some patients may require doses up to 32mg per day.</p> <p>For clinically stable patients at stable doses, one can consider:</p> <p>Alternate-day dosing for patients who are on a stable daily dose of up to 12mg (i.e., within the 24mg/day maximum); and/or gradually increasing take-home doses.</p>
<p>Saskatchewan Manitoba Nova Scotia Prince Edward Island Newfoundland and Labrador</p>	<p>As per CAMH guidelines (see above)</p>		
<p>Quebec</p>	<p>2–4mg</p> <p>Reassess in 2–4 hours; increase by an additional 2–4mg at a time up to max. 8mg total on Day 1.</p>	<p>Dose may be increased by increments of 2–4mg every 2–4 hours to a maximum of 8–16mg/day, depending on patient’s symptoms and previous consumption.</p>	<p>Avg. 12–16mg/day</p> <p>Max. 24mg/day</p> <p>It should be noted that the Health Canada product monograph mentions a maximum dose of 24mg/day, but protocols in various countries (e.g., the U.S. and Australia) mention a maximum dose of 32mg/day.</p> <p>For well-stabilized patients, doses can be given daily, every 2 days (double dosing), or 3 times a week (double dosing on M/W and triple dosing on Friday). Total daily dose should not exceed 32mg/day.</p>

**Optimal dose: can sustain an entire 24-hour dosing interval with no withdrawal symptoms and no medication-related intoxication or sedation.*

Table A6.2. Recommendations for clinical visits, UDT, and take-home dosing (carries) for buprenorphine/naloxone

	Treatment Stage	Schedule of clinical visits	Schedule of UDTs	Take home/Carries
British Columbia	Induction: Day 1	Plan for weekday morning, allowing for reassessment in the afternoon. Reassess 30–60 min from first dose, and 1–3 hours from first dose.	At least monthly during induction and titration, until stable dose is reached; or more frequently as required.	Take-home doses can be gradually increased in clinically stable patients at stable doses. Generally provide for 1–2 weeks’ worth of medication at a time. Some take-home doses may be incorporated into induction when multiple same-day visits for reassessment not feasible.
	Induction: Day 2 onward	Reassess in morning and, if increasing dose, every 2–3 hours.		
	Once optimal dose is achieved	Follow up once per week (or more frequently, as needed).		
	Stabilization	Continue to assess at least every 1–2 weeks; may decrease follow-up visits with increasing clinical stability.	For patients receiving take-home doses: At least 4 random UDTs per year; more frequent if there are safety concerns.	
Saskatchewan Nova Scotia Prince Edward Island Newfoundland and Labrador	As per CAMH guidelines (see below)			
Manitoba	As per CAMH guidelines (see below)		At least 1 UDT before patient is initiated; for stable patients and those receiving carries, min. every 3 mo.	≥2 mo. on MMT First 2 mo. on MMT: only one carry per week (Sunday). After 2 mo.: one additional carry per mo. each month to a maximum of 6 per week i.e., 5 plus Sunday. Very stable patients may receive up to two weeks of carries.

CAMH	Induction: Day 1	As early in the day as possible; reassess 1 hour, and 3 hours, from first dose.	In general, UDT should be performed	May be given once the patient has demonstrated clinical stability.
	Induction: Day 2 onward	Either reassess on Day 2 or write a prescription for observed once-daily dosing for the next 1–2 days	during or immediately following each patient appointment.	Gradual increase in number of weekly take-home doses up to a suggested maximum of 1–2 weeks of consecutive take-home doses.
	Induction	1–2 times/week	More or less frequent testing may be performed for a clinically justifiable reason.	Refer to Health Canada product monograph for take-home dosing guidance; take-home doses should be given once the patient has sufficient clinical stability and is able to safely store the medication.
	Once at stabilization dose	Every 1–2 weeks		Take-home doses should be assessed and reviewed on a regular basis.
	Once achieved clinical stability and eligible for take-home doses	Once every 1–3 months; min. every 3 months. Increase visit frequency if patient demonstrates signs of clinical instability.		
Quebec	Induction: Day 1	The initial dose should be given in the morning; Reassess 2–4 hours after initial dose	UDT should be collected before treatment to confirm opioid intake and randomly during the first two months of treatment.	May be given once the patient has demonstrated ability to manage medication and clinical stability. Unsupervised doses are not allowed during the first 2 months of treatment for a new patient.
	Induction: Day 2 onward	Daily; reduce frequency over time	Frequency of UDT is up to the clinician’s judgment. A frequency of two screenings per month may be useful.	After this period, a first take-home dose may be granted for a period of 1 month. A new take-home dose may be assigned every month, depending on the patient’s stability and treatment progress.
	After stability is achieved	1 per 3 mo.	After the first 2 months of negative UDT, it may be randomly collected at the frequency the clinician deems appropriate.	A patient who switches from MMT to treatment with buprenorphine/naloxone may typically retain the same number of take-home doses as in their MMT dosing schedule. Max. 6 take-home doses in 7 days <i>The physician may expedite a take-home dosing schedule based on their clinical judgment of the patient’s treatment progress and stability, but these exceptional cases must be justified on record, and the pharmacist should be advised.</i>

Sources:

British Columbia: [A Guideline for the Clinical Management of Opioid Use Disorder](#)

Manitoba: [Manitoba Methadone & Buprenorphine Maintenance – Recommended Practice](#)

CAMH: [Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline](#)

Quebec: [La buprénorphine dans le traitement de la dépendance aux opioïdes](#)

Appendix 7: Provincial resources for rapid consultation with addiction medicine specialists

British Columbia: Rapid Access to Consultative Expertise (RACE) Line

- The RACE line allows primary care practitioners in BC to rapidly connect with and receive treatment advice from a specialist, often eliminating the need for a face-to-face specialist or emergency department referral. To connect with an addiction medicine specialist, practitioners may call the RACE line (604.682.2344) or download the RACE app at <http://www.raceconnect.ca/race-app>. Primary care physicians may be eligible to receive CME “Linking Learning to Practice” credit for using RACE in patient care.
- For more information, practitioners can visit the RACE line website at <http://www.raceconnect.ca>.

Champlain, Ontario and Newfoundland and Labrador: Building Access to Specialists through eConsultation (BASE eConsult) Service

- The BASE eConsult service is a secure, web-based tool that allows primary care practitioners (PCPs) in the Champlain region of Ontario and throughout the province of Newfoundland and Labrador to rapidly connect with specialty care for patients, often eliminating the need for a face-to-face appointment. Through eConsult, a practitioner can submit a non-urgent, patient-specific question to a participating specialty. The request will be answered within 7 days (average response time is = 2 days) by the appropriate specialist. Depending on the individual request, the specialist may:
 - Provide the practitioner with patient-specific advice in place of a face-to-face specialist consultation;
 - Request additional information before being able to provide advice; and/or
 - Recommend a formal referral, in which case any additional diagnostic tests, courses for treatment, etc., may be requested and completed before the appointment, leading to a more effective specialist visit.
 - Through this service, PCPs can connect with an addiction medicine specialist with expertise in methadone and buprenorphine treatment.
- For more information or to join the Champlain BASE eConsult service, PCPs can contact iconsultsupport@lhinworks.on.ca or visit <http://www.champlainbaseconsult.com/>.

- For more information or to join the Newfoundland and Labrador BASE eConsult service, PCPs can contact jcook@nlma.nl.ca or visit <http://www.nlma.nl.ca/Physicians/eConsult/>.

