



MANITOBA

OPIOID AGONIST THERAPY

RECOMMENDED PRACTICE MANUAL

QUALITY PRACTICE, COLLABORATION, & COMMUNITY

© 2023 College of Physicians & Surgeons of Manitoba (CPSM)

The College of Physicians & Surgeons of Manitoba Opioid Agonist Therapy Recommended Practice Working Group. *Manitoba Opioid Agonist Therapy Recommended Practice Manual*. CPSM; 2023.
Available at: bit.ly/OATmanual



Phone: (204) 774-4344
Toll Free: (877) 774-4344
Email: cpsm@cpsm.mb.ca

PREFACE

Opioid Use Disorder (OUD) is a chronic illness that adversely impacts every aspect of life for affected individuals. It is a disease associated with guilt, shame, and at times, hopelessness. This experience is compounded by pervasive stigma. Personal and societal barriers can make seeking help feel insurmountable for many patients.

Fortunately, effective long-term treatment is available and now more accessible than ever in Manitoba. Opioid Agonist Therapy (OAT) is an evidence-based treatment that, when delivered by a skilled interdisciplinary team, can effectively stabilize individuals with OUD and support them on the journey to recovery.

BACKGROUND

In 2019, the College of Physicians & Surgeons of Manitoba (CPSM) convened a working group of experts in the treatment of OUD. This working group was tasked with assisting the CPSM Prescribing Practices Program to develop a new *Recommended Practice Manual* for the use of buprenorphine-containing medications in the context of OAT in Manitoba.

By 2021 the same working group was tasked with updating the CPSM publication *Manitoba Methadone and Buprenorphine Maintenance Recommended Practice* (2014). This publication contained minimal guidance on buprenorphine-containing OAT medications and the methadone guidance was outdated.

The resulting combination of these two important projects created this new publication, the [*Manitoba Opioid Agonist Therapy Recommended Practice Manual*](#). This manual is intended to be a dynamic online publication, hosted on this CPSM webpage, to permit more regular revision. It will be updated periodically as evidence and best practices in this field evolve over time. The chapters are divided into key sections and posted individually for providers to find their topic of interest more easily. While many OAT care topics are addressed collectively for overarching guidance, medication-specific recommendations are provided separately as applicable.

The manual is also intended to contribute to **quality assurance** in OAT practice, promote **collaboration** among professionals and with patients, and inspire continued **growth of the OAT community**.

Clinicians are encouraged to adopt and incorporate these recommendations into their OAT practice without delay. Should CPSM registrants have any questions about the interpretation of this guidance, please contact the working group Chair, Dr. Marina Reinecke. We hope all healthcare professionals will find this guidance useful in providing comprehensive care to their patients on OAT.

ACKNOWLEDGEMENTS

Funding for this project was made available through a grant from the Health Canada's Substance Use and Addictions Program (SUAP). CPSM wishes to thank our Provincial and Federal Government partners for making this important project possible.

A sincere thank you is also extended to every member of the working group (as listed below) for their invaluable contribution of time, dedication, and expertise throughout this project – without you, this would not have been possible.

A very special thank you goes to:

- CPSM Registrar, Dr. Anna Ziomek. Without her support this project would not have been possible.
- CPSM for in-kind support to the working group and authors.
- Every author, expert reviewer, and contributor as listed.

DEDICATION

While this OAT Recommended Practice Manual is intended to support the many committed professionals who guide people with OUD along life's path, **it is truly dedicated to our patients – those who fight this illness with bravery and endurance every day. It is our privilege to witness your amazing journey.**

Sincerely,

Talia Carter MOT, BSc, O.T. Reg.(MB)
CHIEF EDITOR & CONTENT REVIEWER

Dr. Marina Reinecke MBChB, CCFP(AM), ISAM
CPSM WORKING GROUP CHAIR & MEDICAL PROJECT LEAD

KEY CONTRIBUTORS

The OAT Recommended Practice Manual is the result of extensive collaboration among regulators, practitioners, and colleagues. The project collaborators provided perspectives from a diverse array of clinical disciplines and professions. The manual would not have been possible without their immeasurable support and contribution.

WORKING GROUP CHAIR, MEDICAL PROJECT LEAD, EDITOR, & AUTHOR

Dr. Marina Reinecke, MBChB, CCFP (AM), ISAM

Medical Consultant, Prescribing Practices Program, CPSM

Medical Director, Opaskwayak Health Authority OAT Program

OAT 101: Introduction to Clinical Practice, Scientific Planning Committee Chair & Educator

Former Medical Director, Addictions Services, Health Sciences Centre

CHIEF EDITOR, CONTENT REVIEWER, & AUTHOR

Ms. Talia Carter, MOT, BSC (Hons), O.T. Reg.(MB)

Prescribing Practices Program Coordinator, CPSM

Occupational Therapist specializing in Addiction Medicine & Mental Health

OAT 101: Introduction to Clinical Practice, Scientific Planning Committee Member & Educator

Former Clinician, Addictions Services, Health Sciences Centre

KEY AUTHORS & ASSISTANT EDITORS

Ms. Kim McIntosh, B.Sc. (Pharm.)

Assistant Registrar, Qualifications & Practice Development, College of Pharmacists of Manitoba

OAT 101: Introduction to Clinical Practice, Scientific Planning Committee Member

Mr. Mike Sloan, BSc. (Pharm), BSc. (Major)

Pharmacist Consultant (Opioid Agonist Therapy), College of Pharmacists of Manitoba

Community Pharmacist specializing in Opioid Agonist Therapy

OAT 101: Introduction to Clinical Practice, Scientific Planning Committee Member & Educator

ADDITIONAL AUTHORS & CONTENT REVIEWERS

Dr. Erin Knight, MD, CCFP(AM), CCSAM

Medical Director, Addiction Services, Health Sciences Centre

Medical Lead, Rapid Access to Addiction Medicine (RAAM), Shared Health

Medical Director, Addiction Program, Four Arrows Regional Health Authority

Program Director, Addiction Medicine Enhanced Skills Residency, University of Manitoba

Assistant Professor, Departments of Psychiatry & Family Medicine, Max Rady College of Medicine, Rady

Faculty of Health Sciences, University of Manitoba

President-Elect, Canadian Society of Addiction Medicine

Dr. Rafiq Andani, MD, MBBS, MSc(c), CCFP(EM)

Assistant Professor, Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba

Dr. James (Jim) F. Simm, MD, FRCPC, CCSAM

Manitoba Provincial Chief Psychiatrist
President, Manitoba Psychiatric Association
Former Medical Director, PACT Logan Team
Former Physician, Health Sciences Centre, Addictions Services & Psychiatry
Former Medical Lead, CARI OAT Clinic

Dr. Joanna Lynch, MD, CCFP(AM), FCFP

Family Physician & Addiction Medicine Consultant
Assistant Professor, Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba

Dr. Steve Melnyk, MD, CCFP

Klinik Community Health
Lecturer, Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba

Dr. Laurie Ireland, MD, CCFP

Medical Director, Nine Circles Community Health Centre
Lecturer, Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba
Primary Care Lead, Manitoba HIV Program
Primary Care Lead, BASE™ eConsult Manitoba

Dr. Bria Sharkey, BSc, MD, CCFP

Former Associate Medical Director, Nine Circles Community Health Centre

Dr. Heather Watson, MD, FRCSC (PDWH)

Psychosocial Obstetrician Gynecologist
Obstetrical Lead, Interprofessional Perinatal Care Clinic
Director, Obstetrics & Gynecology Pre-clerkship, Department of Obstetrics, Gynecology & Reproductive Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba

Dr. Ginette Poulin, RD, MD, CCFP(AM), FCFP, CISAM, CMCBT, CCPE

Former Medical Director, Addictions Foundation of Manitoba
Co-lead, Rapid Access to Addictions Medicine (RAAM) Manitoba, Shared Health.
Prairie Clinical Lead, Canadian Research Initiative for Substance Misuse (CRISM)

Dr. Morag Fisher, MBChB, MCFP(AM), CCSAM

Rapid Access to Addiction Medicine (RAAM) Clinic, River Point Centre, Shared Health
Assistant Professor, Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba

Ms. Caitlin McNeill, RN BN

Director of Health Services, Opaskwayak Health Authority
Former Clinician, Opaskwayak Health Authority OAT Program

Dr. Kernjeet Sandhu, MD, CCFP, ABFM

Harbourview Medical Centre & Waterford Medical Centre
Rapid Access to Addiction Medicine (RAAM) Clinic, Shared Health
Lecturer, Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba

Dr. Stacey Balchen, MD, FRCPC

Shared Care Psychiatry, Community Psychiatry Program
Lecturer, Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba

CPSM OAT RECOMMENDED PRACTICE WORKING GROUP

Members Credentialed as Above

Dr. Marina Reinecke	Dr. Steve Melnyk
Dr. Erin Knight	Dr. Stacey Balchen
Dr. Rafiq Andani	Ms. Talia Carter
Dr. Morag Fisher	Mr. Mike Sloan
Dr. Ginette Poulin	Ms. Kim McIntosh

Additional Members

Dr. Melinda J. Fowler-Woods, MD, CCFP, CPSM/CPSO, DC, B.Sc.N
PGY3 Orthopedic Surgery, University of Manitoba
Director of Ongomiizwin Education & Indigenous Physician Mentor (Ongomiizwin Education)
Assistant Clinical Professor (PT), Department of Family Medicine, Rady Faculty of Health Sciences, University of Manitoba

Ms. Diana Heywood, RN BN MN FRE
Quality Practice Consultant, College of Registered Nurses of Manitoba

Ms. Lynne Leah & Ms. Karen Sorenson
Executive Assistant & Executive Assistant to the Registrar, CPSM

CONTENT SUMMARY

PREFACE

Background, Acknowledgments, & Dedication

Key Contributors

Content Summary

List of Appendices

Glossary of Terms

SECTION 1 – OPIOID AGONIST THERAPY GUIDANCE

- 1.1 [Introduction: Recommendations for OUD](#)
- 1.2 [Application, Training, & Regulatory Requirements to Provide OAT](#)
- 1.3 [Initiating OAT: Comprehensive Assessment, Diagnosis, Informed Consent, & Investigations](#)
- 1.4 [Recommendations for Ongoing Care of Individuals on OAT](#)
- 1.5 [The Relationship with Pharmacy & Prescriptions for OAT](#)
- 1.6 [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#)
- 1.7 [Recommendations for the Use of Urine Drug Testing in the Management of OUD](#)
- 1.8 [Recommendations for In-Hospital Care of Individuals with OUD](#)
- 1.9 [Recommendations for the Treatment of OUD in Pregnancy](#)
- 1.10 [Managing Acute, Chronic, & Perioperative Pain in OAT](#)
- 1.11 [Prevention, Screening, & Management of HIV & Hepatitis C in Individuals with OUD](#)
- 1.12 [Managing Co-Occurring Psychiatric Disorders in the Context of OUD](#)
- 1.13 [Recommendations for Adolescents & OAT](#)
- 1.14 [Managing Older Patients & Patients with Disabilities on OAT](#)
- 1.15 [Recommendations for Continuity of Care: Residential Treatment, Traveling, Incarceration & RAAM Clinics](#)
- 1.16 [Discontinuing Treatment: Voluntary & Involuntary Withdrawal from OAT](#)

SECTION 2 – BUPRENORPHINE-SPECIFIC GUIDANCE

- 2.1 [Introduction: Pharmacology, Precipitated Withdrawal, & Management of Adverse Effects](#)
- 2.2 [Conventional Buprenorphine/naloxone Induction for OUD](#)
- 2.3 [Buprenorphine/naloxone Take-home \(Carry\) Dosing Recommendations](#)
- 2.4 [Recommendations for Unwitnessed Induction with Buprenorphine/naloxone](#)
- 2.5 [Recommendations for Buprenorphine/naloxone Micro-Dosing Inductions](#)
- 2.6 [Recommendations for Sublocade & Considerations for Informed Consent](#)

SECTION 3 – METHADONE-SPECIFIC GUIDANCE

- 3.1 [Introduction: Pharmacology of Methadone & Management of Adverse Effects](#)
- 3.2 [Recommendations for Methadone Induction, Titration, & Stabilization for OUD](#)
- 3.3 [Methadone Take-home \(Carry\) Dosing Recommendations](#)

SECTION 4 – ALTERNATIVE TREATMENT GUIDANCE (SROM)

- 4.1 [Alternative Treatment Approaches to OUD Including SROM \(Kadian®\)](#)

LIST OF APPENDICES

Some appendices repeat within certain chapters for comprehensiveness.

APPENDIX A	DSM-5 CRITERIA FOR OPIOID USE DISORDER
APPENDIX B	OAT COMPREHENSIVE ASSESSMENT TEMPLATE
APPENDIX C	A PATIENT GUIDE: AVOIDING OVERDOSE IN THE FIRST TWO WEEKS OF OAT
APPENDIX D	OAT TREATMENT AGREEMENT & CONSENT FORM
APPENDIX E	AUTHORIZATION TO PHARMACY FOR OAT TAKE-HOME (CARRY) DOSES
APPENDIX F	LETTER TO PHARMACY FOR PATIENTS STARTING OAT
APPENDIX G	BENZODIAZEPINE EQUIVALENT TABLE
APPENDIX H	HARM REDUCTION RESOURCES
APPENDIX I	CLINICAL OPIOID WITHDRAWAL SCALE (COWS)
APPENDIX J	NON-OPIOID MEDICATION FOR SYMPTOMATIC MANAGEMENT OF OPIOID WITHDRAWAL
APPENDIX K	ADDITIONAL RESOURCES FOR HIV & HEPATITIS C
APPENDIX L	ADDITIONAL MENTAL HEALTH RESOURCES
APPENDIX M	BUPRENORPHINE/NALOXONE INDUCTION FLOW DIAGRAM
APPENDIX N	CLINICAL OPIOID WITHDRAWAL SCALE (COWS)
APPENDIX O	NON-OPIOID MEDICATION FOR SYMPTOMATIC MANAGEMENT OF OPIOID WITHDRAWAL
APPENDIX P	TAKE-HOME (CARRY) DOSING AGREEMENT
APPENDIX Q	PHARMACY UNWITNESSED INDUCTION NOTIFICATION
APPENDIX R	STARTING BUPRENORPHINE/NALOXONE (SUBOXONE®) AT HOME
APPENDIX S	SAMPLE WALLET UNWITNESSED INDUCTION NOTIFICATION CARD
APPENDIX T	PHARMACY MICRO-DOSING INDUCTION NOTIFICATION
APPENDIX U	BUPRENORPHINE/NALOXONE (SUBOXONE®) MICRO-DOSING INSTRUCTIONS
APPENDIX V	SAMPLE WALLET MICRO-DOSING INDUCTION NOTIFICATION CARD
APPENDIX W	TREATMENT WITH SUBLOCADE® CONSENT FORM: GENERAL VERSION
APPENDIX X	TREATMENT WITH SUBLOCADE® CONSENT FORM: REPRODUCTIVE AGE VERSION
APPENDIX Y	A PATIENT GUIDE: AVOIDING OVERDOSE IN THE FIRST TWO WEEKS OF OAT
APPENDIX Z	CLINICAL OPIOID WITHDRAWAL SCALE (COWS)
APPENDIX AA	NON-OPIOID MEDICATION FOR SYMPTOMATIC MANAGEMENT OF OPIOID WITHDRAWAL
APPENDIX BB	TAKE-HOME (CARRY) DOSING AGREEMENT

GLOSSARY OF TERMS

Abstinence: Refraining from an activity typically associated with giving pleasure (e.g., refraining from the use of a substance, or activity such as gambling or sexual intercourse). In the context of opioid use disorder, abstinence is typically considered the cessation of all opioid use. A common treatment goal for OAT programs is abstinence from non-prescribed or illicitly acquired opioids and other substances. However, cessation of drug use or complete abstinence from non-prescribed substances may be a later goal along the treatment continuum, or it may not be realistic or achievable for some patients, but they can still benefit from harm-reduction and the OAT program.

Accidental Polypharmacy Overdose: Ingestion of multiple substances (prescribed, non-prescribed, and/or over-the-counter medications/substances) with sedating and/or psychoactive properties, wherein the combined central nervous system effects (especially in individuals with predisposing health conditions) cause unintended respiratory depression, possibly leading to death.

Addictions Medicine Specialist: A physician with robust training, knowledge, and clinical experience in the management of substance use disorders, including OUD, *and* who has passed an addiction medicine exam proctored by the International Society of Addiction Medicine (ISAM), the American Board of Addiction Medicine (ABAM), or the American Board of Preventive Medicine (ABPM), *or* with Canadian Society of Addiction Medicine certification (CCSAM), *or* a Certificate of Added Competence in Addiction Medicine (CCFP(AM)).

Adolescence: The phase of life between childhood and adulthood, from ages 10 to 19, a unique stage of human development and an important time for laying the foundations of good health. However, for healthcare purposes in Manitoba, and medicine in general, patients are treated as adults by age 18.

Alcohol: Alcohol (containing ethanol) acts as a drug and is produced by fermentation of grains, fruits, or other sources of sugar. May refer to beer, wine, spirits, home-brew, and be potable/non-potable.

Alpha-agonists: Alpha-adrenergic agonists are a class of medications that selectively stimulates alpha adrenergic receptors, used in the management of a variety of disorders. In the context of opioid use disorder, alpha-agonists like clonidine are occasionally prescribed for off-label indications, for symptom management (e.g., diaphoresis/sweating, insomnia).

Antidepressants: Medications with psychoactive properties typically prescribed to treat mental-health related conditions (e.g., Bupropion, Tricyclics, SSRI/SNRIs).

Benzodiazepines: A class of depressant medications with anxiolytic and sedative-hypnotic properties, whose core chemical structure is the fusion of a benzene ring and a diazepam ring, commonly prescribed to treat anxiety, insomnia, and seizure disorders (e.g., alprazolam, lorazepam, diazepam, clonazepam, temazepam). It is not uncommon for patients with opioid use disorder to use benzodiazepines and/or (the closely related) Z-drugs (e.g., zopiclone or zolpidem). This can vary from intermittent use to alleviate the discomfort of opioid withdrawal, to a concurrent sedative-hypnotic use disorder. Benzodiazepines/Z-Drugs are generally contraindicated with OAT and a thorough history of their use may be required as part of a comprehensive medication management plan.

Bioavailability: The extent and/or rate at which an active drug accesses its site of action (commonly the systemic circulation).

Buprenorphine: A long-acting semi-synthetic opioid that is a partial agonist with high affinity at the mu-opioid receptor. Some buprenorphine formulations are prescribed for the treatment of opioid use disorder as OAT, and others as analgesia for the treatment of pain.

Buprenorphine/naloxone Micro-dosing: A buprenorphine/naloxone induction using lower than typical induction doses (at least initially) that overlap with the continued use of a full opioid agonist by the patient (commonly referred to as the “Bernese method”). Unlike a conventional buprenorphine induction, this approach does not require a period of abstinence from other opioids or the required clinical evidence of opioid withdrawal prior to starting buprenorphine/naloxone (to avoid precipitated withdrawal).

Cannabis: A psychoactive drug from the cannabis plant, also known as marijuana, that may be commercially or illicitly acquired, and used for recreational, medicinal, and entheogenic purposes. Cannabis products can be smoked, vaped, or ingested orally.

Ceiling Effect: A point at which increasing amounts/higher doses of a substance/drug does not increase the pharmacological/physiological effect; essentially the substance/drug’s impact on the body plateaus. Methadone does not demonstrate a ceiling effect and thus accumulation may lead to opioid toxicity and respiratory depression, especially if the induction dose is too high, or the dose is increased too rapidly.

Centre for Addiction and Mental Health (CAMH): Canada's largest mental health and addiction teaching hospital and one of the world's leading research centres in the field. CAMH is affiliated with the University of Toronto and is a Pan American Health Organization/World Health Organization Collaborating Centre, setting standards for care, research, education, and leading social change.

Clinical Opioid Withdrawal Scale (COWS): A clinical tool to help clinicians measure the severity of opioid withdrawal. COWS is an 11-item scale designed to be administered by a clinician, that can be used in both inpatient and outpatient settings to reproducibly rate common signs and symptoms of opioid withdrawal and monitor symptoms over time.

Complex Addiction & Recovery Medical Assessment (CARMA) Clinic: Winnipeg Health Sciences Centre Addiction Services outpatient clinic that offers assessment, diagnostic clarification, and treatment recommendations for problematic substance use including assistance with prescription medications, illicit substances, and/or alcohol, where medical review is warranted.

Comprehensive Urine Drug Screen (C-UDS): A test utilizing liquid chromatography-high resolution mass spectrometry to determine the presence or absence of specific medications in a urine sample. C-UDS is recommended when initiating OAT therapy. Confirmatory testing with C-UDS is also recommended in the case of unexpected point-of-care (POC) test results, either positive or negative, when further information is needed to formulate an appropriate treatment plan for a patient. However, given comparatively greater costs, it is not recommended to use C-UDS routinely for the follow-up of OAT patients, including for the routine determination of clinical stability.

Controlled Dispensing: Dispensing lesser quantities of medications at more frequent intervals so that fewer medications are available at one time, to ultimately improve patient safety. For example, dispensing other medications on the same schedule as the OAT medication is dispensed for witnessed self-administration versus unwitnessed take-home doses.

Conventional Buprenorphine/naloxone Induction: A buprenorphine/naloxone induction process wherein the first dose is administered following a period of abstinence from other opioids and/or clinical evidence of sufficient opioid withdrawal, to avoid precipitating withdrawal.

Detox/Detoxification: Withdrawing from a substance, either via a taper or completely abstaining from a substance, often associated with admission to an institutional setting (e.g., community-based “detox” facility or a hospital). However, this can also occur outside of a clinical or institutional setting (see **Home-Based Detox**). In the context of opioid use disorder, “detox” towards the goal of abstinence from opioids without transition to OAT and long-term treatment is *not recommended* as it has been associated with increased morbidity, such as HIV transmission, and mortality secondary to overdose.

Down: Common slang terminology for an illicit combination of fentanyl and other analogues, heroin, and possibly benzodiazepines. May include a combination of (diverted) prescription medications and/or non-prescription/non-pharmaceutical grade substances produced and acquired illicitly.

Drug Program Information Profile (DPIN): A provincial record of medications dispensed in Manitoba to an individual patient.

Electrocardiogram (ECG): A non-invasive medical test that records the electrical activity of the heart. ECG can be used to assess the QTc interval in OAT patients, as methadone and buprenorphine (to a lesser degree) may cause QTc interval prolongation. (See **QTc Interval** and **QTc Prolongation** below).

Gabapentinoids: Antiepileptic drugs, including gabapentin and pregabalin, that can be used as treatment for the management of neuropathic pain.

Guest Dosing: Providing a pharmacy, other than the patient’s typical/regular community pharmacy, with an OAT prescription so that the patient may attend the interim host pharmacy for witnessed guest dosing for a limited time, often to facilitate travel.

Hallucinogens: A large and diverse class of psychoactive drugs that can produce altered states of consciousness that can include major alterations in thought, mood, and perception. May be categorized as psychedelics, dissociative, or deliriants, and can include LSD/acid, psilocybin/magic mushrooms, phencyclidine (PCP)/angel dust, synthetic cathinone/bath salts, and ketamine.

Harm Reduction: Evidence-based interventions that are intended to reduce an individual’s risk of harm from substance use (e.g., education of safer use techniques, sterile drug-consumption equipment and supply distribution, supervised consumption, take-home naloxone training and distribution, and connection to other medical care and resources). Harm reduction is considered the standard of care for all people at risk of opioid/substance use related harms.

Health Sciences Centre Consult Team/Service: A group of Addiction Medicine Physicians associated with Health Sciences Centre (HSC) that can provide assessment, diagnostic clarification, and treatment recommendations for problematic substance use, including assistance with prescription medications, illicit substances, and/or alcohol, where medical review is warranted. This service is available to in-patients at HSC and St Boniface General hospital. They also take calls from healthcare providers outside of these facilities to provide expert advice/recommendations regarding the treatment of opioid use disorder and the appropriateness of OAT induction and/or titration. Healthcare professionals can reach the HSC Consult Team through HSC paging.

Hepatitis C: An RNA virus that infects the liver, primarily transmitted via blood and/or blood exposure. As with all Sexually Transmitted and Blood Borne Infections (STBBIs), comprehensive screening should be offered to all patients with opioid use disorder. Initial and intermittent STBBI screening, including treatment referrals as appropriate, form an important part of ongoing OAT care.

Home-Based Detox: A self-guided process of tapering a low to moderate dose of opioids, or abstinence from opioids over a predetermined period, outside of an established clinical or institutional setting (see **Detox** above). This approach has limited evidence and carries significant risk, and is not the recommended standard of care for the treatment of opioid use disorder.

Human Immunodeficiency Virus (HIV): Retrovirus transmitted by blood, genital or rectal fluids, and breast milk. As with all Sexually Transmitted and Blood Borne Infections (STBBIs), comprehensive screening should be offered to all patients with opioid use disorder. Initial and intermittent STBBI screening, including treatment referrals as appropriate, form an important part of ongoing OAT care.

Hyperhidrosis: Excessive sweating, not necessarily related to heat or exercise, which may be associated with opioid withdrawal or side-effects of opioids/OAT medications (more commonly with methadone).

Illicitly Acquired Opioids: Can be another patient's diverted prescription medication (e.g., morphine, hydromorphone, codeine, fentanyl, diverted methadone or buprenorphine/naloxone) that may be acquired by purchase, borrowed, or traded with other medications. Also includes non-prescription/non-pharmaceutical grade opioids produced illicitly, such as illicit fentanyl, carfentanil, heroin, or "down" (as above, slang terminology for an illicit combination of fentanyl, heroin, possibly benzodiazepines).

Informed Consent: A process of communication between healthcare providers and patients that may lead to agreement or permission to proceed with medical care, treatment, or services. This involves providing patients with information regarding the care, procedure, or treatment, including possible risks and benefits of treatment vs. non-treatment, and potential outcomes. Patients (or an appropriate substitute decision maker) must understand this information in order to decide whether to take part in the medical care, treatment, or services.

Injectable OAT (iOAT): Injectable diacetylmorphine or hydromorphone prescribed as OAT for individuals with severe opioid use disorder, who have not achieved adequate benefit from OAT trials (i.e., with buprenorphine, methadone, and slow-release oral morphine), and/or who are considered treatment refractory with ongoing risk related to opioid injection drug use. Use of iOAT under supervision in a structured and supported clinical environment has shown some benefit as a harm reduction treatment strategy, however, it is not currently available in Manitoba.

Medication Diversion: The illicit/illegal transfer or distribution of prescription medication and the use of these medications for purposes not intended by the prescriber, for example, when a patient provides their prescribed medication(s) to another person for their own use or further diversion, either voluntarily or involuntarily (e.g., by coercion or theft).

META-PHI: Mentoring, Education, and clinical Tools for Addiction: Partners in Health Integration. An initiative to support healthcare providers in treating people struggling with substance use disorders, through the development of care models (e.g., developed the RAAM clinic model), clinical tools, and resources.

Methadone: A full agonist and long acting synthetic opioid, with actions predominantly at the mu-opioid receptor. Methadone is prescribed for the treatment of opioid use disorder as OAT, and also as analgesia for the treatment of pain.

Muscle Relaxants: Skeletal muscle relaxants which commonly cause central nervous system depression (e.g., cyclobenzaprine, baclofen, methocarbamol).

NIHB: The Non-Insured Health Benefits program provides eligible First Nations and Inuit clients with coverage for a range of health benefits that are not covered through other social programs, private insurance plans, and/or provincial/territorial health insurance.

NIHB Client Safety Program: Patients on OAT whose medications are covered by Non-Insured Health Benefits (see **NIHB**) for First Nations and Inuit are enrolled in the NIHB Client Safety Program. These patients are required to have a sole prescriber (or identified group of prescribers) as a provision for coverage of opioids, benzodiazepines, stimulants, gabapentinoids, and/or nabilone (i.e., restricted medications). When patients are initiated in a community pharmacy on buprenorphine/naloxone, methadone, or slow-release oral morphine to treat opioid use disorder, they are automatically enrolled in this program.

OAT: Opioid Agonist Therapy, formally known as opioid replacement therapy. The recommended evidence-based treatment of opioid use disorder with opioid medications specifically prescribed for the indication of OUD, including sublingual buprenorphine/naloxone, methadone, slow-release oral morphine (SROM) or injectable buprenorphine formulations.

OAT Taper (Involuntary): When a patient is not requesting withdrawal from treatment, but given significant safety concerns (for the patient, treatment team, or the community), the treatment team determines that continuing OAT is either unsafe or inappropriate.

OAT Taper (Voluntary and clinically reasonable): A taper requested and directed by a stable patient, in collaboration with the treatment team. In this context, the patient and provider agree that many treatment goals, including clinical stability, have been achieved and that a trial of tapering is a reasonable option.

OAT Taper (Voluntary with clinical concerns): A taper requested by the patient before many important treatment goals are achieved, and/or before clinical stability is reached. The patient thus wishes to taper off of OAT but remains at high risk of relapse to non-prescribed opioid use and other harms.

Opaskwayak Health Authority OAT Program (OHA OAT Program): A northern remote program serving individuals with opioid use disorder and providing OAT to patients in Opaskwayak Cree Nation, The Pas, Moose Lake, Easterville, Grand Rapids and surrounding areas.

Opioid Agonist Therapy 101: An Introduction to Clinical Practice: This two-day interdisciplinary continuing professional development event is aimed at healthcare professionals who are interested in treating and supporting individuals with opioid use disorder. The workshop is accredited for pharmacists, family physicians, and Royal College fellows. The workshop is for those interested in prescribing or dispensing OAT, or for those who want to learn more about opioid addiction and the resources available to patients, and will arm participants with new knowledge and skills to support this vulnerable patient population.

Opioid Use Disorder (OUD): A substance use disorder involving a problematic pattern of opioid use that causes significant impairment and/or distress, consistent with diagnostic criteria as outline in the Diagnostic and Statistical Manual of Mental Disorders (DSM). OUD is a chronic and potentially life-threatening illness that can affect anyone. OAT is an evidence-based and effective long-term treatment for OUD.

Over the counter (OTC) Medications: Medications available over the counter and without a prescription. Some sedating/psychoactive OTC medications when combined with OAT and other medications can contribute to overall sedation, impairment, and accidental polypharmacy medication overdose. OTC medication use must be evaluated and considered when planning an OAT induction and as part of the ongoing medication management plan. Sedating/psychoactive OTC medications commonly contain ingredients such as diphenhydramine, dimenhydrinate, dextromethorphan, and other antihistamines.

Pain: “An unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage” (International Association for the Study of Pain, 2020). Pain management issues form part of the scope of practice of OAT providers. OAT prescribers should play an active role in the management of acute, chronic, and peri-operative pain for patients on OAT.

Personal Health Information Act (PHIA): Manitoba legislation governing the use and dissemination of personal health information.

Pill/Carry Bottle Counts: A clinical intervention that assists with monitoring medication compliance and identifying potential medication diversion. It may involve periodic pill counts, or methadone carry bottle checks, for patients with take-home doses. Patients may be asked to bring medications dispensed as take-home doses or labelled methadone carry bottles to a clinic visit or to the pharmacy for inspection. A healthcare professional may physically count pills/examine bottles to ensure the correct amount of medication is in the patient’s possession (to confirm that medications and carries are being taken as prescribed).

Point-of-Care (POC) Urine Drug Test: An immunoassay-based urine drug test that often detects classes of drugs (e.g., opioids, benzodiazepines, stimulants) rather than a specific drug or medication. For most purposes, POC is the preferred method of testing, ideally ordered upon initiation of OAT treatment and for follow-up testing as clinically indicated, as it provides immediate results that can be shared with the patient and used in the development of a timely management plan.

Polypharmacy: For the purposes of this manual, the concurrent prescribing of five or more medications with sedating and/or psychoactive properties. Importantly, the inherent risks of polypharmacy also apply in situations where licit (e.g., alcohol and cannabis), or illicit drugs/prescription medications and/or over-the-counter medications with sedating and/or psychoactive properties, are combined with prescribed medications with similar properties. When prescribing OAT, it is important for the prescriber to educate patients regarding these risks on a regular basis and develop a comprehensive medication management plan.

Post Exposure Prophylaxis (PEP): Antiretroviral medications prescribed to HIV-negative individuals who has had a potential exposure to HIV. PEP must be initiated within 72 hours of potential HIV exposure. Patients should be referred to urgent care or an emergency department if they meet the criteria for PEP.

Precipitated Withdrawal: As a partial agonist with high affinity for the mu-opioid receptor, buprenorphine has the potential to displace full agonists with lesser affinity (e.g., morphine, heroin, fentanyl) at receptor level, and precipitate clinically significant opioid withdrawal symptoms. This occurs when an initial dose of buprenorphine is taken by a patient who has recently consumed other opioids. This experience can be very distressing to patients and may negatively impact treatment retention. This risk can be minimized with appropriate clinical assessment and treatment planning around induction. All patients eligible to start treatment with buprenorphine-containing OAT medications must first be adequately counselled regarding this risk as part of the informed consent discussion.

Pre-Exposure Prophylaxis (PrEP): Medications prescribed for the prevention of HIV in HIV-negative individuals who are at high-risk of acquiring HIV.

Prescriber: For the purpose of this manual, a regulated healthcare professional who is authorized by their regulatory body (i.e., CPSM, CRNM) to prescribe medications.

Prescription Opioids: Pharmaceutical-grade (quality controlled) opioids obtained via a legitimate prescription from an authorized practitioner (e.g., morphine, hydromorphone, codeine, fentanyl, methadone, buprenorphine/naloxone).

QTc Interval: The QT interval is a measurement made on an electrocardiogram (ECG) used to assess a component of the electrical activity of the heart. The corrected QT interval (QTc) calculates the QT interval at a standard heart rate of 60 bpm. This allows comparison of QT interval values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

QTc Prolongation: The QTc is prolonged if > 440ms in men or > 460ms in women, and a QTc > 500 is associated with an increased risk of serious cardiac arrhythmia (i.e., torsades de pointes).

RAAM Clinics: Rapid Access to Addiction Medicine Clinics are low-barrier, walk-in style clinics that individuals can attend to get help for substance use disorders, including opioid use disorder. No appointment or formal referral is required. RAAM clinics provide time-limited medical addiction care, including pharmacotherapy such as OAT, brief counselling, and referrals to community services.

Sexually Transmitted and Blood Borne Infections (STBBI) Screening: Laboratory-ordered tests to identify STBBIs. Given a higher prevalence in individuals with substance use disorders, comprehensive STBBI screening should be offered to all patients with opioid use disorder. Initial and intermittent STBBI screening, including treatment referrals as appropriate, form an important part of ongoing OAT care.

Slow Release Oral Morphine (SROM): Refers to the 24-hour formulation of the extended-release morphine capsules (i.e., brand name Kadian®). SROM is a specialist-led third-line OAT treatment option for carefully selected patients with opioid use disorder, subject to specific prescribing and dispensing requirements outlined in this manual.

Stimulants: Stimulant/psychostimulant substances that can enhance the activity of the central and peripheral nervous systems, with common effects of increased alertness, awareness, wakefulness, pleasure, and endurance. Including but not limited to cocaine powder, crack cocaine, methamphetamine, amphetamines, methylphenidate, MDMA, and ecstasy.

Street Drug (Immunoassay) Urine Drug Screen: An immunoassay-based urine drug test that is preformed by a laboratory and typically detects classes of drugs (e.g., opioids, benzodiazepines, stimulants) rather than a specific drug or medication.

Sublocade (Buprenorphine Extended-Release Injection): A partial opioid agonist for the management of moderate to severe opioid use disorder (prescribed as OAT) that is administered subcutaneously in the abdominal region by a trained health care professional.

Take-Home Doses (Carry Doses): Dose(s) of OAT medications authorized by an OAT prescriber to be taken home by the patient for unwitnessed self-administration. Generally, OAT doses should be dispensed as daily witnessed doses to be self-administered under the direct supervision of a pharmacist, approved prescriber, or a nurse, until the patient has demonstrated sufficient clinical stability to be considered for take-home doses. Take-home doses must be authorized by the prescriber or a member of the clinical treatment team. The pharmacist cannot authorize take-home doses, and the prescriber/clinic staff should clearly explain this to the patient to avoid misunderstanding.

Trauma-Informed Care/Practice: Practices such as attention, caring awareness, and sensitivity to a patients' past experiences, that promote a healthcare environment that is culturally safer, empowering, and healing. "Trauma is often closely tied to substance use, mental illness, stigma, health care access barriers, and other challenges. Trauma-informed practice means recognizing this link, making sure that people feel safe and are not re-traumatized by their care". (BC Mental Health & Substance Use Services, Provincial Health Services Authority, 2023).

Treatment Agreement: A written agreement reviewed collaboratively between the patient and prescriber/treatment team that outlines behaviour expectations, boundaries, and mutual responsibilities. Such agreements are recommended for patients treated with OAT, to foster transparency, trust, and safety in care. While the expectations of the agreement apply to the clinical setting and extend to the pharmacy setting, the pharmacy may also utilize a pharmacy-specific treatment agreement with OAT patients.

Urine Drug Testing (UDT): Testing for the presence/absence of substances in a patient's urine sample to support assessment and care planning throughout the course of OAT. UDT is recommended during initial assessment, ideally prior to induction, however lack of feasible availability of UDT should not delay treatment if the patient meets diagnostic criteria for opioid use disorder and OAT is indicated. UDT is also recommended upon routine follow up, as clinically indicated, to contribute to the provider's overall assessment of patient stability.

UDT False Negative Result: When a substance is not detected by a urine drug test despite being consumed by a patient. This can occur when the drug is present below the threshold of the test, when the drug is not detected by the particular test, when the test occurs outside the window of exposure, and occasionally with individual variabilities in metabolism (e.g., with certain prescribed medications or medical illnesses). Caution is advised before making impactful treatment decisions based on results of UDT; generally, a pattern of unexpected results is more reliable than a single aberrant test.

UDT False Positive Result: When a substance is reported as being present by a urine drug test but was not (knowingly) consumed by a patient. This may occur as a result of cross-reactivity, when the supply is contaminated with an unexpected substance, or when a patient intentionally tampers with the sample. False positives are rare in cases of passive exposure. It is important to note that cross-reactivity is only possible with immunoassays, not with comprehensive urine drug screens. Caution should be used before making impactful treatment decisions based on results of UDT; generally, a pattern of unexpected results is more reliable than a single aberrant test.

Unwitnessed Induction/Home Induction: Induction with buprenorphine/naloxone that does not require the patient to take the first dose(s) of buprenorphine/naloxone under the direct supervision of a pharmacist, approved prescriber, or nurse. This approach is useful in engaging select patients in care who are unable to appear for a traditional witnessed induction schedule at a pharmacy or with an approved prescriber, due to a variety of patient characteristics or systemic barriers.

Winnipeg Health Sciences Centre Addiction Unit (AU): An inpatient unit specializing in medical management of substance use disorders. Patients requiring specific medical intervention for withdrawal management, stabilization, and access to treatment services are considered for admission.

Withdrawal Management: Medical and symptomatic management while a patient withdraws from a substance, either via a taper or abstaining from the substance. This can be associated with community-based programs in primary care or specialty addiction care, or admission to an institutional setting (e.g., a community-based “detox” facility or hospital). In the context of opioid use disorder, “detox” towards the goal of abstinence from opioids without transition to OAT and long-term treatment is *not recommended* as it has been associated with increased morbidity, such as HIV transmission, and mortality secondary to overdose (see also **Detox** and **Home-Based Detox**).

Witnessed dosing: Generally, OAT doses should be dispensed as daily witnessed doses to be self-administered under the direct supervision of a pharmacist, approved prescriber, or a nurse, until the patient has demonstrated sufficient clinical stability to be considered for take-home doses (see also **Take-Home/Carry Doses**).

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.1 Introduction: Recommendations for Opioid Use Disorder

EVIDENCE SUMMARY

The treatment of choice for people with opioid use disorder (OUD) is opioid agonist therapy (OAT), ideally, though not necessarily, in combination with psychosocial interventions such as counseling, contingency management, and/or peer support. The main options for OAT include buprenorphine/naloxone (Suboxone) and methadone, with Sustained Release Oral Morphine (SROM) as a third line option. Novel long-acting formulations of buprenorphine are also available.

First-line Treatment

Due to its comparable effectiveness and an enhanced safety and side-effect profile, buprenorphine/naloxone is the preferred first-line treatment for OUD. For the majority of people with OUD, it should be used preferentially. Further reasons to strongly consider buprenorphine/naloxone as the optimal pharmacologic treatment include significant alcohol, benzodiazepine, or other sedative/hypnotic use, or significant respiratory disease.

Consideration for methadone as an alternative agent may be appropriate in the presence of:

- Significant cirrhosis (where activity of the naloxone component is enhanced due to reduced first pass effect, causing problematic withdrawal symptoms),
- Previous failed treatment with buprenorphine/naloxone, or
- Very high opioid tolerance unlikely to stabilize on a partial opioid agonist.

Personal preference should also be considered, though it is important to ensure that people understand the risks and benefits of the various OAT medications and make an informed choice.

In rare situations, a third-line option such as SROM or injectable OAT (iOAT) may be appropriate, *in consultation with an addiction medicine specialist*. Please see [Alternative Treatment Approaches for OUD Including SROM \(Kadian®\)](#) for detailed recommendations.

Opioid Antagonists

Alternative pharmacologic options that have been studied include opioid antagonists. While there is emerging evidence to support sustained release injectable naltrexone as an alternative to OAT in some populations, it is not currently available in Canada.

Oral naltrexone is available but is not supported by the evidence. However, in people who decline OAT in favour of abstinence-based treatment, oral naltrexone may be considered as an adjunct to reduce risk of overdose in the event of resumption of opioid use.

Detox NOT Recommended

Withdrawal management, or detox, without transition to OAT and long-term treatment is **specifically NOT recommended as it has been associated with increased morbidity, such as HIV transmission, and mortality secondary to overdose.**

If people decline OAT despite the risks, a slow outpatient taper of opioids is a safer approach than admission to a hospital or residential detox setting. Other considerations to improve safety include the use of oral naltrexone for overdose protection, take-home naloxone for overdose treatment, and enrolment in intensive psychosocial interventions including long-term residential treatment or recovery housing. Please refer to [Alternative Treatment Approaches for OUD](#) for further considerations around home-based withdrawal management.

Harm-Reduction is Paramount

Finally, there is **ample evidence to support harm-reduction interventions for all people who use opioids**, including those engaged in OAT or other treatment.

Specific interventions with strong evidence include:

- Harm reduction supply distribution (e.g., needle/syringe programs)
- Supervised consumption/overdose prevention sites, and
- Take-home naloxone training.

These interventions should be made widely available with low barriers to help reduce opioid related harms.

Furthermore, the Centre for Addiction and Mental Health (CAMH) guideline for OUD describes a comprehensive harm-reduction approach as:

- Outreach services,
- Access to naloxone (naloxone kits),
- Sterile drug consumption equipment,
- Supervised consumption services,
- Education on harm reduction practices,
- Infectious disease testing,
- Access to primary care,
- Vaccinations, and
- Appropriate referrals to other health and social services¹.

In Summary

For the treatment of opioid use disorder, the evidence suggests:

- OAT with buprenorphine is the preferred first-line treatment.
- OAT with methadone is an alternative first-line treatment.
- OAT with SROM or injectable options are *specialist-led approaches* for severe or complex disease.
- Oral naltrexone is not recommended as primary treatment. It may be used to reduce the risk of overdose if OAT is refused.
- Withdrawal management (i.e., detox), without immediate transition to OAT and long-term treatment, is *NOT recommended*.
- Harm reduction interventions, including supply distribution, supervised consumption, and take-home-naloxone training should be widely available, promoted, and considered standard of care for all people at risk of opioid related harms.

References

1. Centre for Addiction and Mental Health (CAMH). *Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*. CAMH; 2021. Available at: <https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf>

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.2 Application, Training, & Regulatory Requirements to Provide Opioid Agonist Therapy

REGULATION OF OAT PRESCRIBING & DISPENSING

In Manitoba, specific training and a regulatory approval is required to prescribe Opioid Agonist Therapy (OAT), including buprenorphine/naloxone, other buprenorphine-containing OAT treatments, methadone, and slow-release oral morphine (SROM) when used as OAT. Training requirements must also be met to dispense these medications as a pharmacist. This chapter addresses the application, training, and approval processes involved in providing OAT from a tri-college perspective.

Please note that the federal exemption for prescribing methadone no longer exists. Both methadone and buprenorphine prescribing approvals/authorizations are now provincially regulated by the prescriber's regulatory authority. In Manitoba, this includes the College of Physicians & Surgeons of Manitoba (CPSM) for physicians and the College of Registered Nurses of Manitoba (CRNM) for RN(Nurse Practitioners).

In compliance with the Manitoba Pharmaceutical Regulation and the College of Pharmacists of Manitoba (CPhM), dispensing of OAT by a pharmacy requires that at least one of the pharmacists at the pharmacy has specialized training and is extensively knowledgeable to provide OAT. The pharmacist with specialized training at a pharmacy is then responsible for training all pharmacists who will be dispensing methadone and/or buprenorphine. All pharmacists dispensing methadone or buprenorphine for OAT must be knowledgeable in all pertinent aspects of OAT.

Tri-College Resources & Approved Courses

Details of the application and training process, for both buprenorphine and methadone, are outlined in these tri-college documents from CPSM, CRNM, and CPhM:

- [OAT Approval Training Process](#)
- [OAT Approval Training Process Flow Chart](#)

To prescribe or dispense OAT, the prescriber or pharmacist must complete an approved, theoretical course tailored to their intended practice and complete all assigned readings as required. If the practitioner intends to provide both methadone and buprenorphine, they must complete the *OAT 101: An Introduction to Clinical Practice Workshop*. This course, along with other requirements, can qualify the practitioner to provide both OAT medications.

Practitioners interested in providing treatment with buprenorphine-containing OAT medications *only* have the option to take the OAT 101 Workshop or complete a College-approved online course (as listed below). As of December 2022, *physicians* applying to prescribe *only* buprenorphine are no longer required to provide proof of training to CPSM *prior* to being granted prescribing approval. However, an approved course remains **strongly recommended** by CPSM for physicians to ensure clinical competency in the treatment of opioid use disorder (OUD) with buprenorphine/naloxone.

Prescribers have an additional component of required training, clinical preceptorship (optional for pharmacists). While proof of completed preceptorship/mentorship is no longer required for *physicians* pursuing buprenorphine-only approval, it remains recommended by CPSM. Given the more complex pharmacology and greater risks associated with methadone compared to buprenorphine, the training requirements for methadone are more comprehensive than those for buprenorphine-only prescribing approval.

TRI-COLLEGE APPROVED OAT TRAINING COURSES

[Opioid Agonist Therapy 101: An Introduction to Clinical Practice](#), offered by the University of Manitoba's CPD Medicine Program. The required course for methadone prescribing and dispensing.

To prescribe or dispense buprenorphine *only*, practitioners can take the above course, or:

[Provincial Opioid Addiction Treatment Support Program](#), offered by the British Columbia Centre on Substance (BCCSU); or

[Buprenorphine Treatment for Opioid Use Disorder](#), offered by The Centre for Addiction and Mental Health (CAMH); or

[Addiction Care and Treatment Online Certificate](#), offered by the BCCSU. This is more of a time commitment for more detailed learning on other substance use disorders beyond OUD; or

[Buprenorphine Prescribing Course](#), offered by the Canadian Society of Addiction Medicine (CSAM). May be offered in conjunction with the CSAM Annual General Meeting (no link available).

FOR PHYSICIAN PRESCRIBERS

As outlined in the CPSM Practice Direction for [Prescribing Methadone or Buprenorphine/naloxone](#), a physician can apply and train towards two approvals for the treatment of OUD:

1. Methadone Prescribing Approval and/or
2. Buprenorphine/naloxone Prescribing Approval.

Step One – Apply to the Registrar

The first step towards either or both approvals is applying **by letter to the Registrar. In this application the physician must request permission to pursue prescribing approval(s) for OAT.**

This letter can be submitted electronically, via email, and should outline the applicant's:

- Educational background (year of graduation, residency, specialty).
- Current practice and location(s).
- Plans for OAT Training and how OAT can be incorporated into their practice (e.g., target population for treatment, settings, if working with other OAT providers).
- For **methadone**, this letter must also contain the contact information for **two physician references** who can speak to the applicant's character and competency. These do **not** need to be OAT prescribers. CPSM will contact these references directly.

A written application requesting permission to pursue prescribing approvals and the relevant training is an essential first step, as the *Registrar has the authority to decline a candidate's application to proceed with training*. Contacting CPSM *before* initiating the training process ensures that physicians' time and financial resources are invested appropriately.

For buprenorphine-only approval, the applicant's request will be reviewed by CPSM to ensure suitability to provide OAT to this vulnerable patient population, prior to Registrar approval.

CPSM CRITERIA FOR METHADONE APPROVAL

1. Application by letter to the Registrar and 2 physician references of character and competency.
2. Proof of Completion of the Approved Theoretical Training Course.
3. Documentation of Clinical Preceptorship Completion.
4. Active registration as a Full-Regulated Member (or active provisional registration, with an OAT Practice Supervisor identified).

CPSM CRITERIA FOR BUPRENORPHINE APPROVAL

1. Application by letter to the Registrar.
2. Active registration as a Full-Regulated Member (or active provisional registration, with an OAT Practice Supervisor identified).
3. Training/education towards clinical competency in the treatment of OUD with buprenorphine *strongly recommended*, but proof of same no longer required *prior* to approval.

Physicians can start prescribing buprenorphine/naloxone upon receipt of a formal letter from the Registrar indicating their prescribing approval was granted. However, physicians must ensure they possess the knowledge, skills, and clinical judgment to prescribe buprenorphine safely to patients as OAT. Therefore, *Step Two* and *Step Three* below are recommended to build clinical competency in the treatment of OUD with buprenorphine/naloxone.

Step Two – Complete an Approved Course

Physicians pursuing training must select a theoretical course approved for the specific OAT approval(s) they are seeking. Physicians seeking a methadone prescribing approval must complete the OAT 101 Workshop as outlined above.

This course is also useful to build clinical competency in the treatment of OUD with buprenorphine/naloxone, but is not required for approval. While physicians are no longer required to submit proof of a completed course *prior* to buprenorphine prescribing approval, a CPSM-approved course remains strongly recommended.

Step Three – Complete Preceptorship for Methadone

Again, given the more complex pharmacology and greater risks associated with methadone compared to buprenorphine, the preceptorship requirements for methadone approval are more comprehensive than the requirements for buprenorphine-only.

Physicians seeking a **methadone approval must complete four half-day preceptorship clinics**, shadowing an experienced OAT prescriber, selected from the CPSM-approved preceptor and site list. This list is available by contacting the CPSM Prescribing Practices Program (it is not available online for privacy reasons as preceptors provide personal contact information to arrange clinics). These four clinics should ideally be **completed within six months of the theoretical workshop**.

Typically, physicians seeking a methadone approval are also seeking a buprenorphine approval. This is strongly encouraged, given that buprenorphine is considered first-line therapy for treatment of OUD. Completion of the OAT 101 Workshop and preceptorship clinics would certainly support clinical competency in the treatment of OUD with both medications. Ideally, preceptorship clinics can expose the candidate to the full spectrum of methadone and buprenorphine care, including inductions, titrations, and maintenance care.

Physicians seeking **only buprenorphine prescribing approval are encouraged to seek preceptorship/mentorship as needed to build clinical competency** for the treatment of OUD with buprenorphine/naloxone. Proof of completed preceptorship or mentorship is no longer required by CPSM prior to approval.

Preceptorship clinics are also a practical way to learn the administrative, pragmatic, psychosocial, and therapeutic aspects of OAT care. These clinics can build connections and mentorship relationships with experienced providers.

Step Four – Notify CPSM of Completed Training for Methadone

Once the theoretical course and preceptorship clinics are completed for **methadone training**, the applicant can notify CPSM by providing confirmation and specific details via email. Physicians should submit their certificate of completion for the OAT 101 Workshop. They should also provide details of their preceptorship, including the dates of the clinics, the site(s), and name(s) of the physician(s) shadowed.

Final approval will be confirmed with the Registrar. **Physicians can start prescribing methadone upon receipt of a formal letter from the Registrar indicating their prescribing approval was granted.**

Prescribing Renewals – Every Three Years

CPSM prescribing approvals expire on a specified date over a three-year cycle, regardless of when a physician obtained the approvals. For example, the next expiry date is June 1, 2024, and every three years thereafter. Renewals are granted upon completion of a questionnaire to evaluate continued competency through ongoing prescribing and participation in Continuing Professional Development (CPD) relevant to OAT prescribing and addictions medicine.

FOR NURSE PRACTITIONER PRESCRIBERS

RN (Nurse Practitioners) can review the tri-college training process documents linked above and the CRNM document [Prescribing Controlled Drugs and Substances](#).

Step One – Apply to CRNM

The first step towards prescribing either methadone or buprenorphine for RN(NP)s is **submission of the relevant application form**; the [Methadone Prescribing for OUD](#) form (Part A) and/or the [Buprenorphine Prescribing for OUD](#) application form.

RN(NP)s seeking a methadone prescribing exemption must also **provide two references for character and competency**, who will be contacted directly by CRNM. One reference must be a supervising manager and the other a professional with whom the applicant has worked or trained with recently.

CRNM CRITERIA FOR OAT PRESCRIBING AUTHORIZATION

1. Submission of Application Forms to CRNM and 2 references of character and competency.
2. Proof of Theoretical Training Course Completion.
3. Documentation of Clinical Preceptorship Completion.
4. Active Registration with CRNM and authorization to prescribe controlled substances (including M3P and controlled substances education as directed by CRNM).

Step Two – Complete an Approved Course

RN(NPs) pursuing training must select a theoretical course approved for the specific OAT authorization they are seeking. RN(NP)s seeking a methadone prescribing exemption must take the OAT 101 Workshop as outlined above. This will also qualify them for a buprenorphine authorization. RN(NP)s seeking an authorization to prescribe *only* buprenorphine can complete any one of the CRNM-approved courses listed above, including the online options.

Step Three – Complete Preceptorship

The clinical preceptorship requirements for RN(NPs) seeking methadone exemption are the same as the requirements for physicians. Likewise, the requirements for methadone are more comprehensive than the requirements for a buprenorphine-only prescribing authorization.

RN(NPs) pursuing **methadone prescribing must complete four half-day preceptorship clinics**, shadowing an experienced OAT prescriber from the approved preceptor and site list. These four clinics should ideally be **completed within six months of the theoretical workshop**.

Typically, RN(NP)s seeking a methadone exemption are also seeking buprenorphine authorization. This is strongly encouraged, given that buprenorphine is considered first-line therapy for treatment of OUD. Completion of the OAT 101 Workshop and four preceptorship clinics would qualify a RN(NP) for both authorizations. Ideally, these preceptorship clinics should expose the candidate to the full spectrum of methadone and buprenorphine care, including inductions, titrations, and maintenance care.

The preceptorship is also a practical way to learn the administrative, pragmatic, psychosocial, and therapeutic aspects of OAT care. These clinics can build connections and mentorship relationships with experienced providers.

RN(NP)s pursuing *only* buprenorphine prescribing must complete **one half-day preceptorship clinic**, shadowing an approved buprenorphine prescriber, ideally within three months of finishing the theoretical course. RN(NP)s must also formally identify a **CRNM-approved mentor** (with OAT experience) for their first year prescribing buprenorphine, for support and guidance as needed. Contact CRNM at practice@crnm.mb.ca for a list of approved preceptors and mentors. (Please note the CRNM requirements for buprenorphine-only prescribing authorization may be revised at a later date.)

Registrants must also continue to demonstrate the [Practice Expectations for RN\(NP\)s](#).

Step Four – Notify CRNM of Completed Training

Once the theoretical course and preceptorship are completed, the applicant can notify CRNM by submitting any outstanding application forms, a mentor's name as applicable, and relevant completed course certificates to practice@crnm.mb.ca. RN(NP)s will receive a formal email from CRNM confirming their methadone and/or buprenorphine prescribing privileges.

FOR PHARMACISTS

Pharmacists seeking to dispense methadone and/or buprenorphine can review the tri-college training documents linked above and complete the required readings as found in the [OAT Guidelines for Manitoba Pharmacists](#).

Step One – Complete an Approved Course

The Manitoba Pharmaceutical Regulation states that a member may only engage in the aspects of pharmacy practice for which they have the requisite knowledge, skill, and judgment to provide or perform, and that are appropriate to their area of practice.

At least one pharmacist must be extensively knowledgeable at each pharmacy that provides OAT. Similar to prescribers, the pharmacist must complete a theoretical training course approved for the specific OAT they plan to dispense:

- If the pharmacist wishes to dispense methadone, they are required to take the OAT 101 Workshop. This will also qualify them for buprenorphine dispensing.
- If the pharmacist wants to dispense *only* buprenorphine, they can complete any one of the tri-college approved online courses already listed. (Please note these CPhM requirements for buprenorphine-only dispensing are presently being revised.)

The pharmacist with specialized training is then responsible for training all pharmacists who will be dispensing OAT at their pharmacy.

If a pharmacy must provide OAT for continuation of care and it is not possible for the pharmacist to complete the approved specialized training in advance, they must have a formal agreement with a pharmacist with specialized training at another pharmacy who agrees to act as a mentor. Training must be completed within 6 months.

Step Two – Preceptorship, Mentorship, & Documentation

Clinical preceptorship or mentorship is optional for Pharmacists.

Additionally, pharmacists do not need to provide confirmation of completed clinical training to CPhM. However, they must maintain documentation of completion of the required training for record keeping and compliance with the Regulation. Proof of completion may be requested at a later date.

While not a formal requirement, pharmacists who are new to dispensing OAT can also seek a mentor; another trained pharmacist can be helpful in setting up early practice and for guidance as needed. Contact CPhM if assistance is needed in finding a mentor.

PROVIDING OTHER FORMS OF OAT

To prescribe other formulations of buprenorphine, such as Sublocade® (buprenorphine extended-release injection) or Probuphine® (buprenorphine implant), prescribers must hold a buprenorphine/naloxone prescribing approval/authorization from their respective College and pursue additional training as outlined below.

If third-line options such as slow-release oral morphine (SROM) or injectable OAT (iOAT) are considered, prescribers must already hold both methadone and buprenorphine/naloxone approvals/authorizations. Prescribers **MUST** discuss such treatment *in consultation with an addiction medicine specialist*.

Additionally, see [Recommendations for Sublocade®](#) and [Alternative Treatment Approaches including SROM \(Kadian®\)](#) for further guidance.

Pharmacists should contact CPhM for more information on training requirements for dispensing other forms of OAT.

INFORMATION ON SUBLOCADE® TRAINING

More information on Sublocade® use and administration is available **for prescribers and pharmacists** in this document: [Joint Guidance on Sublocade Administration](#).

- Prescribers must hold a current, active buprenorphine/naloxone prescribing approval/authorization from CPSM/CRNM to prescribe Sublocade®.
- Currently, approved/authorized prescribers wanting to prescribe Sublocade® must complete the non-accredited certification program, **a Health Canada requirement**, available at www.sublocadecertification.ca. The completed program certificate must be faxed to the pharmacy along with the M3P prescription when prescribers first order Sublocade® from a particular pharmacy.

INFORMATION ON PROBUPHINE® TRAINING

More information on Probuphine® (buprenorphine implant) is available **for prescribers and pharmacists** by contacting the CPSM's Prescribing Practices Program directly.

- Please note that prescribers must hold a current, active buprenorphine/naloxone prescribing approval/authorization from CPSM/CRNM to prescribe/implant Probuphine®.
- Because of the risks associated with insertion and removal, Probuphine® must be prescribed, implanted, and removed only by trained prescribers who have successfully completed a training program on the insertion and removal of Probuphine®.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.3 Initiating Opioid Agonist Therapy: Comprehensive Assessment, Diagnosis, Informed Consent & Investigations

GENERAL CONSIDERATIONS

Before starting opioid agonist therapy (OAT) a thorough intake assessment is critical to safe patient care. This section summarizes key aspects of the initial comprehensive assessment of a patient with opioid use disorder (OUD), as well as key clinical investigations that should be considered in early treatment.

The importance of informed consent and treatment agreements is also discussed. Establishing a mutual understanding of the treatment plan and goals with the patient, as well as behavioural expectations, is essential to safe care. This also lays the foundation of the therapeutic relationship for ongoing treatment.

THE COMPREHENSIVE ASSESSMENT

INITIAL ASSESSMENT

The comprehensive patient assessment should address the **KEY COMPONENTS** listed below.

Assessment should confirm a diagnosis of OUD, consistent with DMS-5 criteria (see **Appendix A**), and explore key safety considerations, *before* starting OAT. With this established, a discussion of treatment options and goals can follow, including review of pharmacotherapy, psychosocial interventions, and harm reduction strategies.

Set the Stage for the Interview

Addiction medicine care requires a compassionate, non-judgmental, and sensitive approach to gathering information. Building a therapeutic alliance with the patient starts with the initial interview and is important to effective care.

Before delving into questioning, take a moment to help the patient settle into the interview space:

- Welcome the patient and introduce yourself and whomever may be joining for the interview.
- Let them know how long the assessment may take.
- Let them know what to expect and the type questions you will ask (e.g., about their medical history, life circumstances, and the substances they may be using).
- Determine if they would like a support person to join the interview and/or treatment discussion, as appropriate.

The assessment will be affected by the clinical setting, time limitations, and, of course, the patient's readiness to share information. Patients struggling with substance use disorder may feel guarded and reluctant to share certain information about themselves, their family, or their substance use, at least initially. Offer reassurance that the more shared, the better the treatment plan can align with their individualized needs, preferences, and values.

KEY COMPONENTS: THE COMPREHENSIVE ASSESSMENT

The following areas should be reviewed to determine a diagnosis of OUD and to establish a safe and realistic treatment plan with the patient:

PSYCHOSOCIAL HISTORY

Review age, housing, family/friends, finances, education, employment, legal issues, illicit activity, supports, stressors, interests, and valued life roles.

SUBSTANCE USE & TREATMENT HISTORY

Screen all drug classes. Ask for details if using/used a substance regularly: length of use, pattern of use, amount, route (oral, insufflation, IV, other), access (prescribed and/or illicit), last use, periods of abstinence, cessation symptoms.

Screen for behavioural addictions.

Review past experience with addiction treatment.

MEDICAL HISTORY

Review physical & psychiatric/mental health history, hospitalizations, surgeries, other healthcare providers involved, and the status of current issues or diagnoses.

MEDICATION REVIEW

Review prescribed medications. Link current meds to active clinical issues. See, "An Approach to Polypharmacy in the Context of OAT" in [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#), for guidance on medication reviews.

FOCUSED PHYSICAL & MENTAL STATUS EXAM

Check vitals, heart, lungs, focused pain assessment (as appropriate), focused lab tests.

Special attention should be given to signs of opioid withdrawal, cardiovascular and respiratory status, pupil size, alertness, affect, speech, agitation, skin (injection sites, infection, abscess), malnutrition, jaundice, hepatosplenomegaly.

TREATMENT GOALS & PLAN

Identify goals, safety considerations, and plan.

Additionally, substance use and trauma often overlap. It is important to be mindful of adverse childhood experiences and other trauma during the interview. This should also be approached with sensitivity and consideration of the patient’s readiness to share, using a person-centered and trauma-informed lens.

Incorporating trauma-informed principles into care is also recommended by the Centre for Addiction and Mental Health (CAMH) guidelines for OUD, including “trauma awareness, choice, collaboration and connection, safety and trustworthiness, skill building, and strengths-based approaches”¹. Cultivating this care starts with the initial interview.

Templates & Documentation

Documenting the details of the assessment, diagnoses, and rationale for the treatment approach is critical to quality care. This can be done in narrative form or on templated assessments forms. Templates, either in electronic or paper format, are an effective way to ensure the **KEY COMPONENTS** of the initial interview are covered. They can prompt you to remember important topics and questions. See **Appendix B** for a template example.

Please note that while templates are useful tools, **quality contemporaneous documentation in the medical record is required**. Details of the patient’s specific history, physical, substance use, as well as diagnoses, problem list, and plan/goals must be captured in the medical record.

In general, medical record keeping should align with the CPSM Standards of Practice for [Documentation in Patients Records](#) and [Maintenance of Patients Records In all Settings](#), as highlighted in the box below.

STANDARD OF PRACTICE: DOCUMENTATION IN PATIENT RECORDS²

For **accuracy and completeness**, the Standard for Documentation emphasizes:

- 2.9. In creating an entry, the use of templates or macros carries substantial risk that information not relevant to the specific patient’s actual clinical circumstance or the specific encounter may inadvertently be included in the patient record, rendering the entry unreliable or inaccurate. For this reason:
 - 2.9.1. Templates or macros prepopulated with clinical information should be avoided.
 - 2.9.2. Registrants who use templates or macros must review them and ensure that the content accurately and comprehensively reflects the care given.
- 2.10. Registrants must not copy and paste an entry related to a prior visit with a patient unless the copied entry is modified to remove outdated information and include current information which reflects the actual circumstances the visit entry is meant to reflect.

Substance Use History – Get Details

Templates can also help the clinician complete a detailed review of substance use. Asking patients about each class of drug, and giving examples of specific types, common names, or local slang terminology, will often yield more definitive information about substance use.

While the patient may present for help with opioids, the OAT provider should be aware that polysubstance use is very common. Patients may be using more than one type of drug on a regular basis. It is important to screen all classes of drugs, then focus on gathering details about the substances used regularly. The **QUICK REFERENCE** below lists commonly used substances that should be reviewed in most initial interviews. **Evaluating polysubstance use, including sedating and psychoactive medications, is critical to treatment planning and establishing safeguards during OAT induction and early recovery.**

QUICK REFERENCE: DRUG CLASSES FOR SUBSTANCE USE HISTORY

It is best practice to screen for substance use within all drug categories during initial interviews. The list below is not exhaustive but covers commonly used substances. The clinician should acknowledge that polysubstance use is common. If there is a significant history of use, gather more details about the specific substance(s) (e.g., frequency, amount, route, length of use, access, cessation, abstinence).

While not all listed here, using trade names and local slang (acquired over time), or asking patients to describe shapes, sizes, or colours of pills, can often help identify what patients are using and improve communication. If patients use unfamiliar terms, ask them to clarify to build mutual understanding.

Opioids	prescribed or illicit sources, e.g., morphine, codeine, hydromorphone, oxycodone, fentanyl, heroin, “down” (typically an illicit combination of fentanyl, heroin, possibly benzodiazepines), diverted methadone or buprenorphine.
Benzodiazepines	prescribed or illicit sources, e.g., alprazolam, lorazepam, diazepam, clonazepam, temazepam, zopiclone.
Alcohol	beer, wine, spirits, home-brew, potable/non-potable.
Stimulants	cocaine powder, crack cocaine, methamphetamine, amphetamines, methylphenidate, MDMA, ecstasy.
Hallucinogens	LSD/acid, psilocybin/magic mushrooms, phencyclidine (PCP)/angel dust, synthetic cathinone/bath salts, ketamine.
Cannabis	commercially acquired or illicit sources, smoked, vaped, oils, edibles.
Over the counter	diphenhydramine, dimenhydrinate, dextromethorphan/cough syrups, sleep aids/acetaminophen or ibuprofen PM.
Nicotine	cigarettes, cigars, vaping.
Other	gabapentinoids, quetiapine, trazodone, muscle relaxants (cyclobenzaprine, baclofen), caffeine, kratom, solvents, steroids.

Additionally, understanding the patient's life circumstances or history around substance use can be a helpful framework to better understand the patient and, ultimately, tailor a recovery plan. When and why did they start using a particular substance? What led to opioid use? What positive benefits did substance(s) have and when did it start affecting their life in a negative way? The answer may not always be clear to the patient but asking will typically offer insights and useful information.

List of Active Issues & Medication Review

The history and physical completed upon initial assessment should assist in generating an updated **list of active clinical issues/diagnoses** that require management. Ideally, a detailed review of the patient's medication record (e.g., DPIN or E-Chart) must occur in conjunction with the review of active clinical issues. This provides the clinician and patient an opportunity to clarify how medication is being used, and to determine where a particular medication ranks in terms of importance in managing the clinical concerns.

The section, "An Approach to Polypharmacy in the Context of OAT" in [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use](#), provides useful recommendations to support medication reviews. This section's feature box, "**MEDICATION REVIEW - KEY QUESTIONS**", can be used to explore each medication on the patient's DPIN.

It is important to also note that the absence of prescribed medications on DPIN does not rule out polypharmacy; the patient may be using sedating and/or psychoactive medications from a non-prescribed source.

In collaboration with the patient, identifying the active clinical issues, setting priorities, and making a medication management plan are critical steps of the comprehensive assessment, *particularly in the context of polypharmacy*. These are often the final steps as assessment moves towards treatment planning.

DIAGNOSIS & TREATMENT GOALS

Diagnosis of OUD

The comprehensive assessment should gather enough information about the patient's substance use, health, and psychosocial status to make a diagnosis of OUD. The clinician needs to develop an understanding of the patient's function and the consequences experienced because of substance use, and identify the strengths and barriers that will impact recovery. Several helpful checklists for DSM-5 OUD criteria (**Appendix A**) are available to help practitioners make a clear diagnosis, as listed in the box below.

Co-occurring conditions can certainly complicate diagnosis. For example, mental health issues, psychiatric disorders, and chronic pain conditions will impact patient function and blur diagnostic lines.

If questions remain regarding definitive diagnosis, further investigations or consultations may be needed to sort out the diagnoses.

A diagnosis of OUD must be confirmed to start OAT. In many circumstances, by the time patients are seeking help for opioid use, they will likely meet at least two to three criteria to diagnose mild OUD, at minimum. Of note, tolerance and withdrawal, in the context of taking opioids solely under appropriate medical supervision, do not qualify as criteria towards diagnosis of OUD. This would be something to consider in a patient prescribed opioids for chronic pain – evaluating if they meet other diagnostic criteria is important to confirm a concurrent diagnosis of OUD.

ONLINE RESOURCES: OUD DIAGNOSTIC CHECKLISTS

British Columbia Centre on Substance Use ([BCCSU](#))
[DSM-5 Clinical Diagnostic Criteria for Opioid Use Disorder](#)

University of Colorado – [IT MATTRs™](#)
[DSM-5 Criteria for Diagnosis of Opioid Use Disorder](#)

Boston Medical Centre – [Massachusetts Consultation Service for Treatment of Addiction and Pain \(MCSTAP\)](#)

[DSM-5 Checklist of Diagnostic Criteria: Opioid Use Disorder](#)

Treatment Goals

Identify the goals of treatment in collaboration with the patient. Harm-reduction – improving patient safety and reducing harms through addiction care and/or while on OAT – is paramount. Both provider and patient-driven goals are important to document and revisit periodically.

Cessation of drug use or complete abstinence from non-prescribed substances may be a later goal along the treatment continuum, or it may not be realistic or achievable for some patients, but they can still benefit from harm-reduction and involvement with the OAT program now.

The CAMH describes a comprehensive harm-reduction approach as:

- Outreach services,
- Access to naloxone (naloxone kits),
- Sterile drug consumption equipment,
- Supervised consumption services,
- Education on harm reduction practices,
- Infectious disease testing,
- Access to primary care,
- Vaccinations, and
- Appropriate referrals to other health and social services¹.

Treatment goal areas to discuss include:

- 1) **Safety Goals.** This includes safety of self and others so that OAT medications are safely used, stored, and not diverted. Providers and team members must ensure that patients receive adequate education regarding the risks involved with OAT treatment, as care plans are negotiated and adjusted over time.

This education must be provided in a manner that is easy to understand and relevant to the patient's circumstances and literacy level. Handouts that patients can share with family, friends, and roommates, may be especially useful. See **Appendix C**, "A Patient Guide: Avoiding Overdose in the First Two Weeks of OAT", as an example to facilitate this teaching. Treatment agreements will also explicitly address safety considerations for treatment.

- 2) **Substance Use Goals.** Discuss the patient's goals around opioid and other drug and alcohol use. What changes are they ready for? What substances to do they hope to cut-back, reduce, stop? This also involves discussion around safe use and harm-reduction teaching, supplies, and provision of naloxone kits and associated education, as above.
- 3) **Medication Management Goals.** How will current medications be managed for safety? If polypharmacy concerns exist, what can be stopped, reduced, or tapered first? Discuss this collaboratively with the patient for increased engagement with the medication management plan.
- 4) **Other Health Goals.** Discuss the other active issues or diagnoses that require further assessment, work-up, and management, as applicable. What does the patient feel ready to address?
- 5) **Psychosocial Goals.** Consider goals to improve psychosocial function for **pragmatic reasons** (e.g., how will they pay for their medication? How stable is housing?), **safety** (e.g., who will care for the children if they go to a treatment program? How will medication be safely stored?), and for overall **recovery** (e.g., how will they abstain from illicit drug use if their partner is still using? How will they spend their time if not using anymore?).

The OAT provider should give attention to the following needs, as applicable:

- Addressing family or relationship problems or need for supports,
- Housing issues,
- Financial needs,
- Legal concerns,
- Employment or educational needs or skills training,
- Mental health, peer supports, cultural supports, and/or spiritual health.

INFORMED CONSENT & TREATMENT AGREEMENTS

As with any treatment in the practice of medicine, informed consent prior to starting OAT is essential. The British Columbia Centre on Substance Use (BCCSU) explains that “seeking informed consent to trial an intervention requires disclosing the relevant information that will allow the patient to make a voluntary choice to accept and consent or decline the intervention”³.

Individualized treatment plans that incorporate patients’ preferences, values, and choice must be balanced with evidence-informed treatment and safety considerations. Treatment agreements can be useful tools to support informed consent and treatment planning. They can also be used to, “delineate expectations, negotiate boundaries, and minimize conflicts between providers and patients with OUD”⁴.

See **Appendix D** for an example Treatment Agreement & Consent Form.

The BCCSU clinical guideline for OUD also provides examples of treatment agreement and consent forms specific to OAT medications, including methadone, buprenorphine/naloxone, and slow-release oral morphine (see [Appendix 8, pages 61-69](#))⁵. However, these BC resources should be considered within the local provincial context and Manitoba guidelines and standards applied accordingly.

Boundaries & Expectations

Compassion combined with clear boundaries is often needed to support patients with OUD.

Treatment agreements are also useful tools to help providers role model healthy boundaries and effective communication with patients. They can also foster trust and transparency at the forefront of treatment.

It is important that all patients and prescribers understand their respective expectations and responsibilities when it comes to participating in OAT care. Mutual respect is essential and worth an investment of time and effort. Reviewing and signing a treatment agreement that includes behavioral expectations can assist in clarifying roles and expectations. A clear discussion of boundaries around behavior may be needed so that patients understand that threats or aggression directed at staff, pharmacists, or co-patients, will not be tolerated and may result in discontinuation of care.

Reviewing agreements should be adapted to meet patients’ cognitive abilities, literacy level, and psychosocial needs. These agreements can be also revisited in early treatment as patients are stabilizing on OAT, ideally when not in withdrawal, more clear-headed, and able to retain information, to ensure mutual understanding of expectations.

Information on urine drug testing parameters, expectations, and management should also be included in treatment agreements, using a patient centered, non-punitive, and non-stigmatizing approach⁶.

The Circle Of Care

Treatment agreements can also help address confidentiality, circle of care, and circumstances where providers have a duty to report. Upon intake, patients should be made aware of the importance of communicating and collaborating with their other care providers. Discuss openly with the patient the importance of communicating with their circle-of-care providers as needed (e.g., family physician, pharmacist, psychiatrist, counsellors, and other professionals involved).

This requirement for transparency facilitates patient safety for OAT induction and ongoing care and can be outlined in the treatment agreement. If patients decline to participate in treatment because of the need for such communication, OAT induction is not recommended as it puts both the patient and provider at risk and jeopardizes safety. Focusing on harm-reduction education and resources, clarifying treatment expectations, and ensuring patients know where they can access future care then becomes paramount.

The CPSM [Standard of Practice for the Duty to Report Self, Colleagues, or Patients](#) provides more information about the ethics and legalities of reporting. The Standard highlights that honesty and compassion are fundamental to the patient-physician relationship and encourages communication with patients around reporting duties and potential breaches as appropriate, to foster a trusting relationship between patient and provider⁷. Please see this Standard for more information around mandatory reporting with patients.

It is also important to note that sharing patient information to their benefit within the circle of care is permissible and still fulfills the duty of confidentiality⁷.

INVESTIGATIONS & LABORATORY TESTS

The following minimum investigations are recommended in early treatment:

- Urine Drug Testing (UDT)
- Sexually Transmitted and Blood Borne Infections (STBBI) screening
- CBC, liver function, renal function, and blood sugar tests
- Urinalysis
- Pregnancy test (as appropriate)

While the above investigations are ideal, they should not delay access to timely treatment⁵.

Urine testing that identifies the presence of opioids is also ideal prior to initiating OAT, however, if testing cannot be feasibly completed and OAT is indicated, treatment should be initiated promptly regardless.

UDT can then be arranged as soon as it is feasible – not only to help evaluate opioid use, but to inform the polysubstance use history.

Of note, if urine testing *does not* detect opioids upon intake, this does not preclude a patient from starting OAT if clinically indicated. There may be clinical reasons for this, such as recent abstinence, or failure of the test to reliably detect certain opioids.

Consideration must be given to select the type of UDT that will be most effective for the clinical context (e.g., point-of-care, street drug screen, or comprehensive). The benefits and drawbacks of each type of test must be considered along with the clinical context and utility. See the [Use of UDT in the Management of OUD](#) for a general approach to testing, including the recommended frequency and important issues to consider when interpreting results.

Importance of STBBI Screening

It is important to note that OAT providers must offer comprehensive screening for STBBIs to all patients with OUD. This can occur around intake and periodically thereafter based on ongoing risk assessment. Initial screening should include testing for HIV, hepatitis A, B, and C, as well as syphilis, chlamydia, and gonorrhea, including throat and rectal swabs if indicated.

Patients at significant and ongoing risk of infection should be offered STBBI screening every 6 to 12 months. Repeat testing may be customized based on individual risk factors. Please see [Prevention, Screening, & Management of HIV & Hepatitis C in Individuals with OUD](#) for further guidance. Again, such testing should not delay access to OAT, and should a patient present for help and then decline OAT, offering STBBI screening is still part of a comprehensive harm reduction approach.

Other Investigations

Other investigations can be considered as clinically relevant or indicated.

Baseline and monitoring electrocardiograms (ECG) may be warranted and are recommended in the context of methadone (particularly at higher doses), QT prolonging medications, and other risks factors. Further considerations for ECG and clinical management of the QT interval with methadone treatment are discussed in detail in the Maintenance Phase recommendations of this manual.

In the context of new-onset mental health symptoms, standard lab work including thyroid, kidney, and liver function, and any other investigations suggested by a review of systems, can be helpful to rule out if physical health conditions are contributory. Chronic pain conditions may also benefit from further investigations and referral to relevant specialists.

Individuals with substance use disorders may not routinely access healthcare, and may in fact avoid it given past negative or stigmatizing experiences. While OAT may not be offered in conjunction with primary care in some settings, the OAT prescriber could be the one trusted provider who is seen routinely enough to offer basic screening lab work and facilitate a connection with primary care for follow-up, if possible and available.

ONGOING ASSESSMENT AT REGULAR CLINIC VISITS

Upon routine follow up, the OAT provider should review and document, as applicable:

- The current OAT dose.
- Any signs or symptoms suggestive of need for dose change.
- Current medications, review DPIN or E-Chart, and communication with pharmacy as needed.
- Use of illicit opioids or other drugs, alcohol, prescribed and/or non-prescribed medications, and/or OTC medications.
- Recent urine drug testing as clinically indicated.
- Presence of signs or symptoms of intoxication or withdrawal.
- Presence of any acute stressors or acute medical problems.
- Current psychosocial status/stability (e.g., housing, finances, relationships, legal concerns, productivity, coping, recovery activities, as applicable).
- Appropriateness of change in take-home dosing (carries).
- Any safety concerns including the safe storage of medications or psychosocial stability as above.

The provider should also document the new OAT prescription and any other prescriptions given.

Physicians are encouraged to utilize narrative notes for follow up visits. Careful attention should be paid to ensure documentation on forms or electronic records is patient-specific and detailed.

Quality contemporaneous documentation in the medical record upon follow up is imperative.

Please refer to the earlier box regarding the [STANDARD OF PRACTICE: DOCUMENTATION IN PATIENT RECORDS](#) and the importance of accuracy and completeness.

Periodically the OAT provider should also review:

- Common potential side effects (e.g., constipation, sexual difficulties, weight gain).
- Need to consider referral for treatment of chronic health conditions and/or for primary care (e.g., hepatitis C, HIV, pain, mental health).
- If there is a need for ECG, other laboratory tests, or serum levels.
- If more intensive counseling or other treatment support would be appropriate.

References

1. Centre for Addiction and Mental Health (CAMH). *Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*. CAMH; 2021. Available at: <https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf>
2. College of Physicians & Surgeons of Manitoba. *Standard of Practice: Documentation in Patient Records*. CPSM; 2022.
3. British Columbia Centre on Substance Use (BCCSU). *Opioid Use Disorder Practice Update*. BCCSU and BC Ministry of Health; 2022. Available at: <https://www.bccsu.ca/wp-content/uploads/2022/02/Opioid-Use-Disorder-Practice-Update-February-2022.pdf>
4. Korownyk C, Perry D, Ton J, et al. Managing opioid use disorder in primary care: PEER simplified guideline. *Canadian Family Physician*. 2019; 65(5):321-330.
5. Provincial Opioid Use Disorder Treatment Guideline Committee. *A Guideline for the Clinical Management of Opioid Use Disorder*. British Columbia Centre on Substance Use (BCCSU) and BC Ministry of Health; 2017. Available at: <https://www.bccsu.ca/care-guidance-publications/>
6. British Columbia Centre on Substance Use (BCCSU). *Urine Drug Testing in Patients Prescribed Opioid Agonist Treatment – Breakout Resource*. BCCSU, BC Ministry of Health, and Ministry of Mental Health and Addictions; 2021. Available at: <https://www.bccsu.ca/wp-content/uploads/2021/07/Urine-Drug-Testing-Breakout-Resource.pdf>
7. College of Physicians & Surgeons of Manitoba. *Standard of Practice: Duty to Report Self, Colleagues, or Patients, Contextual Information and Resources*. CPSM; 2021.

Appendix A

DSM-5 CRITERIA¹ FOR OPIOID USE DISORDER

- A. A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by **at least two** of the following, occurring within a 12-month period:
1. Opioids are often taken in larger amounts or over a longer period than was intended.
 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 or urge 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 opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
 10. Tolerance*, as defined by either of the following:
 - a) A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
 - b) A markedly diminished effect with continued use of the same amount of an opioid.
 11. Withdrawal*, as manifested by either of the following:
 - a) The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal, pages 259-260).
 - b) Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

* **Note:** These criteria are not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Specify current severity

305.50 (F11.10) Mild:	Presence of 2-3 symptoms
304.00 (F11.20) Moderate:	Presence of 4-5 symptoms
304.00 (F11.20) Severe:	Presence of 6 or more symptoms

¹ The criteria are reprinted with permission from American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Washington, DC: Author.

Appendix B

OAT COMPREHENSIVE ASSESSMENT TEMPLATE

Name: _____ DOB: Y/M/D: _____

Date/Time	Focus	Progress Notes
	Pre-screen	
	Social History	
	Age	
	Partner	
	Children	
	Main supports	
	Childhood	
		Adverse Childhood Experiences:
		Other Trauma:
	Education	
	Job history	
	Last worked	
	Current job	
	Income	
	Medication coverage	
	Driver's licence	Yes No
	Legal history	
	Current charges	
	Upcoming court dates	
	Substance Use History	
	Cannabis	
	Alcohol	
		Ever in ER or admitted for alcohol withdrawal:
		Seizures: DT's:

	Cocaine powder	
	Crack	
	Methamphetamines	
	MDMA	
	Hallucinogens	
	Benzodiazepines	
	Opioids	
		Last Use:
		DOC:
		Overdoses:
		Clean Supplies:
		Naloxone kit:
	Nicotine	
	Ketamine	
	Solvents	
	OTCs	
	Previous substance use treatment	
	Current treatment involvement	
	Self-help groups	
	Co-occurring issues	Gambling:
		Shoplifting:
		Disordered eating:
	Medical History	
	IVDU	Complications of IV use:
	Previous STI panel	
	Fertility control	
	Other care providers	
	Family history	
	Current medications	

	DPIN/EChart Review	
	Allergies	
	Hospitalizations	
	Surgeries	
	Psychiatric history	
	Previous suicide attempt/ideation	
	Notable on review of systems	
	Physical Exam	
	General appearance	
		BP: Pulse: Temp: Weight:
		H & N: Pupils:
		Chest:
		CVS:
		Abdomen:
		Skin: IV sites:
	Point of care UDS	
	Goals	
	Assessment	
	Plan	
	Additional comments	
	Signed	

Appendix C

A PATIENT GUIDE: AVOIDING OVERDOSE IN THE FIRST TWO WEEKS OF OPIOID AGONIST THERAPY

This clinic provides opioid agonist therapy (OAT) care *as safely as possible*, but accidental overdoses sometimes happen in the first two weeks of treatment. This is especially important when starting methadone treatment, but many of the same safety ideas should also be applied when starting buprenorphine/naloxone (Suboxone).

The questions and answers below will help you to get through this period safely. Share this information sheet with a friend or family member.

Why can't my doctor increase my dose more quickly?

When you first start taking methadone or buprenorphine/naloxone, you want to get on the right dose as soon as possible. With buprenorphine/naloxone your doctor may only need a few days to get you to the right dose while making sure you can safely tolerate the medication. With methadone, however, your doctor must increase your dose slowly over several weeks, because your body takes time to adjust to the methadone and (unlike other opiates), methadone builds up slowly in your bloodstream over several days. A dose that may feel like too little on a Monday could put you in hospital by Thursday.

What can I take to relieve withdrawal and help me sleep until the OAT medication begins to work?

Your doctor may discuss taking certain medications to assist with your symptoms. These medications may include plain Tylenol® (acetaminophen) and Advil® (ibuprofen). Drinking lots of water is important to stay hydrated. Occasionally, your doctor may prescribe other medications to help with specific symptoms – **only take medications that are approved by your OAT doctor**. If you're on a medication prescribed by another doctor, your OAT doctor needs to approve it because it could interact with the buprenorphine/naloxone or methadone.

Substances that make you relaxed or sleepy can be dangerous. This includes:

- Alcohol, opioids, and benzodiazepines (e.g., Ativan®, Valium®, Xanax®, Restoril®, etc.).
- Antihistamines, cold medications, and sleeping pills (such as, but not limited to, Gravol™, Benadryl®, Nyquil™, Benlyn®, or Tylenol® PM, zopiclone).
- Certain types of antidepressants and tranquilizers.

Even certain antibiotics can be dangerous as they block the breakdown of methadone in the body. **Make sure to check all your medications with your OAT doctor.**

What if I feel like I still need to use other opioids while starting OAT?

If you feel like you need to use other opioids in addition to the OAT medication, particularly while at a lower methadone dose, talk to your doctor about this honestly at every visit. Your doctor understands that your buprenorphine/naloxone or methadone dose may not last 24 hours in early treatment. Knowing that you are using other opioids and how much, will help your doctor to increase your OAT medication dose as needed, while being safe. Your doctor can also help you to determine the safest way to use additional opioids if this is needed. **However, if you can cope with your OAT dose only, that is the safest option.**

Isn't OAT, especially methadone, supposed to make you sleepy?

No. You are supposed to feel normal on your OAT medication, not high or sleepy. This applies to both buprenorphine/naloxone and methadone. When taken as prescribed by your doctor, OAT medications build up slowly in your system and should not make you feel drowsy. You should take the following precautions to help the clinic staff keep you safe:

- Take your OAT at the same time each day.
- See your doctor or case manager at least once a week for the first two weeks. (Many clinics will require visits that are more frequent.)
- Discuss your OAT treatment with a close friend or family member. If they see that you are drowsy, they must call your OAT doctor or 911.
- Discuss naloxone kits with your doctor and with a close friend or family member. Make sure you and your friend/family know how and when to use naloxone (your doctor or trained clinic staff can teach you this).

I'm starting methadone...What are some of the symptoms if my dose is too high?

- You may feel sleepy and nod off several times during the day.
- You may be forgetful.
- You may be difficult to wake up from your sleep.
- You may experience slurred speech, stumbling walk, or appear drunk.

If these things are occurring, you must call your doctor immediately and call 911 for help.

I've been offered a small amount of methadone by a methadone patient at the pharmacy. This can't hurt – I know I need 80 mg?

Above all, don't take any extra methadone! What is safe for your friend could be lethal for you. It may be true that you took 80 mg **once** and were okay. If you had taken 80 mg every day for three or four days, you might have overdosed. Remember, it takes *five or more days* for a certain dose to build up in your blood.

Appendix D

OAT TREATMENT AGREEMENT & CONSENT FORM

Adapted with acknowledgment and permission from Manitoba Programs including MOST, HSC, & OCN

The prescribing and dispensing of methadone/Suboxone/Sublocade is regulated by provincial guidance documents, as well as policies unique to this Opioid Agonist Therapy (OAT) Program.

This treatment agreement has been prepared to both inform you about opioid agonist therapy, as well as to document that you agree to the rules/obligations contained in this agreement.

ACKNOWLEDGEMENTS

I acknowledge that:

- 1) Methadone and buprenorphine (Suboxone/Sublocade) are opioids (opioids are drugs like heroin, codeine, morphine, oxycodone, hydromorphone, fentanyl, etc.), and that I will develop a physical dependence on the medication. Sudden decreases in dose or discontinuation of this medication will likely lead to symptoms of opioid withdrawal.
- 2) I am already physically dependent on at least one opioid, and I am unable to discontinue the use of opioid(s).
- 3) I have had the opportunity to review and determine whether abstinence-based treatment is appropriate for me.
- 4) Taking any mood-altering substance with OAT medications can be dangerous. There have been reported deaths caused by the combination of medications with alcohol, opioids, cocaine, barbiturates, and/or tranquilizers.
- 5) It is important to inform any physician/dentist who is prescribing any other medication(s) that I am taking an OAT medication.
- 6) My DPIN history (pharmacy record) will be reviewed on admission to prevent potential adverse drug interactions. For safety reasons, my DPIN may be reviewed periodically while I am on the program.
- 7) I may voluntarily withdraw from the OAT program at any time.
- 8) Regarding pregnancy, I understand that the newborn baby may experience opioid withdrawal as a result of my methadone/buprenorphine treatment. This withdrawal is usually mild, but if more severe, specialized care may be required for some days after birth. For this reason, I am aware that I may be required to deliver away from my hometown, in a hospital able to provide an elevated level of care.

- 9) If my treatment team and I decide to switch to Sublocade (buprenorphine extended-release injection), I understand that is not considered safe to receive Sublocade injections while pregnant. My treatment team will rule out pregnancy before administering Sublocade and will require me to use a reliable fertility control method for the duration of my Sublocade treatment.
- 10) It is unsafe to drive a motor vehicle or operate machinery during the stabilization period after starting methadone/Suboxone/Sublocade and during dose adjustments. My OAT prescriber will advise me when it is safe to drive after starting methadone/Suboxone/Sublocade and during dose adjustments.
- 11) The common side effects of methadone are sweating, constipation, decreased sexual function, drowsiness, increased weight, and water retention. These are usually mild and can be lessened with help from my OAT prescriber. Methadone can cause serious cardiac arrhythmias (irregular heartbeat), particularly at high doses. Methadone can also cause long-term hormonal changes that may increase risk of osteoporosis. Suboxone/Sublocade has similar but milder side effects.
- 12) I acknowledge that my OAT prescriber is not my family doctor/primary care provider.
- 13) Treatment will be tapered and discontinued if my physician determines that it has become medically unsuitable (i.e., the treatment is not effective, or I develop a medical condition that could make further methadone/Suboxone/Sublocade administration unsafe).
- 14) Treatment may also be tapered and discontinued if my physician determines that continuing treatment poses a risk to the community (i.e., I am selling or giving away my medication).
- 15) I acknowledge that the cost of my medication (methadone/Suboxone/Sublocade) is my responsibility if I do not have medication coverage in place, for example through EIA, FNIHB, or a private medication insurance plan.

BEHAVIOR WHILE AT THE CLINIC & PHARMACY

I understand the following behavior is not acceptable in the clinic or pharmacy, and may result in the termination of treatment:

- 1) Any violence or threatened violence directed toward staff or other clients.
- 2) Disruptive behavior in the clinic or the surrounding vicinity of the clinic.
- 3) Any illegal activity, which includes selling or distribution of any kind of street drug or substance or prescription drug, in the clinic or the surrounding vicinity of the clinic.
- 4) Any behavior that disturbs the peace of the clinic or the surrounding vicinity of the clinic.

- 5) Illegal activity or disruptive or threatening behavior at the pharmacy.
- 6) Any diverting, selling, or misuse of methadone/Suboxone/Sublocade.

I agree to maintain positive, respectful behavior towards other program clients and staff at all times when in the clinic and pharmacy. I understand that threats, racist or sexist remarks, physical violence, theft, property vandalism or mischief, the possession of weapons, and selling, buying, or distributing illicit substances while on clinic property are extremely serious program violations and may result in the termination of my treatment.

OBLIGATIONS OF BEING ON THE OAT PROGRAM

I agree to:

- 1) Take only one dose of methadone/Suboxone a day unless additional doses are prescribed for use, and to have the ingestion of my dose witnessed on those days that I don't have take-home doses of methadone/Suboxone (carries).
- 2) Inform any prescribing physician or dentist who may treat me for any medical or psychiatric condition that I am receiving methadone/Suboxone/Sublocade, so that my treatment can be tailored to prevent potentially dangerous interactions with methadone/Suboxone/Sublocade.
- 3) Provide a urine sample for a drug screen when I receive a prescription for methadone/Suboxone/Sublocade or when I am asked to do so by program staff.
- 4) Recognize that failure to provide a urine sample will result in my record being marked as a sample assumed to contain drugs other than my prescribed medication(s) and this could reduce the number of carries I receive.
- 5) Not tamper with my urine sample. To tamper with my urine sample in any way is a serious violation of the program, and it may affect my future status in the program.
- 6) Keep all my appointments with the OAT prescriber. Repeatedly missing appointments may result in reduction of my carry doses, changes to my prescribed medication(s), and could interfere with the prescriber-patient relationship. The prescriber is not obligated to supply a prescription without an in-person assessment.
- 7) Have my methadone/Suboxone dose witnessed by my nurse or pharmacist 7 days per week until stability has been determined by the treatment team, unless otherwise directed by the treatment team.
- 8) To attend the clinic for administration of my Sublocade injection by my doctor or a program nurse (if applicable). In some cases, a program nurse may visit my community (at a nursing station or other medical space) to administer my Sublocade injection there.