Alberta: Referral, Access, Advice, Placement, Information & Destination (RAAPID)

- RAAPID allows PCPs and nurse practitioners in Alberta to access expert consultation with an opioid dependency physician specialist over the phone. Practitioners can call this consult service for advice regarding:
 - Initiating and managing opioid agonist therapy
 - Prescribing medications, such as buprenorphine/naloxone, methadone or naloxone
 - Treating patients with existing opioid dependency
 - Managing opioid withdrawal and consideration of opioid agonist therapy
- Opioid dependency physician specialists are available:
 - Monday through Friday 0800 to 2200 hours
 - Weekends and Statutory holidays 0800 to 1800 hours
- To access this service, practitioners north of Red Deer can call RAAPID North at 1-800-282-9911 or 780-735-0400. Practitioners in and south of Red Deer can call RAAPID South at 1-800-661-1700 or 403-944-4488.
- For more information, visit <http://www.albertahealthservices.ca/info/Page15558.aspx>.

Appendix 8. DSM-5 Clinical Diagnostic Criteria for Opioid Use Disorder

To be eligible for methadone, buprenorphine/naloxone or slow release oral morphine agonist treatment, patients should meet DSM-5 criteria for opioid use disorder.

Opioid Use Disorder (OUD) Diagnostic Criteria¹

1	Opioids are often taken in larger amounts or over a longer period than was intended	OUD severity MILD: The presence of 2 to 3 symptoms MODERATE: The presence of 4 to 5 symptoms SEVERE: The presence of 6 or more symptoms
2	There is a persistent desire or unsuccessful efforts to cut down or control opioid use	
3	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects	
4	Craving or a strong desire to use opioids	
5	Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home	
6	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids	
7	Important social, occupational, or recreational activities are given up or reduced because of opioid use	
8	Recurrent opioid use in situations in which it is physically hazardous	
9	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids	
10	Tolerance*, as defined by either of the following: Need for markedly increased amounts of opioids to achieve intoxication or desired effect Markedly diminished effect with continued use of the same amount of opioid	
11	Withdrawal*, as manifested by either of the following: Characteristic opioid withdrawal syndrome Same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms	

**This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision*

¹ Reprinted with permission from: American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5™*. 5th ed. Arlington, VA: American Psychiatric Publishing, Inc.

Appendix 9: Guideline methodology and development process

Funding

Guideline development activities were entirely supported by internal funding from the Canadian Institutes of Health Research (CIHR) Canadian Research Initiative in Substance Misuse (CRISM) Regional Nodes (British Columbia, Ontario, Prairies and Quebec-Atlantic), without support from the pharmaceutical industry or associated stakeholders.

Review Committee Selection

The Nominated Principal Investigators (NPIs) from each CRISM Node nominated a Clinical Lead to coordinate committee formation and review activities in each region (Table 1a). The NPIs and the Clinical Leads, hereby referred to as the Guideline Development Group (GDG), identified and invited seven to 13 expert candidates from each region to form a regional guideline committee (Table 1b). Overall, 44 practicing clinicians and key facilitators, including primary care physicians, addiction-medicine physicians and psychiatrists, nurse practitioners and registered nurses, social workers, pharmacists, program managers and administrators, and policymakers, were invited to participate in the regional review committees. All 44 completed conflict of interest declarations and assessments prior to participation. Of these, 43 completed the full guideline development, review, and approval process. Committee members reviewed and discussed guideline materials via email and teleconference. CRISM staff provided operational and administrative support.

Table 1a. CRISM Guideline Development Group Membership List*

Region	Clinical Lead
British Columbia NPI: Evan Wood, MD, PhD	Keith Ahamad, MD
Ontario NPI: Benedikt Fischer, PhD	Peter Selby, MBBS, MHSc
Prairies NPI: T. Cameron Wild, PhD	Ginette Poulin, RD, MD
Quebec-Atlantic NPI: Julie Bruneau, MD, MSc	Marie-Ève Goyer, MD, MSc

Table 1b. CRISM Guideline Regional Committee Membership List*

Region	Committee Members
British Columbia	<p>Nadia Fairbairn, MD, FRCPC, CISAM</p> <p>Ramm Hering, MD, MSc, CCFP, Dip. PH, Dip. ABAM, FASAM, CCSAM</p> <p>Leslie Lappalainen, MD, CCFP, Dip. ABAM</p> <p>Zak Matieschyn, BSN, MN, RN, NP(Family)</p> <p>Nader Sharifi, MD, CCFP, Dip. ABAM</p> <p>Kenneth W. Tupper, PhD</p>
Ontario	<p>Sharon Cirone, MD</p> <p>Curtis Handford, MD, CCFP, MHSc</p> <p>Meldon Kahan, MD, CCFP, FRCPC</p> <p>Alice Ordean, MD, CCFP, MHSc, FCFP, Dip. ABAM, FASAM</p> <p>Kathy Pouteau, MD, DTMH</p> <p>Sheryl M. Spithoff, MD</p> <p>Beth A. Sproule, BScPhm, PharmD</p>
Prairies	<p>Marita Athaide, BN, BGS, MD, CCFP, FCFP</p> <p>Kulvir Badesha, MD, FRCPC, ABAM Candidate</p> <p>Peter R. Butt, MD, CCFP, FCFP</p> <p>Laura D. Evans, MD, CCFP, Dip. ABAM, CCSAM, CISAM</p> <p>Morag Fisher, MBChB, CCSAM</p> <p>Michael R. Isaac, MD, MPH, FRCPC</p> <p>Ronald Lim MD, CCFP, Dip., ABAM, FASAM, DFISAM, CCSAM</p> <p>Richard A. Martin, MD, CCFP, FCFP</p> <p>Matt Rose, MD, CCFP</p> <p>Michael Trew, MD, FRCPC</p>

Quebec-Atlantic	Peter Barnes, MD, MEd, CCFP
	Patrick Boudreault, BPharm, MSc
	Joeseeph Cox, MD, MSc, FRCPC, FASAM
	Jacques Dumont, MD, CCFP
	Serge Dupont, MD
	Samuel Hickcox, MD
	Bruce Hollett, MD
	Peter Hooley, MD, CCFP
	David Martell, MD, CCFP
	Lynn Miller, DNP, NP, FRE
	Marie-Chantal Pelletier, MD, LLB
Duncan Webster, MD, MA, FRCPC	

**Note: Committee members participated in guideline development activities in their individual capacities and not as institutional representatives.*

Conflict of Interest Policy

Conflicts of interest were assessed using the Guidelines International Network’s Principles for Disclosure of Interests and Management of Conflicts.¹ For this Guideline, committee members were required to disclose all sources and amounts of direct and indirect remuneration received in the past five years from industry, for-profit enterprises, and other entities (e.g., direct financial conflicts) that could introduce real, potential, or perceived risk of bias. In addition, committee members were asked to disclose possible indirect conflicts of interest, such as academic advancement, clinical revenue, and professional or public standing that could potentially influence interpretation of evidence and formulation of recommendations.

Before the draft guideline was circulated for review, two CRISM staff members independently reviewed the disclosure forms to screen potential committee members who should be precluded from participation due to ongoing or current financial relationships (e.g., employment, paid consultancy or advisory board membership, stock ownership, intellectual property) with industry or commercial entities that could theoretically benefit from the guideline recommendations. Consistent with the Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines,² any individual with a current, ongoing relationship with industry, who had received any remuneration or non-monetary support from industry within the past 12 months, or with a history of significant remuneration or non-monetary

support from industry (defined for our purposes as cumulative receipt of more than \$10,000 or equivalent value within the past five years), was excluded from participation on the guideline committee prior to the review process. No committee members were excluded during initial screening as none met these criteria for exclusion.