OBLIGATIONS FOR DOSING & SAFETY

I understand that I will not be given a dose of methadone/Suboxone/Sublocade if:

- 1) I appear to be intoxicated or under the influence of some other substance. I may be asked to see a physician, nurse, or pharmacist for assessment before receiving my medication. For my own safety, I may be asked to return later to receive my dose or be refused a dose for that day.
- 2) I arrive late, after my pharmacy's dispensing hours. **NO EXCEPTIONS!**
- 3) I exhibit threatening or disruptive behavior towards any staff member or another patient at the clinic or pharmacy.
- 4) I do not show proper identification before receiving methadone/Suboxone/Sublocade, if asked for identification.
- 5) I miss three or more doses of methadone or miss five or more doses of Suboxone in a row (the dose of medication needs to be lowered after multiple missed doses in a row).
- 6) I am late for my Sublocade injection, my treatment team will provide me with instructions on how to proceed in order to resume treatment.

I further understand that OAT is most effective when combined with psychosocial interventions (participating in activities that can improve my mind, health, and life) and clinic staff will encourage participation in things like:

- Individual or group counselling,
- Peer-support or self-help groups,
- Formalized treatment programs, and/or
- Working on personal goals related to my health, family, work, school, etc.

OBLIGATIONS FOR TAKE-HOME DOSES (CARRIES) & SAFETY

I agree that:

- 1) Methadone and Suboxone are potent medications. **A single dose taken by a person who is not used to taking opioids can be fatal, especially if taken by a child.** For this reason, I agree to store take-home dose(s) in a locked box, in a location where it is unlikely to be stolen or accidentally taken by another person. For methadone, an ice pack can be included in the box to keep the liquid/juice fresh.
- 2) The number of take-home doses I receive will be decided by my prescriber, with input from the clinic staff (e.g., OAT nurse, counsellor, and pharmacy staff) as my treatment progresses.

- 3) I will not give, lend, or sell my take-home dose(s) to anyone.
- 4) I will consume the methadone/Suboxone on the dates specified on the medication label and in the appropriate manner – that is, a full dose is taken within 24 hours.
- 5) I will return all empty methadone/Suboxone bottles to the pharmacy, on my next day back at the pharmacy after receiving take-home dose(s).
- 6) Take-home doses will **only** be given if I provide urine screens as requested by my OAT prescriber or nurse.
- 7) If an appointment is missed and a prescription runs out, I may be asked to attend the clinic in-person before a new prescription is given. Most commonly take-home doses of methadone/Suboxone will also be restricted.

CIRCLE OF CARE CONSENTS

I hereby give my consent for the following:

- For my OAT prescriber to speak to any other doctors or healthcare professionals involved in my care, regarding my care. I understand this is very important to ensure my safety, especially around medication use.
- For OAT clinic staff to speak to pharmacists or other health care providers to verify my recent methadone/Suboxone dose(s), which I received in another pharmacy or institution, and to communicate appointment information. Nurses, therapists, and other OAT clinic staff follow PHIA (Personal Health Information Act) and clinic policies regarding privacy and may ask for specific signed consents as necessary.
- For OAT clinic staff to review my DPIN (pharmacy prescription record) as deemed necessary by staff. I am aware that a DPIN will be reviewed on upon intake into the program and intermittently while on OAT to prevent potential adverse drug interactions.

CONFIDENTIALITY

Everything that you tell OAT clinic staff is confidential (private) and protected by PHIA. However, it is important to realize that there are some exceptions to this rule of confidentiality. Under exceptional circumstances clinic staff may have to report something you share to the appropriate authority. This can occur under the following circumstances:

- If we suspect that a child is at risk of emotional or physical harm or neglect – it is the law that we report this information.

- If you become suicidal, homicidal, or are unable to take care of yourself due to a medical or psychiatric condition, you may be held to be assessed by an emergency room physician or psychiatrist against your will.
- If you reveal to staff that you intend to harm another person, we will be obliged to protect that person by notifying the appropriate authority.
- If a court subpoenas your medical chart, we must release it in accordance with the subpoena.
- If it is suspected that you are unable to safely drive an automobile due to a medical condition (which includes intoxication from alcohol or drugs), we are obliged to notify the appropriate authority.
- Certain infections must be reported to the local public health department.

AGREEMENT & CONSENT

My signature below indicates that I understand and agree to the information contained in this treatment agreement, including my personal responsibilities while participating in treatment. Should I fail to meet the terms of this agreement, I understand that I may be discharged from the Opioid Agonist Therapy (OAT) Program.

I also agree to respect the confidentiality of other clients in the program.

I have had an opportunity to discuss and review this agreement with my OAT prescriber and my questions (if any) have been answered to my satisfaction.

Client Information & Consent

Name (PRINT)

DOB (D/M/Y)

Patient Signature

Date (D/M/Y)

OAT Prescriber Information

Physician Name (PRINT)

Physician Signature

Date (D/M/Y)

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.4 Recommendations for the Ongoing Care of Individuals on Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Once the induction and early stabilization phases of treatment have been completed, the patient is typically on a stable daily dose of opioid agonist therapy (OAT) and enters the maintenance phase of treatment. During the maintenance phase, treatment goals shift from early engagement and medical stabilization to the ongoing work of recovery. Appointments are spent managing all the biopsychosocial components of addiction treatment, with an overarching goal of establishing and nurturing clinical stability.

This section addresses key features of assessment and ongoing care during the maintenance phase of treatment. Several common issues that may arise as patients navigate life, while participating in OAT, are also discussed. Specifically, recommendations are provided for dose optimization, split dosing, rapid metabolism, prolonged QTc, missed doses, vomited doses, and rotation between different OAT medications.

SPECIFIC RECOMMENDATIONS

ASSESSING CLINICAL STABILITY

The following issues should be reviewed at follow-up appointments to assess and support clinical stability. In the earlier maintenance phase, a structured approach to follow-up will ensure that no important issues are neglected. Most issues on the list below should be reviewed at each appointment and are addressed throughout this chapter.

- 1) OAT Dose
- 2) Potential Side Effects
- 3) Current Substance Use

- 4) Urine Drug Testing (UDT)
- 5) Medication Review
- 6) Psychological Stability
- 7) Physical Health & Pain Management
- 8) Sexually Transmitted and Blood Borne Infection (STBBI) Screening
- 9) Social Stability
- 10) Treatment Goals
- 11) Revisit the Treatment Agreement

However, as the patient progresses in treatment and increasingly re-engages in healthy activities of daily living, follow-up appointments may be used to address the most pressing issues the patient and provider wish to discuss. Some follow-up appointments may simply be used to check in on the patient's life and to further strengthen the therapeutic alliance, often by highlighting the treatment goals realized over time.

1) OAT DOSE

The goal is to establish a stable dose of OAT medication. A stable dose is achieved when opioid withdrawal is eliminated or adequately suppressed for a complete 24-hour period following the dose, allowing patients to further engage in ongoing medical and psychosocial treatment. At a stable dose, drug cravings should be under control. The patient will likely still have regular thoughts about using (*this is very normal in early treatment*), but they should not experience regular, intense, and "physical" cravings for opioids. Opioid use will have stopped or be dramatically reduced.

The right OAT dose achieves these clinical goals without causing daytime sedation or excessive tiredness, and with minimal or at least manageable side-effects. Tolerance to common side-effects often develops over time, and reassuring patients of this in early treatment can be helpful.

Buprenorphine Dose Stability

A stable dose of buprenorphine/naloxone may be reached within the first few days of induction, but sometimes further small adjustments are required later in treatment. If it becomes apparent that withdrawal symptoms are breaking through prior to the next dose, further increases may be required. Dose increases of **2 to 4 mg may be needed up to 24 mg daily**. At this later stage of treatment, depending on the severity of withdrawal symptoms or the extent of opioid use, dose increases are typically smaller with longer intervals between increases. **A one-week interval between smaller dose adjustments allows for adequate serum accumulation to fully assess the effect of each increase.**

In some exceptional circumstances (for instance patients with higher opioid tolerance), dose increases up to an absolute maximum of 32 mg daily may be useful. It is important to note the clinical benefit associated with dose increases beyond 24 mg is significantly diminished. Therefore, if a patient does not actually benefit from increases beyond 24 mg daily, the increases should be reversed.

For patients who do identify benefit from doses between 24-32 mg daily early in treatment, it is important to later attempt a slow trial of tapering down to 24 mg after the first 6 to 12 months in treatment. Patients are often able to thrive on a lower dose once they have benefitted from treatment for an initial period. Reducing the dose to within a normal dose range may minimize side effects and the common medical complications associated with long-term opioid use.

Discomfort Despite Dose Stability

Some patients will continue to report feeling unwell, despite being at a clinically stable dose of OAT. Such distress may be described as ongoing craving, or feeling “not right”, or “not comfortable in my own skin”. It may also manifest as ongoing drug use, including intermittent opioid use. It is important to understand *if these feelings/behaviors are consistently present, or more episodic* and related to circumstantial or emotional triggers. For example, running into previous contacts or friends associated with drug use, or the emotional upset tied to any number of normal life experiences. Consider if an underlying mental health disorder may need to be addressed.

Generally, once withdrawal is eliminated further dose increases are rarely effective in addressing this type of discomfort, which can manifest psychologically and physiologically. Behavioral change and counselling interventions may be more effective strategies to support patients in coping with the stress and distress of early sobriety. **It is important for providers to remember that not all forms of discomfort can be addressed with medication.** A consistent strategy of non-judgmental support, framed by predictable boundaries, is often the best treatment plan. The section on [Managing Co-Occurring Psychiatric Disorders](#) offers detailed guidance to help determine if mental health symptoms are a natural part of the recovery process in opioid use disorder (OUD) or rather indicative of a psychiatric disorder requiring specific medication or psychotherapy.

Some patients, particularly those with long-standing and/or high-dose use of potent opioids, may not achieve a dose of buprenorphine/naloxone that eliminates withdrawal symptoms and significantly reduces ongoing opioid use. Such patients may need to consider switching to a different opioid agonist. Methadone has been found to be more effective in some circumstances. For inexperienced prescribers, consultation with an experienced prescriber may be helpful for advice. Transitioning from buprenorphine to methadone is discussed later in this chapter (see [ROTATION OF OAT MEDICATIONS](#) below).

Methadone Dose Stability

While buprenorphine/naloxone often allows for more rapid dose titration, **methadone induction and titration MUST be approached slowly and cautiously**, as recommended in [Methadone Induction, Titration, & Stabilization](#). It may take several weeks to address opioid withdrawal effectively. It is important to be upfront with patients about this requirement and to discuss ways to cope with ongoing withdrawal and cravings, to help maintain engagement in treatment. Again, a stable dose is achieved when opioid withdrawal is eliminated or adequately suppressed for 24 hours, to allow patients to further engage in ongoing medical and psychosocial treatment. In the later stages of treatment most patients have substantially reduced opioid use, they are largely tolerant to methadone, and experience no withdrawal symptoms for most of the day.

With experience, prescribers can typically establish a stable dose for many patients within four to eight weeks of initiating methadone. The stable dose range for most methadone patients is 50-120 mg, however **the focus should be on clinical indicators of stability, not the dose**. Patients may occasionally ask for dose increases because of episodic subjective withdrawal symptoms, opioid cravings, or a relapse to opioid use. During the maintenance phase, or if the dose is 80 mg or higher, dose adjustments are **typically between 3-5 mg every three to seven days**. Patients who use high-potency opioids (e.g., fentanyl) regularly, may require higher overall doses and larger dose increases for stability.

Given the high degree of variability in methadone pharmacokinetics and metabolism, "the optimum methadone dose can vary significantly between patients, necessitating careful, individualized dose titration as opposed to standardized dosing regimens"¹.

Lower Methadone Doses (Below 50 mg)

Some patients stabilize at lower-than-average doses. Low maintenance doses may be suitable for some patients, such as those with lower opioid tolerance and a contraindication to buprenorphine/naloxone, or intolerable side-effects on buprenorphine/naloxone.

Some patients may choose methadone treatment despite education about the benefits of buprenorphine/naloxone. This may be due to past treatment success on methadone, or familiarity with methadone treatment due to a close family member or friend on methadone.

Treatment should not be withheld when a patient specifically requests methadone. If the patient has received adequate education about the benefits of buprenorphine/naloxone, methadone is a reasonable second-line treatment option.

Methadone doses below 50 mg are generally less effective than higher doses at reducing high-potency opioid use and retaining patients in treatment¹.

Higher Methadone Doses (Above 120 mg)

Patients may require maintenance doses above 120 mg either due to a higher innate tolerance secondary to long-standing or high-potency opioid use, or increased metabolism of methadone secondary to certain conditions or medications (see [Rapid Metabolism & Serum Levels](#)).

Patients on higher doses should be granted dose increases if they *consistently* report a cluster of withdrawal symptoms that occur at a predictable time at the end of a dosing interval. The cluster should include both physical and psychological symptoms. Assess the patient for other conditions that are commonly confused with withdrawal symptoms (also see [Discomfort Despite Dose Stability](#) section above).

Patients with particularly high tolerance of high-potency opioids (e.g., injecting or smoking primarily illicitly sourced fentanyl) may require higher doses for stabilization and treatment retention and/or [Alternative Treatment Approaches](#) to care. **Consultation with an addiction medicine specialist should be sought to best support these patients**, particularly if patients continue to have difficulty stabilizing on doses around 150 mg.

Tapering Methadone Doses

For patients who do benefit from higher doses of methadone, it is important to attempt a slow trial of tapering to a lower dose, after the first 12 months in treatment. Patients are often able to thrive on a lower dose once they have benefitted from treatment for an initial period. Reducing the dose in such cases will minimize side effects and common medical complications associated with long-term high-dose opioid use.

Clinically, some patients report feeling more alert and energetic after tapering from higher doses, and some can decrease their dose by 20-40 mg with relative ease, over time. Dose reductions should be *no more* than 5-10% of the total remaining dose every one to two weeks. The taper should be held or reversed if the patient reports persistent and uncomfortable withdrawal symptoms, to avoid risk of destabilization or relapse, even if the dose is >120 mg.

Taper attempts should also be considered in elderly patients, given age-related changes to metabolic, cardiac, respiratory, and cognitive functions. Prescribers should review the clinical picture with ageing patients to determine if a trial of a slow taper to a lower dose would be beneficial. See [Recommendations for Older Patients](#) for further guidance.

Methadone Split Doses

Split dosing should be considered rarely, in select patients, and a thorough clinical assessment is required when evaluating potential indications for split dosing. This should include review and documentation of the risks and benefits of split dosing, discussed in collaboration with the patient. **Inexperienced prescribers are strongly advised to seek expert guidance.**

If a trial of split dosing is warranted, collaboration with pharmacy is essential to discuss the indication and practical implications for pharmacy attendance/take-home doses. Further to this collaboration, the prescriber must be clear on the prescription as to which doses (i.e., AM and/or PM doses) are expected to be witnessed and take-home doses.

In determining if a trial of split dosing is appropriate in the community setting, the OAT prescriber should consider:

- The overall stability of the patient,
- The number of regular take-home doses,
- The nature and duration of the patient’s condition/indication for split dosing,
- The patient’s overall mobility, and
- Public safety, including the safety of other adults and children in the home.

Split dosing is *rarely recommended* in patients without sufficient clinical stability to earn take-home doses, as split dosing in such patients would require multiple trips per day to the pharmacy, which is usually impossible or impractical.

There are three *possible* clinical indications for split dosing:

- **Patients with pain:** Patients typically experience analgesia from methadone in the first 6-8 hours immediately post-dose and split dosing can be considered in *clinically stable* patients who suffer from chronic pain. **This should only be considered as an adjunct if all other non-opioid/non-pharmacological modalities of treatment are not effective or appropriate.**

In certain situations, clinically stable patients who suffer from acute or post-operative pain may also benefit from temporary split dosing. However, once the pain is improved/resolved, once-daily dosing should be resumed. The section [Managing Acute, Chronic, & Perioperative Pain](#) provides detailed recommendations for managing pain in the context of OAT. Inexperienced providers are strongly encouraged to consult with an addiction medicine specialist when considering split dosing for pain.

- **Pregnant patients:** Dose increases may be required during pregnancy as the body and metabolism change, particularly in the third trimester and especially in pregnant patients on methadone. Some patients may report ongoing withdrawal symptoms in the evening or overnight despite dose titration, and split dosing may be effective in addressing this scenario. Typically, the smallest dose that eliminates withdrawal is prescribed as the second dose in this context. Patients in the third trimester must be assessed regularly by the treatment team to ensure appropriate and timely dose adjustments are made, including split dosing if required. See the [Treatment of OUD in Pregnancy](#) chapter for further guidance.

- **Rapid metabolizers:** Split dosing can also be considered in patients with clinically relevant symptoms of rapid metabolism, or those who take medications known to significantly induce methadone metabolism (see **hepatic inducers** section of [Methadone Pharmacology](#)). Consultation with an experienced prescriber and/or pharmacist is recommended. See section below for further details.

Rapid Metabolism & Serum Levels

Rapid methadone metabolism may occur in a small portion of patients, who otherwise would be expected to stabilize but continue to experience withdrawal near the end of their 24-hour dosing interval. While most patients will tolerate and adjust to this mild withdrawal, some require further investigation and intervention if suitable, such as split dosing or switching to other treatments (e.g., buprenorphine). Consulting with an experienced OAT prescriber can be helpful to navigate such cases.

Rapid metabolism is clinically suspected when patients on methadone report sedation or early signs of methadone toxicity at the dose peak (typically 2-4 hours after dosing), and then experience withdrawal at the end of the dosing interval the following morning.

It may be clinically useful for OAT providers to schedule a time to observe the patient when the emergence withdrawal can be witnessed – this should occur following a *witnessed* dose at a *confirmed* time. Similarly, if post-dose sedation is reported as part of the issue, arrange a visit to assess for sedation when peak methadone levels are anticipated, typically 2-4 hours after a *witnessed* dose. The patient's pharmacist may be able to assist in this process (e.g., confirming the time of the preceding witnessed dose).

In these situations, further dose increases risk the patient developing more pronounced methadone toxicity, or even overdose.

If clinical observation and collateral information raises suspicion of rapid methadone metabolism, serum methadone levels should be ordered when possible and available². A peak/trough ratio of > 2:1 may be indicative of rapid metabolism. **However, it is important to note that peak/trough levels are not a definitive measure of rapid metabolism in all patients, given the high degree of variability in methadone pharmacokinetics and metabolism. Assessment of the patient's whole clinical picture is needed to effectively determine if rapid metabolism is contributing to their difficulty stabilizing.**

Collecting accurate peak and trough serum methadone levels also requires planning and pharmacy collaboration:

- Arrange for three to five consecutive days of *witnessed* ingestion of methadone at a consistent time of day.
- Draw the trough level just before the next scheduled ingestion.
- On the same day, draw the peak level approximately four hours post dose.

These written instructions, along with local laboratory locations and operating hours, should also be provided to the patient to assist them in the process. Calling the lab to discuss what is desired, may also facilitate accurate results.

2) POTENTIAL SIDE EFFECTS

Asking patients about possible side effects at follow-up appointments and addressing their concerns through reassurance, education, and medical management promotes treatment adherence and retention. Nausea, constipation, fatigue or drowsiness, headache, sweating, and sexual dysfunction are the most common side effects. Asking about these routinely and normalizing the experience can facilitate discussion around topics that patients may find uncomfortable to bring up.

Side effects are often dose-dependent, so a dose reduction may be appropriate management. However, if a dose reduction would put the patient's stability at risk, medical management with other medications or lifestyle strategies may be preferred. See the respective [ADVERSE EFFECTS & MANAGEMENT](#) sections of the chapters on [Buprenorphine Pharmacology](#) and [Methadone Pharmacology](#) for a practical approach to managing common side effects.

3) CURRENT SUBSTANCE USE

Review current substance use patterns during follow-up appointments, including checking on substance use disorders in early remission. Brief motivational interviewing techniques can be effective to highlight successes and create awareness of how ongoing substance use is impacting the patient's life or stated goals. Support the patient to set manageable goals for change, however small they may be. Asking them to actively track substance use in a private journal can be insight building and a small step toward change. See [Managing Polysubstance Use](#) for further guidance.

Remember that relapse is a common and normal part of substance use disorders as chronic diseases, and that periods of instability are manageable. For patients in early remission, discuss practical relapse prevention strategies. Additional supportive counselling and/or mutual-help groups can also be effective ways to support behaviour change and early remission.

4) URINE DRUG TESTING

UDT should be performed at most assessment appointments. Under certain circumstances, practitioners may also opt to perform a pill/bottle count at appointments if there is concern about diversion of take-home medications.

See the [Use of UDT in the Management of OUD](#) for a general approach to testing, including the recommended frequency and important issues to consider when interpreting results.

An advantage of using point-of-care UDT cups/strips is the immediate availability of results. This allows for open discussion with the patient at the time of the appointment, rather than when results are received from the laboratory at a later date. This is particularly useful if results are unexpected or suggest illicit substance use, as it allows for more timely discussion and adjustments to the treatment plan (as needed) during the appointment.

If the appointment is being conducted virtually, the patient may be asked to attend a local lab to submit a sample. Patients may experience practical challenges around attending off-site labs and thus collecting samples in this manner can be more challenging.

5) MEDICATION REVIEW

An important component of the OAT intake assessment is establishing a plan for managing other sedating/psychoactive medications prescribed to the patient starting OAT. This plan often involves ongoing tapers or medication adjustments to simplify polypharmacy regimens over time and reduce/control the use of less desirable medications such as benzodiazepines/Z-drugs.

Ongoing care appointments are ideal opportunities to review the medication management plan with the patient, stay on track with planned tapers, and discuss/address any difficulties that may arise. See [Managing Polypharmacy, Benzodiazepines, Alcohol & Polysubstance Use](#) for discussion of issues related to medication management, specifically [AN APPROACH TO POLYPHARMACY IN THE CONTEXT OF OAT](#).

6) PSYCHOLOGICAL STABILITY

The patient should be periodically assessed for co-occurring mental health symptoms, possible mental health conditions, and the ability to emotionally regulate while navigating life stressors. When the patient is no longer experiencing the cycle of intoxication and withdrawal, symptoms of anxiety, depression, and insomnia may improve spontaneously over time. Many of these symptoms may have been related to withdrawal symptoms and the feelings of helplessness and desperation that accompany active substance use disorder. Conversely, previously unrecognized mental health issues that were masked by drug use may become more apparent in time.

Know Resources & Refer

Once the patient has established trust with their care providers, they may be more forthcoming with other issues, so ongoing assessment and treatment planning are crucial. Appropriate pharmacotherapy and referral to culturally appropriate and trauma-informed counselling services may be indicated. Practitioners should be familiar with local resources for counselling services, e.g., CBT, DBT, and services with a focus on trauma recovery. Many patients new to treatment also benefit from focused work to build emotional regulation and distress-tolerance skills.

Referral for psychiatric consultation, with psychiatry services knowledgeable about substance use disorders, should be considered in more complex cases.

Peer support networks such as 12-step groups and alternatives can also be valuable support to patients in recovery. Remind patients that working on self-care and coping skills are the building blocks of recovery, along with participation in OAT.

See [Managing Co-Occurring Psychiatric Disorders](#) for further insight on navigating mental health issues in patients with OUD.

7) PHYSICAL HEALTH & PAIN MANAGEMENT

Patients starting OAT often suffer from undiagnosed physical health problems that have been neglected in the context of living with OUD. Practicing self-care is a cornerstone of recovery and referral to primary care can assist in facilitating routine medical care if the OAT provider does not offer primary care services.

Pain management issues form part of the scope of practice of OAT providers, and as such, they need to play an active role in the management of acute, chronic, and peri-operative pain for patients on OAT. See [Managing Pain in OAT](#) for specific guidance in this topic.

8) STBBI SCREENING

OAT providers must offer comprehensive screening for STBBIs to all patients with OUD. Initial and intermittent STBBI screening, including treatment referrals as appropriate, form an important part of ongoing OAT care. This can occur periodically after intake, based on ongoing risk assessment. Initial intake screening should include testing for HIV, hepatitis A, B, and C, as well as syphilis, chlamydia, and gonorrhea, including throat and rectal swabs if indicated.

Patients at significant and ongoing risk of infection should be offered STBBI screening every 6 to 12 months. Repeat testing may be customized based on individual risk factors. Please see the chapter [Prevention, Screening, & Management of HIV & Hepatitis C in Individuals with OUD](#) for further guidance.

9) SOCIAL STABILITY

Advocacy and practical support around psychosocial issues is an important part of ongoing OAT care. This includes issues related to relationships with family and friends, housing, finances, transport, employment, education, medication coverage, and navigating social services.

Support and referral to other agencies should be provided as needed.

10) TREATMENT GOALS

Goals of treatment should be reviewed periodically. It can also be useful to identify short- and long-term goals with the patient. It is important to recognize that the provider's goals of treatment may not be the same as the patient's goals or priorities. Cessation of drug use or complete abstinence from non-prescribed substances may be a later goal along the treatment continuum, or it may not be realistic or achievable for some patients, but they can still benefit from harm-reduction and involvement with the OAT program. Patient goals should be documented and honored in a non-judgmental fashion.

Discussing the patient's goals in a supportive manner can contribute to patient buy-in when addressing the provider's treatment goals. Collaboration, finding common ground, and celebrating small gains is the foundation of an effective therapeutic relationship.

11) REVISIT THE TREATMENT AGREEMENT

Reviewing adherence to the treatment agreement keeps safety, mutual expectations, and boundaries at the forefront of care. The fundamentals of succeeding in treatment include:

- Attendance at appointments as scheduled.
- Attendance for UDT at the agreed upon frequency.
- Regular attendance at the pharmacy for witnessed doses and to receive take-home doses, as applicable.

Revisiting these expectations and why they are important is time well spent with patients. Review the schedule of take-home doses with the patient and assess whether this should be adjusted. Discuss the reason for changes in a transparent manner.

Treatment agreements are effective tools to review behavioural/safety expectations with patients when initiating OAT and throughout the course of care, particularly if concerns arise that may warrant changes to the treatment plan. See the [Comprehensive Assessment](#) chapter section on treatment agreements for further guidance. If the patient is not adhering to the treatment agreement, explore barriers and potential solutions. Consider whether this might be due to an active substance use disorder, work/life responsibilities, or other reasons that need to be addressed.

The Continuum of Stability

Patients engaging with OAT care will present along a continuum of clinical stability. The same patient's stability may also change over time. Even when patients are not achieving many of the treatment goals identified and promoted by providers, clinically unstable patients can still benefit from OAT care from a harm reduction perspective.

In the extremely unstable patient, the provider may truly question if the patient is benefitting from treatment. If this is the case, an overall more in-depth risk-benefit assessment can be conducted to decide if treatment should be continued. This risk-benefit assessment, decision, and the associated risks should be documented. When in doubt, a second opinion from an experienced colleague should be sought and documented as well. Seeking input from the pharmacy team may also provide a valuable additional perspective, as pharmacy staff typically see the patient more frequently. See [Discontinuing Treatment](#) for guidance on managing safety concerns in unstable patients and recommendations around involuntary withdrawal of treatment.

FREQUENCY OF ASSESSMENTS

The frequency of assessments will vary according to the stability of the patient and any changes in management that need to be monitored. In the initial months of treatment, appointments at intervals of one to four weeks are often required. More frequent appointments will be needed when the patient is unstable or when treatment changes are made.

For the most stable patients, with no changes in treatment, follow-up appointments every three months are appropriate. Clinical judgement should be applied.

Patients may have difficulty attending regular in-person appointments in certain situations, such as:

- Rural and remote living where geographic distance and transport are barriers,
- Health or mobility issues that make attendance at the clinic difficult,
- Work or childcare responsibilities that make attendance difficult, and/or
- Extreme social instability that interferes with keeping appointments.

Blended Models & Flexibility

The practitioner should be prepared to be flexible and employ novel approaches to providing OAT in the above circumstances, to promote equity in access to care. **This can include a blended model of virtual appointments, on screen and/or by phone, and in-person assessment.** Occasionally, partnerships with local healthcare providers who are willing to assist with in-person assessment may also be a useful strategy. Remember to ask for collateral information from the pharmacist and utilize UDTs that can be submitted at a local laboratory.

Drop-in capacity, if possible, is also a useful strategy to engage patients who struggle to keep scheduled appointments. If feasible, providers should schedule clinics with a combination of booked visits for patients who rely on scheduling appointments around work, childcare, or other responsibilities, and flexible drop-in time to see patients who present without an appointment, and to discuss cases as a team.

Seeking patient input regarding the ideal frequency and type of clinic appointments is also important. Often the final decision is a compromise between what the provider feels is ideal for quality care and what the patient feels they can reasonably manage.

ECG MONITORING FOR PROLONGED QTc

Methadone and buprenorphine, to a lesser degree, may cause QTc interval prolongation. In rare cases, a prolonged QTc interval can result in serious cardiac arrhythmia (i.e., torsades de pointes).

The Centre for Addiction and Mental Health (CAMH) guideline, [*Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*](#), recommends obtaining an electrocardiogram (ECG) before initiating OAT and throughout ongoing care when monitoring is warranted, however, **lack of access should not be a barrier to receiving OAT**². Providers should use clinical judgment, risk-benefit analysis in collaboration with the patient, and document the rationale for treatment decisions and attempts at obtaining ECGs.

Dose Dependent & Often Multifactorial

The effects of methadone on QTc prolongation are dose dependent. Doses above 100 mg/day are frequently reported in cases of torsade de pointes, and some case reports show that the QTc interval normalizes when methadone is discontinued or reduced in dose³. However, when possible, modifiable risk factors like drug-drug interactions should be rectified first.

The risk of torsade de pointes is often increased when other risk factors for QTc prolongation are present. Collaborating with pharmacists and other care providers around polypharmacy and risk factors can help mitigate the overall risk in patients with concerning QTc intervals. In addition to a higher dose of methadone, other risk factors for QTc prolongation include:

- The presence of other drugs that prolong QT interval,
- Hypokalemia,
- Female sex,
- Advancing age,
- Genetic predisposition,
- Hypomagnesemia,
- Heart failure, and
- Bradycardia⁴.

Frequency of Monitoring

CAMH recommends considering the following conditions when deciding to obtain additional ECGs and to determine frequency of monitoring²:

- Patient has a family history of prolonged QTc or sudden death.
- Patient has had previous arrhythmias/hospitalizations.
- Patient has unexplained symptoms that suggest cardiac involvement (e.g., syncope, presyncope, palpitations, seizure activity, blurred vision without other explanations) or a predisposition to poor cardiac health.
- Patient is initiated on (or already takes) medications known to prolong the QTc interval.
- Patient is using illicit substances known to prolong the QTc interval (e.g., cocaine, methamphetamine).
- Patient develops a medical condition that increases the risk of QT prolongation (e.g., excessive vomiting).
- Methadone daily dose meets or exceeds 120 mg.

For patients requiring higher doses of methadone to stabilize, where daily doses exceed 120 mg, more frequent monitoring of QTc is recommended, if obtaining ECG is feasible. For QTc intervals between 450 msec to 500 msec, review the risks and benefits of ongoing care, monitor more frequently, and consider dose reductions of other QTc prolonging medications preferentially over changes to the OAT medication. Consulting a cardiologist is recommended if the QTc interval exceeds 500 msec².

Benefits of OAT May Outweigh Theoretical Risk

It is important to review the risk and benefits of continued treatment with the patient and collaborate on the best approach. Some patients may elect to accept the theoretical risk of a prolonged QTc over jeopardizing their stability or recovery, particularly if asymptomatic. Discuss transitioning patients on methadone to buprenorphine/naloxone, or possibly slow-release oral morphine (SROM) if buprenorphine is not appropriate. If dose reductions or changes are made, monitor more closely for destabilization or relapse.

If the patient does not wish to alter treatment options, the risk of mortality from non-retention on OAT may outweigh the mortality risk of the prolonged QTc². Clinical judgment should be applied, taking into consideration the patient's wishes. When in doubt, a second opinion from an experienced colleague should be sought and documented as well.

CONSIDERATIONS FOR BUPRENORPHINE EXTENDED-RELEASE FORMULATIONS

Sublocade[®] (buprenorphine extended-release injection, or depot) or Probuphine[®] (buprenorphine implant) can enhance medication adherence and convenience for some patients. These options can be explored with both clinically stable patients and those struggling with stability and/or regular pharmacy attendance (see [MISSED OAT DOSES](#) below).

CAMH notes that there is not yet evidence about the long-term safety and effectiveness of depot or implant buprenorphine therapy and encourages prescribers to review existing evidence to counsel patients accordingly for informed consent². Patients may find these options preferable for less frequent medication administration. If patients switch to depot or implant buprenorphine therapy, consider the overall medication management plan for patients on other sedating/psychoactive medications and determine a reasonable dispensing schedule for these medications.

Other considerations include the patient's comfort with an invasive procedure or device and available medication coverage options².

Depot buprenorphine therapy can be considered in patients stabilized on 8-24 mg sublingual buprenorphine/naloxone daily, for at least 3-7 days. The injection does not require abstinence from other opioids before initiation, but it is preferable. Alternatively, the subdermal implant can be considered in patients stabilized on ≤ 8 mg of sublingual buprenorphine/naloxone daily, noting the implant requires a period of abstinence from opioids before initiation².

MISSED OAT DOSES

Missed doses of OAT (due to patients not attending the pharmacy for witnessed self-administration and possible take-home doses) can indicate a variety of problems that warrant exploration, including:

- Relapse to substance use,
- Psychosocial instability,
- Financial reasons (e.g., the patient is unable to pay for the prescription),
- Limited access to the pharmacy due to geographic distance or mobility issues,
- Limited pharmacy hours,
- Work hours resulting in an inability to attend the pharmacy,
- Lack of transportation, and/or
- Childcare or other caregiver issues.

Pharmacists must report missed doses to the prescriber/clinic staff daily. Missed doses present an opportunity to reach out to the patient and reassess stability, particularly if doses are missed frequently or unexpectedly. The prescriber should explore reasons for missed doses and make every effort to problem solve with the patient. This may include switching to a pharmacy with different hours and/or closer to home, work, school, or even on a more accessible bus route. Re-evaluate take-home dosing candidacy and schedules, depending on patient stability. Note that more flexibility exists with buprenorphine formulations.

Document the patient's reasons for frequently missing doses and potential attempts at solutions. If there has been a significant relapse to substance use, treatment intensification should be offered to the patient, along with discussion of relapse-prevention and harm-reduction strategies.

After 6 consecutively missed days of buprenorphine/naloxone, 3 consecutively missed days of methadone, and 2 consecutively missed days of SROM, the pharmacist will cancel the OAT prescription. A new prescription will be required from an approved prescriber to restart OAT.

Providers should use clinical judgement to determine if in-person assessment by the prescriber or nurse, and/or collateral information from the pharmacist, is indicated to assess withdrawal and recent drug use, and to conduct point-of-care UDT.

Risks of precipitated withdrawal when restarting buprenorphine/naloxone must be weighed against the benefits of resuming OAT as soon as possible. Similarly, when restarting methadone, a risk-benefit assessment based on the unique patient situation should guide decisions about in-person assessment and the best approach to resuming OAT.

Buprenorphine Missed Doses

If the patient is on buprenorphine/naloxone and sufficiently stable, but struggling to attend the pharmacy due to work or family responsibilities, consider accelerating the provision of take-home doses as outlined in [Take-home Dosing Recommendations](#).

Additionally, consider and discuss alternative treatment approaches, as appropriate:

- 1) Alternate-day dosing is an option for patients who are clinically stable at doses ≤ 12 mg/day (e.g., 12mg/day could be prescribed as 24 mg every other day) and who require/desire less frequent visits to the pharmacy for dosing. This approach should be balanced with the challenges of managing missed doses. The patient should be assessed for sedation when given this higher dose and timely communication with the pharmacist is paramount to discuss the plan².
- 2) Consider switching to an extended-release buprenorphine formulation if the main reason for alternate-day dosing is to facilitate fewer pharmacy visits, and if the patient is not a candidate for accelerated take-home doses. Assess and discuss with the patient if switching to the extended-release monthly injection or the six-month subdermal buprenorphine implant would be suitable and preferable.

Given the partial agonist properties of buprenorphine, re-stabilizing a patient after missed doses does not require the same vigilance as for methadone, but prescribers must stay mindful of loss of tolerance to buprenorphine after 6 or more consecutively missed days^{1,2}.

Again, **pharmacists must notify the prescriber/clinic staff of any missed doses daily.**

The following is recommended for consecutively missed daily doses of buprenorphine:

- For **≤ 5 consecutively missed days**, continue the same buprenorphine/naloxone dose. The current prescription remains valid. The pharmacist must report all missed doses to the prescriber/clinic team daily and if providers are able contact the patient, they can advise them to return to the pharmacy as soon as possible to resume buprenorphine dosing *before or by day 6*.

If the patient has relapsed to substance use (of opioids or other substances) offer assessment and treatment intensification as appropriate. With relapse to full opioid agonist use, as the number of missed consecutive daily doses increases, the theoretical risk of precipitated withdrawal also increases. However, experientially, the benefits of resuming buprenorphine/naloxone within this time frame tend to outweigh this theoretical risk, even with resuming dosing on day 6.

- For **≥ 6 consecutively missed days**, the prescription will be cancelled. Encourage the patient to connect with the treatment team when they are able/desire to resume OAT. A new induction will be required using either a [Conventional Buprenorphine Induction](#) or a [Micro-dosing Induction](#), as appropriate. **A new prescription is required for the buprenorphine/naloxone restart.**

After assessing the patient’s response to dosing with the restart, the dose can be increased toward the previous stable dose more rapidly, as applicable, in the absence of other safety concerns and with reassessment as needed.

An approach to missed doses of buprenorphine/naloxone is summarized in the **PRESCRIBING ESSENTIALS** below.

PRESCRIBING ESSENTIALS: MISSED BUPRENORPHINE DOSING APPROACH

Missed Days	Previous Prescribed Dose	Suggested Adjustment
1-5	Any dose	Same dose (no change)
≥ 6	Any dose	Restart buprenorphine/naloxone*

*The pharmacist will cancel the prescription. A new prescription is needed to restart OAT. The pharmacist must report all missed doses to the prescriber/clinic team daily.

For patients on alternate-day dosing of buprenorphine who missed two alternate-day doses, suspend prescribing until the patient can be reassessed. Accordingly, the prescription will be cancelled, and a new OAT prescription is required. The patient should resume daily dosing, possibly at a lower dose, to restabilize before considering return to every-other-day dosing².

Methadone Missed Doses

As outlined above, missed methadone doses may indicate a variety of problems requiring review with patients. Tolerance to methadone is lost rapidly and may occur in as little as three days, so restarting at the previous stable dose may be excessive or dangerous¹.

Again, **pharmacists must notify the prescriber/clinic staff of any missed doses daily.**

The following is recommended for consecutively missed daily doses of methadone:

- For 1 to 2 consecutively missed days, continue the usual prescribed dose, provided there is no other reason (e.g., intoxication) to withhold methadone. The current prescription remains valid.
- **For 3 consecutive missed days, the pharmacist will cancel the methadone prescription and the patient must follow up with the prescriber/clinic team.** Remind patients of this regularly. Before restarting methadone, providers should use clinical judgement to determine if in-person assessment by the prescriber or nurse, and/or collateral information from the pharmacist, is indicated to assess withdrawal and recent drug use, and to conduct point-of-care UDT.

A new prescription is required to restart:

- If the usual dose is ≤ 30 mg, the patient may be continued at the same dose following appropriate assessment.
- **For doses > 30 mg, patients can typically be restarted at 50% of their previous dose.** Generally, the reduced dose should be no less than a starting dose of 10-30 mg. After tolerance to the reduced dose has been demonstrated, the dose can be rapidly increased (by no more than 5-10 mg per day) if daily supervision occurs. Slower dose escalation is suggested for patients with clinical instability and/or concurrent use of alcohol, benzodiazepines/Z-drugs, or other sedative/hypnotics. The patient should be assessed as needed during titration and re-stabilization, and more frequent UDT may be warranted if clinically appropriate.
- **For ≥ 4 consecutive missed days, restart methadone at 30 mg or less.** Again, a new prescription is required. After assessing the patient's response to this new dose, the dose can be increased toward the previous stable dose more rapidly, in the absence of other safety concerns, with reassessment as needed.

The CAMH guideline summarizes an approach to missed methadone doses as outline in the **PRESCRIBING ESSENTIALS** below.

PRESCRIBING ESSENTIALS: MISSED METHADONE DOSING APPROACH²

Missed Days	Previous Prescribed Dose	Suggested Adjustment
1-2	Any dose	Same dose (no change)
3	Any dose	Decrease dose by 50% of previous dose*
≥ 4	Any dose	Decrease dose to 30 mg or less*

*The pharmacist will cancel the prescription. A new prescription is needed to restart OAT. The pharmacist must report all missed doses to the prescriber/clinic team daily.

VOMITED DOSES

Patients may experience nausea as a symptom of withdrawal or as a side effect of OAT, or as a symptom of another medical condition (such as commonly experienced in pregnancy). If changes to OAT medications are considered to manage nausea, the risks to the patient’s stability should be evaluated, and medical management and/or lifestyle strategies may be preferred. Collaboration with the pharmacy is recommended, particularly if considering changes between different brands or formulations of medications.

Buprenorphine, Nausea, & Vomiting

If a patient vomits after their buprenorphine/naloxone is fully dissolved, no replacement dose is indicated, as the dose should be adequately absorbed sublingually.

Very rarely a patient may vomit before the tablets have fully dissolved. If this is witnessed by the pharmacist and it is reasonable to assume that the patient would not have had time to absorb the full buprenorphine dose, the practitioner may exercise clinical judgement and prescribe a replacement dose of 25-50% of the original dose. **Replacement doses require a new prescription.** The prescriber should note on the prescription that it is a “replacement dose”.

If the patient reports persistent nausea which is not related to withdrawal, several strategies could be considered:

- Use of a non-sedating antiemetic prior to taking the buprenorphine/naloxone dose.
- A small dose reduction in the buprenorphine dose, weighed against the potential for destabilization.
- Switching to a different brand, as some patients find taste triggers nausea and the taste varies between brands.
- Switching to a different formulation, e.g., buprenorphine/naloxone film, depot or implant buprenorphine therapy.

Methadone & Vomited Doses

Vomited methadone doses are not replaced unless emesis is *witnessed* by a healthcare provider or support staff. **It is impossible to entirely empty the stomach, even with projectile emesis right after dosing, therefore full dose replacement is *not recommended*.**

Please refer to the [Pregnancy Chapter](#) for specific guidance on vomited doses in pregnancy, as avoiding opioid withdrawal is more critical in this context.

The following is recommended for *non-pregnant* patients:

- If emesis occurs less than 15 minutes after consumption, consider replacing 50-75% of the full dose. If the dose is ≥ 120 mg, consider replacing only 50% of the full dose.
- If emesis occurs at between 15-30 minutes after consumption, consider replacing 25-50% of the full dose.
- If emesis occurs at more than 30 minutes after consumption, do not replace the dose.

After a replacement dose, the patient should be observed for 30 minutes. Repeated dose replacement increases the risk of unexpected overdose. If emesis is a recurrent reason for dose replacement, observing the patient for 15-20 minutes after dosing may be warranted¹. Use of a non-sedating antiemetic prior to dosing may be helpful. Providers may elect to not replace a vomited dose.

All replacement doses require a new prescription. The prescriber should note on the prescription that it is a "replacement dose".

Again, potential underlying causes of the vomiting should be addressed, and dose reductions to offset nausea should be weighed against the potential for destabilization. Sometimes it may be helpful to speak with the pharmacist about trying a different diluent with the methadone concentrate (e.g., apple juice instead of Tang), or switching to a cherry-flavored concentrate that does not require dilution. However, remember that switching between methadone brands should be approached cautiously and in collaboration with the pharmacist. **Methadone products are not interchangeable from a clinical perspective nor a coverage perspective.**

A new prescription from an approved methadone prescriber would be required to switch a patient from one product to another. **Such changes will often require collaboration and communication between the prescriber, pharmacy team, and patient.**

A [safety review completed by Health Canada](#) found that there may be a link between switching methadone-containing products used to treat OUD and the risk of lack of effect, which may present as withdrawal symptoms, although the reason for this is unclear⁵.

OAT providers should be aware that:

- Some patients may experience withdrawal symptoms after being switched from one methadone-containing product to another; these patients should be clinically managed and monitored regularly.
- Dose adjustments may be necessary in some patients.
- Withdrawal symptoms can lead to a failure to remain in treatment and subsequent problematic substance use, which can lead to serious harms.

ROTATION OF OAT MEDICATIONS

Some patients may benefit from transitioning from methadone to buprenorphine/naloxone and vice-versa, for several reasons:

- To manage intolerable side effects, patients may elect to transition between either medication.
- For more flexibility with take-home dosing and to decrease the burden of treatment, patients may elect to transition from methadone to buprenorphine/naloxone, or to eventually transition to depot or implant buprenorphine therapy.
- For safety reasons, if patients become increasingly at risk of overdose, providers may promote transitioning from methadone to buprenorphine.
- To manage withdrawal and cravings more effectively, patients may transition from buprenorphine to methadone, particularly patients with high tolerance and regular use of high-potency opioids.

Collaboration between the prescriber, patient, and pharmacist is required to review the goals of treatment and a transition plan. Recognizing the principle of patient autonomy, while promoting retention in treatment and harm reduction, is essential when making such decisions.

Regardless of the clinical approach taken, this can be a challenging process for patients and can increase risk of relapse. Patients therefore need to be carefully selected and all appropriate options discussed.

Prescribers who are inexperienced with transitions are advised to seek expert guidance for complex situations.

Patients Transitioning from Methadone to Buprenorphine

Transitioning from the full-agonist methadone to the partial-agonist buprenorphine can be challenging. The methadone dose should ideally be gradually tapered to ≤ 30 mg/day, and the patient should be advised to abstain from methadone for 48-72 hours prior to a [Conventional Buprenorphine Induction](#).

Alternatively, patients may transition from methadone to buprenorphine/naloxone using a [Micro-dosing Induction](#), as appropriate, or switching from methadone to SROM (the 24-hour formulation) for five days prior to transitioning to buprenorphine.

Again, this process can be very challenging for patients. The risk of relapse must be discussed with the patient and the discussion documented. Prescribers who are inexperienced with transitioning patients from methadone to buprenorphine/naloxone are strongly advised to seek expert guidance.

Inpatient admission for transitions may be helpful for patients with psychosocial instability, ongoing polysubstance or polypharmacy concerns, or patients with complicated or poorly managed medical conditions. See [In-Hospital Care](#) for details, specifically **PLANNED HOSPITAL ADMISSIONS IN THE CONTEXT OF OUD**.

Transitioning From Buprenorphine to Methadone

Comparatively, transitioning patients from buprenorphine to methadone is less complicated, going from a partial to full agonist. Generally, the first dose of methadone can be administered within 24 hours of the last buprenorphine/naloxone dose¹. Dosing can then follow the guidance for [Methadone Induction](#) for patients with established opioid tolerance, typically 10-30 mg per day for the first three days, and titrated based on assessment of individual patient factors.

The BCCSU guideline summarizes that a “stepped care strategy (i.e., treatment initiation on buprenorphine/naloxone and escalation to methadone if necessary)” is equally efficacious and given the greater safety profile of buprenorphine, it is recommended as first-line treatment¹. Methadone can then be explored as a second-line option for patients as needed, with SROM serving as a third-line treatment option for carefully selected patients. Please see [Alternative Treatment Approaches for OUD Including SROM \(Kadian®\)](#) for detailed recommendations.

IN SUMMARY

The ongoing care of patients on OAT certainly requires investment from the provider and the patient. This work necessitates therapeutic alliance, collaboration, mutual respect, and problem solving, not only between the provider and patient, but along with the whole care team, pharmacy, and community. Providers are encouraged to seek advice from experienced colleagues in challenging situations to optimize patient outcomes, as they navigate the long road of recovery.

References

1. Provincial Opioid Use Disorder Treatment Guideline Committee. *A Guideline for the Clinical Management of Opioid Use Disorder*. British Columbia Centre on Substance Use (BCCSU) and BC Ministry of Health; 2017. Available at: <https://www.bccsu.ca/care-guidance-publications/>
2. Centre for Addiction and Mental Health (CAMH). *Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*. CAMH; 2021. Available at: <https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf>
3. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med*. 2009; 150(6):387-95. doi: 10.7326/0003-4819-150-6-200903170-00103.
4. Trinkley KE, Page RL, Lien H, Yamanouye K, Tisdale JE. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin*. 2013 Dec;29(12):1719-26. doi: 10.1185/03007995.2013.840568.
5. Health Canada. *Methadone Treatment of Opioid Dependence and Potential Risk of Lack of Effect when Switching between Different Products*. Government of Canada; 2020. Available at: <https://recalls-rappels.canada.ca/en/alert-recall/methadone-treatment-opioid-dependence-and-potential-risk-lack-effect-when-switching>

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.5 The Relationship with Pharmacy & Prescriptions for Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Pharmacy staff are integral members of the care team and play a crucial role in the provision of Opioid Agonist Therapy (OAT). A trusting professional relationship between the patient and pharmacist plays an important role in promoting treatment goals, while reinforcing boundaries and patient safety. The pharmacy team will see patients more frequently than other members of the OAT care team and they can be a great source of support to patients. They can also provide valuable collateral information to the OAT prescriber and clinic team to augment the care provided in the clinic setting.

Although the pharmacy team is often geographically removed from the clinic, they are part of the circle of care under the *Personal Health Information Act* (PHIA). Sharing information within the circle of care, to the patient's benefit, is permissible and still fulfills the duty of confidentiality¹. As such, information required for the safe and effective provision of care should be shared freely between the pharmacist and prescriber/clinic staff.

Treatment agreements are effective tools to review behavioural and safety expectations with patients throughout the course of care, and these expectations extend to the pharmacy team. **The same respectful behaviour expected in clinic is also expected in and around the pharmacy.** This can be clearly communicated with patients when reviewing treatment agreements (see [Comprehensive Assessment](#) for further guidance). Disruptive behavior or theft from the pharmacy may result in the pharmacist terminating the patient relationship. Unacceptable behavior in pharmacy may also result in consequences and changes to the treatment plan with the clinic. For example, if a patient behaves in a threatening manner toward pharmacy staff, this may constitute grounds for involuntary withdrawal of treatment (see the [Discontinuing Treatment](#) chapter for detailed guidance).

Information sharing and collaboration between the pharmacy and clinic enables care providers at both locations to reinforce consistent boundaries and provide clear guidance on patients' rights and responsibilities when participating in treatment.

SPECIFIC RECOMMENDATIONS

PHARMACY & PRESCRIBER COMMUNICATION

Clear communication between the OAT prescriber/clinic staff and pharmacist is crucial. Issues that require prompt communication between prescriber and pharmacist are outlined below.

- 1) **Dose Changes:** All dose changes must be clearly communicated/highlighted to the pharmacist. Using an up (↑) or down (↓) arrow on the prescription instructions can be useful to indicate to the pharmacy that a dose change is intentional and not an error. This is particularly important during transitions between different pharmacies or treatment sites where the dose may have been adjusted (e.g., discharge from hospital or a residential treatment program).
- 2) **Missed Doses:** The pharmacist must report missed doses to the prescriber daily as they occur. The prescriber/clinic staff can then reach out to the patient to assess wellbeing and screen for issues that could be contributing to missed doses. This can also help providers plan ahead in case a prescription for a reduced OAT dose is needed in the near future. See the [Ongoing Care](#) section on **MISSED OAT DOSES** for specific recommendations.
- 3) **New Prescriptions for Concerning Medications:** The pharmacist must inform the OAT provider of any concerns when the patient is prescribed a medication by another prescriber that may interact with OAT, including all medications with sedating and/or psychoactive properties. This allows for collaborative discussion so that treatment adjustments can be made as necessary in the interest of patient safety. For example, the OAT prescriber may request that a new psychoactive medication be dispensed at intervals that match the witnessing schedule of the patient's OAT.
- 4) **Changes in Pharmacy Attendance:** A change of pharmacy or travel plans should be communicated promptly between the pharmacy and clinic team. This allows the clinic team to appropriately support the patient in planning for travel/guest dosing. It also prompts pharmacy staff to appropriately communicate with the new pharmacy, or the pharmacy responsible for guest dosing if indicated during travel.
- 5) **Take-home (Carry) Doses:** The schedule of take-home doses must be clearly communicated to the pharmacy. This can be done by either writing the instructions for witnessed and take-home doses directly on the prescription, or by sending it to the pharmacy as a separate note or letter (see **Appendix E** for an example). The latter is

especially useful when the current prescription is still valid and the treatment team wishes to authorize changes to take-home doses, such as a new permanent carry or one-time carry doses for travel or another reason. The schedule must indicate *both* the witness and take-home dates using specific days of the week (e.g., Monday, etc.) or calendar dates.

Take-home doses must be authorized by the prescriber or a member of the prescriber's treatment team. The pharmacist cannot authorize take-home doses, and the prescriber/clinic staff should clearly explain this to the patient to avoid misunderstanding. Pharmacists can often provide valuable input on the appropriateness of take-home doses. Discussion is thus encouraged, especially when the prescriber/clinic staff are questioning the safety of releasing carries in certain situations.

- 6) **Collateral About Stability:** As the pharmacy team interacts with the patient regularly between appointments, they can provide valuable observations regarding the patient's physical and mental health, apparent social stability, and episodes of intoxication/sedation. Concerning presentations or behaviors should be promptly communicated to the prescriber.

Occasionally, the prescriber/clinic team may elect to send a letter to the patient's pharmacy of choice at the start of treatment, or to facilitate guest dosing during travel. Such a letter serves to communicate the prescriber's treatment expectations to the pharmacy, as discussed with the patient. This may be particularly useful for out-of-province pharmacies who may operate with different expectations than Manitoba, or for pharmacies with minimal OAT experience (see **Appendix F** for an example letter). Pharmacists may also require patients on OAT to sign a pharmacy treatment agreement to outline expectations (contact the College of Pharmacists of Manitoba for an example).

It is also important for prescribers/clinic staff to discuss practical expectations about care with patients *periodically* to ensure understanding. This reinforces the safety measures, boundaries, and predictable structure that anchors OAT treatment.

OTHER CONSIDERATIONS FOR PHARMACY

Intoxicated Patients & Withholding Doses

Patients may present at the pharmacy for their dose appearing intoxicated from alcohol or other substance use. Concurrent use of sedative-hypnotics, such as benzodiazepines/Z-drugs, alcohol, or other opioids greatly increases the risk of overdose when combined with OAT medication.

Patients appearing somnolent, sedated, or intoxicated (slurred speech, stumbling gait, disorientation) will not be given their OAT dose if the pharmacist deems it unsafe, based on their assessment of the patient. The pharmacist may elect to ask the patient to return for

reassessment at a later time or the dose for that day may be withheld altogether. The pharmacist must inform the prescriber/clinic of such presentations as soon as they occur and may request additional collaboration from the prescriber/clinic to resolve the matter.

If a patient is administered their OAT dose and impairment/intoxication is noted after, the prescriber/clinic should be consulted and/or the pharmacist may choose to call 911 for emergency assistance. Consideration may also be given to clinic or emergency room attendance for assessment and further observation, as appropriate.

Management of Wrong Dose & Overdose

On occasion, dosing errors may occur at the pharmacy, and this may necessitate further assessment and monitoring. **Dosing errors must be reported to the OAT prescriber.** Particular caution must be taken with overdosing of methadone and slow-release oral morphine (SROM), given the full-agonist effects and comparatively greater risk of opioid toxicity.

The pharmacist, in consultation with the prescriber, should be actively involved in ensuring that the patient receives the appropriate medical intervention, which may include finding transportation to the OAT clinic, emergency department, or calling an ambulance.

Methadone and buprenorphine/naloxone can have peak effects that begin in 1-2 hours, and this can last for several hours. When an overdose occurs, adverse effects will be most apparent during these peak times. Early signs of toxicity include drowsiness or “nodding” during low stimulus activities. Ataxia, nausea/vomiting, slurred speech, euphoria, and slow or laboured breathing (respiratory depression) may be signs of progressive toxicity and require urgent medical attention.

If the patient refuses to seek medical attention, such as attending their OAT clinic or hospital, the pharmacist and prescriber/clinic staff can collaborate on the following:

- Educate the patient on the risks involved.
- Involve a trusted person (e.g., family member or friend), as able, who can stay with them and monitor for adverse effects, particularly during dosing peaks.
- Ensure the patient has a naloxone kit and someone who can stay with them who knows how to use it.
- Educate the patient and/or trusted person regarding signs of overdose, naloxone kit use, and when to call 911.
- Instruct the patient to avoid any other sedative/psychoactive substances for the remainder of the day and/or until the peak effects are expected to subside.
- Contact the patient throughout the day to check in and provide further support.

OAT providers/clinics and pharmacies should have an **overdose response plan** in place. A clear protocol for appropriate action supports staff and increases safety. **For high dose ingestions or if the patient shows any signs of sedation, OAT providers/clinics should adhere to the following steps:**

- Ensure naloxone is available on-site and administered if needed.
- Monitor patient vitals accordingly.
- Clinic staff should recommend and help arrange transfer to an emergency department, and provide appropriate information to the receiving institution.
- Consider the need for involuntary transfer to a hospital if the prescriber or clinic staff have significant concerns.
- If the patient is referred to the emergency department, the OAT prescriber/clinic staff should communicate with the emergency room physician to advise that:
 - The patient should be observed for a minimum of 10 hours.
 - The patient should not be discharged with ongoing signs of lethargy or sedation.
 - The patient should not receive any other sedative/psychoactive medications.

The risk of opioid toxicity is also affected by other factors, such as the patient's age, stage of treatment, concurrent health conditions, prescribed medications, and/or concurrent substance use. **Patients in the early stabilization phase (e.g., first 2-3 weeks), using other sedative-hypnotic substances/medications, the elderly, and patients with respiratory illness are more prone to toxicity.** Even a small "extra" OAT dose could cause harm in such patients.

OAT PRESCRIPTION WRITING & TRANSMISSION

OAT Medications Are M3P Drugs

Methadone, buprenorphine, and SR0M (Kadian®) are drugs covered by the Manitoba Prescribing Practices Program (M3P), and therefore prescriptions must be written in one of the approved M3P formats. See the [CPSM Practice Direction for Manitoba Prescribing Practices Program](#) and page 3 for a list of M3P drugs².

The following resources are available electronically by contacting the CPSM Prescribing Practices Program (phone 204-774-4344):

- Guidance on approved methods and formats for faxing M3P medications.
- Templates for faxing that can be tailored to prescribers' practice locations.
- Teaching examples of M3P OAT prescriptions.

Please note these instructional resources are not available online for forgery prevention.

The M3P form exists to minimize diversion of controlled and narcotic medications, and to facilitate communication among healthcare professionals. Historically, the original, hardcopy M3P form had to be received by pharmacies for the prescription to be valid. Since 2016, OAT prescribers were permitted and **strongly advised to fax OAT prescriptions directly to the pharmacy of the patient's choice**. This decreases the chance of prescriptions being lost, stolen, or altered, and improves access to care for patients on OAT, especially when providers are caring for patients over a distance. See [Faxing M3Ps](#) below for more details on faxing OAT prescriptions.

Since the COVID-19 pandemic, it has been permissible to fax prescriptions for all drugs on the M3P schedule directly to the patient's pharmacy of choice, *without sending the original*.

M3P prescriptions can now be faxed as the M3P form (from the duplicate prescription pad) affixed to a template, or the provider can generate an EMR or handwritten prescription for faxing, **provided all requirements are met per the M3P form** and the [Joint Statement for Facsimile Transmission of Prescriptions](#).

OAT Prescription Requirements

OAT prescriptions must contain the following information, consistent with M3P form fields, including:

- Patient demographics (name, address, PHIN, DOB).
- Name and daily dosage of the drug, in numbers and words, e.g., methadone 30 (thirty) mg or Suboxone 18 (eighteen) mg.
- Total quantity of the drug to be dispensed, in numbers and words.
- First and last calendar date of the prescription.
- Specific days of the week or calendar dates for witnessed dosing and take-home doses.
- Therapeutic indication (e.g., opioid use disorder).
- Directions for use.
- Any special instructions specific to the patient.
- Date prescribed.
- Written and signed by an approved OAT prescriber.

Prescribers Must Complete Total Quantity

The total quantity on OAT prescriptions must be filled out (regardless of the faxing format used), including the **total milligram amount** of the entire prescription, written both **numerically** and **alphabetically**. Given the potential for harm to patients, **CPSM requires the total quantity to be completed by the prescriber**. This serves as an additional safety check to ensure the correct daily dose is dispensed to the patient and that the intentions of the prescriber are clear.

As above, OAT prescriptions must clearly state the first and last calendar date of the intended prescription, the indication for the medication (e.g., opioid use disorder), and the daily dose. Completing these fields on the M3P prescription *does not* preclude the prescriber from completing the total quantities field. If the total quantity is not specified, the pharmacy will need to contact the prescriber for clarification, while being mindful not to unnecessarily delay patient care.

Total Daily Dose vs Strength of Drug

It is strongly recommended to write the total *daily* dose in milligrams on the OAT prescription instead of the individual unit strength of the medication, to prevent dosing errors and to provide flexibility for pharmacists. For example, writing Suboxone 18 mg (instead specifying the 8 mg and/or 2 mg tablet strengths) gives the pharmacist flexibility to use the tablet strengths available to make up the dose. Likewise, writing methadone in milligrams (e.g., 30 mg) and not in millilitres (e.g., 3 mL) will help prevent dosing errors. Furthermore, writing the generic name “methadone” (instead of Methadose, for example) also gives the pharmacist options to use available formulations.

If the daily dose is written on an M3P form that is affixed to a prescription fax template, the daily dose must also be written in a *secondary area* on the faxed prescription, to ensure accuracy in case fax artifacts cover the primary notation.

Other Nuances of OAT Prescriptions

The following also applies for prescribers and pharmacists in managing OAT prescriptions:

- No doses are to be given beyond the last calendar date of the prescription (i.e., missed doses cannot be given past the prescription end date).
- Every new prescription must clearly state which doses are to be taken by witnessed self-administration and which may be dispensed as take-home doses.
- A new prescription must be written for any change(s) from a previous dose. Multiple doses written on the same prescription should be avoided. An example of an exception to this may be a pre-planned taper where a number of dose decreases over a specified period of time is clearly written on the same prescription.
- The practice of having pre-signed blank prescriptions in the clinic is unacceptable.
- Any new prescription cancels the previous prescription.
- If the patient is changing pharmacies, the previous prescription will be cancelled. There is an increased risk of error when OAT is regularly dispensed out of two or more pharmacies, and this should be done only rarely if no alternative exists (e.g., geographical constraints). The patient could potentially be double dosed, or the

pharmacist could be unaware of missed doses. As below, one prescriber (or identified group of prescribers) and one pharmacy is considered best practice.

STRONG RECOMMENDATION: ONE PRESCRIBER - ONE PHARMACY

It is best practice for ALL sedating/psychoactive medications to be prescribed by a single prescriber (or group of prescribers) and dispensed from a single community pharmacy. **The prescriber (or group of prescribers) of these medications should generally be the OAT prescriber(s).**

OAT prescribers are **strongly encouraged to provide their cell numbers** (or on-call number for a prescriber group) on *all* prescriptions to facilitate timely communication regarding urgent prescription issues and to minimize delays in patient care. These numbers can be marked as “private” to indicate to the pharmacy team that they should not be shared with patients.

Faxing M3Ps

The requirements outlined in the [Joint Statement for Facsimile Transmission of Prescriptions](#) must be met when M3P OAT prescriptions are faxed to the pharmacy of the patient’s choice and the prescription must contain the usual signed certifications indicating that³:

- i. The prescription represents the original of the prescription drug order,
- ii. The addressee is the only intended recipient and there are no others, and
- iii. The original prescription will be invalidated, securely filed, and not transmitted elsewhere at another time.

The original hardcopy M3P prescription *does not* need to be mailed or couriered to the pharmacy. Once successfully faxed, the original M3P prescription essentially becomes a “copy” and should be labelled as such before being added to a paper chart or scanned into an electronic medical record. The faxed M3P prescription received by the pharmacy is now regarded as the original valid M3P prescription.

Do not provide the original hardcopy M3P prescription to the patient to take to the pharmacy if it has been faxed. This prevents the patient from potentially taking the original hardcopy M3P prescription to a second pharmacy, other than the intended pharmacy.

Buprenorphine Formulations

Buprenorphine/naloxone is currently available as a sublingual tablet or film. While formulations contain both buprenorphine and naloxone at a ratio of 4:1, it should be noted that buprenorphine/naloxone products are commonly referred to by their buprenorphine component only (e.g., 2 mg instead of 2 mg/0.5 mg).

Depending on availability and coverage, the pharmacist will commonly use 2 mg and 8 mg tablets to make up the prescribed strength, however other options may be available. When films are prescribed, the pharmacist may choose from 2 mg, 4 mg, 8 mg, or 12 mg strengths, but may be limited in their choice depending on coverage and availability.

Methadone Formulations

Methadone is available in various formulations, but pharmacists *must* use designated 10 mg/mL liquid concentrates when filling prescriptions for opioid use disorder (OUD). Pharmacists are required to dilute some of these methadone concentrates with a crystalline diluent (e.g., Tang®), while some concentrates may be dispensed safely without further dilution (e.g., cherry-flavored concentrates). Pharmacists will prepare individual daily doses for their patients using this concentrate. An exception to using the methadone concentrate may be made for patients with long-term documented stability; they may be eligible for tablets or capsules at the discretion of the prescriber for reasons such as extended or international travel.

Methadone products are not interchangeable from a clinical perspective nor a coverage perspective. Changes occurred in the Pharmacare drug coverage for brand vs generic methadone products in 2021. Generic methadone products are now listed as a Part 1 (open) benefit. These generic methadone products are *not* interchangeable with each other nor with the brand name methadone products.

As of March 2023, brand name methadone products (e.g., Methadose™) are only a Part 2 benefit for patients who:

- a) Are being treated with the same methadone product already, or
- b) Have previously been treated with two or more generic methadone products listed under Part 1.

Please refer to the [Manitoba Health website](#) for updates to the Pharmacare coverage.

A [safety review completed by Health Canada](#) found that there may be a link between switching methadone-containing products used to treat OUD and the risk of lack of effect, which may present as withdrawal symptoms, although the reason for this is unclear. OAT providers and pharmacists should be aware that⁴:

- Some patients may experience withdrawal symptoms after being switched from one methadone-containing product to another; these patients should be clinically managed and monitored regularly.
- Dose adjustments may be necessary in some patients.
- Withdrawal symptoms can lead to a failure to remain in treatment and subsequent problematic substance use, which can lead to serious harms.

Particular caution should be exercised when the patient is switching between methadone products that require dilution with a crystalline diluent (e.g., Tang[®]) and ones that do not require dilution (e.g., cherry-flavored).

A new prescription would be required to switch a patient from one methadone product to another. If a patient is *new* to taking methadone and presents to a pharmacy with a prescription that does not specify the brand (i.e., written as “methadone”), the pharmacist can dispense whatever generic is usually used by the pharmacy. It is good practice for the pharmacist to notify the prescriber of the generic brand that is being used.

Writing new methadone prescriptions in this format (i.e., written as “methadone”) is recommended, as it may prevent a delay in treatment at the pharmacy.

If the patient is *already* taking methadone and presents with a new prescription, consideration must be given to what brand the patient has been receiving and it may be necessary in some cases to avoid changing the brand, if possible. **If the patient receives a different methadone brand, the patient and prescriber must be made aware so that the patient can be monitored for dose equivalency. This often requires collaboration and communication between the prescriber, pharmacy team, and patient.**

As above, prescribers are **strongly encouraged** to provide their cell numbers (or on-call number for a prescriber group) on *all* OAT prescriptions to facilitate timely communication regarding urgent prescription issues and to minimize delays in patient care. These numbers can be marked as “private” to indicate to the pharmacy team that they should not be shared with patients.

References

1. College of Physicians & Surgeons of Manitoba. *Standard of Practice: Duty to Report Self, Colleagues, or Patients, Contextual Information and Resources*. CPSM; 2021.
2. College of Physicians & Surgeons of Manitoba. *Practice Direction: Manitoba Prescribing Practices Program (M3P)*. CPSM; 2018.
3. College of Pharmacists of Manitoba. *Joint Statement: Facsimile Transmission of Prescriptions*. CPhM; 1998 (Revised 2016).
4. Health Canada. *Methadone Treatment of Opioid Dependence and Potential Risk of Lack of Effect when Switching between Different Products*. Government of Canada; 2020. Available at: <https://recalls-rappels.canada.ca/en/alert-recall/methadone-treatment-opioid-dependence-and-potential-risk-lack-effect-when-switching>

Appendix E

AUTHORIZATION TO PHARMACY FOR OAT TAKE-HOME (CARRY) DOSES

Date: _____
Pharmacy: _____
Phone: _____
Fax: _____

Dear Pharmacist,

RE: _____
DOB: _____
PHIN: _____
Clinic Phone: _____ Fax: _____

Please be advised that the above-named patient has been authorized *one-time* carry dose(s) for the following date(s) _____.

OR

Please be advised that the above-named patient has been authorized a *permanent* carry dose.

They would like to take home their OAT dose on: _____ (day of the week), starting on _____ (date).

The carry schedule moving forward will be:

Day	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Witnessed Dose (W)							
Carry Dose (C)							

Please call us as needed with any questions or concerns, at _____.

Sincerely,

Prescriber or Clinician Signature, credentials

Appendix F

LETTER TO PHARMACY FOR PATIENTS STARTING OAT

Date:

Pharmacy:

Phone:

Fax:

Dear Pharmacist,

RE:

DOB:

PHIN:

Clinic Phone:

Fax:

Our patient has chosen your pharmacy for Opioid Agonist Therapy (OAT).

We encourage regular communication between the pharmacist, OAT prescriber, and clinic staff, for the comprehensive and safe care of our patients. We also ask that the following **clinic expectations** be reinforced with our patients. Please contact the clinic with any questions or concerns at _____.

- 1) Patients are required to self-administer their OAT dose in front of the pharmacist, unless take-home (carry) doses are authorized.
- 2) Please inform us of any OAT doses missed by the patient.
- 3) Please withhold the OAT dose if the patient misses **≥ 3 consecutive doses of methadone** or **≥ 6 consecutive doses of buprenorphine/naloxone**, to prevent overdose due to loss of tolerance. The patient may need to be reassessed before OAT is restarted. Please notify us as soon as possible.
- 4) Please inform us of any diversion or attempted diversion.
- 5) If the patient appears somnolent, sedated, or intoxicated, their OAT dose will not be given if the pharmacist deems it unsafe, based on their assessment. The pharmacist may elect to ask the patient to return for reassessment at a later time or the dose for that day can be withheld altogether. Please notify us of such presentations.
- 6) Patients have been instructed to keep their medication(s) in a locked box or cabinet at home and when travelling. Please inform us of any lost or stolen doses, or if you have any concerns about the patient's ability to lock or secure their doses.

- 7) Changes to the witness/take-home dosing schedule can only be authorized by the prescriber/clinic. Patients are asked to arrange any requests for changes to the schedule directly with our clinic at least 24 hours in advance, if possible.
- 8) Please notify us if pharmacy staff observe the patient vomit their methadone dose within less than 30 minutes from ingesting their dose, or if the patient reports vomiting their dose otherwise.
- 9) Please notify us if you become aware that the patient is prescribed any new medications that interact with OAT, including any new prescriptions for other sedating/psychoactive medications.

Sincerely,

Prescriber or Clinician Signature, credentials

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.6 Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in the Context of Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Polypharmacy* and/or polysubstance use is common in patients with opioid use disorder and patients on opioid agonist therapy (OAT). It is the responsibility of the treating clinician(s), along with all members of the treatment team, to monitor clinical stability and safety on an ongoing basis. This includes screening for substance use that can increase the risk of harm for the patient and/or the community.

Prior to initiating OAT, the prescriber must collect a detailed history of the patient's use of other substances, including alcohol, nicotine, cannabis, prescription medications, over-the-counter medications (OTC), and illicit drugs. The prescriber must also review the patient's prescribing record (DPIN) to verify available prescription history.

It is imperative that the patient's pharmacy, primary care provider, psychiatrist and/or any other specialists involved in their care are notified of the plan to initiate OAT. This ensures that all relevant information is considered when managing medications and other substance use in patients on OAT. It also establishes a clear, mutual understanding regarding the future medication management plan between the OAT treatment team, the patient, and others involved. Ultimately, good communication facilitates patient safety. This is especially important for medications with psychoactive and/or sedating properties.

*For the purpose of this manual, **polypharmacy is defined as the concurrent prescribing of five or more medications with sedating and/or psychoactive properties**. Notwithstanding this definition, it is important to note that the inherent risks of polypharmacy also apply in situations where licit (e.g., alcohol and cannabis), or illicit drugs/prescription medications and/or over-the-counter medications with sedating and/or psychoactive properties, are combined with prescribed medications with similar properties. When prescribing OAT, it is important for the prescriber to educate patients regarding these risks on a regular basis. In this chapter, the authors will outline the risks and provide practical guidance on how to manage these risks.

The Office of the Chief Medical Examiner – Manitoba Data¹

CPSM staff attend the monthly Adult Inquest Review Committee Meetings at the Office of the Chief Medical Examiner (OCME). At this meeting all unnatural deaths of adults between the ages of 18 and 65 are reviewed by an expert panel. CPSM conducts a detailed review of all deaths involving prescription medications, including buprenorphine/naloxone, methadone, and slow-release oral morphine (i.e., Kadian®). The review aims to understand the role that prescribing practices play in accidental overdose deaths. The program is educational and intended to promote quality improvement in prescribing, to ultimately enhance patient safety.

Several important themes have been identified from the review of cases involving prescription medications, including OAT, highlighted in the sidebar.

Additionally, the OCME death reviews indicate that certain combinations of prescription drugs increase the risk of death. Of particular importance, most opioid-related deaths can be attributed to one or more opioids combined with other drugs, often benzodiazepines and/or Z-drugs. The two drug classes that were the top contributors to opioid overdoses between 2014-2017, were benzodiazepines and antidepressants.

The leading prescription sedative-hypnotics contributing to deaths in Manitoba between 2016 and 2018 were alprazolam and zopiclone. Alprazolam has significant street value and has become a significant drug of abuse in Manitoba, along with gabapentin and diphenhydramine.

Lessons learned from Manitoba's provincial death data should transform prescribing practices. **The overall risk of polypharmacy, especially in the context of ongoing illicit substance use, often outweighs the benefit of individual medications.**

OCME DEATH REVIEW THEMES

- The largest category of overdose deaths involving prescription medications are **accidental polypharmacy** overdose deaths.
- Deaths involving polypharmacy most often involve prescriptions written by a **single physician, filled at a single pharmacy**.
- A smaller number of deaths involve multiple sedating prescription medications prescribed to the same patient by **different physicians, filled at multiple different pharmacies** (often including an opioid and one or more benzodiazepines/Z-drugs).
- **OTC medication with sedating properties**, used in combination with prescribed medications (often in polypharmacy situations as defined earlier), increases the risk of accidental overdose death.
- Diphenhydramine, a common ingredient in OTC medications, is of particular concern. **Diphenhydramine contributed to twenty-one deaths in the first three quarters of 2020 alone.**

Polypharmacy Risks

In addition to the above, polypharmacy is known to be associated with:

- Multiple drug interactions.
- **Additive adverse effects**, including memory impairment, falls, confusion, sedation, and additive respiratory depression/death.
- High doses of individual medication, further increasing the risk of diabetes mellitus, metabolic syndrome, and cognitive impairment.³

It is important to note that there is very little evidence that combining agents from the same class increases efficacy (e.g., benzodiazepines, hypnotics, SSRI's). However, evidence does suggest that simplifying therapy without clinical deterioration is possible with medical supervision.

Local OCME findings are in keeping with the literature that demonstrates mounting evidence for the risks associated with prescribed sedative use along with OAT. Prescribed sedatives or psychoactive medications, such as benzodiazepines, Z-drugs, and pregabalin, were significantly associated with overdose deaths in patients on OAT (both methadone and buprenorphine), in a nation-wide 7-year Swedish study.² For patients on methadone maintenance, receipt of any prescription of a psychotropic drug (benzodiazepine, antidepressant, or antipsychotic) in the past year was associated with a twofold increase in the risk of opioid-related death, in a population-based 16-year study in Ontario.³

OAT Providers Must Manage Risks

OAT prescribers must be diligent in managing the risks of polypharmacy and polysubstance use in a patient population that already carries an increased risk of adverse outcomes.

While buprenorphine has a superior safety profile when compared to methadone, it is still important to recognize that psychoactive medications and/or illicit substances increase the risk of accidental overdose death. Review of prescribed and OTC medications, and screening for other substance use, is essential on intake and routine follow up to ensure that all relevant information is taken into consideration when managing medication regimens.

SPECIFIC CONSIDERATIONS

Recommendations for the management of psychoactive/sedating medications and other substance use, will be discussed under the following headings:

- An Approach to Polypharmacy in the Context of OAT
- Managing Prescribed and Illicit Benzodiazepine & Z-drug Use
- Managing Alcohol Use
- Managing Nicotine Use

- Managing Cannabis Use
- Managing Illicit Stimulant Use
- Managing Other Psychoactive Medication Use, both Prescribed and Illicit
 - Gabapentinoids
 - Muscle Relaxants
 - Quetiapine & Trazodone
 - Prescribed Stimulants
 - Antidepressants
- Managing Over-the-Counter Medication Use
- Other Substances to Consider

While the above categories are not an exhaustive list of possible prescription or illicit substances, they have been included for discussion due to their prevalence of use and associated safety risks in the context of OAT.

AN APPROACH TO POLYPHARMACY IN THE CONTEXT OF OAT

Create a List of Active Clinical Issues

To facilitate appropriate discussion and clinical decision making around medication management, the OAT clinician needs to determine the patient's current clinical needs, in order of priority. The comprehensive history and physical completed during the OAT intake process will assist in generating an **updated list of active clinical issues** that require management. Some issues may need to be addressed right away, some may need attention in the coming months, and some may be deferred for ongoing management by the patient's primary care provider or medical specialist.

Conduct a Detailed Review of DPIN Profile

A critical aspect of intake and assessment is a detailed review of the patient's medication record (DPIN). Ideally, a DPIN record including all medication entries over the preceding six months should be reviewed. A longer interval may be required if medications are dispensed infrequently. This review supplements the detailed substance use history collected during the interview process and is ideally conducted together with the patient. **The DPIN review must occur in conjunction with the updated list of active clinical issues** and is therefore often the final step in the treatment planning process. This allows the treating clinician an opportunity to clarify how medication is being used and where a particular medication ranks in terms of clinical importance in managing the list of active clinical concerns.

A detailed DPIN review also gives the prescriber and patient an opportunity to discuss which medications have been stopped (even though they may still be dispensed regularly), which ones

the patient may be selling or sharing, and how the patient feels about stopping or tapering undesirable medications that are no longer clinically relevant or useful. A non-judgemental interview style, along with evidence-informed and patient-centred explanations of why certain medications are undesirable with OAT, can go a long way to promote patient engagement in the plan to simplify a complex medication regimen.

It is crucial to emphasize which medication changes are required to ensure patient safety during OAT induction and ongoing care. Reassure the patient that the treatment team will support them through frequent reassessment and medication adjustments as needed. Combining this strategy with emotional support increases the likelihood of success. Highlighting gains over time, such as improved mental alertness, memory, and cognitive function, can also support the medication management strategy. These benefits are often achieved without any measurable increases in symptoms such as anxiety or insomnia. Some patients may even report a decrease in their baseline anxiety and other forms of mental health distress. The patient's pharmacy should be notified of any medication changes. This ensures consistent messaging from all members of the treatment team and enables pharmacy staff to support the patient with changes.

As below, **KEY QUESTIONS** can be used to explore each medication on the DPIN. It is important to also note that the absence of prescribed medications on DPIN does not rule out polypharmacy; the patient may be using psychoactive medications from a non-prescribed source.

MEDICATION REVIEW – KEY QUESTIONS TO EXPLORE WITH THE PATIENT

Are there psychoactive/sedating medications on the list that they are not taking, selling, or sharing?

Medications that have been stopped by the patient, or that are rarely taken, should be discontinued and the pharmacy notified. The patient should also be encouraged to return any unused medication at home to their pharmacy for safe destruction.

What medications are they taking regularly? What was the initial indication for each medication (why did they start them)? How long have they been taking the medication overall (days, months, years)? How many days of the week do they take them? How many times a day and how many tablets at a time? How do they take them (swallowed, chewed, snorted, injected)? If this is their regular pattern of use, are there ever days when they use a lot more (binge use)?

Do they ever run out of certain medications? What symptoms do they experience when this happens? Do they buy/borrow more from family or friends? What is this costing them? Have they ever found themselves in unsafe situations because of needing these medications?

Do they believe these medications are a problem? Do they feel “addicted”? Are they used as a “rescue” during opioid withdrawal? Do they think they can stop using the medication if opioid withdrawal is eliminated in the context of OAT?

Are they taking any other medications not prescribed to them? Shared, traded, or illicitly acquired? Are they using any OTC medications?

Scope of Practice

The typical scope of practice of an OAT prescriber requires them to be actively involved in the management of the OAT medications, medications prescribed for other substance use disorders, medications prescribed for mental health concerns and insomnia, as well as any medication prescribed for acute, chronic, and/or peri-operative pain.

It is NOT acceptable for OAT prescribers to initiate or continue OAT without a thoroughly documented plan regarding the management of all psychoactive medications during induction and the subsequent stages of treatment. This plan should be regularly updated as part of the cumulative summary of care. This is a requirement of CPSM's [Standard of Practice for Documentation in Patient Records](#).

STRONG RECOMMENDATION: ONE PRESCRIBER - ONE PHARMACY

It is best practice for ALL medications prescribed for the above-mentioned conditions to be prescribed by a single prescriber (or group of prescribers) and dispensed from a single community pharmacy. This is particularly important for all psychoactive/sedating medications. **This prescriber (or group of prescribers) should generally be the OAT prescriber(s).**

If for any reason, some medications must be prescribed by another provider involved in the patient's care, frequent communication must occur between the OAT prescriber, the additional prescriber of psychoactive medications, and the pharmacy. This is essential for patient safety and to ensure that all prescribers participate in the agreed upon plan to manage polypharmacy.

Polypharmacy Management Plan

By updating the list of active clinical issues and completing a DPIN review with the patient, the OAT prescriber can now formulate the polypharmacy medication management plan. This plan must be discussed/negotiated with the patient and other prescribers involved in their care.

In creating the final plan, the prescriber must consider the following:

- After stopping medications that have been discontinued or that are taken infrequently, how many psychoactive/sedating agents remain?
- Can any of these medications be consolidated (e.g., replace 2 or more different benzodiazepines/Z-drugs with a single agent)?
- Can a one-time dose reduction of undesirable medications be considered, especially when prescribed in high doses? Benzodiazepines are a good example; an initial dose reduction can enhance patient safety immediately, followed by a slow taper over time. See [Dosing Recommendations](#) under the subsequent section "Managing Prescribed and Illicit Benzodiazepines & Z-Drug Use" for details.

- Which medications remaining on the list are most beneficial in terms of the list of active clinical concerns? Which medications are no longer clinically relevant or useful? *Ask the patient this question.* Can any of them be discontinued without the need for a taper?
- In the context of significant polypharmacy, were any medications started recently enough that they can be stopped without clinical deterioration?

The above considerations may help simplify a complex medication regimen, especially if the current regimen carries significant risk for accidental polypharmacy overdose death. This risk should also be considered in the context of adding OAT. In some cases, medication changes can be made over time, but in the context of extreme polypharmacy, substantial medication changes may be indicated on day one of the OAT induction.

Communication with the patient's primary care provider or specialist(s) is strongly recommended to review the plan and rationale for the OAT prescriber to take over psychoactive/sedating medications. It is important to emphasize that their ongoing care is essential to the patient's other medical needs, while highlighting that some changes to the medication regimen may be required for safe OAT induction and care. A letter that confirms these arrangements is excellent practice and informs all providers about the plan moving forward.

STRONG RECOMMENDATION: DISPENSE WITH OAT

Typically, all psychoactive/sedating medications should be dispensed with OAT, i.e., on the same schedule as OAT. Communicating with the patient's pharmacy about the plan for managing these medications is essential. Controlled dispensing instructions, such as "dispense as per OAT schedule", must be written on all relevant prescriptions.

There may be occasional circumstances when the prescriber's risk assessment, considering all medication use and psychosocial factors, would safely allow for less controlled dispensing of psychoactive/sedating medications. Clinical judgment can be applied in such circumstances (e.g., when a patient is paying out of pocket for all medications and there are no high-risk behaviours identified, and the additional cost of daily dispensing may not be justifiable). The prescriber must document their risk assessment and rationale for dispensing intervals that diverge from the OAT schedule.

Verbal or written pharmacy communication may also include any dose or medication changes, tapering plans, and specific concerns to highlight, such as monitoring for sedation or withdrawal, notifying the OAT prescriber of new prescriptions for psychoactive agents from other providers, and/or missed or declined doses of medication.

Polypharmacy is typically not a reason to delay induction of OAT, but it must be factored into the documented management plan. Thorough assessment of polypharmacy will inform decisions about the induction approach (starting dose and rate of dose increases) and follow-up intervals.

In the context of extreme polypharmacy and/or novice prescribers, it may be necessary to delay community induction and seek additional support from an experienced prescriber. Extreme polypharmacy may even warrant admission to hospital for induction and medication adjustment under close medical supervision.

A well-documented polypharmacy management plan should outline, where relevant, the following issues discussed with the patient:

- Patient education regarding the risk of polypharmacy in the context of OAT.
- A summary of the DPIN review findings.
- The plan to take over prescribing of psychoactive/sedating medications.
- Communication and/or correspondence with other prescribers and the pharmacy.
- The dispensing interval that will apply to all psychoactive medications, and how this will be adjusted if the patient is awarded gradual take-home doses. Typically, the take-home supply of psychoactive medications will mirror the OAT dispensing schedule. If the prescriber's clinical judgment varies from this approach, they should document the risk assessment and rationale for the dispensing interval applied to each medication.
- Evidence of a treatment agreement, including a single prescriber (or group of prescribers) and single pharmacy agreement.
- Collaborative, prioritized care goals, medication changes, and relevant (eventual) taper plans, noting the benefits of a slow and stepwise approach to deprescribing.

Important Note for Emergent or Brief Care Providers

It may not be feasible or ideal for OAT prescribers treating patients in an emergent or brief care setting to take over prescribing of all psychoactive medications. For example, in Rapid Access to Addiction Medicine (RAAM) clinics, Emergency Departments, or following brief Addictions Medicine Consultation in hospital. An interim prescription for OAT may be provided by the consultant, while other medications are managed by the attending physician or regular community provider(s).

However, even under such circumstances, the consultant remains responsible for appropriate screening, assessment, and documentation around polypharmacy. It is recommended that the consultant connect with the other prescribers and/or pharmacy to discuss relevant expert recommendations around the OAT and other medication plans.

If misuse of prescribed medications or a concurrent substance use disorder is identified (e.g., overuse of gabapentinoids or benzodiazepines), medication changes and/or dispensing interval changes **may warrant immediate intervention in the interest of patient safety**, and further collaboration with other prescribers/pharmacies. The OAT prescriber can offer guidance and support to the other prescribers to implement safer prescribing practices, especially when care is shared or transferred back to primary care.

Urine Drug Screens

Relevant to the assessment of polysubstance use and prescribed polypharmacy, it is worthwhile to note that not all benzodiazepines or other psychoactive agents are detected on a street drug screen or point-of-care urine drug screen (UDS). These tests typically identify drug categories and are subject to false positives and negatives. See the [Use of UDT in the Management of OUD](#) for a general approach to testing, including the recommended frequency and important issues to consider when interpreting results.

When conducting an initial assessment or monitoring for ongoing polysubstance and prescription medication use, a comprehensive UDS (laboratory GC-MS) offers more detailed and clinically useful information about the specific substances/medications detected. Likewise, a comprehensive UDS can also provide useful information about prescribed medications the patient is *not taking* when evaluating medication compliance.

KNOW YOUR TOOL: INTERPRETING COMPREHENSIVE UDS RESULTS

When interpreting comprehensive UDS results, knowledge of which drugs are captured is essential to safe and effective patient care. Previously, Diagnostic Services, under Shared Health, identified most prescription and illicit drugs in samples submitted for comprehensive urine drug screening. This “forensic approach” was very expensive. The lengthy list of substances previously tested for was reduced as of June 17, 2021.

A specific list of the now **80 substances** tested for on a comprehensive screen is available [here](#). This specific panel of drugs is intended to balance clinical utility with a cost-effective approach to testing. This is essential information for prescribers when interpreting comprehensive UDS results to inform clinical judgement, particularly in the context of prescribing medications with psychoactive properties.

NOTE: If prescribers need a specific medication identified that is not included on the list of 80 substances (often to monitor compliance with a prescribed medication), they may request Diagnostic Services test for that medication, by adding a written request on the comprehensive UDS requisition. Date and time of sample collection and the clinical rationale for needing this information should also be documented on the requisition.

Ongoing Monitoring

Like OAT take-home doses, dispensing intervals for psychoactive/sedating medications must be re-evaluated during periods of instability. If circumstances warrant removal of OAT carries, then take-home doses of other psychoactive medications should mirror this approach. Earned take-home doses may need to be removed if concerns arise, such as relapse or a lack of adherence to prescribing agreements. See take-home (carry) recommendations for [Buprenorphine](#) and [Methadone](#) for details. Again, regular comprehensive UDS can help monitor adherence to the polypharmacy management plan. Regular conversations between the patient and treatment team, and **routine evaluation of the DPIN**, are essential components of ongoing monitoring.

MANAGING PRESCRIBED AND ILLICIT BENZODIAZEPINES & Z-DRUG USE

General Considerations

The CPSM [Standard of Practice for Prescribing Benzodiazepines & Z-Drugs](#) came into effect November 1, 2020. In the context of the evolving medical evidence of the risk-benefit ratio of these medications, the Standard establishes the standard of practice and ethical requirements of all members in relation to prescribing benzodiazepines and/or Z-Drugs.

While keeping the Standard in mind, there are some special considerations for the management of benzodiazepines and Z-drugs in patients on OAT. It is not uncommon for patients diagnosed with an opioid use disorder to have a history of benzodiazepine and/or Z-drug use. This can vary from intermittent use to alleviate the discomfort of opioid withdrawal symptoms, to a concurrent sedative-hypnotic use disorder.

Additionally, benzodiazepines and Z-drugs were historically and commonly prescribed for anxiety and insomnia, and many patients with opioid use disorder experience these symptoms. However, the evidence for the long-term use of these medications to treat anxiety disorders and insomnia is poor, and the long-term risks are well known. Notably, the number needed to treat with a benzodiazepine and/or Z-Drug for improved sleep is 13, whereas the number needed to harm is only 6⁴.

Furthermore, individuals seeking treatment for substance use disorders are particularly vulnerable to the addictive potential (and many other known harms) of benzodiazepines and Z-drugs. These harms are exacerbated when these medications are combined with opioids, including OAT. Risks increase even further when this combination is prescribed in the context of sedating polypharmacy or to the elderly.

The known harms of benzodiazepines and Z-drugs include:

- Sedation, confusion, drowsiness, and postural instability contributing to the risk of falls and subsequent fractures.
- Impairment of psychomotor skills, judgment, and coordination increasing the risk of motor vehicle accidents.
- Negative effects on cognition and memory, delirium, drug-related pseudo-dementia and a possible link to cognitive decline and Alzheimer's disease.
- Sleep automatism (in the case of Z-drugs), including food binging, and even driving while asleep or in a sleep-like state.
- Abuse and the potential to develop a sedative-hypnotic use disorder.
- Risky interactions with other psychoactive/sedating medications, increasing the risk of respiratory depression and ultimately, accidental polypharmacy overdose death.

Of note, alprazolam (Xanax®) has been identified as a benzodiazepine with significant risks of abuse and diversion in Manitoba. The rapid onset of action provides a sought-after “high” for some patients, while the relatively short half-life means the effects wear off rapidly, feeding the compulsion to take more for lasting effect. Cycling through this pattern of use regularly can reinforce the patient’s belief that they *need* the drug when they experience rebound symptoms, including anxiety. **Given the risk of abuse, and the role this benzodiazepine continues to play in overdose deaths, prescribing of alprazolam is *not* recommended.** For the purposes of managing sedative-hypnotic use disorders and/or benzodiazepine tapers, longer-acting formulations (diazepam or clonazepam) are preferred for greater clinical stability.

Managing Benzodiazepines & Z-Drugs in the Context of OAT

Not unlike the general approach to polypharmacy, thorough assessment and collaborative decision-making are required to address benzodiazepine and Z-drug use when prescribing OAT. A detailed history of benzodiazepine and Z-drug use will ensure a clinically appropriate plan is made that minimizes the inherent risks of these medications. The **KEY QUESTIONS** below should be reviewed with the patient, as part of a comprehensive intake history.

BENZODIAZEPINE & Z-DRUG REVIEW – KEY QUESTIONS TO EXPLORE WITH THE PATIENT

Do they use any benzodiazepines or Z-drugs? Ask about them by name. If yes, what is the source? Are they prescribed or illicitly acquired, or both?

If prescribed, what was the initial indication? How are they used? How many days of the week do they use these medications? How many pills per day? Are there ever days when they use more (binge use)? What is the effect (what would the patient say it “helps with”)?

Review the DPIN and dispensing frequency; does it align with the patient’s reported pattern of use? Are there any early refills? If the patient runs out early, do they buy or borrow more? Are there multiple prescribers and pharmacies involved? Are multiple benzodiazepines and/or Z-drugs being prescribed concurrently?

If illicitly acquired, can the patient name the benzodiazepines/Z-drugs they are using, or can they describe the pill, and the approximate milligrams? How many do they buy and how long does that supply typically last?

How do they feel between doses or periods of use? What happens if they run out?

Do they think benzodiazepines or Z-drugs are a problem? Do they feel “addicted”? Does the patient meet criteria for a sedative-hypnotic use disorder?

Physical examination can identify signs of opioid withdrawal in the context of the OAT intake or subsequent appointments. Opioid withdrawal symptoms can overlap with benzodiazepine withdrawal signs, and it can be hard to distinguish between these two conditions early on.

As the OAT induction progresses, opioid withdrawal settles and is often eliminated once the patient reaches a stable dose. At this point, residual benzodiazepine withdrawal signs and symptoms may become more apparent. Assessment of these symptoms is then part of the monitoring process if benzodiazepines are prescribed to patients on OAT to promote overall stability.