Summary of disclosures

No current or ongoing direct conflicts of interest were disclosed by the 43 committee members, including the four nominated principal investigators of the CRISM nodes, who participated in the review process upon screening for involvement on the committee. A total of five individuals reported past direct conflict of interests in the form of paid consulting or services as a technical advisor for Indivior Inc. ($n = 2$; total remuneration range \$3,000-\$7,000), and/or paid honoraria or fees to participate in a speakers panel or training seminar ($n = 4$; total remuneration range \$1,000-\$2,000) for Indivior Inc. in the previous five years prior to participation in the committee (one individual received both consulting and training fees). None of these direct conflicts of interest occurred within the 12 months preceding their participation on the committee. No individual reported a history of employment (either self or family member); investment interests; grants-in-aid for research, non-monetary research or program support (e.g., equipment, travel, staff salary, facilities); or intellectual property holdings with industry or any commercial entity that could potentially benefit from guideline recommendations.

In terms of indirect sources of potential interest or bias, overall, 31 individuals disclosed special interests in relation to the guideline content. These mainly pertained to specific expertise (e.g., addiction medicine clinician, academic addictions expert), involvement with provincial OAT programs and committees, or research interests of the individuals that had been selected to participate as review committee members. On review, none of the disclosed potential indirect conflicts of interest or bias were deemed to be of sufficient relevance or weight to warrant exclusion from the committee.

Risk mitigation

On review of disclosures, none of the disclosed potential conflicts of interest were deemed to be of sufficient grounds to warrant exclusion from the committee, particularly due to scope of historical remuneration and given that none were active at the time of participation. To mitigate any real, potential, or perceived risk of bias, the five individuals who disclosed direct financial conflicts of interest contributed to the initial rounds of review and revision of the draft, but were asked to recuse themselves from the final review and approval of guideline. The remaining 38 members of the committee with no disclosed direct conflicts of interest reviewed and granted final approval of the guideline contents and clinical recommendations.

References

- 1 Schünemann HJ, Al-Ansary LA, Forland F, et al. Guidelines international network: principles for disclosure of interests and management of conflicts in guidelines. *Ann Intern Med* 2015;163:548-53.
- 2 Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Board on Health Care Services, Institute of Medicine of the National Academies. *Clinical practice guidelines we can trust*. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, eds. Washington, DC: National Academies Press; 2011. At: <https://www.nap.edu/read/13058/chapter/1>. Accessed 21 Jun 2017.

Content Development

The GDG reviewed and agreed upon the following elements prior to circulation to regional committees:

Intended audience

The guideline is intended for Canadian physicians, nursing and allied healthcare professionals with and without specialized training in addiction medicine. In addition, this guideline is intended to be a resource for Canadian policymakers and healthcare administrators in the development of provincial strategies and programs to best address unmet addiction care needs in an evidence-based, cost-effective manner.

Objective

The purpose of the guideline is to provide recommendations, supported by current and rigorously reviewed evidence, for the full spectrum of medical and psychosocial interventions available to treat OUD. In doing so, the guideline aims to provide comprehensive education and clinical care guidance to healthcare providers spanning the addiction care continuum in the country, which will, in turn, improve access to evidence-based treatment for patients and families, and reduce the significant harms associated with OUD in Canada.

Scope

The guideline reviews the scientific and clinical evidence base for various OUD treatment approaches, including oral agonist and antagonist pharmacotherapies, as well as withdrawal management strategies, psychosocial treatment interventions and supports, and residential treatment. The guideline is directed primarily toward treatment of uncomplicated OUD in adults and youth, including pregnant women. Future work is required to develop and implement best practices in other specific populations, including incarcerated individuals, the elderly, and Indigenous populations (e.g., culturally optimized care pathways), as well as individuals with concurrent medical and mental health disorders, including alcohol and other substance use disorders and severe mental illness.

In addition, evidence-based injectable OAT (diacetylmorphine and hydromorphone) are not reviewed here; these approaches require more specialized clinical expertise and health system infrastructure. In addition, because of the cost and access barriers for patients, other injectable treatment options such as extended-release naltrexone and depot formulations of buprenorphine are not reviewed in this guideline.

Literature search strategy

The national guideline expanded on two previous documents developed in British Columbia: the Vancouver Coastal Health/Providence Health Care Guideline for Clinical Management of Opioid Addiction released in November 2015, and the BC Centre on Substance Use/Ministry of Health [Guideline for the Clinical Management of Opioid Use Disorder](#), released in February 2017. For these provincial guideline documents, an initial literature search was conducted in November 2014, supplemented by literature searches in January 2015 and June 2016. For the national CRISM guideline, updated literature searches were performed June and November 2016.

For all eleven recommendations, relevant search terms and structured search strategies were constructed and used to search PubMed, ISI Web of Science, and the Cochrane Library databases (i.e., the Cochrane Central Register of Controlled Trials including the Cochrane Drugs and Alcohol Group trials register), using a hierarchical approach, where identification and selection of meta-analyses and systematic reviews of randomized controlled trials was prioritized, followed by individual randomized controlled trials, quasi-experimental studies, prospective and retrospective observational cohort studies, and lastly, expert opinion (e.g., clinical practice guidelines, position papers, consensus statements issued by a recognized professional organization or authority).

Initial exploratory searches had no temporal restrictions from initial date of publication index (variable depending on database used) to current date of the search; results were evaluated in a cumulative fashion in order of most recent date of publication. Using the hierarchical approach, once a relevant high-quality meta-analysis or systematic review was identified for a particular topic, clinical question, or recommendation, subsequent structured literature searches were conducted bridging the time period covered by the prior review to date of search, and supplemented by review of selection criteria used in, review of all citations included/excluded from, and review of all citations that subsequently cited that particular meta-analysis or systematic review. If more than one relevant high-quality meta-analysis or systematic review was identified for a particular recommendation, the supplementary review process described above was used for each. CRISM staff members (ranging from 2-4 individuals) conducted literature reviews, independently examined titles, abstracts, and full-text from literature searches, and prepared narrative evidence summaries for the guideline committee's review and consideration.

Development and grading of recommendations

Recommendations were developed and graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool¹⁻³ through an iterative consensus process. The node principal investigators developed draft recommendations and assigned GRADE scores in consultation with clinical leads, and recommendations were then reviewed by the full committee in two consecutive rounds, as described below.

To determine quality of evidence, the GRADE criteria employ a range of factors, including study design, risk-benefit ratios, potential biases, and scope and consistency of results, to assign scores of high, moderate, low, or very low, defined in Table 2.¹⁻³

Table 2. GRADE Hierarchy for Quality of Evidence¹⁻³

Quality level	Definition
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.

As the Cochrane Collaboration uses the GRADE criteria to assess quality of evidence in their systematic reviews, if a Cochrane Review was available for the evidence underlying a particular recommendation, as was the case for most of the recommendations in this guideline, this was used as the baseline for assignment of a quality of evidence score. Additional research evidence considered in developing final recommendations and assigning quality of evidence and strength of recommendation scores using GRADE is detailed in the next section.

Where additional studies were included in the grading process (e.g., for slow-release oral morphine, psychosocial treatment interventions), the GRADE approach was used as follows. Studies were categorized into 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 the treatment effect. Then, factors that would raise or lower a level of confidence were considered. Factors that lowered confidence in evidence included risk of bias, inconsistency across the RCTs, indirectness, and publication bias; factors that increased confidence included large effect size and an observed dose-response effect. The final quality ratings are reflective of the confidence in the estimated effect in the context of bias and limitations that have been identified, as depicted in the table below.