When NOT to Prescribe Benzodiazepines or Z-drugs

Benzodiazepines and Z-drugs are **highly undesirable** medications in patients on OAT and should be avoided whenever possible. The risks of sedative-hypnotics to the vulnerable OAT population have already been discussed. Hence, if the patient's history and UDS results indicate **no benzodiazepine and/or Z-drug use, the patient should be educated regarding the risks of these medications and advised to continue avoiding them.** There are almost NO reasonable indications to start a *new* prescription for a benzodiazepine or Z-drug for a patient on OAT. Even for acute anxiety, there are almost always better options, both non-pharmacological and pharmacological.

When the patient's history and UDS results indicate **infrequent use of benzodiazepines or Z-drugs, the patient should be educated and supported in discontinuing benzodiazepine and/or Z-drug use.** Even when prescribed, patients do not always take a benzodiazepine or Z-drug prescription regularly enough to become physiologically dependent. They may admit to selling or sharing the prescription to facilitate access to other drugs or resources. If the patient uses a current prescription infrequently or not at all, this prescription **MUST** be discontinued. This will sometimes require communication with the current pharmacy and prescriber of the benzodiazepine or Z-drug to explain why this prescription can be discontinued without the need for a taper over time.

Intermittent *illicit* benzodiazepine use, in patients who are not prescribed benzodiazepines by the OAT provider, is treated the same as other forms of intermittent substance use in the context of OAT. This involves non-judgemental education and treatment planning.

When a Trial of Benzodiazepines or Z-drugs May Be Appropriate

A trial of benzodiazepine prescribing is indicated when the patient identifies regular benzodiazepine use for a prolonged period. Regular use is defined as taking a benzodiazepine or Z-drug at least 5 days per week. Prolonged use being more than 6 weeks, but in many cases for months or years. Regular use that occurred over 6 weeks or less can typically be managed with a relatively short-term benzodiazepine taper to zero.

Regular, long-term use is an indication to take over existing prescriptions or prescribe benzodiazepines/Z-drugs as a trial. In the context of illicit use only, interim prescribing for stability may also be considered if the patient describes regular use and physical/UDS findings are consistent with the reported history.

A *stability prescription* can facilitate the patient working a recovery plan if they adhere to expectations and agree to an eventual taper. While benzodiazepines and Z-drugs are overall undesirable medications, a stable prescription has the following potential benefits:

- Reliable, often covered medication access, eliminating the cost and risks associated with illicit access.
- Stable blood levels, facilitating emotional regulation and engagement in psychotherapy.
- It can facilitate a slow taper once more stable on OAT.

When a prescribing trial is indicated, all benzodiazepines and Z-drugs must be consolidated into one long-acting agent, in the lowest-effective dosage. Long-acting agents, such as diazepam, are preferred in clients with substance use disorder(s) and diazepam tablet sizes are helpful for small dose reductions in eventual tapering attempts. Clonazepam is an acceptable alternative if preferred by the patient. The prescriber must account for variable cross-tolerance and note that diazepam can be more sedating than some short-acting formulations.

Dosing Recommendations

Patients can present for OAT intake using variable doses of benzodiazepines and/or Z-drugs. A useful strategy is to start by calculating the overall diazepam dose equivalency the patient is taking; see **Appendix G** for a table of benzodiazepine equivalency.⁵ Typically, 40 mg of diazepam equivalents and higher is considered high-dose benzodiazepine use. This is very risky in the context of OAT. Understanding the range in which a patient's current benzodiazepine use falls is useful context when initiating and monitoring a trial of prescribing.

Despite the variable and high-dose benzodiazepine use patients may describe, moderate doses of diazepam are often enough to stabilize benzodiazepine withdrawal symptoms and maintain alertness, once on a stable dose of OAT. This occurs for several reasons. Firstly, when patients with opioid use disorder are actively using opioids, they may also use benzodiazepines and Z-drugs to manage opioid withdrawal symptoms to some degree. Clinical experience has demonstrated that as patients stabilize on agonist therapy, the overall physiological need for benzodiazepines, or other sedatives, will decrease. Furthermore, the consistent daily dosing of a prescribed long-acting benzodiazepine can provide serum level stability to patients with concurrent sedative-hypnotic use disorder (compared to illicit use), thereby further decreasing the overall need. Lastly, given incomplete cross-tolerance and because diazepam can be more sedating than other (particularly shorter acting) benzodiazepines, a lower dose than the calculated equivalency can be very effective.

Primary care evidence also indicates that it is safe to reduce high-dose benzodiazepines by 25-50% at once, without risking serious complications of withdrawal. Again, the more sedating medications a patient is taking, the more aggressive you can be with initial dose reductions.

For patients with lower dose use, a starting dose of 5-10 mg po OD is often sufficient to prevent benzodiazepine withdrawal. Once-daily dosing is preferred as it can enhance safety with daily dispensing and possibly witnessed ingestion, if warranted, due to diversion concerns.

However, patients with significant benzodiazepine and/or Z-drug use may, initially, require split dosing to achieve stability. For patients with significant use, a practical strategy is to start diazepam 5 mg po BID, along with the OAT induction. If this is not sufficient to prevent benzodiazepine withdrawal, the dose can be adjusted every 1-3 days until the patient is clinically stable. Even for patients with high-dose daily benzodiazepine use, the maximum diazepam dose required for stability should be in the range of 10-15 mg po BID. Very rarely, a patient may require slightly more. Typically, after the first 1-2 weeks on split dosing and once patients are tolerant to the sedating effects of diazepam, consolidating to once-daily dosing is preferred, as outlined above.

In summary, the starting dose for stability and tapering is often much lower than what the patient may report using regularly. Reassuring the patient that regular reassessment will occur can decrease patient anxiety around medication changes and foster therapeutic rapport.

Dispensing Intervals

The dispensing interval of any prescribed benzodiazepines/Z-drugs should mirror the OAT dispensing schedule. As the patient earns OAT take-home doses (carries), they may also receive the same number of take-home doses of benzodiazepines/Z-drugs.

IMPORTANT NOTE: BENZODIAZEPINES/Z-DRUGS & CARRIES

In patients prescribed benzodiazepines/Z-drugs in the context of agonist therapy with methadone, the **maximum number of carries permitted per week is five**. If not medically essential, the patient should be encouraged to slowly taper off benzodiazepines over time. Once a taper to zero is complete, they may be awarded a sixth and final carry dose per week.

In the context of agonist therapy with buprenorphine and prescribed benzodiazepines/Z-drugs, the approach to carries is identical to the recommendations outlined in the [Buprenorphine/naloxone Take-home \(Carry\) Dosing Recommendations](#) section of this manual.

Monitoring & Non-Prescribed Supplementation

In patients who are physiologically dependent on benzodiazepines/Z-drugs, a structured trial of prescribed benzodiazepines is considered beneficial for the reasons already outlined. However, if patients are supplementing their use with non-prescribed sources of benzodiazepines and Z-drugs in addition to their prescribed medication, these benefits are likely offset by greater potential harms, including:

- A larger overall dose, increasing side-effects like cognitive impairment.
- Erratic use of extra medication, leading to exacerbated overdose risk, greater emotional dysregulation, and potentially poorer mental health overall.
- The risk of binge use, which is associated with a higher risk of accidental overdose death.
- The harms of accessing medication from illicit sources are no longer avoided by prescribing an undesirable medication.

Therefore, monitoring patient compliance is important when prescribing benzodiazepines.

Monitoring occurs by:

- **Routine follow up.** Ask patients regularly about additional non-prescribed medication use and observe for sedation or impairment during clinical visits.
- **Reviewing DPIN regularly.** Identify additional medication from other prescribers. Communication with the pharmacy about prescribing agreements and requesting a call if other benzodiazepines/Z-drugs are prescribed can be very helpful.
- **Pay attention to collateral.** Information from family and other care providers/pharmacists about concerning use, sedation, or impairment adds to the clinical assessment.
- **Periodic comprehensive UDS.** Objective monitoring with periodic comprehensive UDS can evaluate use of prescribed medications and rule out illicit supplementation.
- **Pill counts.** This can occur during clinical or pharmacy visits to evaluate take-home dose compliance.

If non-prescribed supplementation or diversion of prescribed benzodiazepines/Z-drugs is suspected or confirmed, the patient should receive education regarding the risks again. Regular discussions with the patient are essential to reinforce the expectation that the patient only use their prescribed medication. **If the patient has ongoing access to illicit benzodiazepines/Z-drugs and they do not adhere to the established treatment agreement, the benzodiazepine prescription should be stopped.**

In the context of ongoing illicit use, stability prescribing of a benzodiazepine is more likely to contribute to a polypharmacy overdose, rather than minimize the harm of illicit substance use. Additionally, the OAT dose and carry schedule may need to be re-evaluated. Patients may require intensification of treatment to address illicit use and build further coping skills.

Benzodiazepines & Z-drug Tapers

During OAT inductions and early recovery, it is reasonable to allow patients time on a stable dose of a long-acting benzodiazepine to adjust to treatment and the many changes recovery can bring (e.g., 3-6 months). Slow tapers of benzodiazepines are recommended in all patients on OAT after 3-6 months.

Tapers may be more urgent in the context of high doses, polypharmacy, reported or observed patient sedation, falls, motor vehicle collisions, other significant side-effects, or for the elderly.

Tapers can be approached very slowly to support the patient, but **must be attempted**, in accordance with the [Standard of Practice for Prescribing Benzodiazepines & Z-Drugs](#). The patient disagreeing with the taper attempt *is not an acceptable reason to indefinitely postpone the attempt*. The goal remains decreasing harms and the overall medication burden, while ideally maintaining or improving function and quality of life. Patients often do not recognize the benefits of the taper themselves until it is well underway.

Recommendations for tapering are outlined in the Standard. In general, gradual dose reductions in small increments can minimize withdrawal symptoms to make tapers more manageable for patients (e.g., 10-25% every 2-3 weeks). Overall, tapers may be highly individualized. Patient circumstances may influence the rate and continuation of a taper.

Even small dose reductions can be beneficial and celebrated with the patient.

Pharmacy collaboration and the direct guidance/supervision the pharmacy team can provide are essential components of a successful taper. Their expertise in dosage forms, equivalencies, and compounding can be useful to individualize tapers. Again, you can ask the pharmacist to alert you to any new prescriptions for benzodiazepines or other psychoactive agents. Ongoing discussion with the patient throughout treatment is essential, as well as documenting changes in the plan and expectations.

If the patient experiences frequent hospital admissions for a comorbid condition, where benzodiazepines may be adjusted or restarted, a care plan can be created in collaboration with hospital clinicians to limit unplanned dose escalations.

Tapering, although difficult for many, is possible. When tapering is attempted and ultimately is not feasible, and there is a documented benefit to the patient outweighing the potential harms, treatment with a long-acting benzodiazepine at the lowest-effective dose can continue.

Collaboration & Documentation Are Key

Overall, when managing benzodiazepines and/or polypharmacy, regular conversations and realistic expectations must be set upon initial assessment and throughout treatment. The patient must know what prescribers can reasonably support for the interim and long-term.

Collaboration and education are crucial, but there may be a degree of unilateral decision making when managing benzodiazepines, especially in the context of OAT and complex polypharmacy. In the end, patient safety must come first.

When prescribing benzodiazepines/Z-drugs to OAT patients, prescribers should ensure quality documentation, as outlined below.

IF PRESCRIBING BENZODIAZEPINES/Z-DRUGS & OAT, PROVIDER SHOULD DOCUMENT:

Patient education regarding the ongoing risks of these medications, interpreted in the context of the entire medication regimen, the patient's age, and other comorbid conditions. Education should highlight the benefits of deprescribing.

Discussion regarding a discontinuation strategy with approximate timeframe to begin tapering.

If available, non-pharmacological treatment modalities (e.g., cognitive behavioural therapy or sleep hygiene strategies) recommended or arranged, and non-benzodiazepine/non-Z-drug medications trialed to support recovery.

Clearly outlined expectations, including dispensing intervals (mirroring the OAT schedule), and a one-prescriber (or group of prescribers) and one-pharmacy agreement.

Discussion regarding the consequences of illicit supplementation and behaviours that will jeopardize ongoing prescriptions.

Communication and correspondence regarding the plan with other care providers, other prescribers, and the pharmacy.

MANAGING ALCOHOL USE

As with other sedatives, it is important to evaluate alcohol use at intake and throughout treatment. A detailed alcohol history will inform decisions about the induction approach and treatment planning. Alcohol use is not a reason to delay OAT induction but must be factored into the treatment plan. When regular and/or heavy alcohol use is suspected or confirmed it may be a reason to seek additional support, particularly for novice prescribers. It may even warrant admission to hospital for induction under closer supervision and for concurrent management of alcohol withdrawal.

Of note, given the improved safety profile, buprenorphine is recommended over methadone for patients with concurrent alcohol use. Furthermore, alcohol use is not an indication for benzodiazepine prescribing, but rather a contraindication if benzodiazepines are being considered for management of other clinical issues. If benzodiazepines are required for the management of alcohol withdrawal, this should be short-term and should occur under close medical supervision, preferably in an inpatient environment.

Alcohol Use & Overdose Risk

Problematic alcohol use, or alcohol use disorder, is a significant safety risk for patients on OAT, including buprenorphine. This risk is compounded by any prescribed or OTC medications with sedating properties and/or polypharmacy. The OAT dose and carry schedule may need to be re-evaluated in the context of persistent alcohol use.

Similarly, the prescribing and dispensing of all psychoactive medications warrants review, as alcohol combined with benzodiazepines or other sedatives substantially increases overdose risk. Tapering of prescribed sedatives may need to occur to offset this risk.

Collaboration with pharmacy is crucial if concerns persist around alcohol. Prescribers should discuss expectations with the patient about holding doses if sedation or intoxication is observed. Making pharmacists aware of alcohol use concerns can increase their vigilance when assessing the patient during pharmacy visits.

It is important to keep in mind that alcohol use can be normalized within patient social circles, and they may not identify their consumption as problematic. Patients may need reminding about the compounding risk of combining alcohol with OAT and other medications. Discuss and document safety considerations, consumption parameters, and treatment options.

Of note, alcohol use is not detected on comprehensive urine drug screens.

Medication-Assisted Treatment

Patients meeting criteria for alcohol use disorder may benefit from relapse-prevention medications to promote abstinence. Patients who are not on opioids/OAT may be appropriate for treatment with naltrexone. Patients on OAT cannot take naltrexone as it is an opioid-receptor antagonist, but they may be suitable for a trial of acamprosate.

Acamprosate can also be considered over naltrexone in the case of severe liver impairment.

Acamprosate is a structural analogue of γ -aminobutyric acid (GABA). The exact mechanism of action of acamprosate is unknown. While the evidence for acamprosate to assist with maintaining sobriety is not as robust as for naltrexone, it may be valuable as an adjunctive treatment in patients who are engaging in psychosocial treatment for alcohol use disorder. One of the advantages of acamprosate is that it does not need to be discontinued if the patient has a brief relapse to alcohol consumption.

Acamprosate is typically well tolerated, with the most common side effect being diarrhea. This is dose-related and usually transient. Starting acamprosate at 333 mg po TID for a few days, before escalating the dose to 666 mg po TID, may be helpful to ameliorate this side effect. In moderate renal impairment the maintenance dose is 333 mg po TID.

Acamprosate is rather costly if a patient does not have public or private medication coverage. This issue needs to be explored with patients as part of the discussion around this treatment option.

Patients with problematic alcohol use may also benefit from more intensive addiction treatment to reduce their drinking or to achieve their goal of abstinence.

MANAGING NICOTINE USE

Cigarette smoking and other forms of tobacco/nicotine use remains common in patients with opioid use disorder. **This continues to be a major cause of morbidity and mortality.** All patients must be asked about smoking and the use of other nicotine products, including vaping.

There are no contraindications to the use of nicotine-containing smoking cessation aids with OAT, including combined nicotine replacement therapy. Other options to consider and review with patients are varenicline and bupropion. Combined therapy may be more effective for some patients, e.g., combined nicotine replacement in combination with varenicline or bupropion.

The treatment plan, potential side-effects of prescribed agents, and discussion regarding complementary non-pharmacological treatment options should be documented.

MANAGING CANNABIS USE

Screening and discussion around the use of cannabis products should be part of an OAT intake assessment and regular follow up. Like other drug use, ask about duration of use, patterns of use, amount, route, source, and the effects. Patients may use cannabis by smoking, vaping, and/or ingestion and may acquire it from a licensed dealer, commercial store front, or illicitly. They may use to offset symptoms or side-effects of the intoxication and withdrawal cycle, or to cope with other mental health symptoms.

Although cannabis use does not typically affect a patient's ability to earn or maintain carries – unless associated with other forms of problematic substance use – it can still negatively impact patients who smoke regularly and/or heavily. Amotivation, psychosis, and heightened anxiety can arise from regular use and exacerbate overall mental health issues.

Additional information can be found in the CPSM [Standard of Practice for Authorizing Cannabis for Medical Purposes](#), which came into effect November 1, 2020.

MANAGING ILLICIT STIMULANT USE

Stimulant use is also common in patients with opioid use disorder. Use may be intermittent or chronic. Stimulants may be used recreationally, to cope with opioid withdrawal symptoms, or patients may meet criteria for a concurrent stimulant use disorder. Stimulant use requires evaluation upon intake and routine screening throughout care. Cocaine and/or methamphetamine use is of particular concern, as it may cause instability and involves risky behaviours that can lead to increased harm or overdose. Presently, methamphetamines play a significant and concerning role in the Manitoba overdose crisis.

Routine monitoring for stimulant use should be factored into take-home dose decisions and the overall polypharmacy management plan. Again, patient safety is paramount.

Patients continuing to use stimulants may also benefit from education regarding harm-reduction strategies. Regular testing for sexually transmitted and blood-borne infections (STBBIs) is recommended for most patients with substance use disorders but can be particularly relevant for people who use stimulants.

More intensive addiction treatment may be warranted to promote abstinence if that is the patient's goal. Patients can also be educated about crisis and emergency services for urgent intervention around substance-related mental health issues or psychosis.

MANAGING OTHER PSYCHOACTIVE MEDICATION USE, BOTH PRESCRIBED AND ILLICIT

The medications included here are commonly prescribed and often part of the polypharmacy picture. The OAT provider may inherit prescribed gabapentinoids, cyclobenzaprine, quetiapine, trazodone, or antidepressants. These medications may also be diverted, and some patients will use them to manage opioid withdrawal symptoms, or they may develop concurrent use disorders. Upon intake, evaluation of these medications is crucial.

Key questions to consider for other psychoactive medications include:

- What is the source; is it prescribed or illicitly acquired, or both?
- What was the initial indication for prescribing?
- Review the DPIN and dispensing frequency; is the medication filled more often than intended? Are there multiple prescribers and pharmacies involved?
- Do they take them as prescribed? Do they skip doses or overuse these medications?
- If illicitly acquired, can they name or describe the pills and the approximate milligrams?
- What symptoms does the medication help with? Do they find them effective?
- Do they think these medications are a problem?

If taking over a prescription, discuss and document the plan with the patient, other care providers, and the pharmacy as described in the [APPROACH TO POLYPHARMACY](#) section. Dispensing intervals should mirror the OAT schedule in most cases.

Gabapentinoids

Gabapentinoids are commonly prescribed, often without a clear indication, and can be part of the polypharmacy picture. Given their sedating and psychoactive properties they can also substantially increase the overall risk of overdose when combined with OAT and/or other sedatives. Patients may use these from prescribed and/or diverted sources, often in high doses, to alleviate opioid or benzodiazepine withdrawal symptoms, or to treat physical and/or emotional pain. If a prescription is inherited, review the DPIN, clarify the indication, ask how they are taking the medication, and if it is effective.

If there is no clear neuropathic pain or other appropriate medical indication, a taper to zero is indicated. Gradual tapers are recommended to prevent unpleasant withdrawal symptoms. Non-urgent tapers are typically well tolerated when the overall dose is reduced by 100 mg daily, per week. In more urgent cases, the dose can be reduced by 300 mg daily, per week. If the initial dose exceeds 3600 mg, an initial larger dose reduction of up to 25% may be considered, especially in the context of polypharmacy.

It is not recommended to prescribe gabapentin when the patient reports exclusively illicit use. Education and support to reduce illicit use is indicated, along with careful management and tight dispensing of OAT and other sedating medications.

If gabapentinoids are indicated for the treatment of neuropathic pain and demonstrated as effective to improve the patient's function and quality of life, ongoing prescribing may be appropriate. Document the benefit to the patient, the discussion regarding the potential harms, and ensure polypharmacy management strategies are in place. Prescribe the lowest-effective dose and do not exceed the maximum recommended daily dose of 3600 mg.

There is some evidence for use of gabapentin to support early abstinence in patients with alcohol use disorder. In the context of OAT, gabapentin is not routinely recommended for this purpose, given the abuse and diversion potential identified in Manitoba. However, in a patient with severe and treatment-resistant alcohol use disorder, a controlled trial of gabapentin for this indication may be reasonable if other options have failed and there is ongoing significant use with harms. Prescribers should discuss such treatment in consultation with an addiction medicine specialist.

Muscle Relaxants

Like gabapentinoids, the use of muscle relaxants (e.g., cyclobenzaprine and baclofen) can be common and warrants review. If inheriting prescriptions, review the DPIN, clarify the indication, ask how patients are taking them, and if they are effective. With all muscle relaxants, document a clear indication for continued prescribing, as well as a discussion of the intended use and risks, and implement safe dispensing practices. **In general, in the OAT population, these medications should be discontinued and avoided whenever possible.**

Quetiapine & Trazodone

These medications are commonly prescribed in lower doses to manage insomnia and/or acute anxiety, in early treatment. This strategy is often used while waiting for a SSRI, SNRI and/or CBT interventions to take effect. Also, sleep often improves naturally once patients stabilize on OAT and establish a healthier diurnal sleep-awake cycle, but this may take several weeks.

It is important to note that given their sedating and psychoactive properties, quetiapine and trazodone can also increase the overall risk of overdose when combined with other sedatives. These medications can also be diverted and may be used illicitly by some patients for the

sedative effects or to cope with opioid-withdrawal symptoms. Ask patients if they have used either quetiapine or trazodone from non-prescribed sources. If inheriting prescriptions, review the DPIN, clarify the indication, ask how patients are taking them, and if they are effective. Again, if prescribing is indicated and effective, dispensing intervals should mirror the OAT schedule in most cases.

Prescribed Stimulants

Patients may be inherited on prescribed stimulants and the same diligence described above must be applied to evaluate appropriate or inappropriate use, addictive potential, and safe prescribing of such medications, if indicated. If concerns exist around attention-deficit symptomology, a referral for psychiatric evaluation and treatment recommendations is strongly recommended prior to initiating prescription stimulants. If a trial is warranted, long-acting tamper-proof formulations are preferred whenever possible. Restricted dispensing of prescription stimulants is also strongly recommended, mirroring the OAT carry schedule.

Antidepressants (Bupropion, Tricyclics, SSRI/SNRIs)

Management of mood and anxiety symptoms or concurrent disorders can be critical to improve the overall well-being for patients on OAT. Treatment with antidepressants is worthwhile, with safe prescribing practices in place as antidepressants can also contribute to overdose deaths. Limited dispensing and routine screening for compliance is warranted. Comprehensive UDS can be a useful tool to supplement clinical monitoring, however, knowledge of what medications are detected is essential – see **KNOW YOUR TOOL** on page 9.

A clear indication should exist when prescribing an antidepressant. Select the medication best suited to the symptoms; is depression, anxiety, insomnia, wakefulness and/or chronic pain the target for intervention? Discuss the intended effect, trial duration, expectations, and safety concerns with the patient, and document the plan.

Note that some antidepressants may carry an increased risk of abuse or diversion; there have been reports of illicit bupropion use for the stimulant properties. Tricyclic antidepressants are commonly used as adjunctive therapy in the management of chronic pain and certain types of headaches. However, **tricyclics remain lethal in overdose and the amount of medication required for a lethal overdose is relatively small. Therefore, in the OAT population, tricyclics should only be prescribed when other options have been exhausted, and dispensing must be tightly controlled.**

IMPORTANT NOTE: LESS IS OFTEN MORE

There is little evidence that prescribing more than one agent from the same class of drug improves clinical outcomes, but it can contribute to polypharmacy and all the associated risks. **If available, non-pharmacological treatment modalities for depression, anxiety, trauma, and pain should be explored to support recovery.** Consider referral to additional services or an addiction-aware psychiatrist for recommendations, especially for patients with complex needs.

MANAGING OVER-THE-COUNTER MEDICATION USE

As noted, the OCME death reviews demonstrate that OTC medication use, combined with illicit and/or prescription drugs, significantly increases overdose risk. The use of OTC medications by patients with opioid use disorder is common to manage a variety of symptoms. Prescribers must screen patients for OTC use upon initial assessment and routinely throughout care.

Diphenhydramine, Dimenhydrinate & Dextromethorphan

In 2018, the OTC medicinal ingredients contributing to the largest number of overdoses included diphenhydramine, dimenhydrinate, and dextromethorphan. Diphenhydramine, an antihistamine and anticholinergic, is widely used in non-prescription sleep aids for insomnia, namely for its sedative and anxiolytic properties. Diphenhydramine is also the primary constituent of dimenhydrinate, an antiemetic, and dictates the primary effect. The main difference relative to pure diphenhydramine is a lower potency in comparison, due to the combination with 8-chlorotheophylline that has stimulant properties.

Dextromethorphan, a cough suppressant commonly found in cold medications, can act as a dissociative anesthetic in doses exceeding the recommended range. Dextromethorphan at high doses and its major metabolite, dextrorphan, can produce similar effects to the dissociative states created by other anesthetics such as ketamine and phencyclidine (or phenyl cyclohexyl piperidine, PCP).

Codeine is also a major contributor to polypharmacy overdose and some codeine-containing products are still available over the counter in many provinces.

Patients with opioid use disorder may use these OTC medications to alleviate opioid-withdrawal symptoms. Symptoms such as anxiety, irritability, restlessness, agitation, or insomnia may be muted by OTC overuse, and this may develop into a concurrent use disorder. Patients may also use dimenhydrinate or loperamide products for nausea or gastrointestinal issues associated with opioid use or withdrawal.

Screen & Manage Like Other Sedatives

Like other sedatives and psychoactive agents, screening for OTC medication use is an important part of comprehensive care. Ask patients if they use any OTC medications to manage the effects of withdrawal or intoxication, perhaps listing common trade name examples such as, but not limited to, Gravol™, Benadryl®, Nyquil™, Benylin®, or Tylenol® PM.

As patients stabilize on OAT, the frequency of OTC use may naturally diminish as the cycle of intoxication and withdrawal normalizes. Conversely, other patients may continue or increase the use of OTC medications while on OAT to escape unpleasant feelings. Some patients may wrongly perceive OTC medications as safe compared to illicit substances, particularly if they continue to struggle with symptoms such as anxiety or insomnia.

As part of regular screening, prescribers should consult with the treatment team, including pharmacists, regarding concerning presentations or behaviours that may suggest OTC medication use. Collateral from family can also be helpful to determine frequency of purchase and the impact on the patient. Routine comprehensive UDS's can also provide useful information.

As noted, OTC medication use can develop into a separate substance use disorder and some patients may require intensification of treatment. Management strategies to increase safety may include removal of carry doses or tapering of other prescribed sedatives to offset the overdose risk. Patients may benefit from referral for more support to develop non-chemical coping skills through counselling and/or residential treatment to break the pattern of use.

OTHER SUBSTANCES TO CONSIDER

As noted, the substances outlined above are not an exhaustive list of possible medications or drugs of abuse. Other medications that may warrant review for safety considerations include, but are not limited to, nabilone, nabiximols (Sativex®), ketamine, and sodium oxybate (Xyrem®), which is the sodium salt of *gamma*-hydroxybutyric acid or GHB.

References

1. Younes J. Manitoba Office of the Chief Medical Examiner (personal communication, 2014-2021).
2. Abrahamsson T, Berge J, Ojehagen A, Hakansson A. Benzodiazepine, z-drug, and pregabalin prescriptions and mortality among patients in opioid maintenance treatment – A nation-wide register-based open cohort study. *Drug and Alcohol Dependence*. 2017; 174:58-65.
3. Leece P, Cavacuiti C, Macdonald EM, et al. Predictors of Opioid-Related Death During Methadone Therapy. *Journal of Substance Abuse Treatment*. 2015; 57:30-35.
4. Glass J, Lanctot K, Herrmann N, Sproule B, Busto U. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ*. 2005; 331(7526):1-7. doi:10.1136/bmj.38623.768588.47 (published 11 November 2005)
5. McMaster MGD National Pain Centre. *Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain: Practice Tool Kit*. Available at: <http://nperesource.casn.ca/wp-content/uploads/2017/01/practicetoolkit.pdf>

Appendix G

BENZODIAZEPINE EQUIVALENT TABLE

from The Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer
PRACTICE TOOL KIT ⁵

Benzodiazepine Equivalent Table

Source: Adapted from Kalvik 1995; Canadian Pharmacists Association 1999.

Benzodiazepine	Equivalent to 5 mg diazepam (mg) *
Alprazolam (Xanax®)**	0.5
Bromazepam (Lectopam®)	3–6
Chlordiazepoxide (Librium®)	10–25
Clonazepam (Rivotril®)	0.5–1
Clorazepate (Tranxene®)	7.5
Flurazepam (Dalmane®)	15
Lorazepam (Ativan®)	0.5–1
Nitrazepam (Mogadon®)	5–10
Oxazepam (Serax®)	15
Temazepam (Restoril®)	10–15
Triazolam (Halcion®)**	0.25

* Equivalences are approximate. Careful monitoring is required to avoid over-sedation, particularly in older adults and those with impaired hepatic metabolism.

**Equivalency uncertain.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.7 Recommendations for the Use of Urine Drug Testing in the Management of Opioid Use Disorder

GENERAL CONSIDERATIONS

Urine drug testing (UDT) is an important clinical tool in the management of patients with opioid use disorder (OUD) who are treated with opioid agonist therapy (OAT). UDT is considered a standard of care in OAT¹ and has the potential to enhance patient and public safety. When used appropriately, UDT helps to confirm or refute patient compliance with the treatment plan and helps assess the overall risk posed by ingested substances. It forms the basis for demonstrating the stability needed for patients to earn take-home doses in OAT. UDT can also help providers understand local drug use patterns and raise red flags for diversion.

However, routine use of UDT should be balanced against the cost to the healthcare system, as well as some associated harms. For example, UDT can undermine the patient's sense of autonomy and trust in providers². A 2014 systematic review of the use of UDT in OAT concluded that there was insufficient evidence to demonstrate the usefulness of the practice³. A critical review of the literature from 2019 supported the use of UDT as a standard of care, but added that the area requires further research⁴.

This chapter outlines recommendations for the use of UDT for OAT providers in Manitoba, based on evidence, cost-benefit balance, and local clinical expertise.

While the principles of UDT identified here may be useful in other clinical situations, the scope is limited to the management of OUD in the outpatient setting with OAT. Recommendations for UDT in the context of polypharmacy and polysubstance use in OUD are reviewed briefly, where clinical overlap is a common challenge. This chapter does not specifically address an approach to patients using opioids for chronic pain exclusively, and is not for application in emergency or palliative care settings.

SPECIFIC CONSIDERATIONS

A PATIENT-CENTERED APPROACH TO UDT

A patient-centered approach to care is essential in the management of substance use disorders, as it leads to improved treatment retention and health outcomes⁵, two of the main goals of OAT. The process of UDT can be stigmatizing and damaging to the development of a therapeutic relationship². As UDT is often perceived negatively by patients, clinicians should take active steps to help patients understand and accept its role in treatment.

From the first visit, OAT providers should ensure that patients understand UDT as a routine practice and that its intent is to optimize their safety. Providers should encourage frank discussion and explain the role of UDT in earning take-home (carry) doses, and the loss of carry doses, according to the clinic policy. Other potential impacts on the management plan should be explained during visits, such as reducing dispensing intervals of other prescribed medications in the interest of patient safety.

Reiterate that any changes in the management plan triggered by UDT results are intended to support patients toward increased clinical stability, not as punishment for bad behavior. It can be helpful to reinforce that OUD is not viewed as a moral failing, but rather as a chronic disease, in which relapse and periods of instability are common and manageable. Clinicians should avoid referring to test results using judgmental terms such as “clean” and “dirty”, preferring neutral terms such as “positive” or “unexpected results”.

Patients can be given the opportunity to disclose drug use prior to providing a sample or reviewing the results, to avoid the appearance that the provider is trying to “catch them in the act”. **Finally, clinicians should exercise extreme caution before accusing patients of dishonesty or implementing punitive measures due to UDT findings alone.** UDT results are subject to false positives and false negatives⁶. Clinicians often make errors in interpretation that can have very unfortunate outcomes if therapeutic relationships break down and patients leave treatment.

Patients should be assured that their UDT results will not be used to withhold OAT treatment. Diversion can be difficult to prove even with regular use of UDT. However, if it becomes clear that patients are not engaged with OAT and are likely diverting their prescription (by using information gathered from UDT, clinical assessment, and/or collateral history), it may be necessary to discontinue prescribing. In these rare cases, where the benefits of continued prescribing are outweighed by the risks to the patient or the community, every attempt should be made to engage the patient in harm reduction strategies and extend the offer of treatment in the future. Treatment agreements are effective tools to review the role of UDT and behavioural/safety expectations with patients when initiating OAT and throughout care, particularly if concerns arise that may warrant withdrawal of treatment. See the [Comprehensive Assessment](#) chapter section on treatment agreements and [Discontinuing Treatment](#) for further guidance on these topics.

TESTING METHODOLOGIES AVAILABLE

The two types of UDT used in the management of OUD with OAT are **immunoassays** and **liquid chromatography high-resolution mass spectrometry** (also known as a comprehensive urine drug screen or C-UDS). Immunoassay testing is available in two formats: point-of-care (POC) kits used in clinic or Immunoassay Drug Screens. The latter is commonly known as a “Street Drug Screen” on older versions of the UDT requisition and is performed at Westman Laboratory and St. Boniface Laboratory, with testing done 24/7. Comparatively, C-UDS is significantly more expensive than POC testing. Therefore, when available and clinically appropriate to do so, POC tests should be used preferentially. In general, comprehensive testing should be reserved for specific clinical scenarios, as detailed below.

Point-of-Care Tests

For most purposes, POC is the preferred method of testing as it provides immediate results that can be shared with the patient and used in the development of a timely management plan¹. It should be ordered upon initiation of treatment and for follow-up testing.

Disadvantages of POC tests include the cost to the provider/clinic and the lack of specificity of information that is sometimes required (see *Interpretation of Results* below). Immunoassays often detect a class of drugs (e.g., opioids, benzodiazepines) rather than a specific drug. They are often *not* equipped to detect semi-synthetic opioids (oxycodone, hydromorphone), synthetic opioids (fentanyl), some common benzodiazepines, or the metabolites of drugs of abuse. Because they are based on antibody detection, there is potential for cross-reactivity (false positives) with other drugs. Where POC testing gives an unexpected result, laboratory confirmation with C-UDS is recommended if it will impact the clinical management of the patient⁷.

There are many POC tests available, and it is important to be familiar with the features of the test used in your practice. Clinicians should consider cost and local drug use patterns in determining the best POC test for their clinical setting. Basic assays usually include some combination of benzodiazepines, amphetamines, methamphetamine, cocaine, opioids (naturally occurring, such as heroin, morphine, and codeine), methadone and its metabolite EDDP, THC and PCP. Since class tests will likely miss semi-synthetic and synthetic opioids, it is **recommended to purchase POC tests that will specifically look for hydromorphone, oxycodone, fentanyl, and buprenorphine for use in the OAT patient population.**

Comprehensive Urine Drug Screens

C-UDS is recommended when initiating OAT therapy. Confirmatory testing with C-UDS is also recommended in the case of unexpected POC test results, either positive or negative, when further information is needed to formulate an appropriate treatment plan for a patient.

It is *not* recommended to use C-UDS routinely for the follow-up of OAT patients, including for the routine determination of clinical stability⁷.

For providers with limited or no access to POC testing, an Immunoassay or “Street Drug Screen” rather than a comprehensive screen can be ordered for this purpose (see the provincial [Urine Drug Screen Requisition Form](#)).

Occasionally, when a patient is known to use a substance that cannot be specified on POC testing, C-UDS will need to be used in place of POC for routine monitoring. As an example, heroin cannot be distinguished from morphine by POC, as both will test positive for naturally occurring opioids. For a patient on slow-release oral morphine (SROM), whose drug of choice is heroin, C-UDS will be needed for monitoring.

The main disadvantage of C-UDS, other than the cost to the healthcare system, is that results can take up to one week and are therefore less helpful in timely treatment planning.

The list of medications which are routinely screened for in a comprehensive drug screen by Diagnostic Services was reduced, as of June 2021, to contain costs. A specific list of the approximately **80 substances** tested for on a comprehensive screen is available [here](#). This specific panel of drugs is intended to balance clinical utility with a cost-effective approach to testing. **This is essential information for prescribers to correctly interpret C-UDS results in the interest of patient care.**

Physicians are encouraged to document all prescription and illicit substances known to be used by the patient and to formulate a clear clinical question on the laboratory requisition. If a physician is interested in the presence or absence of a specific compound not included in the routine test, Diagnostic Services may be able to add the substance of interest to the test. They can only do this if the request is clearly written on the requisition.

The College of Physicians and Surgeons of Manitoba (CPSM) is taking the lead on providing ongoing feedback to Diagnostic Services regarding the list of reported compounds and welcomes feedback from registrants on drugs of interest to be added to the list. To offer feedback, prescribers can contact Dr. Marina Reinecke, Medical Consultant to the CPSM Prescribing Practices Program, at 204-774-4344.

INTERPRETATION OF RESULTS

UDTs should always be interpreted by a clinician who is familiar with the patient’s clinical situation and knowledgeable about the tests used. Caution should be used before making impactful treatment decisions based on results of UDT, such as removal of carries or an involuntary taper from OAT.

In general, a pattern of unexpected results is more reliable than a single aberrant test.

False negatives can occur when:

- The drug is present below the threshold of the test,
- The drug is not detected by the test,
- The test occurs outside the window of exposure, or
- Occasionally, there are individual variabilities in metabolism, such as in the case of certain prescribed medications or medical illnesses.

False positives can occur when:

- Substances cross-react with other drugs,
- The supply is contaminated with an unexpected substance,
- A patient intentionally tampers with the sample in an attempt at diversion, or
- Rarely, in the case of passive exposure.

It is important to note that cross-reactivity is only possible with immunoassays; *not* with C-UDS. Commonly prescribed medications known to cause false positives for opioids on a POC test strip include trazodone, risperidone, paliperidone, quetiapine, and verapamil¹.

The Nature of Detection

Generally, most substances will test negatively if the patient abstains for 2-3 days prior to testing, with some common exceptions. Methadone can be detected up to a week. THC can be detected for days to months, depending on duration and amount used. With chronic use of fentanyl, it can remain detectable in the urine for up to 4 weeks due to its lipophilic properties. Diazepam used in the context of alcohol withdrawal (large quantities administered over days in hospital) will also remain detectable for up to six weeks, depending on the amount used. Therefore, a positive test for these medications does not necessarily mean ongoing use⁸.

POC tests are not quantitative and C-UDS results are not reported quantitatively. Results are reported as the presence or absence of a substance, above a specified threshold level, and therefore cannot be used to determine how much or how often a substance was used. As such, chronic vs. sporadic use (e.g., a single episode of relapse) can only be demonstrated by repeated tests. Additionally, diversion of a portion of the prescribed medication, or supplementing with an illicit supply of the same prescribed medication, cannot be proven or disproven with UDT, since the amount taken cannot be determined.

Metabolites

C-UDS panel includes the metabolites of many drugs of abuse. Results of confirmatory testing must be interpreted cautiously, so that patients are not accused falsely of taking medications that are in fact metabolites of drugs they are known to be using.

For example, codeine breaks down to morphine, and diazepam breaks down into temazepam and oxazepam. Similarly, morphine metabolism includes a small amount of hydromorphone production. A positive result for hydromorphone may be due to high doses of morphine, typical of SROM, and not indicative of hydromorphone use.

C-UDS panel also includes some agents used to “cut” street drugs. The presence of levamisole, an anthelmintic, for example, is indicative of cocaine use. It is commonly used to increase the weight of the cocaine, and unfortunately can cause vasculitis, leading to necrosis of the digits.

CLINICAL INDICATIONS FOR UDT IN OAT

UDT should be used along with clinical assessment (history and focused physical examination) for the monitoring of OAT, to:

- Confirm opioid use during initial assessment prior to initiating therapy.
- Assess clinical stability by:
 - Screening for ongoing non-prescribed or over-the-counter medication use, as well as illicit substance use. Special attention is paid to the use of illicit opioids, as ongoing use may indicate a need for an OAT dose increase.
 - Confirming that prescribed medication is being taken in patients with carry doses.
- Support decision making regarding carry doses.
- Identify local trends in compound availability and use patterns.

Initial Assessment

POC testing is usually performed at the first visit, to confirm recent opioid use. However, false negatives can result if the patient uses in small amounts, intermittently, or uses a semi-synthetic or synthetic opioid not found on the POC test. UDT would also not detect opioids in patients with a recent period of abstinence, such as incarceration or residential treatment.

Providers practicing remotely may not have access to POC tests at the time of presentation of the patient. Clinicians must use clinical judgement in these cases as to whether it is safe to start OAT with a convincing history and physical exam, but a negative or absent POC test. In most cases, the harms of delaying treatment outweigh the risks of starting OAT in the absence of UDT results. **Buprenorphine is strongly preferred over methadone and SROM in this situation.**

In cases where there is no POC available or it is negative for opioids, AND the clinician has doubt as to whether opioids are currently being used, it is strongly recommended to collect a urine sample for C-UDS and await results prior to starting OAT.

In select cases, where POC is not available, lab immunoassays can be ordered *in addition to* C-UDS. Both Westman Laboratory (Brandon) and St. Boniface Laboratory perform immunoassay

UDT. Most rural testing is conducted at Westman Laboratory, where turnaround time for immunoassay results is faster than for C-UDS. Confirming opioid use sooner can facilitate earlier induction. In such cases, C-UDS results may then serve to confirm the immunoassay results and provide a broader analysis of other prescribed and illicit drugs used by the patient.

C-UDS is also recommended at the first visit or shortly thereafter. This panel will provide an accurate picture of the illicit substances being used, as well as any prescribed and over-the-counter medications the patient is currently taking. Results should be compared to the patient's medication record (DPIN) and self-reported substance use history. Ideally, a DPIN record including all medication entries over the preceding six months should be reviewed together with the patient.

Common drugs of concern that are not identified on POC tests include gabapentinoids, dimenhydrinate, tramadol, trazodone, antidepressants, antipsychotics, and Z-drugs. **Each of these may contribute to patients' overall risk and will need to be addressed individually, whether prescribed or illicitly obtained.** This is an opportunity for the provider to engage in harm reduction conversations with patients and to review their overall treatment goals. Safety measures may be instituted when appropriate, such as daily dispensing of psychoactive and/or sedating medications to reduce overdose risk or a monitored taper of unnecessary or contraindicated medications.

The section [AN APPROACH TO POLYPHARMACY IN THE CONTEXT OF OAT](#) in [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use](#) provides useful recommendations to support medication reviews. The [Comprehensive Assessment](#) chapter also provides guidance on collecting a detailed substance history.

The presence of other high-risk substances (including benzodiazepines) is not an absolute contraindication to initiation of OAT, given the relative safety of OAT compared to ongoing opioid abuse, but should always be addressed in the management plan.

The UDT policy of the practice setting should be explained to patients at the first visit, including how unexpected results will be handled. Treatment agreements also present an opportunity to provide a written explanation of the UDT policy, with attention to literacy level. See the [Comprehensive Assessment](#) section on treatment agreements for further guidance. For most patients, any opioid use unless prescribed by a provider, presence of non-prescribed medications with sedative/psychoactive properties and/or abuse potential, or any illicit drug use would be considered a positive test.

Assessment of Clinical Stability

The determination of clinical stability is never based on UDT results alone. Clinicians should rely on patient history, collateral information, and direct observation/clinical examination, which is augmented by information collected from UDT, to formulate treatment plans in partnership with the patient.

Clinicians should monitor for a consistent pattern of presence of the treatment drug(s) and absence of other opioids/drugs of abuse in the urine, together with improvement in overall health status and quality of life. These findings in combination suggest the patient is on an effective management plan. Once the pattern is established, patients can start to receive take-home doses and require less frequent UDT monitoring and clinical follow-up.

Ideally, POC UDT that includes a dedicated buprenorphine strip should be used. If buprenorphine is absent on POC, it is often due to a limitation of the POC test itself and can be clarified with C-UDS.

Historically, C-UDS in Manitoba did not reliably detect buprenorphine. The C-UDS panel now contains the glucuronides of both buprenorphine and norbuprenorphine and can accurately detect these drugs (parent drug and metabolite). For clinical interpretation, however, it may be useful to note that C-UDS *primarily* detects buprenorphine-glucuronide and norbuprenorphine-glucuronide, not the parent compounds.

Absence of the treatment drug, particularly in the case of methadone or morphine, is concerning for diversion in patients with carries. Return to daily witnessed dosing is indicated in the interest of patient and public safety. Furthermore, if patients are diverting a portion of their doses, loss of tolerance can rapidly develop, often requiring a fifty percent or more dose reduction and increased clinical follow-up. Close communication with the pharmacist is also recommended.

After an initial dose reduction, frequent follow-up will allow for appropriate and safe OAT dose adjustments (up or down) depending on how the clinical situation evolves. Where a pattern of repeated attempts at diversion is clear, together with lack of engagement in treatment goals, involuntary withdrawal of treatment may be necessary. See [Discontinuing Treatment](#) for further guidance on these topics.

POC testing is also used to monitor for substances of concern:

- **Ongoing opioid use or intermittent relapses** should prompt non-judgemental discussion about adjustments to the treatment plan. Clinicians should exercise clinical judgement regarding the most appropriate response in each circumstance, such as an OAT dose increase or a different OAT medication for patients experiencing ongoing withdrawal and cravings.

Referral for additional supports for patients experiencing psychosocial stress, or alternate pain management approaches for patients with concomitant pain, may also need to be considered. Returning to previous levels of monitoring and removal or reduction in carries in response to relapse is standard in most settings (see [Decision Making Regarding Take-home Doses](#) below).

- **Use of stimulants, such as methamphetamine or cocaine**, for example, can undermine patient stability and may require implementation of other strategies, such as referral for residential treatment (treatment intensification).

Amphetamines, as a rule, have the highest number of false positives of any class of drug on **immunoassay testing only** (POC UDT and lab immunoassays). A positive result for “amphetamine” on the immunoassay can possibly mean that the analyte detected was amphetamine, MDMA, MDA, MDEA, methamphetamine, etc. Cross-reactivity can also occur with aripiprazole, bupropion, chlorpromazine, fluoxetine, trazodone, and venlafaxine¹. When a POC test is positive for amphetamine, it is essential to compare the results to DPIN and to inquire about use of illicit prescription medications, including those used in the treatment of ADHD.

However, on **C-UDS**, amphetamine, MDMA, MDA, MDEA and methamphetamine, can be identified individually. Only ephedrine and pseudoephedrine cannot be distinguished. Aripiprazole, bupropion, chlorpromazine, fluoxetine, trazodone, and venlafaxine can also be differentiated from amphetamine and methamphetamine with C-UDS. There is no cross-reactivity with this methodology.