1. INITIAL SCORE		2. EVALUATE + ASSESS		3. FINAL DECISION
Study design	Initial Confidence	↓ Lower Score if:	↑ Raise Score if:	Confidence in estimated effect (in context of limitations):
Meta-analyses, RCTs	High (4)	Sparse data	Large effect size	High 
Quasi-experimental	Moderate (3)	Risk of bias		Moderate 
Observational studies	Low (2)	Inconsistency between studies	Dose response, clear signal across studies	Low 
Expert opinion	Very low (1)	Lacks generalizability or specificity (depending on intervention)	Adjustment for bias/confounding variable increases effect size	Very low 
		Imprecision		
		Publication bias		

GRADE uses a binary system to classify strength of recommendations as strong or weak. It is important to note that while 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—additional factors are also considered. To determine strength of recommendations as weak or strong, factors including quality of evidence, risk-benefit ratios, cost and values/preferences were considered in previous documents and again by the GDG, as shown in Table 3.

Table 3. GRADE Criteria for Determining Strength of Recommendations¹⁻³

Factor	Explanation
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.

Examples of how a strong vs. weak recommendation could be interpreted by selected audience or user groups are listed below (adapted from Guyatt et al. 2008a).

A **STRONG** recommendation indicates:

- For **PATIENTS**: Most people in your situation would want the recommended course of action and only a small proportion would not; you should request a 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 **HEALTHCARE ADMINISTRATORS**: The recommendation can be adopted as a policy in most situations.

A **WEAK** recommendation indicates:

- 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 **HEALTHCARE ADMINISTRATORS**: Policy making will require substantial debate and involvement of many stakeholders.

References

- 1 Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ*. 2016; 353.
- 2 Guyatt GH, Oxman AD, Kunz R, et al. GRADE: Going from evidence to recommendations. *BMJ*. 2008a; 336 (7652):1049-1051.
- 3 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008b; 336 (7651):995-999B.

Recommendations with detailed rationale for evidence grade

1. Initiate opioid agonist treatment (OAT) with buprenorphine/naloxone whenever feasible to reduce the risk of toxicity, morbidity and mortality, as well as to facilitate safer take-home dosing.

Clinical Question: Should individuals with opioid use disorder be offered buprenorphine/naloxone as the preferred first-line option for opioid agonist treatment?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed opioid use disorder (OUD) of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment (OAT) at study entry were included. Studies that enrolled pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention: Long term (i.e., “maintenance”) therapy with buprenorphine or buprenorphine/naloxone.

Comparator (Control or Experimental): Long-term (i.e., “maintenance”) therapy with placebo, methadone, treatment as usual, or no treatment or short-term buprenorphine taper.

Outcomes of Interest: Primary outcomes – retention in treatment, abstinence from or reduction in illicit opioid use; Secondary outcomes – side effects, adverse events, morbidity and mortality; Other – direct and indirect costs, health service utilization.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (buprenorphine or buprenorphine/naloxone versus placebo, methadone) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, prospective or retrospective observational cohort study).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: opioid agonist treatment, opioid substitution treatment, opioid replacement treatment – with substitution of treatment with therapy, opioid with opiate and specific opioid agonist medication types (e.g., methadone, buprenorphine, buprenorphine/naloxone) used as appropriate.

Quality of Evidence: High; Strength of Recommendation: Strong. The evidence to support initiating buprenorphine/naloxone as a preferred first-line treatment for individuals with opioid use disorder, which the guideline review committee graded as **high quality**, is from a) systematic reviews of randomized clinical trials reporting safety and efficacy of buprenorphine compared to placebo or methadone for the treatment of opioid use disorder,^{28,30,31,77} b) systematic reviews, toxicological reports, post-marketing surveillance or other safety data comparing relative risk of side effects, adverse events, and drug-drug interactions for buprenorphine compared to methadone,^{28,30,31,52,53,77,102,105,114,116,Table1-4} c) systematic reviews, post-marketing surveillance or other safety data reporting relative risk of diversion to individuals and public for buprenorphine compared to methadone,^{60,88,Table1-7,Table1-8} d) retrospective cohort and national/regional registry studies reporting relative risk of overdose mortality for buprenorphine compared to methadone,^{33-43,54,56,85,86} e) randomized clinical trials comparing safety and efficacy of unobserved versus observed dosing schedules of buprenorphine/naloxone,^{89,91,93} f) a systematic review, prospective and retrospective cohort studies reporting safety and effectiveness of unobserved dosing schedules for buprenorphine,^{90,92,97} and g) expert opinion.^{18,76,80,81,Table1-3,Table1-11}

In determining strength of this recommendation, which the guideline review committee has graded as **strong**, the quality of evidence reviewed above was considered, as was additional research evidence, including a) large observational studies reporting health service utilization, cost-effectiveness, and patient costs for long-term buprenorphine treatment compared to long-term methadone treatment,^{Table1-16,Table1-17} and b) randomized clinical trials and observational studies of effectiveness and cost effectiveness of observed versus unobserved administration of buprenorphine/naloxone,^{89,90,94} as well as formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel.

2. For individuals responding poorly to buprenorphine/naloxone, consider transition to methadone treatment.

Clinical Question: Should individuals with opioid use disorder who are not benefiting from buprenorphine/naloxone be offered the option of transitioning to methadone?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention A: Long term (i.e., “maintenance”) therapy with buprenorphine or buprenorphine/naloxone.

Comparator (Control or Experimental) A: Long-term (i.e., “maintenance”) therapy with placebo, methadone, treatment as usual, or no treatment.

Intervention B: Transition from long-term therapy with buprenorphine or buprenorphine/naloxone to methadone.

Comparator (Control or Experimental) B: Treatment as usual.

Outcomes of Interest: Primary outcomes – retention in treatment, abstinence from or reduction in illicit opioid use; Secondary outcomes – side effects, adverse events, morbidity and mortality; Other – direct and indirect costs, health service utilization.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (A: buprenorphine or buprenorphine/naloxone versus placebo, methadone, treatment as usual, no treatment; B: transition from buprenorphine or buprenorphine/naloxone to methadone versus treatment as usual) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, observational cohort study).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: A: opioid agonist treatment, opioid substitution treatment, opioid replacement treatment – with substitution of treatment with therapy, opioid with opiate and specific opioid agonist medication types (e.g., methadone, buprenorphine, buprenorphine/naloxone) as appropriate; B: opioid agonist treatment and cessation, induction, rotation, switch/ing, transition/ing, transfer/ring, with substitution of terms as described in A.

Quality of Evidence: High; Strength of Recommendation: Strong. *The evidence to support offering individuals with opioid use disorder who are responding poorly to buprenorphine/naloxone the option to transition to methadone, which the guideline review committee graded as **high quality**, is from a) systematic reviews of randomized clinical trials comparing safety and efficacy of buprenorphine to methadone for the treatment of opioid use disorder,^{27,28,30,31,77} b) pharmacological reviews, reports and product monographs for buprenorphine, buprenorphine/naloxone and methadone,^{52,70} c) a randomized clinical trial evaluating safety and efficacy of a stepped-care approach (buprenorphine induction and stabilization, followed by transition to methadone, if needed or preferred) compared to methadone-based treatment as usual,⁸⁴ and d) expert opinion.^{76,80,81,Table1-3,Table1-11} Additionally, when applicable and appropriate, the body of evidence reviewed in development of recommendation no. 1 was also considered in the development and grading process.*

*In determining strength of this recommendation, which the guideline review committee has graded as **strong**, the quality of evidence reviewed above was considered, as well as expert pharmacist review and consultation (on transitioning between OAT medications), formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel.*

3. Initiate OAT with methadone when treatment with buprenorphine/naloxone is not the preferred option.

Clinical Question: Should individuals with opioid use disorder be offered methadone as a first-line treatment option when buprenorphine/naloxone is not preferred?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, or prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention: Long term (i.e., “maintenance”) therapy with methadone.