- **Benzodiazepines/Z-drugs are of particular concern in terms of patient safety and overdose risk**¹. Presence of benzodiazepines/Z-drugs is not a contraindication for starting or continuing OAT, but clinicians should review the type of benzodiazepine/Z-drug used (prescribed vs. illicit), consider the diagnosis of sedative-hypnotic use disorder, and initiate a taper if indicated.

In patients with benzodiazepines detected on POC testing, C-UDS is required to determine which drugs are being taken. As noted, diazepam breaks down into temazepam and oxazepam, so these three cannot be distinguished even on comprehensive testing. Alprazolam and clonazepam each have unique metabolites and can be identified on C-UDS. Note that lorazepam is not currently reliably detected on C-UDS, as lorazepam-glucuronide is not currently tested for. Most benzodiazepines are highly metabolized, so it may be missed if the metabolite is not tested for on C-UDS.

When following patients on a prescribed taper it is recommended to monitor for supplemental benzodiazepine use with regular C-UDS. Some common benzodiazepines, such as alprazolam and clonazepam, are routinely missed on POC tests⁶. Novel compounds, which are typically ordered online, will be missed on both tests. For identification of novel compounds that may be suspected based on patient history, consultation with the lab is recommended. **Clinicians can contact the Shared Health Duty Chemist on-call (phone 431-276-0131)**, available Monday to Friday, 8 am to 4 pm.

In general, a pattern of consistent presence in UDT of substances that are not prescribed should result in continued frequent monitoring of the patient and will preclude authorization of carries.

See [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use](#) for further recommendations.

Presence of THC, now legal, may not be of concern to the OAT provider in the context of a patient who uses cannabis recreationally and who has no cannabis use disorder. Patients who use recreational cannabis may still be granted carries if they are otherwise clinically stable. Of note, most POC tests do not test for alcohol, a substance that should not be ignored in the overall assessment of a patient's stability and should be part of routine history taking.

Decision Making Regarding Take-Home Doses

Patients on OAT, in most cases, start with daily witnessed dosing and progress to take-home doses with demonstrated stability, supported by UDT results. See take-home (carry) recommendations for [Buprenorphine](#) and [Methadone](#) as applicable.

In the case where UDT identifies relapse to opioid or other substance use, reduction and eventual removal of carries has the potential to help restabilize patients by increasing their contact with a healthcare provider (nurse, pharmacist), improving the consistency with which the OAT medication is taken, and reducing risk of diversion.

However, an overly aggressive policy that does not attend to individual patient circumstances (e.g., issues of work, childcare, travel restrictions, or sense of self-efficacy) can have a negative impact on treatment retention. Recently published Canadian data, arising from the COVID-19 pandemic, revealed that loosening restrictions on take-home doses did not increase harm to patients, but did improve retention rates in OAT programs⁹. **Some flexibility in enforcing a policy of carry reduction in response to UDT results is reasonable, especially when overall improvement in stability and attainment of treatment goals is demonstrated. Rationale for decisions to deviate from the policy should be documented.**

Identification of Local Trends

Patients are often unaware of the drugs present in the substances they are using. Many illicitly sourced drugs are pressed using pill presses to appear pharmaceutical grade and marketed as a particular drug, while containing a cocktail of other psychoactive medications. When POC testing is inconsistent with patient history, C-UDS may help identify local trends. Sharing these findings with patients is an important step to establish trust and to engage them in keeping themselves and their community safe.

Some circumstances warrant increased harm reduction planning on the part of local health providers, such as when opioids are found in drugs marketed as stimulants and could result in accidental overdose in opioid-naïve patients. Drugs sourced from the internet may contain substances that do not appear in either POC or C-UDS tests because they are novel. In such cases, providers may need to consult with the provincial laboratory to identify new substances.

RECOMMENDATIONS FOR FREQUENCY OF UDT

UDT, consisting of both a POC and C-UDS, should be collected upon initiation of OAT whenever possible. POC testing provides immediately useful information for safe induction planning. Despite the delayed result, C-UDS can then provide additional and more complete information about the prescribed, over the counter, and illicit substances that a patient is consuming. This comprehensive testing informs appropriate medication management, ongoing treatment planning, and overall risk management.

Subsequently, urine samples for POC testing should be collected when results will affect the management plan, most commonly for the purpose of establishing sufficient stability to authorize carries or to monitor the patient's use of other drugs.

The frequency of UDTs should not interfere with a stable patient's responsibilities to family and work. UDT can be obtained without necessitating a medical appointment.

UDT Frequency for Buprenorphine/naloxone

A minimum of **one C-UDS** is recommended in all patients on buprenorphine during the first three months of treatment. After that, further C-UDS should be based on clinical need/indication.

A **minimum of monthly POC testing** is recommended for all patients during the **first three months** of treatment with buprenorphine/naloxone. However, some stable patients treated with buprenorphine may wish to supply **weekly** samples initially, in order to rapidly earn take-home doses as follows:

- After participating in daily witnessed dosing for the first two weeks of treatment, patients should demonstrate a minimum of **two weeks of clinical stability and two appropriate POC results, 7-10 days apart, per each additional carry earned**, up to **once-weekly witnessed dosing**. A clinically stable patient can thereby attend the pharmacy for witnessed dosing once weekly (i.e., a maximum of six take-home doses) after 12 weeks. After that, UDT may be reduced in frequency to align with opportunities to increase take-home dosing further (see [Buprenorphine Take-home \(Carry\) Dosing Recommendations](#) for details).
- After a further three months of clinical stability (total of six months in treatment) with once-weekly witnessed dosing, and two appropriate POC tests done 7-10 days apart, patients can receive **biweekly witnessed dosing**.
- After one year of clinical stability with biweekly witnessed dosing, and two more follow-up POC tests done 7-10 days apart, patients can receive **once-monthly witnessed dosing**.

The presence of illicitly obtained opioids or other drugs of abuse in a sample should result in stepping back to the previous carry level. If clinical assessment and collateral information indicates an ongoing relapse or use of high-risk opioids (e.g., fentanyl), removal of all carries may be indicated. Patient and public safety must be the primary considerations in these situations.

During such periods of relapse or clinical instability, UDT frequency should be increased to monthly. If patients report that their illicit use is under control and wish to rapidly re-earn carries, more frequent testing (every 7-10 days) may be considered to facilitate the patient's request (if geographically possible).

For patients stabilized on buprenorphine/naloxone with **once-monthly witnessed dosing, a minimum of three to four POC tests per year (approximately every three to four months) is acceptable** to continue the established maximum carry schedule.

For patients with significant barriers to UDT, such as those living remotely or having transportation challenges, less frequent UDT is acceptable but clinical rationale must be documented. Local nursing stations and labs may be able to assist with sample collection, and such opportunities should be explored.

For patients who have no interest in earning carries, or who self-disclose use of other substances and who are therefore ineligible for carries, the frequency of UDT can be reduced. The frequency of testing in this situation, after the first three months of treatment, is determined by the stability of the patient and is at the clinician's discretion. Intermittent monitoring of the urine can encourage discussion regarding high-risk findings and reinforce treatment goals.

Non-judgemental discussion regarding UDT findings can also move patients towards healthy behavior change with substance use overall. Conversely, repeated conversations about ongoing drug use with a patient who is pre-contemplative about change can also be counter productive. **Hence the importance of clinical discretion.**

UDT Frequency for Extended-Release Buprenorphine

For patients on Sublocade® (buprenorphine extended-release injection) or Probuphine® (buprenorphine implant) frequency of UDT is at the clinician's discretion. For example, unstable patients may still require regular monthly UDT to assist with management of other substance use disorders. In a stable patient using Sublocade® or Probuphine® it is reasonable to conduct a UDT two or three times per year during follow-up visits.

Given that co-occurring substance use disorders are common and can arise at any time, the prospect of UDT may encourage disclosure and engage a patient in a new care plan before a clinically evident decline.

UDT Frequency for Methadone & SROM

Patients prescribed methadone and SROM should have **POC UDT every 7-10 days during the induction and stabilization phase of treatment**. Frequency can gradually be reduced as patients demonstrate clinical stability, to a minimum of every two months. Frequency should increase during periods of clinical deterioration.

A minimum of **one C-UDS** is recommended in all patients on methadone and SROM during the first three months of treatment. After that, further C-UDS and POC should be based on clinical need/indication:

- Patients using methadone and SROM are **not eligible for take-home doses for the first two months of therapy**, except under specific circumstances (see sections in [Methadone Induction, Titration, & Stabilization](#) regarding daily witnessed ingestion, and take-home (carry) recommendations for [Methadone](#) and [SROM](#) for specific guidance).
- After that period, once stability is established, a minimum of **three appropriate POC tests (7-10 days apart) is required to earn one additional carry dose per calendar month**, up to the **maximum** allotted carry doses of **six per week for methadone and four per week for SROM**.
- Due to the less favorable safety profiles compared to buprenorphine, methadone or SROM demands a **minimum of six UDTs** per year in clinically stable patients who have achieved maximum carries.

RECOMMENDATIONS FOR COLLECTING URINE SAMPLES

Refusal to comply with UDT requirements can be regarded as a positive urine drug screen, with the same consequences. Opioids can cause urinary hesitancy, so having water available can facilitate obtaining samples. Long wait times in the waiting room may result in patients needing to void before seeing clinic staff, so providing patients with an opportunity to give a sample for UDT upon arrival in clinic may be useful.

Given the significant potential consequences of positive UDT results, **clinical judgement should be exercised in enforcement of clinic policies**, considering real-world barriers to compliance.

Tampering with urine samples will be rare if the use of UDT is perceived as supportive to safe patient care and non-punitive. However, when a patient is diverting medications or attempting to mask their results for other reasons, they may use tactics such as substituting another individual's sample, diluting the sample, or adding compounds to the sample that are known to mask the presence of drugs of abuse. To reduce risk of swapping samples, clinics are encouraged to provide containers that are labeled with the patient's name and to have samples directly passed back to clinic staff. Patients may be asked to leave jackets and bags outside the washroom area.

POC tests are also often equipped with pH, specific gravity, and temperature strips to help detect attempts at tampering. The methadone metabolite, EDDP, will help ensure patients are ingesting carries of methadone, rather than diverting their doses and adding a small amount directly to their own or another individual's sample in order to test positive.

However, sophisticated kits can be purchased online to facilitate a patient providing a warm sample from another patient directly into an appropriately labeled container. It is important to keep in mind that UDT is only one component of assessing stability.

Direct observation of the sample collection is NOT indicated (i.e., witnessed urination)⁷.

Indicators of a tampering can be considered a positive sample and clinicians should discuss concerns frankly with the patients before proceeding with changes to the treatment plan/carry dosing, as appropriate under the circumstances.

True random sampling, which consists of calling patients in without warning, is the most clinically useful way to conduct UDT but is impractical in most clinical circumstances. If this is practiced, it is reasonable to give patients 24-48 hours to present for the test to account for work, travel, and childcare needs¹.

Most clinicians collect samples when patients attend for in-person visits and allow patients to drop in to give samples as able, without a medical visit, when trying to earn carries. In most settings this is preferable to random sampling from a practicality standpoint and achieves most of the objectives of UDT.

Third Party Requests

It is generally advised that patients should not share UDT results with third parties. Patients can be assured that their test results are private and will not be shared with third parties without their explicit consent unless the provider is legally obliged to do so through a court order.

OAT programs do not utilize "chain of custody" capable labs for UDT and requests to do so can be declined, as it is expensive and runs counter to the therapeutic intent of the test.

Organizations such as employers, treatment programs, and Child and Family Services should be instructed to conduct their own testing. However, patients are entitled to a copy of their results upon request. Patient education is important to help them understand the potential risks of sharing their results with third parties.

When in doubt, physicians can consult with the Canadian Medical Protective Association (CMPA) regarding how to proceed with a request for UDT results.

IN SUMMARY

- In general, UDT should not be used without a clear clinical reason⁷, as outlined in this guidance document.
- UDT should be accompanied by discussion with the patient about their substance use and the treatment plan, using non-stigmatizing language to discuss testing and the results¹.
- POC testing, if available, should be performed on initiation of OAT to confirm presence of opioids, and is the preferred UDT for follow-up tests. In circumstances where POC is not available prior to induction, providers can use clinical judgment to ensure timely access to treatment *if OAT is indicated*. UDT should be arranged as soon as it is feasible.
- C-UDS should be performed on initiation of OAT to establish other medication and illicit substance use that may add risk and warrant discussion with the patient, and to clarify uncertainty when POC yields an unexpected result, if it will affect the treatment plan.
- UDT results should be interpreted by a skilled clinician, familiar with both the patient's situation and the strengths and pitfalls of the test used.
- Results should not be used punitively, but rather in the context of promoting patient and community safety, and as a tool to improve stability and achieve shared goals of therapy.
- Direct observation of sample collection for UDT is not necessary and is considered invasive by patients⁷.
- As a general principle, more frequent UDT is indicated at the beginning of treatment and when patients display a change in clinical status.
- Patients receiving maximum take-home doses should have a minimum number of UDT per year (three to four annually for buprenorphine; six annually for methadone and SR/M).

References

1. British Columbia Centre on Substance Use (BCCSU). *Urine Drug Testing in Patients Prescribed Opioid Agonist Treatment – Breakout Resource*. BCCSU, BC Ministry of Health, and Ministry of Mental Health and Addictions; 2021. Available at: <https://www.bccsu.ca/wp-content/uploads/2021/07/Urine-Drug-Testing-Breakout-Resource.pdf>
2. Incze MA. Reassessing the role of routine urine drug screening in opioid use disorder treatment. *JAMA Intern Med*. 2021;181(10): 1282-1283. doi:10.1001/jamainternmed.2021.4109

3. Dupouy J, Mémier V, Catala H, Lavit M, Oustric S, Lapeyre-Mestre M. Does urine drug abuse screening help for managing patients? A systematic review. *Drug and Alcohol Dependence*. 2014;136:11-20. doi:10.1016/j.drugalcdep.2013.12.009
4. McEachern J, Adye-White L, Priest KC, et al. Lacking evidence for the association between frequent urine drug screening and health outcomes of persons on opioid agonist therapy. *Int J Drug Policy*. 2019; 64:30-33. doi: 10.1016/j.drugpo.2018.08.006.
5. Barrio P, Gual A. Patient-centered care interventions for the management of alcohol use disorders: a systematic review of randomized controlled trials. *Patient Prefer Adherence*. 2016;10:1823- 1845. doi: 10.2147/PPA.S109641.
6. Kale N. Urine drug tests: Ordering and interpreting results. *Am Fam Physician*. 2019;99(1):33-39.
7. Canadian Society of Addiction Medicine. Choosing Wisely Canada Website: Addiction Medicine. 2022. <https://choosingwiselycanada.org/recommendation/addiction-medicine/>. Accessed January 2023.
8. Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug Alcohol Depend*. 2020;214:108147 doi: 10.1016/j.drugalcdep.2020.108147
9. Gomes T, Campbell T, Kitchen S, et al. Association between increased dispensing of opioid agonist therapy take-home doses and opioid overdose and treatment interruption and discontinuation. *JAMA*. 2022;327(9):846-855. doi:10.1001/jama.2022.1271

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.8 Recommendations for the In-Hospital Care of Individuals with Opioid Use Disorder

GENERAL CONSIDERATIONS

This section addresses several important issues related to caring for individuals with an opioid use disorder (OUD) in hospital, while highlighting continuity of care between healthcare facilities and the community. **PART 1** will review who can prescribe methadone and buprenorphine/naloxone in hospitals. **PART 2** will provide recommendations for managing the specific care of individuals with OUD while admitted to hospital.

A period of hospitalization can present both opportunities and significant risks for individuals with OUD. In fact, those affected by this illness often fear hospitalization due to the anticipated discomfort of opioid withdrawal and general lack of access to adequate prescribed opioids to treat withdrawal and/or pain, safe spaces to use, harm reduction supplies, and support services that may be more readily available in the community. This can lead to affected individuals avoiding hospitalization despite medical need, or postponing presentation to the emergency department until their illness has progressed to critical severity.

Despite the above-mentioned risks, an emergency room presentation and/or hospital admission presents a valuable opportunity for addiction medicine intervention and harm reduction. Additionally, hospitalization is an opportunity for patients already on opioid agonist therapy (OAT) to be assessed and observed with a view on optimizing OAT dosing. This can also be an opportunity to address concurrent substance use, other medical and mental health issues, and evaluate the need for more intensive community-based supports.

PART 1 – PRESCRIBING OAT IN HOSPITAL

WHO MAY PRESCRIBE METHADONE & BUPRENORPHINE IN HOSPITAL?

Please note that the federal methadone exemption no longer exists. Both methadone and buprenorphine/naloxone prescribing approvals are now provincially regulated by the prescriber’s respective regulatory authority. In Manitoba, this includes the College of Physicians & Surgeons of Manitoba (CPSM) for physicians and the College of Registered Nurses of Manitoba (CRNM) for RN(Nurse Practitioners). Please see [Application, Training, & Regulatory Requirements to Provide OAT](#) for further details.

Prescribing methadone and buprenorphine for OUD in-hospital is specifically discussed in this section to guide patient care for hospital administrators, care providers, and regulators.

Recommendations in this section are guided by the principles of access to care, continuity of care, equity, patient safety, and optimal utilization of current expert resources.

Continuing Care In Hospital

A licensed physician/RN(Nurse Practitioner) practicing in a hospital in Manitoba *does not* need to apply for approval to prescribe methadone or buprenorphine/naloxone for continuation of therapy as long as the patient is:

- An inpatient of the hospital,
- Under their care,
- Currently on methadone or buprenorphine/naloxone in the community, and
- Prescribed the *same dose* or a *lower dose* as in the community.

For dose increases, new methadone or buprenorphine/naloxone starts or restarts in hospital, including take-home (carry) dosing recommendations, please refer to the sections below.

Dose Increases

For methadone and buprenorphine/naloxone, dose increases are permitted in hospital if the licenced physician/RN(Nurse Practitioner) caring for the patient documents a discussion with the patient’s community OAT prescriber or a physician member of the Health Sciences Centre (HSC) Addiction Consult Team. The on-call physician can be reached by contacting HSC paging.

The inpatient order needs to include the phrase “as discussed with Dr. _____ (name of the approved prescriber with whom the increase was discussed)”.

New OAT Starts

For methadone and buprenorphine/naloxone, new starts (inductions) are permitted in hospital if the licensed physician/RN(Nurse Practitioner) caring for the patient documents a discussion with a physician member of the HSC Addiction Consult Team. The on-call physician can be reached by contacting HSC paging.

These on-call physicians have the expertise to determine if a buprenorphine/naloxone or methadone start by an inexperienced prescriber of OAT is advisable with phone guidance from the HSC consult physician. Several factors are considered in this decision, including the patient's overall health and medication regimen, current acute medical and mental health conditions, the hospital environment, in-patient care resources and staffing level, as well as available options for continuing OAT care in the patient's home community post discharge.

A virtual consultation may be suggested by the consulting physician to facilitate an enhanced remote patient assessment and appropriate care recommendations. However, this is at the discretion of the consulting physician and not a requirement.

Inpatient orders for new starts need to include the phrase "as discussed with Dr. _____ (name of the approved physician from the HSC Addiction Consult Team)".

OAT Restarts

An inpatient restart of methadone or buprenorphine/naloxone is defined as a methadone or buprenorphine induction in an inpatient who was prescribed methadone or buprenorphine for OAT in the community during the **30 days preceding hospital admission AND treatment was discontinued for a minimum of 3 days for methadone or 6 days for buprenorphine prior to the admission date.**

For methadone and buprenorphine/naloxone, restarts are permitted in hospital if the licensed physician/RN(Nurse Practitioner) caring for the patient documents a discussion with a physician member of the HSC Addiction Consult Team. The on-call physician can be reached by contacting HSC paging.

These on-call physicians have the expertise to determine if a buprenorphine/naloxone or methadone restart by an inexperienced prescriber of OAT is advisable with phone guidance from the HSC consult physician. Several factors are considered in this decision, including the patient's overall health and medication regimen, current acute medical and mental health conditions, the hospital environment, inpatient care resources and staffing level, as well as available options for continuing OAT care in the patient's home community post discharge.

Inpatient orders for restarts need to include the phrase "as discussed with Dr. _____ (name of the approved physician from the HSC Addiction Consult Team)".

Discharge Prescriptions for OAT Medications

Hospital teams need to notify the patient's community pharmacy and community-based prescriber/clinic of the admission on the first day of admission, or as soon as possible thereafter, to facilitate coordination of a discharge prescription and to notify them that any current OAT prescriptions must be put on hold or cancelled if needed.

It is important for hospital teams to note that **only an approved buprenorphine/naloxone or methadone prescriber may provide a buprenorphine or methadone discharge prescription (utilizing the M3P format) for continuing care at a community pharmacy.** It is therefore important to involve the patient's community pharmacy and community prescriber/clinic in discharge planning *as early as possible*. This communication should **not** happen only at the time of discharge if it can be avoided, especially if a new M3P discharge prescription is needed to facilitate safe discharge.

For hospital admissions during which **no dose changes occurred** for existing methadone or buprenorphine/naloxone prescriptions, the community pharmacy may be able to reactivate the patient's existing OAT prescription that was put on hold during admission, if the end date on the prescription has not lapsed. This needs to be confirmed by the inpatient team (inpatient pharmacist or treating physician if no pharmacist available) prior to discharge, to ensure continuity of care upon discharge.

If a dose change occurs during admission, the inpatient team is responsible for notifying the patient's community pharmacy of the dose change as soon as possible after it occurs. The pharmacy can then cancel their prescription "on hold" and try to acquire a new prescription for discharge in case the patient comes to the pharmacy unexpectedly (e.g., they discharge themselves). In general, a discharge prescription can be arranged by contacting the patient's community prescriber/clinic to request a new prescription be sent to the patient's pharmacy.

The HSC Addiction Consult Team may be able to provide a bridging discharge prescription for patients **on whom they were consulted.**

For both new starts and restarts of methadone and buprenorphine/naloxone in hospital, an approved prescriber from the HSC Addiction Consult Team may be able to provide a bridging discharge prescription to facilitate discharge, *if* arrangements are in place for follow-up with an approved community-based OAT prescriber who will then assume responsibility for the patient's ongoing OAT care.

Clinical Assistants (CAs) & Physician Assistants (PAs)

A clinical assistant (CA) or physician assistant (PA) cannot independently prescribe methadone or buprenorphine/naloxone in hospital and cannot provide a discharge prescription for these medications.

Inpatient orders for continuing care, dose increases, new starts, or restarts of methadone and buprenorphine/naloxone may be signed by a CA or PA if they include the phrase “as discussed with attending physician” on the signature line. Such orders require a documented conversation with the supervising attending physician and **need to be co-signed by the attending physician as soon as possible and within 48 hours.**

The same requirements as for attending physicians apply to CAs and PAs in terms of the need for a documented conversation with an approved prescriber as outlined above for dose increases, new starts, and restarts of methadone and buprenorphine/naloxone.

Residents

A resident may prescribe **buprenorphine/naloxone** in hospital for the purpose of continuing care at the *same or lower dose*.

Inpatient orders for **methadone** for the purpose of continuing care at the *same or lower dose* may be signed by a resident if they include the phrase “as discussed with attending physician” on the signature line. Such orders require a documented conversation with the attending physician and **need to be co-signed by the attending physician as soon as possible and within 48 hours.**

Inpatient orders for dose increases, new starts, or restarts of **buprenorphine/naloxone** or **methadone** may be signed by a resident if they include the phrase “as discussed with attending physician” on the signature line. Such orders require a documented conversation with the attending physician and **need to be co-signed by the attending physician as soon as possible and within 48 hours.**

The same requirements as for attending physicians apply to residents in terms of the need for a documented conversation with an approved prescriber as outlined above for dose increases, new starts, and restarts of methadone and buprenorphine/naloxone.

Residents cannot provide a discharge prescription for methadone or buprenorphine/naloxone.

Fellows

The same recommendations as for residents apply to fellows who hold an educational licence.

Fellows who hold a full licence, but who are not CPSM-approved prescribers of methadone and/or buprenorphine/naloxone, must follow the same requirements as all other licensed physicians/attending physicians in hospital.

Fellows who hold a full licence and who are CPSM-approved to prescribe methadone and/or buprenorphine/naloxone can order continuing care, dose increases, restarts, and new starts of the medication(s) for which they hold a prescribing approval.

Fellows cannot provide a discharge prescription for methadone or buprenorphine/naloxone unless the fellow holds a full licence and the relevant CPSM approval to prescribe methadone and/or buprenorphine/naloxone.

Take-home dosing (carries) for Inpatients

A licensed physician can, at their discretion, prescribe a “pass med” to an inpatient who is temporarily leaving the hospital and is later returning to the hospital. One or more methadone or buprenorphine/naloxone dose(s) must be dispensed by the hospital pharmacy and the patient must still be a patient of the hospital.

Methadone or buprenorphine/naloxone should **only** be provided as a “pass med” if the patient was previously receiving carries in the community and continues to meet the requirements for take-home dosing in the community as outlined elsewhere in this manual (see respective chapters for methadone and buprenorphine take-home dosing recommendations). If the hospital prescriber is in doubt, take-home doses should first be discussed with the patient’s community OAT prescriber. The hospital pharmacy should notify the community pharmacy of any such pass meds provided to prevent double dosing.

Hospitals cannot provide take-home methadone doses to facilitate discharge. A discharge prescription needs to be arranged as outlined above *before* discharge can occur.

For buprenorphine/naloxone, one to two take-home doses provided by the hospital pharmacy is acceptable if discharge is unexpected or occurs on a weekend or holiday and the inpatient team is unable to reach the community OAT prescriber. The community pharmacy needs to be notified of any take-home doses provided upon discharge or as soon as possible to prevent double dosing. The community OAT prescriber/clinic needs to be notified upon discharge or as soon as possible after discharge as well.

CAs, PAs, residents, and fellows with an educational licence can sign pass med orders and orders for one to two take-home doses of **buprenorphine/naloxone** upon discharge if they include the phrase “as discussed with attending physician” on the signature line. Such orders require a documented conversation with the attending physician and **need to be co-signed by the attending physician as soon as possible and within 48 hours.**

CAs, PAs, residents, and fellows with an educational licence can sign pass med orders for **methadone** if they include the phrase “as discussed with attending physician” on the signature line. Such orders require a documented conversation with the attending physician and **need to be co-signed by the attending physician as soon as possible and within 48 hours.**

PART 2 - TREATING PATIENTS WITH OUD IN HOSPITAL

Emergency visits and hospital stays can be difficult for patients with OUD, as outlined in **GENERAL CONSIDERATIONS**. In addition to acute illness, injury, or exacerbations of existing chronic medical conditions, individuals with OUD often present to hospital in withdrawal and/or with serious complications of substance use (e.g., overdose, deep tissue infection, septicemia, endocarditis, osteomyelitis, delirium). This is an opportune time to engage patients in harm reduction and addiction care for overall improved health outcomes. Likewise, patients already on OAT may be admitted for unplanned or planned care, and this can be an opportunity to optimize therapy.

Effective in-hospital care of patients with OUD should use a patient-centered, trauma-informed, and harm-reduction approach. Key components include:

- **Treat Withdrawal.** Manage acute opioid withdrawal. If the patient is already on OAT, ensure treatment is continued.
- **Treat Acute Pain.** Maximize non-opioid pharmacotherapy and other modalities as able and continue/maximize existing OAT dosing as appropriate. If additional opioid analgesia is indicated, patients with baseline opioid tolerance may need greater dose escalation to achieve an adequate response.
- **Offer Harm Reduction.** Provide harm-reduction education, resources, and supplies to all patients as able, even if patients are not ready to engage in addiction treatment (see **Appendix H** for resources).
- **Connect to Addiction Services.** As able/available, consult addiction medicine, facilitate access to OAT induction, and/or refer to community services.
- **Continuity of Care.** Connect with the community pharmacy, current OAT provider/clinic, and/or addiction services in discharge planning. Build safety into the discharge medication plan.

EMERGENCY DEPARTMENT/URGENT CARE OF INDIVIDUALS WITH OUD

Ideally, for patients with OUD seeking emergent care, the emergency department/urgent care (ED/UC) can be a doorway to addiction medicine care. Harm reduction should be emphasized.

Support Access to OAT

OAT induction should be pursued in the ED/UC if patients agree and treatment is indicated. In emergency departments/urgent care settings in Manitoba, ongoing efforts are focused on developing suitable resources, standardized orders, and care maps to support OAT induction and referral for community follow-up.

If possible, consult the HSC Addiction Consult Team as outlined in [PART 1](#), for recommendations regarding the feasibility of a buprenorphine/naloxone induction in your practice setting. The on-call physician can be reached by contacting HSC paging. Alternatively, an ED/UC physician with CPSM approval to prescribe buprenorphine/naloxone can start buprenorphine if indicated. A plan for follow-up with a community-based OAT prescriber or local RAAM clinic is a critical aspect of care planning.

For select patients an unwitnessed (“home”) induction may be considered. Alternatively, others may benefit from a micro-dosing induction over the [Conventional Buprenorphine Induction](#). Please see the respective chapters, [Recommendations for Unwitnessed Induction with Buprenorphine/naloxone](#) and [Recommendations for Buprenorphine/naloxone Induction Using the Micro-dosing Method](#) for details on these approaches. Again, such inductions may be initiated by the HSC Addiction Consult Team, or by an approved buprenorphine/naloxone prescriber.

As buprenorphine/naloxone is considered first-line therapy for the treatment of OUD it should be used preferentially for ED/UC inductions. Please refer to [Recommendations for OUD](#) for further guidance on treatment approaches. Consideration for methadone as an alternative to buprenorphine/naloxone induction may be appropriate in some patients (please see [Recommendations for Methadone Induction, Titration, & Stabilization](#)), however methadone inductions in the ED/UC must be done by a prescriber with a CPSM approval to prescribe methadone or in consultation with the HSC Addiction Consult Team.

If induction cannot be arranged in ED/UC, patients can be directed to a local [Rapid Access to Addiction Medicine \(RAAM\) Clinic](#) or community-based OAT provider in the area. Due to the potentially life-threatening nature of OUD, it is important for emergent care settings to be aware of local resources for OAT induction.

Provide Harm Reduction & Resources

Harm reduction in ED/UC can include access to naloxone kits, sterile drug consumption supplies, and education on safer use (see **Appendix H** for resources). A harm reduction approach can be used with patients irrespective of their readiness to engage with addictions care. Community resource lists for same-day/next-day care and harm reduction supplies can be kept on-hand for ED/UC staff to provide directly to patients.

At minimum, patients can be directed to [Street Connections](#) for information on how to access naloxone kits, safer use supplies, and support in the community. In consultation, the Addiction Consult Team may also be available to offer harm-reduction teaching, supplies, and OAT induction, as appropriate. Again, patients can also be directed to a local RAAM Clinic if these resources cannot be offered in the ED/UC.

Administer Dose for Patients on OAT in ED/UC

Patients already on OAT should have their dose administered in a timely manner if they have yet to receive their daily dose, particularly if an extended stay in the ED/UC is anticipated. Ask patients if they have taken their dose for that day and confirm this with their community pharmacy. Do not rely on DPIN information alone in this regard, as a dose may be entered into DPIN before it is administered to the patient at the community pharmacy. Similarly, check with the community pharmacy if any take-home doses were released and ask the patient if the dose(s) were consumed. **Obtaining collateral from the patient's community pharmacy and community OAT prescriber/clinic is essential**, particularly around take-home doses.

If the patient has take-home doses with them but they have not consumed their dose that day, do not delay the patient's dose if the hospital pharmacy/urgent care setting cannot provide a timely dose. The patient should be allowed to consume the take-home dose in the emergent care setting to prevent withdrawal. Communication with the community pharmacy and community-based OAT clinic is imperative in such situations.

Missed OAT Doses

If the community pharmacy can provide reliable collateral information and the patient has missed one or more doses in community prior to presenting to the ED/UC, refer to the Ongoing Care chapter for recommendations on the management of missed doses.

However, if the available collateral is minimal and the patient's report uncertain, monitor for opioid withdrawal symptoms to determine if further withdrawal management is required. The Clinical Opiate Withdrawal Scale (COWS) can be used to assess and document withdrawal (see **Appendix I**). Withdrawal should be managed using short-acting opioids in this situation, using the approach outlined in the **INPATIENT CARE** section below.

All doses administered in ED/UC must be reported to the patient's community pharmacy and to the OAT provider/clinic to prevent double dosing or miscommunication. Please see the **CONTINUITY OF CARE & DISCHARGE PLANNING** section below for further recommendations.

Treat Opioid Withdrawal

Managing acute opioid withdrawal in the ED/UC is of utmost importance. Adequately treating withdrawal can facilitate the assessment and treatment of other presenting conditions. It enables patients with OUD to engage in their own care, make informed treatment decisions, and stay the course if ongoing or longer-term hospital care is required. See the **INPATIENT CARE** section below for a detailed approach to treating opioid withdrawal.

Treat Acute Pain

In general, acute pain in patients with OUD should be managed similarly to someone who is not on OAT, with additional considerations to ensure adequate analgesia and patient safety.

Patients on OAT with acute pain will typically require pain management *in addition to* their buprenorphine/naloxone or methadone dose. It is important to recognize that the maintenance opioid for OUD is the baseline for preventing withdrawal and does not provide significant pain relief.

If patients present in opioid withdrawal, managing the withdrawal effectively will be essential to treating acute pain.

The initial management of acute pain should take into consideration the type/source of pain and the evidence for managing that particular pain. Often non-opioid analgesics are recommended as first-line treatment and the approach should be the same for someone on OAT. The section [Managing Acute, Chronic, & Perioperative Pain](#) provides detailed recommendations for managing pain in the context of OAT.

For the most part, if acute pain would normally require the use of opioid analgesics, it would also be appropriate for the patient on OAT. **Given the baseline tolerance of patients on OAT to opioids, doses may need to be escalated to achieve an adequate response.** The prescriber should start at doses similar to those used in a patient not on OAT and reassess early in order to provide adequate pain management. Additionally, it is important for the ED/UC prescriber to discuss the short-term nature of the opioid analgesic with the patient, as appropriate.

The [CONTINUITY OF CARE & DISCHARGE PLANNING](#) section below outlines recommendations for medication management, particularly if opioid analgesics and/or sedating/psychoactive medications are provided upon discharge. Generally, prescriptions for such medications from emergent care settings should be short-term (e.g., ≤ 3 days) with controlled dispensing for safety.

Access Mental Health Care

If patients present to ED/UC with psychiatric symptoms of a mental health disorder and consultation with a Psychiatric Emergency Nurse (PEN) and/or Psychiatry is warranted, these services can also provide harm-reduction support and addiction treatment suggestions. Patients with severe psychiatric instability may require preliminary stabilization of their symptoms prior to making informed decisions about their addiction medicine care. However, managing acute opioid withdrawal in these individuals is also helpful to promote stability and engagement in overall care.

INPATIENT CARE OF INDIVIDUALS WITH OUD

Patients in Opioid Withdrawal

Patients who use opioids regularly and who are admitted to hospital typically do not have access to their usual supply, equipment, and supports. This can lead to significant suffering from both physical and emotional symptoms of withdrawal. Managing this withdrawal in

hospital helps patients engage in ongoing medical care. It can decrease higher-risk or drug seeking behaviours, improve presence and compliance with medical care, and decrease the risks associated with illicit use. The HSC Addiction Consult Team can assist with withdrawal management, but **any inpatient team should manage withdrawal if this service is not available or if patients refuse addiction care.**

If patients do agree to treatment of their OUD, ideally OAT can be started in hospital *when indicated*. As outlined in *PART 1, New Starts, Restarts, and Dose Increases* require a documented discussion with a physician member of the Addiction Consult Team. The on-call physician can be reached by contacting HSC paging. Ideally, patients agreeing to treatment can be started on OAT *instead* of treating withdrawal with other opioids, if suitable resources are available to support induction and community follow-up.

Treating Opioid Withdrawal for Inpatients

If OAT induction is not yet indicated or available, acute withdrawal can be managed with scheduled and PRN doses of a short-acting, oral opioid, such as morphine or hydromorphone. Oral liquid formulations, with orders for direct observation of administration, will help limit potential misuse (e.g., intravenous injection) or diversion. **Communicate with nursing staff about the importance of direct observation of each dose for safety.**

Given the baseline tolerance of patients with OUD, opioid doses may need to be escalated to achieve an adequate response. The practitioner can start at doses similar to those used in an opioid-naïve patient but make dosing available at shorter intervals to facilitate rapid dose escalation, if indicated for withdrawal management. Additionally, reassess early and frequently to provide adequate withdrawal management.

An example of an order for harm reduction opioid dosing may be: ‘Morphine oral liquid 10-20 mg po q 1h PRN witnessed, for pain or withdrawal. Hold if sedated or RR < 10’. Note that this is an example only and that many patients will require higher dosing. While some patients may require lower amounts, the use of PRNs (with hold orders based on parameters of opioid toxicity) allows for more liberal dosing to minimize undertreatment of withdrawal, which may limit engagement in care.

The use of PRNs can be monitored to titrate scheduled doses until opioid withdrawal is eliminated or adequately suppressed over a 24-hour period, without sedation. For example, if a patient uses 200 mg of oral morphine through PRNs in the first 24 hours of admission and appears comfortable on reassessment, you may add a scheduled dose of ‘Morphine oral liquid 20 mg po q 3h witnessed’ and continue a smaller amount of PRN morphine.

Alternatively, if that same patient uses 200 mg of oral morphine but is in clinical opioid withdrawal or reports needing to source illicit opioids, you may add a scheduled dose of ‘Morphine oral liquid 25 mg po q 3h witnessed’ and continue a more liberal amount of PRNs, reassessing daily until stable dosing is achieved.

This approach can allow patients to further engage in ongoing medical care and facilitate pain management if needed. If acute opioid withdrawal and pain are adequately managed, PRNs may be reduced or discontinued as dosing stability is achieved.

Discuss this treatment goal transparently with the patient and care team – neither underdosing nor dosing to sedation are appropriate. Additionally, it is important for the prescriber and patient to discuss the interim nature of this opioid therapy as a bridge to OAT induction and/or discharge. Should a patient decline OAT induction, harm reduction opioid dosing should terminate at discharge, or be converted to daily witnessed SROM (i.e., Kadian®) at tapering doses in the community, and the patient should receive information about where they can access OAT. Please see the [CONTINUITY OF CARE & DISCHARGE PLANNING](#) section below, specifically *Discharge Prescriptions*.

The COWS (**Appendix I**) can be used to assess and document the severity of opioid withdrawal while establishing the opioid regimen; this helpful clinical tool utilizes objective and subjective measures of withdrawal and can assist in determining appropriate dosing.

Acute & Perioperative Pain

If acute pain persists, PRNs may still be required for breakthrough pain, procedures (e.g., dressing changes), or sessions with physiotherapy and occupational therapy.

Again, for patients on OAT, it is important to recognize that the maintenance opioid the patient is taking for OUD (e.g., buprenorphine or methadone) is the baseline for preventing withdrawal and does not provide significant pain relief.

If possible, OAT should be continued at the current dose while acute pain is managed *in addition* to this baseline therapy for withdrawal management. The same applies to the perioperative period.

In general, patients should be managed like any other patient who presents similarly but that does not have OUD, with additional considerations to ensure adequate analgesia and patient safety. See [Managing Acute, Chronic, & Perioperative Pain](#) for further recommendations around pain management for patients with OUD.

Other Medications for Symptomatic Management

The risks and benefits of prescribing non-opioid medications for symptomatic withdrawal management must also be carefully considered (see **Appendix J**). Regularly scheduled acetaminophen and ibuprofen may be sufficient. Use extra caution when prescribing symptomatic management medications with sedating properties.

Benzodiazepines and/or Z-drugs should be avoided in patients with OUD and polypharmacy with multiple sedating/psychoactive medications should be minimized.

Benzodiazepines & Z-drugs Increase Risk of Overdose

Patients already using benzodiazepines/Z-drugs are higher-risk and caution is indicated when establishing a suitable opioid regimen to manage withdrawal and/or pain.

A thorough history of benzodiazepine/Z-drug use and further review with the Addiction Consult Team may be necessary. This includes use via prescribed and/or illicit sources. A strategy for benzodiazepine/Z-drug management (even for stable long-term prescriptions), including diagnosis of potential sedative-hypnotic use disorder, must be part of the overall treatment plan. See the [Managing Polypharmacy](#) section **MANAGING PRESCRIBED AND ILLICIT BENZODIAZEPINES & Z-DRUG USE** for detailed guidance.

If significant mood, anxiety, or other psychiatric symptoms persist once opioid withdrawal is adequately suppressed, consultation with the Psychiatric Liaison/Psychiatry may be warranted.

Other Safety Considerations

For safety reasons, case by case, there may be times when hospital teams forgo inpatient administration of opioids to treat withdrawal. Harm-reduction should still be emphasized – see **HARM REDUCTION FOR INPATIENTS** below for details. The Addiction Consult Team can provide guidance for complicated or higher-risk situations. Treatment agreements may be used to encourage communication, delineate expectations, and minimize conflicts between staff and patients. This may be particularly useful for lengthier hospital stays.

For patients on prescribed opioids, benzodiazepines/Z-drugs, and/or OAT, hospital teams must notify the patient’s community pharmacy and prescriber/clinic of the admission on the first day, or as soon as possible thereafter. It is essential to hold or cancel dispensing of these community prescriptions during admission for safety, to avoid potential double dosing or diversion.

Being aware of the hospital admission also allows the community prescriber and pharmacy to plan ahead and potentially assist with the OAT discharge prescription (which can only be written by an approved OAT prescriber). The community OAT prescriber may also be able to advise the hospital provider on discharge medication management to increase patient safety upon discharge.

Inpatients on OAT

Patients who are stable on OAT should generally have their dose continued in hospital, as described under *Continuing Care In Hospital* in **PART 1**.

If a patient is on OAT but unstable (i.e., their dose is subtherapeutic and/or they were supplementing with other opioids prior to admission), they may also require opioid withdrawal management. Ideally, their opioid agonist could be titrated as described in *Dose Increases*, with the guidance of an approved buprenorphine/naloxone or methadone prescriber.

If consultation is not available in a timely manner to make titration possible, a short-acting oral liquid opioid, with witnessed administration, can be used in the interim. Dosing should offset the OAT dose, i.e., if their daily OAT dose wears off by the evening, the additional opioid can be scheduled in the evening and/or before bed to treat withdrawal throughout the night. This should be discontinued prior to discharge.

An inpatient stay can provide valuable observational information about how an unstable patient on OAT is doing on their dose. Collateral information from the in-hospital provider regarding withdrawal observed can alert the community prescriber that further OAT dose titration is indicated.

Perinatal Patients

Pregnancy can be a stressful experience for anyone, but it can also be a time of increased motivation. Pregnancy may present a valuable opportunity to engage individuals who use drugs in addiction care to improve maternal and fetal health outcomes.

Untreated OUD in pregnancy is associated with numerous adverse fetal and maternal outcomes. Significant opioid withdrawal in pregnancy is a medical emergency and requires urgent and effective management to prevent miscarriage/preterm labour, low birth weight, and the associated complications of prematurity.

OAT is the standard of care for pregnant patients with OUD – please refer to the Pregnancy chapter of this manual for detailed recommendations.

Perinatal hospital admissions are an ideal time for OAT induction and/or to optimize OAT dosing. Pregnancy is also an indication for inpatient OAT induction. Admission can also facilitate connection to ongoing addiction care and other services, such as high-risk obstetrics, social work, and primary care.

Individuals already stable on OAT may require dose increases during pregnancy as the body and metabolism change. Titration can proceed as described in *Dose Increases*, with the guidance of an approved buprenorphine/naloxone or methadone prescriber. Reciprocally, some women require *dose decreases* post-partum and should be monitored for sedation.

HARM REDUCTION FOR INPATIENTS

Inpatient admission is an opportune time to engage patients in harm-reduction strategies. Harm reduction is used along the continuum of treatment approaches for OUD, to promote safety and improve health outcomes with patients, regardless of their readiness to stop or decrease substance use. There is **ample evidence to support harm-reduction interventions for all people who use opioids**, including those engaged in OAT or other treatment.

Specific interventions with strong evidence include:

- Harm reduction supply distribution (e.g., needle/syringe programs)
- Supervised consumption/overdose prevention sites, and
- Take-home naloxone training/kits.

These interventions should be made widely available with low barriers to help reduce opioid-related harms – this includes the ED/UC as well as inpatient units.

See **Appendix H** for a detailed list of online resources that can be shared with patients, including downloadable handouts and ways to access naloxone kits. Services and options may vary from location to location, but inpatient harm reduction approaches can include:

- Prescribing/facilitating access to take-home naloxone kits, education, or at minimum connecting patients to community resources to access kits.
- In-hospital access to sterile drug consumption equipment (e.g., clean pipes, glass stems, filters, needles, and other supplies for safer injection techniques). Consider bedside access to supplies.
- Education on safer injection, smoking, and insufflation techniques.
- Supervised consumption spaces in hospital.
- Testing of substances being used, at bedside or through a drug testing service.
- Referrals to addiction medicine or other health and social services, including supporting access to primary care.
- Vaccinations and Sexually Transmitted and Blood Borne Infection (STBBI) testing.

Offer STBBI Testing

Comprehensive testing for STBBIs should be offered to all patients with OUD. Inpatient admission is an excellent time to offer and order this testing and arrange potential follow up with specialized services (e.g., hepatology or HIV clinics).

Initial screening should include testing for HIV, hepatitis A, B, and C, as well as syphilis, chlamydia, and gonorrhea, including throat and rectal swabs if indicated.

Patients at significant and ongoing risk of infection should be offered STBBI screening every 6 to 12 months. Repeat testing may be customized based on individual risk factors. Please see the chapter [Prevention, Screening, & Management of HIV & Hepatitis C in Individuals with OUD](#) for further guidance.

PLANNED HOSPITAL ADMISSION IN THE CONTEXT OF OUD

Planned hospital admission is warranted for some patients with OUD, often to optimize care and to further evaluate and mitigate significant safety concerns. Criteria for inpatient admission can include:

- Pregnancy and perinatally.
- Concurrent polypharmacy or polysubstance use, particularly high-risk alcohol and/or sedatives/hypnotic use.
- Complex medication transitions, such as methadone to buprenorphine/naloxone, or from high-dose long-acting or high-potency opioids (e.g., fentanyl) to buprenorphine or methadone, particularly in the context of complex medical or psychosocial issues.
- Failed and/or higher-risk community OAT inductions (e.g., due to geography/travel, safety concerns, or psychosocial factors).
- Concurrent and/or acute medical conditions that cannot be reliably treated in the community given patient instability within the context of substance use (e.g., pneumonia, endocarditis, osteomyelitis, advanced HIV).
- For emergent investigation of other medical issues with risk of morbidity or mortality, that cannot be reliably investigated in the community given patient instability within the context of substance use.

Some planned admissions may warrant referral for admission to the HSC Addiction Unit for specialized care. Others may be arranged in collaboration with local hospitals, or other services, such as Obstetrics, Surgery, or Medicine, and with or without HSC Addiction Consult Team collaboration.

Winnipeg Health Sciences Centre Addiction Unit

Community providers may consult with the HSC Addiction Unit team to arrange admission for patients who require medical management of their substance use disorder(s), including those who meet the criteria above.

The Addiction Unit (AU) is a small inpatient unit specializing in medical management of substance use disorder. Patients requiring *specific medical intervention* for withdrawal management, stabilization, and access to treatment services are considered for admission. Admissions may be planned following assessment in emergency or through one of the outpatient clinics associated with the program, the Complex Addiction & Recovery Medical Assessment (CARMA) Clinic, the Alcohol Recovery Clinic (ARC), or the Rapid Access to Addiction Medicine (RAAM) clinics.

Given the waitlist for specialist consultation in CARMA, community OAT providers may wish to consult with the HSC Addiction Program Medical Director or the AU attending physician directly to facilitate more urgent admission.

Transfers from other HSC units or St. Boniface General Hospital may also be arranged by the HSC Addiction Consult Team and the AU attending physician. Transfers from attending physicians in other community hospitals may be arranged with the AU attending directly. The on-call physicians can be reached by contacting HSC paging.

Please note that AU is a limited resource that serves all of Manitoba. There may be a wait time for planned admissions and not all admission requests can be accommodated.

Addiction Unit Treatment Agreement

The AU has a treatment agreement that patients must agree to prior to admission. Like other treatment agreements, this is intended to support informed consent and treatment planning, as well as delineate expectations, manage boundaries, and minimize conflicts between staff and patients.

The agreement also promotes safety for this vulnerable patient population. Admission is voluntary and some patients may not agree to admission as the expectations feel too restrictive, particularly around off-ward passes, smoking, and visitors. Since admission is voluntary, patients must have the capacity to agree to admission and contract for safety if needed. The AU cannot admit involuntary patients under the Mental Health Act – these patients would require psychiatric assessment and intervention.

CONTINUITY OF CARE & DISCHARGE PLANNING FOR PATIENTS WITH OUD

Ideally, communication for continuity of care and discharge planning should start on the first day of admission or as soon as possible thereafter. Verifying medications and sharing collateral is essential to safe inpatient care. Likewise, upon discharge, informing the community providers and pharmacy about changes in medical status, medications, or OAT dosing, and highlighting any new safety concerns, promotes a safer transition back to community.

Even for short stays in urgent care or emergency, or brief admissions, when OAT doses are administered in hospital a member of the hospital team must inform the community pharmacy (and ideally the OAT provider/clinic) to prevent double dosing or miscommunications about missed doses.

Discharge Prescriptions

Only an approved buprenorphine/naloxone or methadone prescriber may provide a buprenorphine or methadone discharge prescription for continuing care at a community pharmacy. See the [PART 1](#) section *Discharge Prescriptions for OAT Medications* for details.

If opioids were provided in hospital for interim management of opioid withdrawal, a discharge prescription for this indication is *not an expectation*. As previously described, attempts can be made to help patients access OAT, addiction care, and harm reduction services. Discharge prescriptions for new benzodiazepines/Z-drugs should also be avoided in patients with OUD.

If OAT was not started in hospital for some reason for a patient with OUD (e.g., patient choice, limited resources or length of stay, or discharge is to a rural/remote location without feasible access to OAT), then interim options for bridging or tapering prescriptions may be explored. Please see [Alternative Treatment Approaches for OUD Including SROM \(Kadian®\)](#) for possible approaches to such situations.

Communication is Paramount for Medication Safety

If opioid analgesics or other sedating/psychoactive medications are started in hospital and still indicated upon discharge, prescriptions should be short-term with restricted dispensing for safety.

For patients on OAT, communication with the patient’s community pharmacy and OAT prescriber is essential to build safety and continuity of care into the medication management plan. Ideally the patient has one prescriber, or identified group of prescribers, responsible for their OAT and other sedating/psychoactive medications in the community, including any additional opioids used for pain management. Similarly, best practice is to utilize one community pharmacy for all medications dispensed. The patient’s community pharmacy and OAT prescriber can help determine dispensing intervals upon discharge, which should mirror the OAT schedule in most cases.

STRONG RECOMMENDATION: REMINDER TO DISPENSE WITH OAT

Typically, all psychoactive/sedating medications should be dispensed with OAT, i.e., on the same schedule as OAT. Communicating with the patient’s pharmacy about the plan for managing these medications is essential. Controlled dispensing instructions, such as “dispense as per OAT schedule”, must be written on all relevant prescriptions. Please see the [Managing Polypharmacy in OAT](#) chapter for further medication safety recommendations.

Discharge prescriptions for any opioid analgesics or sedating/psychoactive medications should be time-limited to align with follow up in the OAT clinic. The OAT prescriber can then take over management of any new or continued medications. Discharge prescriptions for any additional opioids should include a note that it is to be used in conjunction with the patient’s OAT, to avoid any interruptions to OAT care at the receiving pharmacy.

Ensuring such information is clearly communicated at the time of discharge from hospital is extremely important. **A “warm handoff” between all parties involved, including the patient, can ensure a common understanding of the care plan, identify potential issues, and set timelines for follow-up.**

NIHB Client Safety Program

Patients on OAT whose medications are covered by Non-Insured Health Benefits (NIHB) for First Nations and Inuit are enrolled in the NIHB Client Safety Program. These patients are required to have a *sole prescriber* (or identified group of prescribers) as a provision for coverage of opioids, benzodiazepines, stimulants, gabapentinoids, and/or nabilone (i.e., restricted medications).

When patients are initiated in a community pharmacy on buprenorphine/naloxone, methadone, or SROM to treat OUD, they are automatically enrolled in this program. Often the sole prescriber will be their regular OAT prescriber (or group of prescribers), and this should be considered when developing the discharge plan. If any of these restricted medications are prescribed by a clinician not listed as the sole prescriber through NIHB, prescription costs will not be covered.

Mitigating Risk of Misuse of Additional Opioids

As noted, additional opioids prescribed upon discharge for pain management **must be dispensed at the same interval as OAT**. Limiting the medication supply dispensed at one time can help mitigate potential misuse of the opioid analgesic.

For example, if the patient is on daily dispensed OAT, the new opioid analgesic should also be dispensed daily. If significant concern for misuse exists, *witnessed* daily dosing may be implemented, depending on the formulation of the opioid. For patients with routine take-home doses (carries) of OAT, the number of days’ supply of the opioid analgesic should not exceed the number of carry days dispensed. If the patient has weekly carries (i.e., OAT is witnessed once weekly), it may be prudent to initially dispense the opioid analgesic at shorter intervals to mitigate risk of misuse.

IN SUMMARY

While emergency visits and hospital stays can be difficult for patients with OUD, they also present a valuable opportunity for addiction medicine intervention and harm reduction. Treating withdrawal and pain as required, providing harm-reduction education, resources, and supplies, and connecting patients to community supports are all essential to overall improved health outcomes for patients with OUD. Diligence in medication management and communication with the community pharmacy and OAT provider/clinic are equally essential for continuity of care and a safe transition back to the community.

Appendix H

HARM REDUCTION RESOURCES

Toward the Heart

Homepage	https://towardtheheart.com/
Resource Page	https://towardtheheart.com/a-z-resource-page
Safer Use	https://towardtheheart.com/safer-use
Safer Tablet Injection Handout	https://towardtheheart.com/assets/uploads/1614902572pDb5cFkV7mmEnHjxavvOVi3tufpOC0dEHfyCNU0.pdf
Safer Smoking Supplies Handout	https://towardtheheart.com/assets/uploads/1603734665AaiyNXgl3ehtneE3DYxXVLbMplwErO8i80bVIGp.pdf

Street Connections

Homepage	https://www.streetconnections.ca/index.php
Van Information	https://streetconnections.ca/van-information
Find a location for supplies, condoms, testing, & naloxone	https://www.streetconnections.ca/service_map.php

CATIE (HIV & Hepatitis C Information)

Homepage	https://www.catie.ca/
Choosing a Vein Handout	http://librarypdf.catie.ca/ATI-70000s/70162.pdf
Safer Use Videos	https://www.catie.ca/safer-substance-use-video-series
Safer Injection & Smoking Information	https://www.catie.ca/prevention-prevention-methods/safer-injecting-and-smoking-supplies

National Harm Reduction Coalition

Homepage	https://harmreduction.org/
Resources	https://harmreduction.org/all-resources/#safer-drug-use
Safer Drug Use Handout	https://harmreduction.org/issues/safer-drug-use/facts/

Manitoba Harm Reduction Network

Homepage	https://mhrn.ca/
----------	---

Appendix I¹



CLINICAL OPIATE WITHDRAWAL SCALE¹

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient's name: _____ Date and Time: ____/____/____:____

Reason for assessment: _____

<p>Resting Pulse Rate _____ beats/minute <i>Measured after patient is sitting or lying for one minute</i></p> <p>0 pulse rate 80 or below 1 pulse rate 81–100 2 pulse rate 101–120 4 pulse rate greater than 120</p>	<p>GI Upset over last ½ hour</p> <p>0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting</p>
<p>Sweating over past ½ hour not accounted for by room temperature or patient activity</p> <p>0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face</p>	<p>Tremor observation of outstretched hands</p> <p>0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching</p>
<p>Restlessness observation during assessment</p> <p>0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds</p>	<p>Yawning observation during assessment</p> <p>0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute</p>
<p>Pupil Size</p> <p>0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible</p>	<p>Anxiety or Irritability</p> <p>0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult</p>
<p>Bone or Joint Aches <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i></p> <p>0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort</p>	<p>Gooseflesh Skin</p> <p>0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection</p>
<p>Runny Nose or Tearing <i>Not accounted for by cold symptoms or allergies</i></p> <p>0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks</p>	<p>Total Score _____</p> <p><i>The total score is the sum of all 11 items.</i></p> <p>Initials of person completing assessment: _____</p>

Score: 5–12 = mild; 13–24: moderate; 25–36 = moderately severe; more than 36 = severe withdrawal

Reference:

1. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35(2):253–259.

More information:
www.bccsu.ca



BRITISH COLUMBIA
CENTRE for EXCELLENCE
in HIV/AIDS



¹. From <https://www.bccsu.ca/wp-content/uploads/2017/08/Clinical-Opiate-Withdrawal-Scale.pdf>

Appendix J

NON-OPIOID MEDICATION FOR SYMPTOMATIC MANAGEMENT OF OPIOID WITHDRAWAL

The following non-opioid medications may be useful to treat symptoms of opioid withdrawal.

Prescribers should exercise caution with all sedating medications during OAT induction, as they may interfere with the assessment of withdrawal severity and increase the risk of fatal overdose. In the absence of precipitated withdrawal (in the context of buprenorphine induction), many prescribers prefer to avoid these medications entirely during induction.

- Acetaminophen 500-1000 mg PO Q4-6h PRN for muscle pain (to a maximum dose of 4000 mg in 24 hours, or as appropriate based on known liver function/impairment).
- Ibuprofen 400 mg PO Q6-8H PRN for muscle pain.
- Ondansetron 4 mg PO Q6H PRN for nausea.
- Loperamide 4 mg PO PRN for diarrhea, then 2 mg PO after each loose stool, up to a maximum of 16 mg in 24 hrs.
- Trazodone 50-100 mg PO QHS PRN for insomnia.
- Quetiapine 25-50 mg PO QHS PRN for anxiety/insomnia.
- Clonidine 0.1 mg PO QHS PRN for opioid withdrawal symptoms and insomnia. Clonidine can be titrated up to 0.2 mg PO BID for severe withdrawal, but caution is advised due to the potential risks of sedation, hypotension, and diversion.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.9 Recommendations for the Treatment of Opioid Use Disorder in Pregnancy

GENERAL CONSIDERATIONS

This chapter aims to empower opioid agonist therapy (OAT) providers to support individuals throughout pregnancy and postpartum with confidence and compassion, while utilizing evidence-based best practices.

The literature reviewed in generating these recommendations include sources dated after 1990 from Medline, Pubmed, The Cochrane Library with word searches including: opioid, morphine, heroin, methadone, Suboxone and pregnancy, postpartum, fetus, mothers and dependence, misuse, addiction and use disorder. Guidelines from the Society of Obstetricians and Gynaecologists, American Conference of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynecologists, Association of Ontario Midwives and Nursing and Midwifery Council (UK) were also searched for recommendations.

Principles of Truth and Reconciliation, patient-centered and trauma-informed care, inter-professionalism, and harm reduction are endorsed in this chapter. The parent-infant dyad is inherently valued and custodial parenting is promoted, when it is the goal of the patient. Not all pregnant individuals identify as female, so most language is intended to be gender-neutral for inclusivity. However, there are elements of lived experience that are specifically gendered, and these will be addressed accordingly.

Substance-involved pregnancy is high risk for social instability, violent exposures, postpartum depression, suicide, and unintended overdose, with a disproportionate and growing burden of maternal morbidity and mortality. Infants born from these pregnancies have a high rate of prematurity, neonatal intensive care unit (NICU) admission, and long-term neurobehavioral sequelae. Stabilizing opioid use disorder (OUD) in pregnancy reduces the likelihood of these negative outcomes, while also reducing the need to rely on emergency services and minimizing NICU admission days. Effective treatment simultaneously serves to enhance patients' experience of dignified care and reduces cost-burdens to the system.

SUMMARY OF KEY RECOMMENDATIONS

The following key recommendations listed here are discussed throughout this chapter:

- 1) All individuals supported on OAT who are of reproductive age should be offered the opportunity for **effective contraceptive and preconception counseling**.
- 2) If pregnancy is discovered after OAT induction, patients should be reassured that their **maintenance therapy is gold standard care** for pregnant persons with OUD, and that there is no need to dose-restrict due to pregnancy.
- 3) For OAT induction during pregnancy, evidence is still emerging. While methadone has a more extensive lineage in the literature, **buprenorphine/naloxone treatment may be considered as a first-line agent in pregnancy**. Micro-dosing with buprenorphine/naloxone may be considered with close supervision over a traditional start to avoid withdrawal.
- 4) Cycles of use and withdrawal impose vasoconstriction and severe fluid shifts in pregnancy. This compromises placental perfusion, and **patients should be educated about the importance of avoiding withdrawal in pregnancy**. They should also be reassured that their prescribers/OAT care teams will treat these presentations.
- 5) Community based opioid weaning should be limited to highly motivated patients who, after thorough risk-benefit discussion, decline OAT therapy. **Cessation, even if closely supervised, is extremely high risk** for relapse to unprescribed opioids, maternal overdose, and placental malperfusion imposed by the requisite withdrawal. This approach has also not been proven to improve newborn outcomes.
- 6) Opioid use is often a barrier to presenting for maternity care. Providers should encourage the **use of all available community resources and make prompt referrals to maternity care** providers who are familiar with OAT. This may include, and is often enhanced by, a shared-care approach with outreach nursing, obstetricians, midwives, and allied health.

- 7) **Smoking cessation counselling should be considered as a first-line intervention** for pregnant smokers, given the synergistic harms of smoking and opioid use in pregnancy. To date there is sufficient safety evidence to also recommend both bupropion and nicotine replacement therapy (NRT) in pregnancy.
- 8) Symptoms common in pregnancy, such as nausea and vomiting, can be distressing and act as provocative triggers for relapse given their overlap with opioid withdrawal symptoms. **Antiemetics should be easily accessible and consider interval EKG studies to assess QT intervals** for patients on OAT (particularly methadone) who require other QT-prolonging medication(s) for symptom control. Typically, non-sedating antiemetics are used first line. However, for severe symptoms a regimen utilizing more than one agent may be required.
- 9) OUD predisposes patients to hyperalgesia so **consultation with anesthesia prior to delivery should be considered**. OAT does not provide effective analgesia in labour.
- 10) The approach to **infant nutrition should be weighed on an individual basis**. OAT is not a contraindication to breastfeeding which is, in turn, associated with reduced neonatal opioid withdrawal scores and increased parent-infant bonding.
- 11) Opioid-involved pregnancies are high risk for postpartum depression and suicide. **Screening for depression should occur at each trimester and postpartum follow-up should be enhanced**. Patients should be screened by a care provider within two weeks of delivery. Neither pregnancy nor breastfeeding are contraindications to antidepressant therapy.
- 12) Intimate partner violence and relationship discord are highly correlated with postpartum relapse and overdose. **Screening for relationship instability should occur in each trimester**, with safety planning as indicated.
- 13) OAT is not a reflection of parenting capacity. Patients should be offered support through local community programs for prenatal and/or parenting classes that are culturally safe and aligned with parenting values. Involvement of Child Protection Services (CPS) should be limited to documented unsafe behavior with infants/children already in the home. **OAT in pregnancy is not an indication to report**.
- 14) Infant apprehension is an important risk factor for maternal mortality in the opioid-involved pregnancy. If CPS are asked to assess for apprehension, **wrap around supports are urgently indicated for maternal welfare**.
- 15) Tapering OAT within the first postpartum year is highly correlated with relapse and unintended overdose. Patients should be advised to titrate the dose to effect as they would non-pregnant, and encouraged to **postpone plans to taper OAT until their newborn is over one year of age**.



Figure 1: More Than One Path to Stability

OAT in pregnancy requires a backbone of dignified, trauma-informed, and culturally safe care with a longitudinal view into the first year postpartum. Dosing is often gradually titrated upwards over time, especially in the third trimester. This approach ensures treatment addresses changing maternal needs. Four induction models are outlined here, including a description of patient features that lend themselves to each modality.

SPECIFIC CONSIDERATIONS

Receptor sensitivity, metabolic rates, drug-drug interaction, and vulnerability to QT-prolongation are different between male and female patients on OAT.¹ This results in a more rapid progression from first opioid use to the development of OUD in women. Women also experience higher rates of fatal overdose (especially with co-ingestion of benzodiazepines), and increased lethality from cardiac effects of opioid use.

These vulnerabilities are further modified by pregnancy, during which opioid metabolism is increased and harmful maternal outcomes are more frequent, such as unintended overdose and violent exposures.² The hormonal milieu exacerbates mental health conditions and can lead to depression, psychosis, and suicide. This extends into the psychosocial world of pregnant persons on OAT. Intersectional theory considers where overlapping marginalization can compound barriers to care and exacerbate negative outcomes. For the opioid-involved pregnancy this is particularly evident amongst Indigenous populations. Social expectations, implicit bias, and systematic racism collide with impact to the maternal-newborn dyad in the context of neonatal care.

However, pregnancy is also a potent motivator for change, and can be a powerful opportunity for recovery and care engagement. Illuminating these differences in pregnancy and adapting OAT to accommodate these needs can provide empowered, nuanced care. OAT care guided by the values and principles described below can cultivate this engagement and empowerment.

Principles of Truth & Reconciliation

The first Call to Action of the Truth and Reconciliation Commission (TRC) is to honour and preserve the family unit and community ties of Indigenous persons. This Call identifies a history of cultural bias and inequity that has been inherent in the work of Canada's CPS agencies, and challenges Canadians to seek healing within and between communities. Patients who have been supported on OAT during pregnancy have had a disproportionate and sometimes unindicated involvement with CPS, exacerbating these racialized inequities.

OAT providers should be aware of the risk of infant apprehension that is linked to substance use disorders, and the **deep sense of anxiety patients feel about losing their child** should they seek out and continue with OAT care during pregnancy and postpartum. Since OAT is the standard of care for the treatment of OUD in pregnancy, this is an important opportunity for advocacy.

Patient-Centred Care

"Patient-centered care puts patients at the forefront of their health and care, ensures they retain control over their own choices, helps them make informed decisions, and supports a partnership between individuals, families, and health care services providers."³

This is actionable through dignity-preservation, information sharing, participation, and collaboration between the patient and their providers. In maternity care, there is still outdated language such as physicians “letting” patients labour, deliver vaginally, and even continue with OAT. It is important to invite patients to identify their goals of care and then align with them as safely as possible.

Cultivating a care plan together, not only for pregnancy but also for the first year postpartum, keeps patient values at the centre of the therapeutic alliance.

Trauma-Informed Care

Traumatic life experiences are those which fundamentally have an element of terror, isolation and helplessness.⁴ The features of the event itself are not an important defining factor, but rather how they are experienced and processed by the survivor. “[Trauma] is not a thing that you have. This is a process that expresses your life experience.”⁵ Subsequent experiences that literally or symbolically recapitulate the traumatic experience can trigger post-traumatic symptoms and create powerful barriers to care.

Many of the events of childbearing are high risk for unintended re-traumatization. For example, intimate exams, overwhelming physical symptoms with limited ability to suppress them, and pain that can mimic opioid withdrawal. These experiences can destabilize an OUD in remission or decompensate mental health. Seeking opportunities to maximize safety, therapeutic relationships, and agency are meaningful antidotes to the features of trauma.

Inter-Professionalism

Opioid-involved pregnancy represents a clinical situation that arises from a multifaceted pathogenesis. Elements of childhood adversity, social inequity, genetic endowment, and familial coping all contribute to the development of addiction. Pregnancy is a collision of changing physiology, social roles, and personal identity. Both have vulnerability to complex infections, mental health instability, and intimate partner violence. Together these comorbidities can be significant.

One patient may require support from Addiction Medicine, Cardiology, Obstetrics, Social Work, Endocrinology, Psychiatry, Public Health, and Neonatology, all before the baby is even born. Medical silos result in care-redundancies, lack of continuity, and missed treatment opportunities, all of which exacerbate negative outcomes. **Increasing timely, reciprocal communication between providers, including case conferencing with patients leading the discussion, can help optimize care-efficiencies and improve outcomes.**

Harm Reduction

The recovery journey is a spectrum of goals and experiences that range from frequent, high-dose, unregulated use to absolute abstinence with a wide variety of use- and care-engagement along the way.

For some patients, their definition of recovery may not include abstinence; for others, anything short is considered failure. Meeting patients where they are at, on *their path* to the recovery *they value*, is a requisite first step in harm reduction.

Identifying behaviors which increase the risks of overdose, complex infection, violent exposures, criminal engagement, and/or housing and food insecurity can illuminate opportunities to intervene to minimize these harms.

In the setting of pregnancy, harm reduction also considers the developmental impact of opioid exposure to the fetus, the perfusion effects of use or withdrawal upon the placenta, congenital infection secondary to intravenous use, and the interplay between substance use and preeclampsia or gestational diabetes. **OAT providers can collaborate with maternity care professionals to optimize harm reduction together as it aligns with patient care goals.**

1) ALL INDIVIDUALS SUPPORTED ON OAT WHO ARE OF REPRODUCTIVE AGE SHOULD BE OFFERED THE OPPORTUNITY FOR EFFECTIVE CONTRACEPTIVE AND PRECONCEPTION COUNSELING.

OAT providers can provide essential counselling to reduce the risk of blood borne infections for their patient, their patient's sex/use partners, and their unborn children. By supporting reproductive planning, OAT providers can promote social stability and optimize parenting outcomes. OAT itself improves obstetrical outcomes for both maternal and newborn benefit. While ongoing study is needed to define long-term neurobehavioral effects of fetal OAT exposure, current evidence supports long-acting opioids as decidedly superior to unregulated use in pregnancy. This counsel is meaningful for expectant patients, those considering future fertility, and anyone who might be involved with an unplanned pregnancy.

Infection Risk Reduction

The frequency of Sexually Transmitted and Blood-Borne Infection (STBBI) that follows unregulated opioid use impacts males and females equally. The implications of subsequent sexual transmission should be addressed by care providers. Risk is not limited to intravenous drug use (IVDU). Unregulated oral opioid use is associated with increased unprotected sex, survival sex trade, and sexual violence leading to increased infection rates.⁶

OAT providers must offer comprehensive screening for STBBIs to all patients with OUD. Initial and intermittent STBBI screening, including treatment referrals as appropriate, form an important part of ongoing OAT care. This can occur periodically after intake, based on ongoing risk assessment.

Patients at significant and ongoing risk of infection should be offered STBBI screening every 6 to 12 months. Repeat testing may be customized based on individual risk factors. The chapter on [HIV & Hepatitis C Prevention, Screening, & Management in OUD](#) provides further guidance, along with the recommendations below.

Patients with a diagnosis of STBBI should be provided with barrier prophylaxis (some coverage providers may honour a prescription for condoms) and education about the risk of congenital transmission/harms and the impact of pregnancy on treatment options. Traditionally, these discussions are limited to female-presenting patients who are already pregnant, which negates male agency in transmission and treatment, and misses an essential audience for public health education.

Online resources (CATIE.ca)⁷ can help facilitate these discussions, and shared-care models may induce obstetrical referral for more in-depth counselling.

- **Human Immunodeficiency Virus (HIV):** Manitoba has the second highest rate of HIV infection in Canada,⁸ a growing statistic in step with the opioid crisis in Western Canada. Risk of acquisition is gendered, with male HIV primarily associated with men who have sex with men (MSM), with about 11% linked to IVDU. Female infection is a consequence of heterosexual sex (63%) and IVDU (27%).

The risk of vertical transmission of HIV is about 45% in absence of treatment⁹, which can be reduced to 2% with effective antiretroviral therapy (ART) and appropriate delivery planning. Regular screening, prompt referral to wrap-around HIV care programs, and continued efforts to de-stigmatize HIV are all effective harm reduction strategies. Administration of ART in the same clinic/pharmacy as OAT improves medical adherence.¹⁰

- **Hepatitis C Virus (HCV):** 80% of HCV infection in Canada is secondary to IVDU¹¹ with a 52:48 distribution between the sexes (F:M), and significant overrepresentation among Indigenous communities.¹² The risk of transmission to a fetus can be as high as 38% particularly if the maternal viral load is >1 million IU/L, if alcohol use is concurrent to infection, if HIV is comorbid, and obstetrical interventions are used which increase fetal exposure to maternal blood (scalp clips/sampling, vacuum extraction, prolonged rupture of membranes).¹³

Male patients can protect future offspring with timely treatment and barrier contraceptives to avoid exposing their sex partner(s). Female patients should use effective contraception to prevent a pregnancy until their HCV treatment is complete as both pregnancy and breastfeeding are contraindications to HCV antiviral therapy. Other harm reduction initiatives include alcohol abstinence, at least until the conclusion of antiviral therapy, and comprehensive treatment of HIV. Repeat testing in the third trimester is indicated, given the 2-3 month interval for seroconversion with new infection.¹⁴

- **Hepatitis B Virus (HBV):** HBV affects approximately 200,000 Canadians at present, with a higher risk for fulminant liver disease than HCV.¹⁵ Alcohol use disorder, IVDU, and comorbid HIV/HCV are risk factors for acute HBV infection.

Less obviously, major mental illness is an independent risk factor for HBV, likely a consequence of maladaptive coping with high-risk behaviours.

Opportunistic vaccination is the most important harm reduction intervention for the OAT provider,¹⁶ and is safe during pregnancy. High maternal viremia ($>3.8 \times 10^8$ copies/mL) has an odds ratio of 147 for fetal co-infection.¹⁷ Tenofovir and Telbivudine are pregnancy class B drugs¹⁸ and can prevent vertical transmission when administered in late pregnancy.¹⁹

- **Syphilis:** In 2019 a syphilis outbreak was announced in Alberta, following a 10-fold increase in this infection across the prairies.²⁰ What was considered an eradicated disease has returned to rates not seen since 1948. This is largely attributed to increased laxity in barrier prophylaxis use following the advent of ART, pre- and post-exposure prophylaxis, and the perceived survivability of HIV.²¹

Congenital syphilis is now, likewise, on the rise, with social determinants such as poverty, unstable housing, substance use, and trauma contributing to both increased infectious exposure and decreased prenatal care.²²

An important gap in congenital syphilis prevention is the male partner. Minimal screening and refusal of treatment increase maternal re-exposure despite prenatal care and maternal treatment. Counselling all patients with syphilis about the risks to an unborn child (miscarriage, still birth, blindness, deafness, and/or bone deformities)²³ may help motivate male and female carriers alike to complete treatment.²⁴

CLINICAL PEARL: WHY WON'T MY PATIENT ACCEPT TREATMENT?

Acting against medical advice (AMA) can threaten the therapeutic alliance between providers and their patients. For clinicians, the linear equation of Diagnosis + Treatment = Health seems obvious, and refusal of care can be experienced as a personal rejection.

Instead, this care-disengagement can be viewed through a trauma-informed lens. For marginalized patients “the traumatogenic effects of oppression that are not necessarily overtly violent or threatening to bodily well-being [can] do violence to the soul and spirit”²⁵ and may not only impair trust in the medical system, but also can erode self-preservation.

Recognizing AMA as a potential manifestation of trauma or colonization, rather than simply a difference of opinion can motivate more nuanced discourse. **An assumption that patients make their decisions for important reasons helps preserve the relationship.**

Trust is a therapeutic agent and measurably improves obstetrical outcomes.²⁶

Social Instability Reduction

Patients who are new to OAT are embarking on a journey of recovery that may be complicated by untreated mental illness, trauma, poverty, violent exposures, criminal engagement, and homelessness. All of these factors impart an increased burden of morbidity and mortality.²⁷

Approximately 65% of pregnant persons with OUD have co-occurring psychiatric conditions such as anxiety, depression and suicidal ideation.²⁸ All of these social comorbidities worsen obstetrical outcomes, contributing to prematurity, low birth weight, and increased pregnancy loss.²⁹ Similarly, pregnancy with its complement of mental health vulnerabilities, can destabilize one's recovery. While pregnancy is an important motivation for change, the **postpartum period is particularly high-risk for relapse and unintended overdose** (see **Maternal Benefits of OAT** below).

Exploring patient goals to start or grow their family can lead to more strategic planning for the OAT supported patient. Establishing psychosocial stability prior to pregnancy is associated with a greater likelihood of custodial parenting, term delivery, and a lower-risk postpartum interval.³⁰

Advocating for long-acting reversible contraception (LARC) as the most efficacious option, hormone therapy for persons with irregular or symptomatic menses (co-administered with daily-dosing), and barrier prophylaxis for all can be a useful starting place. Depot injection contraception may be triggering for patients recovering from IVU, but is otherwise very effective especially for those with chronic pelvic pain. It is important to remember, however, that marginalized populations may have negative experiences with coercive contraception planning, and **great care must be taken to champion autonomy**.³¹

- **Maternal Harms of Disordered Opioid Use:** In Canada, opioid overdose rates have increased by 50% over the past decade, now surpassing motor vehicle accidents as a leading cause of death among young Canadians.^{32 33} In the general population, unregulated opioid use is associated with sex trade, HIV and HCV infection, violent exposures, incarceration and socioeconomic marginalization.³⁴ During pregnancy, the consequences are grave with a 3.6-fold increase in cardiac arrest and a 4.6 times increase in mortality rates.

Prenatal care is significantly limited, delaying diagnosis for complex infections such as cellulitis and endocarditis with a consequent increased risk for sepsis, ICU admission, and mortality. A study between Canada and Britain revealed that the risks of opioid-involved pregnancy had a long-reaching effect. Using neonatal opioid withdrawal syndrome (NOWS) as a surrogate for severe, active OUD in pregnancy, they identified a mortality rate of 1:20 over the subsequent 10 years.³⁵

- **Fetal Harms of Opioid Exposure:** Fetal opioid exposure in pregnancy has grown by 16-fold over the past decade, and is associated with fetal growth restriction, low birth weight, preterm birth, and intrapartum fetal distress.³⁶ There is also growing evidence that associates first trimester opioid exposure with fetal cardiac and neural tube defects and gastroschisis^{37 38} though this is not consistent throughout the literature.^{39 40}

Withdrawal itself compromises placental perfusion, resulting in intrauterine growth restriction (IUGR). The risk of placental abruption increases by about 2.4 times, which increases both maternal and neonatal ICU admissions and demise. Neurodevelopment is compromised, with reduced brain volumes than unexposed peers.⁴¹

- **Maternal Benefits of OAT:** The opioid crisis has driven more research in the area of opioid-exposed pregnancies. The majority of literature focuses on the fetal harms of opioid exposure in pregnancy. Advocating for maternal needs and best interests is of particular importance for marginalized populations.

In pregnancy OAT:

- Reduces relapse⁴²
 - Reduces HCV/HIV⁴³ transmission
 - Reduces risk-taking activities⁴⁴
 - Reduces overdose⁴⁵
 - Increases prenatal care⁴⁶
 - Increases custodial parentage⁴⁷
- **Fetal Benefits of OAT:** Fetal impacts of opioid-involved pregnancy are still being explored. Prenatal exposure modifies several neurobehavioral systems in the newborn including sensory integration, state and motor/tone control, and autonomic activation. This manifests in hyper-stimulation response, resistance to being soothed, tremor, difficulty sustaining latch, and suppressed appetite. These are measured in feeding and sleeping behaviours, social and emotional interactions (neonatal abstinence syndrome [NAS] and NOWS scores), and often result in failure to thrive.⁴⁸ Concurrent nicotine, benzodiazepine, and antidepressant exposures may worsen these presentations.⁴⁹

Studies which contrast OAT-supported pregnancy with unregulated opioid-involved pregnancy, however, show reproducible fetal benefits. In the fetal environment, OAT:

- Decreases miscarriage, stillbirth, and neonatal demise⁵⁰
- Improves birth weight⁵¹
- Improves neurological development⁵²
- Decreases prematurity⁴⁷
- Reduces NOWS^{53 54}

- 2) IF PREGNANCY IS DISCOVERED AFTER OAT INDUCTION, PATIENTS SHOULD BE REASSURED THAT THEIR OPIOID AGONIST THERAPY IS GOLD STANDARD CARE FOR PREGNANT PERSONS WITH OUD, AND THAT THERE IS NO NEED TO DOSE-RESTRICT DUE TO PREGNANCY. IN FACT, PHYSIOLOGICAL CHANGES OF PREGNANCY CAN NECESSITATE A DOSE-INCREASE.

Obstetrical advisory bodies in Canada, the US, and the UK all identify OAT as the **gold standard** for opioid-involved pregnancies^{55,56,57} yet pregnant patients fear discrimination in the maternity care environment if they continue their OAT. This perceived stigma becomes a barrier to OAT adherence⁵⁸ and can limit participation in prenatal care, which is the single-most important protective factor for a positive obstetrical outcome.

OAT providers can validate that prioritizing maternal health naturally prioritizes fetal well-being and that maternity care providers and child protective agencies alike increasingly look favorably upon OAT engagement.⁵⁹

- **Avoid dose-restriction:** Effective, adequately dosed OAT suppresses withdrawal and cravings for 24 hours, and prevents or significantly reduces unregulated use. This care goal is unchanged by pregnancy. Patient perception is often that dose-reduction will minimize fetal harms. Pregnant persons thus often endure increasingly severe withdrawal symptoms in the intent to spare their unborn child.

OAT tapers in pregnancy are associated with a dramatic relapse rate. For those who completely wean, the relapse rate is 96%.⁶⁰ Fetal exposure to withdrawal is associated with the deleterious effects of unregulated use such as prematurity and growth restriction.⁶¹

- **Anticipate dose increase in third trimester:** Methadone metabolism, particularly, changes over the course of pregnancy, frequently requiring a need to increase the OAT dose, typically starting around 28-weeks gestation.^{62 63} Patients should be counselled ahead of time to anticipate this shift, and to interpret it as a physiological interaction with pregnancy, not a sign of failed recovery.

Pregnant patients should be seen more frequently, starting at 28 weeks, to ensure regular evaluation of dose adequacy and to facilitate timely dose adjustments. Specifically, in the absence of other significant complications, these patients should be seen **every 2 weeks starting at 28 weeks** gestation, and **weekly starting at 34 weeks** gestation. A blended model of in-person and virtual care appointments may be offered to decrease the travel and financial burden of regular assessments during the third trimester. Video visits are preferable when assessing withdrawal, but may not always be practical or accessible for the patient. Pregnant patients on methadone especially may require *multiple* small dose increases over the course of the third trimester.

Conversely, there is a risk for somnolence with increased potency of OAT following the dramatic fluid shifts of delivery and subsequent volume contraction. **Postpartum patients should be counselled regarding, and monitored for, excess sedation in the postpartum period.** Patients must be advised how to reach their OAT provider if urgent dose reductions are required.

- **Consider increased dosing frequency (split dosing):** New studies suggest that physiologic changes of pregnancy alter the half-life of buprenorphine, with less durable effects of OAT to suppress withdrawal symptoms.⁶⁴ This may be a consequence of plasma expansion, increased eGFR, or both, but serum concentrations can drop below a therapeutic threshold after 8 hours, particularly if the daily dose is less than 12 mg. This effect is more pronounced in the second trimester when plasma volume peaks.

Consideration of divided doses may be more beneficial in pregnancy than just a dose-increase. A 50/50 split is *not* usually required to address withdrawal associated with altered metabolism. A much smaller evening dose is often sufficient to address withdrawal symptoms not alleviated by further increases to once daily dosing.

Similarly, methadone metabolism is increased in pregnancy and patients may likewise benefit from divided doses. This effect is typically more pronounced toward the latter part of the third trimester. Typically, when withdrawal is reported at the end of the dosing interval, the **once daily methadone dose is optimized first.** However, if further AM dose increases cause sedation at the serum peak without adequately suppressing withdrawal towards the end of the dosing interval, consideration may be given to adding a small PM dose of methadone to eliminate withdrawal before the next day's dose.

Patient stability needs to be carefully considered when considering divided doses in pregnancy, including the patient's ability to safely store take-home doses (carries) of methadone or buprenorphine. These considerations, including an overall risk-benefit analysis, must be documented when authorizing evening carries in pregnant patients who do not routinely qualify for take-home doses.

Inexperienced providers or those uncertain of the safety/appropriateness of take-home doses in pregnancy are strongly encouraged to seek guidance from an experienced OAT provider who frequently cares for pregnant patients. See the [Ongoing Care](#) chapter, specifically the section on split-dosing for further recommendations.

- 3) FOR OAT INDUCTION DURING PREGNANCY, EVIDENCE IS STILL EMERGING. WHILE METHADONE HAS A MORE EXTENSIVE LINEAGE IN THE LITERATURE, BUPRENORPHINE/NALOXONE MAY BE CONSIDERED AS A FIRST-LINE AGENT IN PREGNANCY. BUPRENORPHINE/NALOXONE MICRO-DOSING MAY BE FAVOURED OVER A TRADITIONAL START TO AVOID WITHDRAWAL.

In 2020 a randomized controlled trial (RCT) was launched in Canada to contrast traditional versus micro-dose induction of OAT with buprenorphine/naloxone. The study goals are to measure withdrawal symptoms, adherence, durability of abstinence, and patient satisfaction, however pregnancy (as it is in most RCTs) is an explicit exclusion criterion.^{65 66} While maternity care organizations lobby for inclusion of pregnant persons in medical research, in the interim care necessarily requires action in the face of some uncertainty.

OAT providers can engage in a comprehensive risk-benefit discussion with patients, being clear about what is well known versus what is presumed to apply to OAT in pregnancy. Together an induction strategy that aligns with patient goals and prescriber experience can be developed.

- **Buprenorphine/naloxone may be superior to methadone:** Studies in this field are inherently fraught with low quality data, with case-control and retrospective studies comprising the majority of the literature. However, trends increasingly favour buprenorphine use particularly for its association with reduced care costs due to shorter hospital stays.⁶⁷

TABLE 1: OBSTETRICAL OUTCOMES WITH BUPRENORPHINE VS METHADONE OAT - TWO CONSECUTIVE CASE SERIES⁶⁸

METHADONE	OUTCOME	BUPRENORPHINE/NALOXONE
38w6d	Gestational Age @ birth	39w5d
2941 g	Newborn birth weight	3250 g
77.8%	Any NOWS	40.4%
52.8%	NOWS requiring medication	14.9%
19.7	Newborn days in hospital	9.4

- **Methadone is still an important treatment option:** High-dose unregulated opioid use may require methadone therapy⁶⁹ as these patients are not always sufficiently stabilized on buprenorphine/naloxone due to its “ceiling effect”. Patients may have had negative experiences with buprenorphine in the past, or simply have a strong preference.⁷⁰ **Aligning with patient care goals has a more significant association with positive outcomes than use of one drug over the other.** While a comparison, as illustrated in [TABLE 1](#), makes methadone appear dramatically inferior, the lack of high-quality evidence and importance of patient autonomy should preserve methadone as a reasonable care option according to a Cochrane review.⁷¹
- **Micro-dosing in pregnancy:** Micro-dosing induction of buprenorphine/naloxone is associated with increased access to OAT, reduced withdrawal symptoms, and rapid achievement of stabilization.⁷² However, a literature review revealed only one paper,

reflecting a single case, regarding the safety of buprenorphine micro-dosing/rapid induction in pregnancy.⁷³

Extrapolation from non-pregnant data is reasonable, however, **the risk of precipitated withdrawal is important to review during informed consent, given its association with prematurity.** Motivated and well-supported patients may be considered for outpatient induction.

TABLE 2: OUTPATIENT VS INPATIENT BUPRENORPHINE/NALOXONE INDUCTION IN PREGNANCY⁷⁴

OUTPATIENT	OUTCOME	INPATIENT
0%	Precipitated withdrawal	13%
96%	Attend 1wk follow up	63%
72%	Buprenorphine positive urine at follow up	60%
53%	Illicit opioid positive urine at follow up	80%
87%	3-months adherence	63%

- 4) CYCLES OF USE AND WITHDRAWAL ARE ASSOCIATED WITH FETAL STRESS. THIS IS PRESUMED TO BE A CONSEQUENCE OF COMPROMISED PLACENTAL PERFUSION; PATIENTS SHOULD BE EDUCATED ABOUT THE IMPORTANCE OF AVOIDING WITHDRAWAL IN PREGNANCY AND REASSURED THAT THEIR PRESCRIBERS/OAT CARE TEAMS WILL TREAT THESE PRESENTATIONS.

Withdrawal relief is an important care goal on which providers and patients can often align, offering reassurance that opioid withdrawal is an appropriate indication for therapy. During pregnancy this discussion must be additionally nuanced as patients may be motivated to dose-restrict for fetal sparing. Self-induced suffering can be valued as “motherly sacrifice.”

Opioid exposure in pregnancy modifies metabolic function of the placenta, likely through selective methylation, and can compromise oxygen delivery to the fetus overall.⁷⁵ The highs and lows of use and withdrawal impose acetylcholine vasoconstriction.⁷⁶ Given the maternal hypovolemia associated with acute withdrawal, placental perfusion is further compromised. Cerebral oxidative stress has been shown in animal models during fetal exposure to maternal opioid withdrawal.^{77 78}

OAT providers can reinforce the clinical importance of suppressed withdrawal from a recovery perspective, while also relieving mothers of the misconception that withdrawal is a necessary part of pregnancy. Withdrawal management in the obstetrical patient is most appropriate in a hospital setting with oral opioids as a bridge to OAT induction. Other medications to ameliorate symptoms can be utilized with the *exception of clonidine*. This potent antihypertensive is relatively contraindicated in pregnancy due to its association with hypotensive placental malperfusion.

- 5) COMMUNITY BASED OPIOID WEANING SHOULD BE LIMITED TO HIGHLY MOTIVATED PATIENTS WHO, AFTER THOROUGH RISK-BENEFIT DISCUSSION, DECLINE OAT THERAPY. CESSATION, EVEN IF CLOSELY SUPERVISED, IS EXTREMELY HIGH RISK FOR RELAPSE TO UNSTABLE OPIOID USE, MATERNAL OVERDOSE, AND PLACENTAL MALPERFUSION IMPOSED BY THE REQUISITE WITHDRAWAL.^{79 80} THIS APPROACH HAS ALSO NOT BEEN PROVEN TO IMPROVE NEWBORN OUTCOMES.⁸¹

Previous dogma linking “detoxification” (medication-assisted withdrawal for opioid-dependent patients⁸²) with placental abruption have largely been disproven. The primary concern is with practical feasibility and **relapse risk**. Few patients actually complete the process and the overwhelming majority relapse to unstable use.⁸³

However, in the interest of patient autonomy, for the highly motivated and very well-supported individual, cessation can be a treatment option with appropriate counselling. The term “detoxification” is predominantly used in the literature, but itself can have valiative connotations, as though OAT might be considered “intoxication.” Identifying implicit bias is meaningful to empower patients to make care decisions based on their own values and not prejudices in the community.

Risks versus benefits of opioid cessation in pregnancy:

- Emerging studies suggest structural brain changes in opioid-exposed newborns, however findings are not yet clinically correlated to meaningful developmental effects; studies compare exposed and naive newborns, rather than OAT supported versus tapered pregnancies.⁸⁴
- Acute maternal withdrawal results in high circulating catecholamines, uterine contractions and decreased placental perfusion which paradoxically increases fetal activity and oxygen demand. Similarly, lasting clinical consequences of these stress events are unknown.⁸⁵
- In contrast with either OAT or unregulated use, cessation does not improve/affect rates of prematurity or NOWS severity.⁸⁶
- Preoccupation with NOWS scoring can be a distractor – this condition is treatable and not associated with enduring sequelae. Neonatal sepsis, however, is increased 30-fold in unstable opioid use in pregnancy, and these risks should be considered when foregoing OAT.⁸⁷
- Duration of symptomatic withdrawal can last up to 16 weeks which precipitates relapse⁸⁸
- Maternal relapse rates are extremely high, up to **90% return to unstable use by delivery**.⁸⁹

- **Risk of maternal death by overdose increases as OAT decreases; opioid tolerance is lost rapidly over days to weeks and what previously was a usual dose can become a lethal one.**⁹⁰
- Only one study included fetal monitoring in its protocol, and did not reveal fetal distress, but this was too small to be representative.⁹¹ Fetal effects of cessation are not well understood, and guidance is lacking. It is reasonable to refer to fetal assessment for a well-being scan if primary withdrawal results in prolonged dehydration, and to consider fetal heart auscultation during intervals of enduring maternal tachycardia or hypotension.
- Robust wrap-around supports with a culturally-safe care team are required for risk reduction.⁹² This might include frequent check-ins either virtually or in-person regarding symptom tolerability, social stability, and mood assessment.
- Outpatient cessation is favoured given the lengthy time course. Recent study designs suggest 10% weekly or more, as per symptom profile.⁹⁶ **A safe and tolerable taper should not require inpatient intervention.**
- Preservation of the therapeutic alliance between patient and provider is essential and has a mortality benefit.⁹³ Patients who decline both OAT or a supported taper and either elect ongoing unregulated use or “cold-turkey” cessation need to know they still have a medical resource to return to when needs change or complications emerge.
- A contingency plan for OAT induction in the event of maternal/fetal distress should be in place. Where methadone and buprenorphine/naloxone are unavailable, slow-release oral morphine (SROM) and MS Contin can be acceptable off-label alternatives.⁹⁴

One Canadian study followed a cohort of >100 pregnant patients who were offered long-acting morphine (SROM or MS Contin) on a taper with a goal of cessation.⁹⁵ **Fewer than 10% of participants were off of all opioids at the time of delivery.** Statistically significant outcomes included decreased birth weight, increased NOWS scores, and increased length of stay in the taper group.

Finally, rapid **inpatient** opioid tapers to zero over 7-14 days (so-called “detoxification admissions”) are **NOT recommended for patients with OUD, and this includes pregnant patients with OUD.** Withdrawal management, or “detox”, without transition to OAT and long-term treatment is associated with increased morbidity, such as HIV transmission, and mortality secondary to overdose.

If patients decline OAT despite the risks, a slow outpatient taper of opioids, as discussed above, is a safer approach than admission to a hospital or residential detox setting.

- 6) OPIOID USE IS OFTEN A BARRIER TO PRESENT FOR MATERNITY CARE.⁹⁶ PROVIDERS SHOULD ENCOURAGE THE USE OF ALL AVAILABLE COMMUNITY RESOURCES AND MAKE PROMPT REFERRALS TO MATERNITY CARE PROVIDERS WHO ARE FAMILIAR WITH OAT. THIS MAY INCLUDE AND IS OFTEN ENHANCED BY A SHARED-CARE APPROACH WITH OUTREACH NURSING, OBSTETRICIANS, MIDWIVES, AND ALLIED HEALTH.