Comparator (Control or Experimental): Long-term (i.e., “maintenance”) therapy with placebo, buprenorphine or buprenorphine/naloxone, treatment as usual, or no treatment.

Outcomes of Interest: Primary outcomes – retention in treatment, abstinence from or reduction in opioid use; Secondary outcomes – side effects, adverse events, morbidity and mortality; Other – direct and indirect costs, health service utilization.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, and observational cohort studies (prospective and retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (buprenorphine or buprenorphine/naloxone versus placebo, methadone, or treatment as usual) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, prospective and retrospective observational cohort studies).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: opioid agonist treatment, opioid substitution treatment opioid replacement treatment – with substitution of treatment with therapy, opioid with opiate and with specific opioid medications (i.e., methadone, buprenorphine) as appropriate.

Quality of Evidence: High; Strength of Recommendation: Strong. *The evidence to support initiating methadone a) as a second-line treatment option for opioid use disorder when individuals are responding poorly to buprenorphine/naloxone, or b) as a first-line treatment option for opioid use disorder when buprenorphine is not preferred, which the guideline review panel graded as high quality, is from a) meta-analyses and systematic reviews of randomized clinical trials comparing safety and efficacy of methadone to placebo or buprenorphine for the treatment of opioid use disorder and prescription opioid use disorder,^{27-31,52,53,77,102,105,114,116,Table1-4} b) systematic reviews, toxicological data and safety data reporting relative risk of side effects, serious adverse events, and drug-drug interactions for methadone compared to buprenorphine,^{31,52,53,105,116} c) systematic reviews, post-marketing surveillance and safety data reporting relative risk of diversion to individuals and public for methadone compared to buprenorphine,^{58,60,88,Table1-7,Table1-8} d) retrospective cohort and national/regional registry studies reporting relative risk of overdose mortality for methadone compared to buprenorphine,^{33-43,54,56,85,86} e) a randomized clinical trial evaluating safety and efficacy of unobserved compared to observed dosing schedules of opioid*

agonist treatment with methadone and buprenorphine/naloxone,⁹¹ f) pharmacological reviews, reports and product monographs for buprenorphine, buprenorphine/naloxone and methadone,^{52,70} g) a systematic review of clinical trials and uncontrolled studies that reported feasibility of transitioning from buprenorphine or buprenorphine/naloxone to methadone,⁷⁹ and h) expert opinion.^{49,76,80,81,Table1-3,Table1-11}

In determining strength of this recommendation, which the guideline review committee graded as **strong**, the evidence above was considered, as was additional research evidence, including a large observational studies reporting cost and health service utilization for methadone versus buprenorphine,^{Table1-16,Table1-17} as well as formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel.

4. For individuals with a successful and sustained response to methadone who express a desire for treatment simplification, consider transition to buprenorphine/naloxone, since its superior safety profile allows for more routine take-home dosing and less frequent medical appointments.

Clinical Question: Should individuals with opioid use disorder who have achieved sustained clinical and social stability on methadone, and who express a desire for lower-intensity treatment or treatment simplification, be offered the option of transitioning to buprenorphine/naloxone?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention A: Long term (i.e., “maintenance”) therapy with methadone.

Comparator (Control or Experimental) A: Long-term (i.e., “maintenance”) therapy with placebo, buprenorphine, buprenorphine/naloxone, treatment as usual, or no treatment.

Intervention B: Transition from long-term (i.e., “maintenance”) therapy with methadone to buprenorphine or buprenorphine/naloxone.

Comparator (Control or Experimental) B: Treatment as usual.

Outcomes of Interest: Primary outcomes – retention in treatment, abstinence from or reduction in illicit opioid use; Secondary outcomes– side effects, adverse events, morbidity and mortality; Other – direct and indirect costs, health service utilization.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (A: methadone versus placebo, buprenorphine, buprenorphine/naloxone, treatment as usual, no treatment; B: transition from methadone to buprenorphine or buprenorphine/naloxone versus treatment as usual) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, prospective or retrospective observational cohort study).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: A - opioid agonist treatment, opioid substitution treatment, opioid replacement treatment – with substitution of treatment with therapy, opioid with opiate and specific opioid agonist medication types (e.g., methadone, buprenorphine, buprenorphine/naloxone) as appropriate; B - opioid agonist treatment and cessation, induction, rotation, switch*, transition*, transfer*, with substitution of terms as described in A.

Quality of Evidence: Moderate; Strength of Recommendation: Strong. *The evidence to support offering individuals with opioid use disorder who have achieved clinical stability on methadone and who desire treatment simplification the option to transition to buprenorphine/naloxone, which the guideline review committee graded as **moderate quality**, is from a) systematic reviews of randomized clinical trials comparing safety and efficacy of methadone to placebo or buprenorphine for the treatment of opioid use disorder and prescription opioid use disorder,^{27,28,30,31,77} b) systematic reviews, toxicological reports, post-marketing surveillance or other safety data comparing relative risk of side effects, adverse events, and drug-drug interactions for methadone compared to buprenorphine,^{28,30,52,53,77,102,105,114,116,Table1-4} c) systematic reviews, post-marketing surveillance or other safety data reporting relative risk of diversion to*

individuals and public for buprenorphine compared to methadone,^{60,88,Table1-7,Table1-8} d) retrospective cohort and national/regional registry studies reporting relative risk of overdose mortality for buprenorphine compared to methadone,^{33-43,54,56,85,86} e) randomized clinical trials comparing safety and efficacy of unobserved versus observed dosing schedules of buprenorphine/naloxone,^{89,91,93} f) a systematic review, prospective and retrospective cohort studies reporting safety and effectiveness of unobserved dosing schedules for buprenorphine,^{90,92,97} and g) expert opinion.^{49,76,80,81,Table1-3,Table1-11}

In determining strength of this recommendation, which the guideline review committee has graded as **strong**, the quality of evidence reviewed above was considered, as was additional research evidence, including a) large observational studies reporting health service utilization, cost-effectiveness, and patient costs for long-term buprenorphine treatment compared to long-term methadone treatment,^{Table1-16,Table1-17} and b) randomized clinical trials and observational studies of effectiveness and cost effectiveness of observed versus unobserved administration of buprenorphine/naloxone,^{89,90,94} as well as expert pharmacist review and consultation (on transitioning between OAT medications), formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel.

5. In patients for whom first- and second-line treatment options are ineffective or contraindicated, OAT with slow-release oral morphine (ideally prescribed as once-daily witnessed doses) can be considered. Slow-release oral morphine treatment should only be prescribed by physicians with a Section 56 exemption to prescribe methadone, or following consultation with an addiction practitioner experienced in OAT with slow-release oral morphine.

Clinical Question: Should individuals with opioid use disorder who have not benefited from treatment with first- and second-line treatment options (buprenorphine/naloxone and/or methadone), be offered the option of opioid agonist treatment with slow-release oral morphine?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, or prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention: Long term (i.e., “maintenance”) therapy with slow-release oral morphine.

Comparator (Control or Experimental): Long-term (i.e., “maintenance”) therapy with placebo, methadone, buprenorphine or buprenorphine/naloxone, treatment as usual, or no treatment.

Outcomes of Interest: Primary outcomes – retention in treatment, abstinence from or reduction in opioid use; Secondary outcomes – side effects, adverse events; Other – quality of life, patient preference, physical and mental health, social functioning, other substance use, cravings.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (slow-release oral morphine versus buprenorphine, buprenorphine/naloxone or methadone, placebo, treatment as usual, or no treatment) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, observational cohort).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: opioid agonist treatment, opioid substitution treatment, opioid replacement treatment – with substitution of treatment with therapy, opioid with opiate and with specific opioid medications as appropriate – slow-release oral morphine, extended-release oral morphine, sustained-release oral morphine, Kadian®, Substitol retard®, Sevre-Long®, Mundidol® UNO retard, Kapanol™, methadone, buprenorphine, buprenorphine/naloxone.

Quality of Evidence: Moderate; Strength of Recommendation: Strong. *The evidence to support offering individuals with opioid use disorder the option of initiating OAT with slow-release oral morphine when first- and second-line treatment options have been found to be ineffective, contraindicated, or otherwise not preferred, which the guideline review committee graded as moderate quality, is from a) systematic reviews of randomized clinical trials comparing efficacy of slow-release oral morphine to methadone, buprenorphine or placebo for the treatment of opioid use disorder,^{126,132} b) a large, multisite randomized cross-over clinical trial comparing safety and efficacy of slow-release oral morphine to methadone for the treatment of opioid use disorder,¹²⁷ c) systematic reviews and randomized clinical trials reporting relative risk of side effects and adverse events for slow-release oral morphine versus methadone,^{126,127,130,132} d) secondary analyses of randomized controlled trials reporting mental health symptoms, physical*

health symptoms, quality of life, other substance use (e.g., stimulants, benzodiazepines, alcohol), patient satisfaction, and cravings for slow-release oral morphine compared to methadone,^{126,128-130} e) quasi-experimental studies reporting safety and effectiveness of slow-release oral morphine compared to methadone.^{130,133,134,136,137}

In determining strength of this recommendation, which the guideline review committee graded as **strong**, the evidence above was considered, supplemented by direct communication with several principal investigators of the above-cited clinical trials regarding risks, benefits, clinical care guidance and regional/national experiences with slow-release oral morphine as OAT, as well as formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel.

Following review and discussion, the guideline review committee reached consensus that in order to assign this recommendation as **strong**, that additional requirements should be met. First, acknowledging that the evidence base for safety and efficacy of slow-release oral morphine in the treatment of opioid use disorder is not as substantive as that for buprenorphine and methadone, the guideline review committee recommended that **slow-release oral morphine should only be considered for those patients who have not benefited from, or have contraindications to, first-line treatment options (buprenorphine/naloxone and methadone)**. Second, due to a lack of empirical data on relative risk of overdose mortality and the putative risk of diversion associated with slow-release oral morphine, the guideline review committee stipulated that **slow-release oral morphine should ideally be prescribed as once-daily witnessed doses** (i.e., daily witnessed ingestion at a pharmacy). Finally, as prescribing slow-release oral morphine for the treatment of opioid use disorder is a relatively new approach in Canada and is considered “off-label”, the guideline review committee recommended that prescribing clinicians should be experienced in the clinical management of individuals with opioid use disorder so as to optimize patient safety and treatment outcomes. For this reason, the guideline review committee included a directive that: **Slow-release oral morphine treatment should only be prescribed by physicians with a Section 56 exemption to prescribe methadone, or following consultation with an addiction practitioner experienced in prescribing slow-release oral morphine for the treatment of opioid use disorder.**

6. Offering withdrawal management alone (i.e., detoxification without immediate transition to long-term addiction treatment) should be avoided, since this approach has been associated with increased rates of relapse, morbidity, and mortality.

Clinical Question: Should individuals with opioid use disorder be offered the option of withdrawal management as a stand-alone treatment?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, or prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention: Tapered dose regimens of opioid agonist treatments (buprenorphine, buprenorphine/naloxone, or methadone) or alpha2-adrenergic agonists (clonidine).

Comparator (Control or Experimental): Tapered dose regimens of treatment as usual (for within-class comparisons of opioid agonist treatments and alpha2-adrenergic agonists), tapered dose regimens of symptomatic medications (e.g., anti-anxiolytic, anti-emetic, anti-diarrheal, and/or non-opioid analgesic medications), no pharmacological treatment or long-term (i.e., “maintenance”) opioid agonist treatment.

Outcomes of Interest: Primary outcomes – completion of or retention in treatment, sustained abstinence from or reduction in opioid use; Secondary outcomes – side effects, adverse events, morbidity and mortality.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (retrospective and prospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (opioid agonist taper, alpha2-adrenergic agonist taper versus placebo, no treatment, treatment as usual, long-term opioid agonist treatment) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, observational cohort).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: detoxification; medically-managed, -supervised, or -assisted withdrawal; withdrawal management; tapered opioid or alpha2-adrenergic agonist, opioid agonist taper or alpha2-adrenergic agonist taper, with substitution

of opioid with opiate and with specific opioid and alpha2-adrenergic agonist medications as appropriate – methadone, buprenorphine, buprenorphine/naloxone, and clonidine.

Quality of Evidence: Moderate; Strength of Recommendation: Strong. *The evidence to support a recommendation against offering individuals with opioid use disorder the option of withdrawal management as a stand-alone treatment (without linkage to ongoing or continuing addiction care), which the guideline review committee scored as **moderate quality**, is from a) systematic reviews of randomized clinical trials reporting relative risk of drop-out and/or relapse to illicit opioid use for withdrawal management (opioid agonist tapers and alpha2-adrenergic agonists) compared to placebo, treatment as usual, or long-term opioid agonist treatment,^{31,77,138,143,144,155} b) randomized clinical trials reporting i) relative risk of drop-out and/or relapse to illicit opioid use for withdrawal management with transition to or continuation of ongoing addiction treatment (pharmacological and/or psychosocial) compared to withdrawal management alone or ii) rates of drop-out and/or relapse to illicit opioid use for withdrawal management with opioid agonist and/or alpha2-adrenergic agonist tapers compared to placebo, treatment as usual, or long-term opioid agonist treatment,^{140,146,147,152,153} c) retrospective cohort and national/regional registry studies reporting i) relative risk of drop-out and/or relapse to illicit opioid use for withdrawal management with and without ongoing addiction treatment (pharmacological and/or psychosocial) or ii) rates of drop-out and/or relapse to illicit opioid use for withdrawal management,^{139,141,145,148,151} d) a retrospective cohort study reporting relative risk of overdose mortality for withdrawal management alone compared to no treatment.¹⁴⁹*

*In determining strength of this recommendation, which the guideline review committee graded as **strong**, the evidence above was considered, as well as formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel.*

7. When withdrawal management (without transition to OAT) is pursued, provide supervised slow (>1 month) opioid agonist taper (in an outpatient or residential treatment setting) rather than a rapid (<1 week) taper. During opioid-assisted withdrawal management, patients should be transitioned to long-term addiction treatment to help prevent relapse and associated health risks.

Clinical Question: Should individuals with opioid use disorder who wish to pursue withdrawal management be offered the option of an extended opioid agonist taper (i.e., gradual dose reduction over a period of one month or more) in an outpatient or residential setting?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity

(mild, moderate, or severe) with primary use of illegal heroin, or prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention: Buprenorphine, buprenorphine/naloxone or methadone taper regimens administered at variable amounts, duration, or rates. Alpha2-adrenergic agonist taper regimens were excluded.

Comparator (Control or Experimental): Where applicable, treatment as usual (for within-class comparisons of opioid agonist tapers) or long-term (i.e., “maintenance”) opioid agonist treatment.

Outcomes of Interest: Primary outcomes – completion of or retention in treatment, sustained abstinence from or reduction in opioid use; Secondary outcomes – side effects, adverse events, morbidity and mortality.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (variable opioid agonist taper schedules versus treatment as usual [where applicable]) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, prospective or retrospective observational cohort).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: detoxification or medically-managed, -supervised, or -assisted withdrawal and schedule, duration, pattern, or rate; opioid agonist taper and schedule, duration, pattern, or rate, with substitution of opioid with opiate and with specific opioid agonist medications as appropriate – methadone, buprenorphine, buprenorphine/naloxone.

Quality of Evidence: Moderate; Strength of Recommendation: Strong. *The evidence to support offering supervised slow (>1 month) opioid agonist taper to individuals with opioid use disorder who wish to pursue a withdrawal management approach, which the guideline review committee has graded as **moderate quality**, is from a) systematic reviews of randomized clinical trials reporting relative risk of drop-out and/or relapse to illicit opioid use for brief compared to extended withdrawal management,^{138,142} b) randomized clinical trials reporting relative risk of drop-out and/or relapse to illicit opioid use for brief compared to extended withdrawal management,^{93,154} c) retrospective cohort or national/regional registry studies that reported associations between variable opioid agonist taper schedules and duration with risk of drop-out and/or relapse to illicit opioid use,^{65,151} and d) expert opinion.^{80,81} Additionally, the body of research evidence reviewed in development of recommendation no. 6 regarding comparative effectiveness and risks of withdrawal management compared to placebo, no treatment, treatment as usual, and longer-term opioid agonist treatment was considered.*

*In determining strength of this recommendation, which the guideline review committee scored as **strong**, the evidence above was considered, as was the body of research evidence reviewed in development of recommendation no. 6. Formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel also informed the final consensus.*

*Following review and discussion, the guideline review committee reached consensus that in order to assign this recommendation a score of **strong**, inclusion of an explicit statement on patient safety was necessary, due to the known risks and harms associated with withdrawal management when delivered as a stand-alone intervention. To address this, the guideline review committee added the following text: **During opioid-assisted withdrawal management, patients should be transitioned to long-term addiction treatment to help prevent relapse and associated health risks.***

8. For patients with a successful and sustained response to OAT who wish to discontinue OAT (i.e., desiring medication cessation), consider a slow taper approach (over months to years, depending on the patient). Ongoing addiction care should be considered upon cessation of opioid use.

Clinical Question: Should individuals with opioid use disorder who have sustained clinical stability on but wish to discontinue opioid agonist treatment be offered the option of a long-term stepped-tapering schedule (i.e., individually tailored, alternating schedule of gradual dose reduction and stabilization periods with a total duration of months to years)?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, or prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention: Buprenorphine, buprenorphine/naloxone or methadone taper regimens administered at variable duration, rates, and schedules.

Comparator (Control or Experimental): Not applicable.

Outcomes of Interest: Primary outcomes – completion of or retention in treatment, sustained abstinence from or reduction in opioid use.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (variable opioid agonist taper schedules versus treatment as usual [where applicable]) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, observational cohort).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: cessation, discontinuation, detoxification or medically-managed, -supervised, or -assisted withdrawal and schedule, duration, pattern, or rate; opioid agonist taper and schedule, duration, pattern, or rate, with substitution of opioid with opiate and with specific opioid agonist medications as appropriate – methadone, buprenorphine, and buprenorphine/naloxone.

Quality of Evidence: Moderate; Strength of Recommendation: Strong. *The evidence to support offering individuals with opioid use disorder who wish to discontinue opioid agonist treatment the option of a long-term stepped-tapering schedule (i.e., individually tailored, alternating schedule of gradual dose reduction and stabilization periods with a total duration of months to years), which*

*the guideline review committee has graded as **moderate quality**, is from a) systematic reviews of randomized clinical trials reporting relative risk of drop-out and/or relapse to illicit opioid use for brief compared to extended opioid agonist taper schedules,^{138,142} b) randomized clinical trials reporting relative risk of drop-out and/or relapse to illicit opioid use for brief compared to extended opioid agonist taper schedules,^{93,154} c) retrospective cohort studies that reported associations between variable opioid agonist taper schedules and duration with risk of drop-out and/or relapse to illicit opioid use,^{65,151} and d) expert opinion.⁸⁰ Additionally, the body of research evidence reviewed in development of recommendations no. 6 and 7 regarding comparative effectiveness and risks of a) withdrawal management compared to all other treatments, and b) brief withdrawal management compared to extended withdrawal management or longer-term opioid agonist treatment.*

*In determining strength of this recommendation, which the guideline review committee scored as **strong**, the evidence above was considered, as was the body of research evidence reviewed in development of recommendation no. 6 and 7. Formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel also informed the final consensus.*

*Following review and discussion, the guideline review committee reached consensus that in order to assign this recommendation a score of **strong**, inclusion of an explicit statement on patient safety was necessary, due to the known risks of relapse following cessation of opioid agonist treatment. To address this, the guideline review committee added the following text: **Ongoing addiction care should be considered upon cessation of opioid use.***

9. Psychosocial treatment interventions and supports should be routinely offered but should not be viewed as a mandatory requirement for accessing OAT.

Clinical Question: Should individuals with opioid use disorder who are engaged in opioid agonist treatment be offered the option to access or participate in psychosocial treatment interventions?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, or prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion) receiving opioid agonist treatment with buprenorphine/naloxone, methadone, or slow-release oral morphine. Pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and

community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention: Psychosocial treatment interventions were defined as structured and/or manualized counselling that incorporates principles of psychoanalytic therapy, cognitive behavioural therapy, interpersonal therapy, dialectic behavioural therapy, contingency management, biofeedback, hypnotherapy/subliminal, twelve-step facilitation, family/group counselling delivered in conjunction with long-term opioid agonist treatment. Studies of psychosocial treatment interventions or supports delivered in conjunction with withdrawal management – short-term opioid agonist or alpha2-adrenergic agonist tapers – were excluded.

Comparator (Control or Experimental): Treatment as usual – long-term opioid agonist treatment with methadone, buprenorphine, or buprenorphine/naloxone.

Outcomes of Interest: Primary outcomes – retention in treatment, abstinence from or reduction in opioid use; Secondary outcomes – side effects, adverse events, morbidity and mortality; Other – direct and indirect costs, health service utilization, quality of life, mental health, social functioning, risk behaviors, HIV and hepatitis C infection, and criminality.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, and observational cohort studies (prospective and retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention (OAT with and without adjunct psychosocial treatment interventions) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, prospective or retrospective observational cohort).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: psychosocial treatment, counselling, motivational interviewing, motivational enhancement therapy [MET], psychoanalytic therapy, cognitive behavioural therapy, interpersonal therapy, dialectic behavioural therapy, contingency management, biofeedback, hypnotherapy/subliminal, twelve-step facilitation, narcotics anonymous, methadone anonymous, family/group counselling, and opioid agonist treatment, opioid substitution treatment, opioid replacement treatment – with substitution of treatment with therapy, and opioid with opiate and with specific opioid medications (i.e., methadone, buprenorphine, or buprenorphine/naloxone) as appropriate.

Quality of Evidence: Moderate; Strength of Recommendation: Strong. The evidence to support offering individuals with opioid use disorder engaged in opioid agonist treatment the option of participating in psychosocial treatment interventions, which the guideline review committee has graded as **moderate quality**, is from a) systematic reviews of randomized clinical trials reporting retention in treatment and illicit opioid use for opioid agonist treatment delivered in combination with psychosocial treatment interventions compared to opioid agonist treatment alone,^{143,164} b) randomized clinical trials reporting retention in treatment and illicit opioid use for opioid agonist treatment delivered in combination with psychosocial treatment interventions compared to opioid agonist treatment alone,^{153,165-173} and c) non-randomized and prospective observational studies reporting effectiveness of 12-step programs in improving treatment outcomes individuals with opioid or other substance use disorders,¹⁸⁶⁻¹⁸⁸ and d) expert opinion.^{161,162}

In determining strength of this recommendation, which the guideline review committee has graded as **strong**, the evidence above was considered, as was additional evidence from systematic reviews of randomized clinical trials reporting effectiveness of pharmacological treatment for substance use disorders (reported as pooled interventions, but including at least one trial of opioid agonist treatment) delivered in combination with psychosocial treatment interventions in specific populations (i.e., individuals with concurrent substance use disorders [alcohol, stimulants], mental health diagnoses [post-traumatic stress disorder, severe mental illness]).^{78,180-182} Additionally, formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel informed consensus. In order to assign a score of strong, and in line with the evidence base reviewed above, the guideline review committee included the directive that **participation in psychosocial treatment should not be viewed as a mandatory requirement for accessing OAT**. Further, although psychosocial support services - defined as non-therapeutic support services that aim to improve overall individual and/or familial stability and quality of life, including community services, social services, temporary and supported housing, income assistance programs, vocational training, life skills, legal services, etc. – have not been empirically studied in the context of opioid agonist treatment, the guideline review committee opted to include that **referrals to psychosocial supports may be routinely provided** as part of standard care, acknowledging research literature that supports importance of addressing housing and other survival needs in improving opioid agonist treatment outcomes and supporting overall health and recovery.^{183,184}

10. Oral naltrexone can also be considered as an adjunct medication if cessation of opioid use is achieved.

Clinical Question: Should individuals with opioid use disorder who have achieved cessation of

opioid use be offered the option of treatment with oral naltrexone to prevent lapse or relapse to illicit opioid use?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, or prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Pregnant women were excluded.

Setting: Studies conducted in a range of treatment settings, including primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs. No geographical restrictions were applied.

Intervention: Long term (i.e., “maintenance”) therapy with oral naltrexone. Injectable naltrexone was excluded.

Comparator (Control or Experimental): Long-term (i.e., “maintenance”) therapy with placebo, methadone, buprenorphine, buprenorphine/naloxone, treatment as usual, or no treatment.

Outcomes of Interest: Primary outcomes – retention in treatment, abstinence from or reduction in opioid use; Secondary outcomes – side effects, adverse events, morbidity and mortality.

Study Design: Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective or retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention (naltrexone, buprenorphine, buprenorphine/naloxone, methadone, placebo, treatment as usual, or no treatment) and study type (meta-analysis, systematic review, randomized controlled trial, quasi-experimental study, prospective or retrospective observational cohort).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: opioid antagonist treatment, with substitution of treatment with therapy, and opioid with opiate and with specific opioid medications (i.e., naltrexone) as appropriate

Quality of Evidence: Low; Strength of Recommendation: Weak. *The evidence to support the recommendation that individuals with opioid use disorder who have achieved abstinence or cessation of opioid use (including both opioid agonist treatment and illicit opioid use) should be offered the option of oral naltrexone to prevent relapse, which the guideline review committee has graded as **low quality**, is from a) systematic reviews of randomized clinical trials reporting safety and efficacy of oral naltrexone compared to placebo, treatment as usual, opioid agonist treatment with methadone, buprenorphine, buprenorphine/naloxone for the treatment of opioid use disorder,^{157,159} b) a randomized clinical trial reporting safety and efficacy of oral naltrexone compared to placebo and injectable naltrexone,¹⁵⁸ c) systematic reviews and randomized clinical trials reporting relative risk of side effects, serious adverse events, and drug-drug interactions efficacy of oral naltrexone compared to placebo, treatment as usual, or opioid agonist treatment with methadone, buprenorphine, or buprenorphine/naloxone,^{157,159} d) a retrospective cohort study reporting relative risk of overdose mortality for oral naltrexone compared to opioid agonist treatment with methadone for the treatment of opioid use disorder,¹⁶⁰ and e) expert opinion.⁸¹*

*In determining strength of this recommendation, which the guideline review committee has graded as **weak**, the evidence above was considered, as was additional research evidence reviewed in development of recommendations no. 1-4, as well as formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.), and, finally, the expert opinion of the guideline review panel.*

11. Information and referrals to take-home naloxone programs and other harm reduction services (e.g., sterile injection supplies), as well as other general healthcare services, should be routinely offered as part of standard care for opioid use disorders.

Clinical Question: Should individuals with opioid use disorder be offered harm reduction services?

Population: Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, or prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Pregnant women were excluded.

Setting: Studies conducted in a range of community and treatment settings, including community-based organizations, community pharmacies, governmental organizations, and health systems organizations – primary care and community-based outpatient clinics, specialized drug-treatment outpatient and inpatient programs, residential treatment facilities and hospital-based programs.

Studies conducted in closed environments such as prisons or correctional institutions were included. No geographical restrictions were applied.

Intervention: Direct and indirect (information, referral and/or linkage with services) provision of harm reduction services (e.g., supervised consumption sites, take-home naloxone, overdose prevention education, safer injection education, HIV and hepatitis C prevention education, sterile injection or smoking supplies distribution).

Comparator (Control or Experimental): Not applicable (omitted by design and/or study specific ethical reasons).

Outcomes of Interest: Primary Outcomes – Morbidity and mortality, fatal and non-fatal overdose events, HIV and hepatitis C infection, risk behaviors; Other – direct and indirect costs, health service utilization, and criminality.

Study Design: Meta-analyses, systematic reviews, quasi-experimental studies, observational cohort studies (prospective and retrospective).

Search Strategy: Search strategies, terms and vocabulary specific to the database used (PubMed, ISI Web of Science, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention (harm reduction services as listed above) and study type (meta-analysis, systematic review, quasi-experimental study, prospective or retrospective observational cohort).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate, people or persons who use drugs, people or persons who inject drugs, etc.

General examples of intervention search terms used include: needle and/or syringe exchange, needle and/or syringe distribution; overdose prevention, overdose education; take-home naloxone, community naloxone, naloxone programs; safe or safer injection site, supervised injection site, with substitution of injection with consumption and site with facility, services; etc.

Quality of Evidence: Moderate; Strength of Recommendation: Strong. *The evidence to support offering individuals with opioid use disorder information about and/or referrals to harm reduction services as part of routine care, which the guideline review committee has graded as **moderate quality**, is from a) systematic reviews of the effectiveness of harm reduction services in reducing or preventing opioid- and/or injection-related harms (fatal and non-fatal overdose, high risk behaviours, HIV and HCV infection, other infections),^{11,13,15,20,44,Figure2-12,Figure2-13} b) program evaluations and reviews reporting effectiveness of harm reduction services in reducing or preventing opioid-*

and/or injection-related harms (fatal and non-fatal overdose, high risk behaviours, HIV and HCV infection, other infections),^{14,18,19} and c) expert opinion.^{12,16,17}

*In determining strength of this recommendation, which the guideline review committee has graded as **strong**, the evidence above was considered, as well as formal and informal consultations held by the four CRISM nodes (British Columbia, Prairie Provinces, Ontario, and Quebec/Atlantic) with stakeholder groups (e.g., clinicians, people with lived experience who currently use or have used opioid drugs, individuals and family members who are or have been affected by OUD, policymakers, researchers, etc.) and the expert opinion of the guideline review panel.*

Review and Consensus Process

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. Following each round of review, NPIs edited and approved the next version of recommendations, for subsequent committee review. Differences in opinion or interpretation with regards to the guideline recommendations or the evidence review were resolved through facilitated discussions in regional committee teleconferences or through direct communication. A final decision was reached for all cases without the need for arbitration. Following the two rounds of committee review, two international academic experts and two stakeholder organizations representing people affected by OUD reviewed and provided input on the final draft.

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