Fear of stigma, infant apprehension, and lack of agency all collude to inhibit disclosure of opioid use in pregnancy. In addition to these more existential barriers to care, childcare is an important obstacle both for OAT adherences and prenatal (PN) care.⁹⁷ Medical adherence and maternity care attendance both improve when care occurs in the same place. Optimizing patient engagement can include shared OAT-PN care.

Patients describe moral inhibition around their use of OAT during pregnancy, the inclusion of this history on PN charts, and presumed stigma. "It is shamed-based, you know. You are made to feel ashamed for making poor choices and you have to carry that for the rest of existence."⁹⁸

Stakes are also inflated during pregnancy with the threat of custody loss looming as an enduring stressor. "I had child protection tell me that if I relapsed one more time that they were going to take my children and I would never see them again... and that was it." For some patients this is a potent motivator, but for most it **recapitulates the powerlessness that is entrenched in marginalization, trauma, and addiction itself**. Evidence shows that child welfare agencies can unintentionally compromise recovery.⁹⁹

Engagement with community support for cultural safety, group parenting programs to reduce isolation, and **reassurance that OAT is not reportable** can help bolster that vulnerability.

CLINICAL PEARL: VALUE OF TRUST

"Women in recovery from OUD may experience deeper engagement in outpatient perinatal services when they perceive that their providers are invested and collaboratively engaging in their recovery and personal growth."¹⁰⁰

Cultivating trust in the setting of unregulated drug use is a clinical skill that OAT providers exercise with each care encounter – it is a particular type of expertise.

When patients transition to other providers – either for maternity care, antiviral treatment of their hepatitis, or an echo for their cardiomyopathy – OAT providers can help leverage that trust with shared-care encounters. Utilizing virtual platforms, the specialist can be invited into an OAT visit to create a setting of safety with a new face, protected from judgment and stigma by the provider they trust.

- 7) SMOKING CESSATION COUNSELLING SHOULD BE CONSIDERED AS A FIRST-LINE INTERVENTION FOR PREGNANT SMOKERS, GIVEN THE SYNERGISTIC HARMS OF SMOKING AND OPIOID USE IN PREGNANCY. TO DATE THERE IS SUFFICIENT SAFETY EVIDENCE TO ALSO RECOMMEND BUPROPION AND NRT IN PREGNANCY.

OAT providers can debunk the myth that cessation should happen one substance at a time. Use is often paired, and concurrent use-reduction can improve outcomes synergistically. In pregnancy the most important co-use is cigarette smoking – a known teratogen with association with placental insufficiency. Smoking in pregnancy increases cardiac defects, limb malformations, and a variety of errors of visceral organogenesis.¹⁰¹ Pulmonary compromise, reproductive impairment, and neurobehavioral effects last beyond childhood.¹⁰²

As many as 95% of pregnant persons on OAT smoke cigarettes¹⁰³ with the lifetime cardiovascular maternal harms that smoking can impart.

Opioid use with concurrent smoking:

- Increases ectopic pregnancy rates.¹⁰⁴
- Increases placenta previa and placental abruption.⁹¹
- Increases rates of miscarriage, stillbirth, and neonatal demise.¹⁰⁵
- Increases premature birth, intrauterine growth restriction, and SIDS.^{106 107}

Smoking cessation in pregnancy:

- Is more likely to succeed with NRT which has good safety data.¹⁰⁸
- May require higher NRT dosing due to increased nicotine metabolism.¹⁰⁹
- Before 15-weeks gestation has the greatest magnitude of fetal benefit but cessation and use reduction at any gestational age also improve outcomes.¹¹⁰
- Patients may benefit from bupropion according to many observational trials and one small RCT.¹¹¹
- Varenicline has insufficient data to recommend during pregnancy/breastfeeding.¹¹²

- 8) SYMPTOMS COMMON IN PREGNANCY, SUCH AS NAUSEA AND VOMITING, CAN BE DISTRESSING AND ACT AS PROVOCATIVE TRIGGERS FOR RELAPSE GIVEN THEIR OVERLAP WITH WITHDRAWAL SYMPTOMS. ANTIEMETICS SHOULD BE EASILY ACCESSIBLE AND CONSIDER INTERVAL EKG STUDIES TO ASSESS QT INTERVALS FOR PATIENTS ON OAT (PARTICULARLY METHADONE) WHO REQUIRE OTHER QT-PROLONGING MEDICATION(S) FOR SYMPTOM CONTROL. TYPICALLY, NON-SEDATING ANTIEMETICS ARE USED FIRST LINE. HOWEVER, FOR SEVERE SYMPTOMS A REGIMEN UTILIZING MORE THAN ONE AGENT MAY BE REQUIRED.

Symptoms that resemble opioid withdrawal can induce panic in the recovering individual. Such symptoms, from morning sickness to hyperemesis, can decrease confidence that OAT is working, increase the need for QT-prolonging drugs, and can be exacerbated by the constipating effects of OAT.¹¹³

Increased Risk for Vomited Doses in Pregnancy

Given the ubiquity of nausea and vomiting in pregnancy (NVP), patients should be educated about the timing of emesis in relation to their OAT dose. Methadone and SROM are of particular concern, as a portion of the dose may be lost if the patient vomits within 15-20 minutes after dosing. Given that buprenorphine absorbs sublingually, vomiting is less of a concern for dosing stability if the dose was fully dissolved prior to emesis.

Regardless of the specific OAT medication, NVP is distressing to patients and warrants aggressive treatment. Vomited doses are also discussed in [Ongoing Care](#), however **recommendations vary in pregnancy**, as described below:

- If NVP is a concern, consider pre-dosing with ondansetron 4-8 mg PO daily to prevent OAT dose losses, especially in the setting of hyperemesis gravidarum (HG).
- It may be useful for patients on methadone to consume 50% of their dose, wait 10 minutes in the pharmacy before consuming the rest, then wait another 10-15 minutes in pharmacy post dose. This way, if emesis occurs within 15 minutes after dosing, it can be observed by the pharmacist and be replaced appropriately in collaboration with the prescriber. Discussing this dosing arrangement with the pharmacist beforehand is essential, so as to make them aware of the situation and to consider the practical implications of having the patient wait in the pharmacy during the witnessed self-administration process.
- It is important to note that all replacement doses require a *new* OAT prescription. The prescriber should note that it is a “replacement dose” on the prescription.
- As some patients identify that certain smells/tastes trigger emesis, it may be helpful to speak with the pharmacist about trying a different diluent with the methadone concentrate (e.g., apple juice instead of Tang), or switching to a cherry-flavored concentrate that does not require dilution. However, remember that switching between methadone brands should be approached cautiously and in collaboration with the pharmacist. **Methadone products are not interchangeable from a clinical perspective nor a coverage perspective.** A new prescription would be required to switch a patient from one product to another. **Such changes will often require collaboration and communication between the prescriber, pharmacy team, and patient to monitor for dose equivalency.**
- Pregnant patients may also vomit take-home doses. **Pregnancy is the one circumstance in which a partial replacement dose may be considered for unwitnessed emesis.** Patients should be educated to check the time that they self-administer a take-home dose, so that they can report the time lapse between dosing and emesis more accurately. Ensure the patient has multiple contacts for assistance, particularly for dose losses due to unwitnessed emesis, to strategize the utility of a partial replacement dose.

- Treating NVP can be a key component of early treatment retention. Opioid withdrawal causes nausea that can exacerbate pregnancy-related nausea and vomiting. Vomiting is even more common during the induction phase of treatment. Therefore, during the induction and titration phase, dose retention is crucial to establish early benefit from treatment and to promote patient engagement.
- OAT providers should have a low threshold for referring pregnant patients starting OAT for IV rehydration in hospital or urgent care, as the combination of withdrawal and emesis may result in significant fluid deficits and affect overall coping.

Non-Prescription Treatment for NVP

Ginger in the form of tea, chews, and capsules are excellent first-line options for NVP. Acupressure and antihistamines are safe and effective. These methods should be exhausted before starting phenothiazines, dopamine, and serotonin 5-hydroxytryptamine type 3 receptor antagonists, particularly for QT-sparing in the setting of OAT.¹¹⁴

Many pregnant patients utilize cannabis for GI complaints. While the majority report symptom relief, **THC crosses the placenta readily and is associated with growth restriction, long-term neurobehavioral disorders, and an increased lifetime risk in the offspring for disordered substance use.**^{115 116} As such, [national guidance](#) discourages cannabis use in pregnancy.

Cannabinoid hyperemesis syndrome (CHS) has distinct clinical features from HG. CHS tends to be associated with significant pain, and features three phases of (1) abdominal pain prodrome, (2) emesis, and (3) exhaustion that tend to cycle through in 2-3 day intervals.¹¹⁷ CHS rarely responds to traditional antiemetics, alleviated more by hot water bathing. The mainstay of therapy is cannabis cessation. HG on the other hand features nausea more prominently, is less cyclic in nature, responds to routine medications, and tends to improve after 20-weeks gestation. A simplified table below highlights features of CHS to distinguish it from HG.^{118 119 120}

TABLE 3: DISTINGUISHING CANNABINOID HYPEREMESIS FROM HYPEREMESIS GRAVIDARUM IN PREGNANCY

HG	FEATURE	CHS
Primiparous non-smokers	Risk Factors	Cannabis >1x/wk for >1 year
First half of pregnancy	Gestational onset	Any gestational age
Absent	Pain Prodrome	Classic
Dextrose rehydration	Alleviating factors	Hot water bathing
<i>H. Pylori</i> co-infection	Aggravating factors	Increased cannabis use
Serotonin/dopamine antagonists	Effective medication	Limited role for medication

9) OUD PREDISPOSES PATIENTS TO HYPERALGESIA SO CONSULTATION WITH ANESTHESIA PRIOR TO DELIVERY SHOULD BE CONSIDERED.¹²¹ OAT DOES NOT PROVIDE EFFECTIVE ANALGESIA IN LABOUR.

Patients have a variety of anxieties regarding analgesia in labour. They worry that they will be denied pain relief, that it will not be effective, and that opioid analgesia will cause them to relapse. Historically, OAT has been mistaken for pain control in labour, but current obstetrical guidance has clarified this matter. **Most importantly, opioids when used for acute pain in labour or post-operatively are not associated with OUD relapse.**¹²²

Recommendations for analgesia in labour include:

- Analgesic activity of methadone and buprenorphine is much shorter (8 hours)¹²³ than that for withdrawal suppression. In pregnancy this can be even shorter due to metabolic acceleration. Again, it is important to recognize that the maintenance opioid for OUD is the baseline for preventing withdrawal and does not provide significant pain relief. As above, **patients on OAT with acute pain will typically require pain management in addition to their buprenorphine/naloxone or methadone dose.**
- Essentially all routine methods of analgesia are still available except for morphine in the patient on buprenorphine, as it may not have sufficient binding affinity to compete¹²⁴. A remifentanyl PCA can be offered for those who decline epidural.
- Despite opioid tolerance, patients can be reassured that acetaminophen and naproxen are usually sufficient postpartum for vaginal birth.¹¹⁵
- On average, patients on methadone require 70% more analgesia post c-section. Those on buprenorphine require a 47% increase.¹²⁵
- Epidural is an excellent option for pregnant patients on OAT, and should be offered when appropriate.
- It is important to establish IV access early for patients with OUD in labour, as IV access may be challenging in individuals with a history of intravenous drug use.
- Pregnant patients on OAT should be referred for delivery in a center with the appropriate level of neonatal care capacity, as determined in consultation with the obstetrical care provider.

Delays in OAT dosing can cause unnecessary withdrawal on the labor delivery unit or birth center. In sufficiently stable patients, OAT providers may consider prescribing one take-home dose to be kept in the patient's hospital bag to bridge until reliable dosing is available.

Detailed recommendations for [Managing Pain](#) and the [In-Hospital Care](#) of individuals with OUD are discussed in these respective chapters.

10) APPROACH TO INFANT NUTRITION SHOULD BE WEIGHED ON AN INDIVIDUAL BASIS. OAT IS NOT A CONTRAINDICATION TO BREASTFEEDING WHICH IS, IN TURN, ASSOCIATED WITH REDUCED NOWS SCORES AND INCREASED PARENT-INFANT BONDING.^{126 127 128 129}

OAT providers are not expected to offer expertise in breastfeeding, but can support patient goals and reinforce that OAT is not a contraindication. In contrast, in the setting of unregulated opioid use, nursing is relatively contraindicated given the high risk for poisoned supply and unknown contaminants. It is unknown how long one should permit clearance before attempting to resume breastfeeding after an isolated use, particularly if methamphetamines contaminate the dose. This is an emerging field of active research and harm-reduction planning should be frank about what medicine does not yet know. However, **the benefit of skin-to-skin care in the first weeks of life is well demonstrated**; this helps to regulate newborn temperature and heart rate, allowing them to conserve calories for weight gain.

Maternal benefits of breastfeeding:¹³⁰

- Decreased postpartum depression.*
- Increased maternal-newborn bonding.*
- Decreased postpartum bleeding.
- No cost, portable, complete nutrition for the first 6 months of life.
- Decreased risk of pregnancy in the first 6 months postpartum.
- Decreased lifetime risk of breast and ovarian cancers, diabetes, and hypertension.

Fetal benefits of breastfeeding:¹³¹

- Decreased Nows severity.*
- Decreased SIDS.*
- Improved heart rate and temperature regulation.*
- Increased maternal-newborn bonding.*
- Reduced risk for respiratory infections.
- Decreased lifetime risk for type 1 diabetes, asthma, and obesity.

**These benefits can also be achieved at least in part with skin-to-skin bottle feeding.*

11) OPIOID-INVOLVED PREGNANCIES ARE HIGH RISK FOR POSTPARTUM DEPRESSION AND SUICIDE. SCREENING FOR DEPRESSION SHOULD OCCUR AT EACH TRIMESTER AND POSTPARTUM FOLLOW UP SHOULD BE ENHANCED; PATIENTS SHOULD BE SCREENED BY A CARE-PROVIDER WITHIN TWO WEEKS OF DELIVERY. NEITHER PREGNANCY NOR BREASTFEEDING ARE CONTRAINDICATIONS TO SSRIS.

Maternal mortality is 8:100,000 and is 9% higher in Manitoba than the national average.^{132 133} This risk is increased to 20:100,000 for those who deliver a newborn symptomatic for Nows.¹³⁴

Most major centers offer robust services during antepartum, but routine postpartum follow up is limited to a solitary 6-week visit. In the opioid-involved pregnancy, it is the postpartum year that is the highest risk for psychosocial decompensation. Postpartum depression (PPD) impairs attachment and response to newborn cues¹³⁵ and has lasting consequences for attachment.

Due to anxiety about infant apprehension, mothers are reluctant to reach out for mental health supports. The risk of depression, relapse, suicide, and unintentional overdose is effectively doubled amongst Indigenous populations.¹⁸

SSRIs are indicated for moderate to severe depression in pregnancy and postpartum, and are compatible with breastfeeding but associated with *slightly* increased NOWS scoring.¹³⁶ Given that suicide is a complication of undertreated depression, this small risk is appropriately accounted in risk-benefits assessment. **The exception is paroxetine which has been linked with equivocal findings of cardiac defects¹³⁷ and is generally avoided during pregnancy.** It is not contraindicated in breastfeeding. SSRIs with minimal QT-interval impact are favoured for patients on methadone. Education about and monitoring for serotonin syndrome is important for this population.¹³⁸

TABLE 4: RISK FOR DEPRESSION, SUICIDE, AND OPIOID OVERDOSE IN THE OAT POPULATION.

RISK	GENERAL POPULATION	OAT POPULATION	RED FLAGS
PPD	5.6% ¹³⁹	32% ¹⁴⁰	Missed OAT doses
Suicidal Ideation	3-7% ¹⁴¹	23% ¹⁴²	Repeat ED visits with non-specific complaints
Overdose	6.5:10,000 ¹⁴³	281:10,000 ¹³⁰	Loss to follow up

12) INTIMATE PARTNER VIOLENCE AND RELATIONSHIP DISCORD ARE HIGHLY CORRELATED WITH POSTPARTUM RELAPSE AND OVERDOSE. SCREENING FOR RELATIONSHIP STABILITY SHOULD OCCUR IN EACH TRIMESTER, WITH SAFETY PLANNING AS INDICATED.

Lamentably, pregnancy is the highest risk interval for intimate partner violence (IPV) over the reproductive lifespan, with increasing severity with advancing gestation. This is disproportionately burdensome for women with socioeconomic disadvantage. The general population has a risk of IPV in pregnancy of 9% whereas those living in poverty suffer 50%.¹⁴⁴

Additionally, **for those dependent on opioids, lifetime risk of IPV is as high as 95% with violence in the past year up to 75%.**¹⁴⁵ This reveals a “bidirectional” risk where violence perpetuates increased unstable use, and instability is a key risk factor for violence. Adult male violence is a manifestation of childhood toxic stress and is modifiable¹⁴⁶ with often favourable outcomes with therapy and behaviour modification strategies; screening males for violent histories can potentially further reduce events suffered in peripartum.

CLINICAL PEARL: HARM REDUCTION ALONG THE CONTINUUM

Intimate partner violence increases postpartum suicidality by nine-fold.¹⁴⁷

IPV care, such as safety shelters and support groups, often requires the patient to abstain from their relationship. As with opioid use, recovery from violence exists on a continuum with varied stages of readiness for change and actionable agency. Acceptance of referral may require time. In the interim, **safety planning and advocating for patient agency fit well within the skills of the OAT provider - meeting patients where they are at, in a spirit of harm reduction.**

Provider interventions to reduce maternal mortality due to IPV include:¹⁴⁸

- **Universal screening (see Table 5) and referral for IPV.**
 - Collaborate on [Safety Plans](#) with patients.
 - Provide 24-hour crisis helpline in Manitoba (phone 1-877-977-0007).
 - Provide up-to-date shelter contact information, available at the Ending Violence Association of Canada link to [Getting Help](#).

TABLE 5: [HITS](#) FOUR-QUESTION SCREENING TOOL FOR INTIMATE PARTNER VIOLENCE ¹⁴⁹

DOES YOUR PARTNER...	NEVER (1)	RARELY (2)	SOMETIMES (3)	OFTEN (4)	FREQUENTLY (5)
Hurt you					
Insult/talk down to you					
Threaten you with harm					
Scream/curse at you					

A total **score of 10** is considered “positive” for IPV

- **Recognize emergency room visits in the postpartum year as flags for IPV.** Optimize these encounters as opportunities for brief intervention and referral. Consider the role of traumatic brain injury in opioid recovery/relapse.¹⁵⁰
- **Increase ease of access to naloxone kits** and treatment programming.
- **Refer to trauma informed community services.** Recognize the intergenerational and collective trauma lived by marginalized populations and offer culturally safe/embedded programming. See [Managing Co-Occurring Psychiatric Disorders in OUD](#) for a list of resources and additional guidance.

13) OAT IS NOT A REFLECTION OF PARENTING CAPACITY.^{151,152,153} PATIENTS SHOULD BE OFFERED SUPPORT THROUGH LOCAL COMMUNITY PROGRAMS FOR PRENATAL AND/OR PARENTING CLASSES THAT ARE CULTURALLY SAFE AND ALIGNED WITH PARENTING VALUES. INVOLVEMENT OF CHILD PROTECTIVE SERVICES (CPS) SHOULD BE LIMITED TO DOCUMENTED UNSAFE BEHAVIOUR WITH INFANTS/CHILDREN ALREADY IN THE HOME. OAT IN PREGNANCY IS NOT AN INDICATION TO REPORT.

In 1997, a Manitoban case was escalated to the level of the Supreme Court¹⁵⁴ to assess whether or not illicit drug use in pregnancy was a reportable offense, and if child protection agencies could mandate treatment in service of the needs of an unborn child. In this instance, Manitoba's Queen's Bench had granted CPS the power to enforce involuntary residential addictions treatment, later revoked by the Supreme Court. This decision included harsh criticism of Manitoban courts, stating the "intervention was on behalf of the fetus with no evidence of concern for maternal wellbeing". Despite this highly publicized case and ruling, prevailing attitudes assume that women who use drugs in pregnancy lack maternal commitment, emotional maturity, and are inherently deceitful.¹⁵⁵

Managing Misconceptions & Shame for Relapse Prevention

In the US, adoptive parent Barbara Harris founded Children Requiring a Caring Community, (CRACK, later termed Project Prevention), a program that pays women with addictions cash to engage in long-acting contraceptive use or undergo sterilization.¹⁵⁶ She was famously quoted on the television program *60 Minutes*, comparing her program to community neuter-spay clinics, and repeatedly used the phrase "having litters" in reference to the grand multiparity she observed in this population.¹⁵⁷ As of May 2021, over 7000 women with substance use histories had been paid to either accept an IUD or tubal ligation, and the initiative has branched into the United Kingdom. These attitudes are internalized by women of reproductive age, and can compound the self-loathing that often features in addiction:

You can't be raised by an alcoholic, like there are people who have been raised by alcoholics and grown up to be good people, but those are stories you put in books and don't happen as often as you'd like to think. Then there are people who are raised by alcoholics, and become alcoholics because it's what they know, or that their kids go on welfare because their parents are on welfare – (16-year-old subject, Dee).¹⁵⁸

Appreciating the myriad of reasons that women engage with unstable opioid use, and why pregnancy can stimulate recovery in some and relapse in others, is extremely poorly understood. We know there are important roles that familial substance use and childhood/intergenerational trauma play,^{159 160} but it is unclear how best to intervene and which risk factors can be modified in terms of impact.

A modicum of research has been committed to Indigenous communities, exploring the potential for intergenerational care in recovery. Formal "grannies", female elders who take on a

grandmotherly role, seem to increase care-engagement and fulfill a care gap left by the treatment community:

I don't think, without Elders... our race our culture can survive. Let's face it, there are very few young people who are interested in culture nowadays. And with Elders like, no matter of how bad of a kid you are, almost all native kids looked up to their Kokum or their Mushum, almost all of them did – (17-year-old subject, Cherish).¹⁴⁹

Indigenous doulas also appear in the literature as important advocates to navigate the inherent racial bias in medicine that influences maternity care and amplifies marginalization for OAT supported mothers. Their involvement can decrease barriers to care such as transportation needs, improve trust experiences in clinical environments, and help clients navigate encounters with CPS.¹⁶¹

This translates partly into relapse prevention planning between the patient and OAT provider. Extrapolating from alcohol-based literature, **shame is a potent risk factor for relapse to unstable use.**¹⁶² Entering into pregnancy is not only triggering for old shame (such as childhood abuse¹⁶³), but often exposes patients to countless microaggressions and direct insults about their capacity to parent. Erroneously, care providers may assume older children are in care, that fathers are not involved, and that the patient will not plan to parent.¹⁵² Active listening, reframing, and fact-checking are important strategies to help patients navigate these hurts.

14) INFANT APPREHENSION IS AN IMPORTANT RISK FACTOR FOR MATERNAL MORTALITY IN THE OPIOID-INVOLVED PREGNANCY. IF CPS ARE ASKED TO ASSESS FOR APPREHENSION, WRAP AROUND SUPPORTS ARE URGENTLY INDICATED FOR MATERNAL WELFARE.

Preservation of the mother-infant dyad and effective attachment requires “engaged mothering, recognition of risk, affection, and respectful maternity care”. The result of attached parenting is increased discharge home of the newborn with biological family, experience of love and security, and increased enduring sobriety.¹⁶⁴ OAT providers can validate patient parenting goals and priorities, reinforce the role of motherhood, and help patients navigate local supports to prepare for parenting. However, at the time of delivery, unanticipated intervention from CPS can be intensely destabilizing to the family unit and to maternal recovery and psychiatric safety.

Increased PPD & Unintentional Overdose

Postpartum patients with a substance use history are subjected to disproportionate monitoring and apprehension from child protection agencies.^{165 166} **Infant removal is not simply “distressing” but is experienced with equally intense grief symptoms as those endured when an infant has died.**¹⁶⁷ The impact of this complex grief experience is measured in PPD (effectively doubled¹⁶⁸) and unintentional overdose that is increased by 55% and further doubled in the Indigenous population¹⁶⁹ in the setting of apprehension.

Nearly 90% of children in foster care in Manitoba are Indigenous,¹⁷⁰ linking to intergenerational traumas like the Residential School Act and Sixties Scoop.¹⁷¹

The most significant risk factors for permanent loss of parental custody are more important in combination rather than any single factor, and include:¹⁷²

- a) Incarceration history with comorbid substance use.
- b) Maternal childhood abuse history with less than grade 12 education.
- c) Psychiatric history requiring hospitalization in setting of depressive symptoms.

These patients require multidisciplinary care throughout pregnancy and long into the postpartum period. Collaboration with social work, spiritual care, grief counseling and culturally appropriate community programs such as [The Mothering Project](#) are essential.

One of the most important protective factors for preserved custody is simply rooming-in with easy and close contact and skin-to-skin engagement with the newborn. “Given that a growing body of literature suggests rooming in can reduce NAS scores, and that higher NAS scores are associated with an increased risk of maternal overdose, we believe rooming in should be considered a critical factor in future analyses looking at risk for maternal overdose.”¹⁷³ Champions for the maternal-infant dyad are required at the level of patient care and hospital policy.

15) TAPERING OAT WITHIN THE FIRST POSTPARTUM YEAR IS HIGHLY CORRELATED WITH RELAPSE AND UNINTENDED OVERDOSE. PATIENTS SHOULD BE ADVISED TO TITRATE DOSE TO EFFECT AS THEY WOULD NON-PREGNANT, AND ENCOURAGED TO POSTPONE PLANS TO TAPER THEIR OAT DOSE UNTIL THE NEWBORN IS OVER ONE YEAR OF AGE.

Postpartum relapse risk in the setting of an OAT-supported pregnancy is high, along with the risk for fatal overdose.¹⁷⁴

Traumatic birth experiences increase this risk,¹⁷⁵ and sleep deprivation with the intense demands of new parenting certainly play a role,¹⁷⁶ but there are also counterintuitive risks with addiction treatment. Residential treatment during pregnancy is *negatively correlated* with treatment retention and custody beyond the first 6 months of life.¹⁷⁷ Those supported in the community on OAT had significantly improved outcomes, without the dose itself impacting the result.

Risk features in the postpartum year:

- 1:7 will experience overdose.¹¹
- The risk of overdose increased by 4x after the first 6 months of life.¹⁰
- Indigenous ethnicity increases postpartum overdose by 2.1x.¹⁷⁸

Red flags for relapse: ¹⁷⁹

- Bottling up emotions,
- Socially isolating,
- Failing to attend/participate in programming,
- Focusing on others rather than self, and
- Poor eating/sleeping habits.

Relapse prevention: ¹⁸⁰

- Changing lifestyle/environment to make it easier to avoid use,
- Being completely honest,
- Asking for help,
- Practicing self-care, and
- Avoiding rule bending.

There is very little in the literature to guide clinicians about when it is advisable to consider weaning OAT in general, and even less regarding the postpartum family. Recommendations, such as the recent publication from Mayo Clinic,¹⁸¹ lump together multiple populations on opioids such as those treated for chronic pain and OUD across the age continuum.

Again, OUD is a chronic medical condition that requires long-term treatment, and no recommendations exist to indicate a specific optimal treatment duration. However, it is encouraged and recommended that treatment continue for as long as desired by the patient to provide stability, functionality, and reduce harms. See [Discontinuing Treatment](#) for guidance on helping patients decide when to attempt tapering and detailed recommendations for withdrawal of OAT.

Patient goals, functional/quality of life impairments, polypharmacy, or cardiovascular complications of opioid use may all be motivators to taper, but must outweigh the risk of destabilizing recovery. Ensuring stability in other domains, such as housing, income, relationships, mental health, and custody, are all likely protective features to increase the likelihood of a successful taper, but data in this area is scarce and poorly nuanced. Case-by-case risk-benefits analysis is required, as is reassurance that OAT support can be an important feature of a healthy and happy home.

CLINICAL PEARL: COMPASSION IS AS IMPORTANT AS OAT IN THE OPIOID-INVOLVED PREGNANCY

I think you should know that your belief in me and your kindness and your non-judgement played a huge part in how my life is today. When I first met you, I thought of myself as worthless and was quite used to being treated that way by every person that I had come in contact with. Your easy kindness was felt immediately, and I remember that you gave me that shred of hope that I so desperately needed. Somehow ‘thank you’ seems hardly sufficient. (Former patient BC Women’s Fir Square, 2005)¹⁷.

FURTHER CONSIDERATIONS & ONGOING AREAS OF RESEARCH

SROM In Pregnancy

SROM (name brand Kadian®) is an oral alternative to methadone and buprenorphine/naloxone and regarded as a *third-line therapy* in the general population. There is scant literature regarding the utility of SROM in non-pregnant individuals and even less regarding OAT with SROM in pregnancy.

- **Consideration of RISK:** A Cochrane Review conducted in 2013 identified only three studies, representing 197 *non-pregnant* subjects comparing first-line OAT with SROM. These demonstrated relatively equivalent outcomes regarding remission and treatment engagement, but identified significantly worse abdominal cramping, aches & pains, insomnia and (in one study) depression with SROM compared to methadone and buprenorphine.¹⁸² Given the predisposition to these complaints inherent to pregnancy, there is concern that the side effects of SROM could be deleterious. In two small observational studies in the late 1990s, however, this was not the case.¹⁸³
- **Anticipation of BENEFIT:** One observational trial followed 24 pregnancies supported on SROM and *no clinically significant* maternal or newborn differences were found in contrast to buprenorphine and methadone.¹⁸⁴ However, there are also practical and safety issues to consider for SROM in comparison with first-line therapy.

Practical Considerations of SROM

Like other forms of OAT, **daily witnessed dosing is required with SROM**. With TID induction, short-term hospital admission may be considered for safety. However, for community-based induction once-daily dosing and subsequent titration of SROM is preferred. Frequent clinical assessment is required for safety. If the pregnant patient is *agreeable to admission*, the following titration approach is recommended as applicable:

- **If the daily use is relatively consistent and dosing is known:**
 - Convert to equivalent dose of short-acting liquid morphine (for ease of witnessed administration in hospital and to reduced risk of diversion).
 - Reduce equivalent dose of liquid morphine by 50% (due to incomplete cross tolerance when switching to a new opioid).
 - Divide into three scheduled doses of immediate-release (IR) liquid morphine.
 - Add three PRN doses of liquid morphine (30-50% of scheduled dose).
- **Alternatively, if no consistent daily dose is known** (i.e., variable daily dose depending on availability or uncertainty regarding use history):

- Start with a smaller dose (e.g., 15 mg IR liquid morphine TID with 5 mg liquid morphine TID PRN).
- **Titrate similarly to the [Conventional Buprenorphine Induction](#):**
 - Tabulate all of Day 1 scheduled + PRN doses to a 24-hour total consumed.
 - Divide total value into three scheduled doses.
 - Add three PRN doses of 5-15 mg TID (again, utilize liquid morphine as above).
- **Once an optimal dose is reached** (opioid withdrawal is adequately suppressed for 24 hours), convert daily IR liquid morphine dose to equivalent daily SROM.

See [Alternative Treatment Approaches to OUD](#) for further SROM guidance.

STRONG RECOMMENDATION: BUPRENORPHINE VS SROM IN RURAL & REMOTE COMMUNITIES

When no local access to traditional OAT programs exists in rural/remote locations for pregnant patients agreeable to buprenorphine/naloxone, local care providers are strongly encouraged to reach out to regional and urban OAT services to explore options for shared care. Buprenorphine/naloxone could be prescribed virtually, in partnership with the local care providers who can provide the in-person assessment/support.

RAAM clinics or RAAM on-call services, the HSC Addiction Medicine Consult Service on-call physician, and the MOST program are all valuable resources. These resources can be explored to arrange OAT access for pregnant patients living in rural or remote areas. When limited pharmacy/nursing station access makes daily witnessed dosing impractical, **liberal prescribing of buprenorphine/naloxone with multiple early take-home doses is preferred over take-home doses of SROM, as the latter poses a much greater safety risk to the patient and local community, in comparison.**

However, given barriers to access especially for rural/remote communities, SROM is a reasonable model for OAT in pregnancy where conventional treatment with buprenorphine or methadone is refused, or has failed, or is not practically accessible, either as a bridging strategy or for ongoing maintenance. **It is important to note that access to daily witnessed dosing of SROM is required for patient and community safety.** Given safety concerns regarding opioid tapering in pregnancy and postpartum, utilizing SROM to this end must only be considered in careful consultation, on a case-by-case basis, with an addiction medicine specialist.

Sublocade® In Pregnancy

Sublocade® (buprenorphine extended-release) is a depot injection, administered subcutaneously once per month to replace buprenorphine/naloxone dosing up to 24 mg daily. Presently, there is no dose equivalency for patients requiring 26-32 mg daily.

- **Consideration of RISK:** In general, pregnancy and breastfeeding have been viewed as relative contraindications to Sublocade[®], as one of its excipients, *N*-methyl-pyrrolidone (NMP), has been identified as potentially teratogenic in animal studies. Human data is extremely limited: two cases of undiagnosed pregnancy treated with Sublocade[®], up to 18 weeks gestation, had normal obstetrical and pediatric outcomes.¹⁸⁵
- **Anticipation of BENEFIT:** The motivation to explore Sublocade[®] in pregnancy is not only for the perceived benefits that apply to non-pregnant patients (more stable steady-state than daily dosing, fewer pharmacy visits and associated stigma, and reduced risk for theft/diversion of sublingual tablets).¹⁸⁶ The pharmacokinetics are also theorized to result in decreased neonatal withdrawal severity. Clinical trials of a novel formulation without NMP are underway at the time of writing. CAM2038 has a weekly depot formulation that replaces NMP with ethanol at a clinically irrelevant concentration; the maximum fetal exposure over 9 months gestation is one tablespoon.¹⁸⁷ This is being studied in a randomized control trial compared with daily sublingual buprenorphine/naloxone.

Practical Considerations for Sublocade[®]

It is not uncommon to have breakthrough withdrawal during the first month of Sublocade[®] treatment, requiring supplementation with sublingual buprenorphine/naloxone.¹⁸⁸ For some patients, breakthrough withdrawal may even last longer than the first month of treatment. This may obviate some of the improved convenience of Sublocade[®] during pregnancy. In a case series with three subjects, Sublocade[®] started after 12 weeks gestation produced euphoria in the first 1-3 days post injection similar to intoxication.¹⁸⁹ This was **not** observed in the case study of Sublocade[®] use prior to pregnancy diagnosis, but does amplify the controversy surrounding this method of treatment. Reliable data is not expected to be imminently available.

STRONG RECOMMENDATION: USE OF SUBLOCADE[®] IN PREGNANCY

Given the paucity of data for antepartum efficacy, maternal tolerance, and fetal safety, introduction to Sublocade[®] during pregnancy should be deferred to the postpartum interval.

Continuation of Sublocade[®] may be considered when pregnancy is identified after treatment is well-established with Sublocade[®], if alternative therapy is not available, and gestation is already greater than 12 weeks (beyond embryogenesis). Patients who are breastfeeding are encouraged to further defer until 6 months postpartum when breastfeeding is no longer exclusive nutrition.

As data emerges, these **STRONG RECOMMENDATION** statements will be revised accordingly.

IN SUMMARY

Pregnancy can be a very motivating but equally challenging time for patients with OUD.

OAT providers are encouraged to support individuals throughout pregnancy and postpartum with compassion, non-judgment, and collaboration, while utilizing the evidence-based best practices discussed in this chapter. Using a patient-centered, trauma-informed, harm-reduction, and culturally-safe approach is essential, as with all patients on OAT. The OAT provider and team can be effective advocates for pregnant patients, promoting autonomy, agency, and comprehensive care during a vulnerable time in their patients' lives.

References

- ¹ Unger, A., Jung, E., Winklbaur, B., & Fischer, G. (2014). Gender issues in the pharmacotherapy of opioid-addicted women: buprenorphine. In *Women, Children, and Addiction* (pp. 113-126). Routledge.
- ² Campbell, J., Matoff-Stepp, S., Velez, M. L., Cox, H. H., & Laughon, K. (2021). Pregnancy-associated deaths from homicide, suicide, and drug overdose: review of research and the intersection with intimate partner violence. *Journal of Women's Health, 30*(2), 236-244.
- ³ https://www.health.gov.bc.ca/library/publications/year/2015_a/pt-centred-care-framework.pdf
- ⁴ Staff, A., Volunteers, K. O. P., & KOB, B. (2016). Clinic Community Health's Statement on Trauma-Informed Practice. https://trauma-informed.ca/wp-content/uploads/2013/10/Trauma-informed_Toolkit.pdf
- ⁵ Maté, G. (2008). *In the realm of hungry ghosts: Close encounters with addiction*. Random House Digital, Inc.
- ⁶ Mateu-Gelabert, P., Guarino, H., Jessell, L., & Teper, A. (2015). Injection and sexual HIV/HCV risk behaviors associated with nonmedical use of prescription opioids among young adults in New York City. *Journal of substance abuse treatment, 48*(1), 13-20.
- ⁷ https://www.catie.ca/sites/default/files/2022-01/CATIE_SaferSexGuide_2022_English_WEB.pdf
Accessed Feb 20, 2022
- ⁸ Bourgeois, A. C., Edmunds, M., Awan, A., Jonah, L., Varsaneux, O., & Siu, W. (2017). Can we eliminate HIV?: HIV in Canada—surveillance report, 2016. *Canada Communicable Disease Report, 43*(12), 248.
- ⁹ Barral, M. F et al (2014). Risk factors of HIV-1 vertical transmission (VT) and the influence of antiretroviral therapy (ART) in pregnancy outcome. *Revista do Instituto de Medicina Tropical de Sao Paulo, 56*(2), 133–138.
- ¹⁰ Mohd Salleh NA, Fairbairn N, Nolan S, et al. Dispensation of antiretroviral therapy and methadone maintenance therapy at the same facility in a low-barrier setting linked to optimal adherence to HIV treatment. *HIV Medicine*. 2019; in press.

- ¹¹ Remis RS. *Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007*. Ottawa, ON: Public Health Agency of Canada; 2007. Available from: www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf. Accessed 2015 Apr 10.
- ¹² Gordon, J., Bocking, N., Pouteau, K., Farrell, T., Ryan, G., & Kelly, L. (2017). First Nations hepatitis C virus infections: Six-year retrospective study of on-reserve rates of newly reported infections in northwestern Ontario. *Canadian Family Physician, 63*(11), e488-e494.
- ¹³ Boucher, M & Gruslin, A No. 96-The Reproductive Care of Women Living With Hepatitis C Infection *SOGC Clinical Practice Guidelines*. 2017; 39(7): E1-E25.
- ¹⁴ Wong S, Ordean A, Kahan M, SOGC clinical practice guidelines: Substance use in pregnancy: no. 256, April 2011. *Int J Gynaecol Obstet*. 2011 Aug; 114(2):190-202.
- ¹⁵ Binka, M., Butt, Z. A., Wong, S., Chong, M., Buxton, J. A., Chapinal, N., & Janjua, N. Z. (2018). Differing profiles of people diagnosed with acute and chronic hepatitis B virus infection in British Columbia, Canada. *World Journal of Gastroenterology, 24*(11), 1216.
- ¹⁶ Centers for Disease Control and Prevention. Washington, DC: Public Health Foundation; 2015. *Chapter 10: Hepatitis B*. Jennifer Hamborsky, Kroger A, Wolfe C, editors. Epidemiology and prevention of vaccine preventable diseases. 13th ed.
- ¹⁷ Tram T. Tran, Hepatitis B in Pregnancy, *Clinical Infectious Diseases*, Volume 62, Issue suppl 4, June 2016, Pages S314–S317
- ¹⁸ Antiretroviral Pregnancy Registry Steering Committee. *Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2015*. Wilmington, NC: Registry Coordinating Center, 2015. Accessed 6 February 2016
- ¹⁹ Han G-R , Cao M-K, Zhao W et al. A prospective and open label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. *J Hepatology*. 2011; 55:1215–21.
- ²⁰ Giovannetti J. Alberta declares provincewide syphilis outbreak amid surge across Canada. *Globe and Mail* (Calgary Ed.) [Internet]. 2019 Jul 17 [cited 2022, Feb 20].
- ²¹ Traeger MW, Cornelisse VJ, Asselin J, et al. Association of HIV preexposure prophylaxis with incidence of sexually transmitted infections among individuals at high risk of HIV infection. *JAMA*. 2019;321(14):1380–90.
- ²² Mill, J, Singh AE, Taylor M. Women in the shadows: prenatal care for street-involved women. *Can J Urban Res*. 2012;21(2):68–89.
- ²³ Torrone, E.A. and W.C. Miller, Congenital and Heterosexual Syphilis: Still Part of the Problem. *Sexually Transmitted Diseases*. 2018. 45: p. S20-S22
- ²⁴ Park, E., Yip, J., Harville, E., Nelson, M., Giarratano, G., Buekens, P., & Wagman, J. (2021). *Gaps in the Congenital Syphilis Prevention Cascade*. Qualitative Findings from Kern County, California.

- ²⁵ Brown, Laura S. Not Outside the Range: One Feminist Perspective on Psychic Trauma. *Trauma: Explorations in Memory*. Ed. Cathy Caruth. Baltimore: Johns Hopkins UP, 1995.100-12
- ²⁶ Jones HE, Deppen K et al. Clinical care for opioid-using pregnant and postpartum women: the role of obstetric providers. *Am J Obstet Gynecol*. 2014 Apr; 210(4):302-310.
- ²⁷ Grande LA, Thompson EC, Au MA, Sawyer D, Baldwin L-M, Rosenblatt R. Problem Drug-related Behavior and Discontinuation of Opioids Following the Introduction of an Opioid Management Program. *J Am Board Fam Med*. 2016;29(6):718–726. pmid:28076255
- ²⁸ Benningfield MM et al Co-occurring psychiatric symptoms are associated with increased psychological, social, and medical impairment in opioid dependent pregnant women. *Am J Addict*. 2010 Sep-Oct; 19(5):416-21
- ²⁹ Spyridou, A., Schauer, M., & Ruf-Leuschner, M. (2015). Obstetric care providers are able to assess psychosocial risks, identify and refer high-risk pregnant women: validation of a short assessment tool—the KINDEX Greek version. *BMC pregnancy and childbirth*, 15(1), 1-17.
- ³⁰ Chatterjee, A., Yu, E. J., & Tishberg, L. (2018). Exploring opioid use disorder, its impact, and treatment among individuals experiencing homelessness as part of a family. *Drug and Alcohol Dependence*, 188, 161-168.
- ³¹ E Charron, et al. It's a very nuanced discussion with every woman: Health care providers' communication practices during contraceptive counseling for patients with substance use disorders. *Contraception*, 102 (2020), pp. 349-355
- ³² Canadian Institute for Health Information. *Opioid-Related Harms in Canada* [Internet]. CIHI, Ottawa, ON, 2017. https://secure.cihi.ca/free_products/opioid-harms-chart-book-en.pdf
- ³³ Statistics Canada. *Table 102-0551 Deaths and mortality rate, by selected grouped causes* [Internet]. 2018. <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039201>. Accessed February 20, 2022
- ³⁴ Committee opinion No. 711: Opioid use and opioid use disorder in pregnancy. *Obstet Gynecol*. 2017;130(2):e81-e94
- ³⁵ Guttman, A., Blackburn, R., et al. (2019). Long-term mortality in mothers of infants with neonatal abstinence syndrome: A population-based parallel-cohort study in England and Ontario, Canada. *PLoS medicine*, 16(11), e1002974.
- ³⁶ Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In: *Medication-assisted treatment for opioid addiction in opioid treatment programs*. Treatment Improvement Protocol (TIP) Series, No. 43 . Rockville (MD): Substance Abuse and Mental Health Services Administration; 2005. p. 211–24.
- ³⁷ Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. *Obstet Gynecol*. 2013;122(4):838-844

- ³⁸ Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol.* 2011;204(4):314.e1-314.e11.
- ³⁹ Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. *Eur J Epidemiol* 1992;8:757–60
- ⁴⁰ Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. *Eur J Clin Pharmacol* 2011;67:1253–61
- ⁴¹ Caritis, S. N., & Panigrahy, A. (2019). Opioids affect the fetal brain: reframing the detoxification debate. *American journal of obstetrics and gynecology*, 221(6), 602-608.
- ⁴² Newman RG Methadone treatment. Defining and evaluating success. *N Engl J Med.* 1987 Aug 13; 317(7):447-50
- ⁴³ Marshall BD, et al (2011). Reduction in overdose mortality after the opening of North America’s first medically supervised safer injecting facility: a retrospective population-based study. *Lancet.* 377(9775):1429-1437
- ⁴⁴ Kaltenbach K, Berghella FL. Opioid dependence during pregnancy: effects and management. *Ob Clinics of NA.* 1998 March;25(1)
- ⁴⁵ ACOG Committee on Health Care for Underserved Women. (2012). ACOG Committee Opinion No. 524: opioid abuse, dependence, and addiction in pregnancy. *Obstetrics and gynecology*, 119(5), 1070-1076.
- ⁴⁶ Lindsay MK, Burnett E The use of narcotics and street drugs during pregnancy. *Clin Obstet Gynecol.* 2013 Mar; 56(1):133-41.
- ⁴⁷ Nathoo, T., et al (2015) *Harm Reduction and Pregnancy: Community-based Approaches to Prenatal Substance Use in Western Canada*: University of Victoria School of Nursing and British Columbia Centre of Excellence for Women’s Health.
- ⁴⁸ Velez, M., & Jansson, L. M. (2008). The opioid dependent mother and newborn dyad: non-pharmacologic care. *Journal of addiction medicine*, 2(3), 113.
- ⁴⁹ Bagley SM, Wachman EM, Holland E, Brogly SB. Review of the assessment and management of neonatal abstinence syndrome. *Addict Sci Clin Pract.* 2014;9:19
- ⁵⁰ Kandall SR, Akbin RS, Gartner LM, Lee KS, Eidelman A, Lowinson J, et al. The narcotic dependent mother: fetal and neonatal consequences. *Early Hum Develop.* 1977;1:159–169
- ⁵¹ Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In: *Medication-assisted treatment for opioid addiction in opioid treatment programs*. Treatment Improvement Protocol (TIP) Series, No. & Rockville (MD): Substance Abuse and Mental Health Services Administration; 2005. p. 211–24

- ⁵² McCarthy JJ, Leamon MH, Finnegan LP, Fassbender C (2017) Opioid dependence and pregnancy: minimizing stress on the fetal brain. *Am J Obstet Gynecol*. Mar; 216(3):226-231.
- ⁵³ Balfour-Boehm J, Rea S, Gordon J, Dooley J, Kelly L, Robinson A. The evolving nature of narcotic use in northwestern Ontario. *Can J Rural Med* 2014;19(4):158-60.
- ⁵⁴ Jumah NA, Edwards C, Balfour-Boehm J, Loewen K, Dooley J, Gerber-Finn L, et al. Observational study of the safety of buprenorphine and naloxone in pregnancy in a rural and remote population. *BMJ Open* 2016;6(10):e011774
- ⁵⁵ Ordean, A., Wong, S., & Graves, L. (2017). No. 349-substance use in pregnancy. *Journal of Obstetrics and Gynaecology Canada*, 39(10), 922-937.
- ⁵⁶ American College of Obstetricians and Gynecologists. (2017). *ACOG Committee Opinion, Number 711. Opioid use and opioid use disorder in pregnancy*. ACOG.org.
- ⁵⁷ National Institute for Health and Clinical Excellence. *Drug misuse: psychosocial interventions* London: NICE, 2007.
- ⁵⁸ O'Connor, M., Czarnik, M., Morrow, B., & D'Angelo, D. (2021). Opioid use during pregnancy: An analysis of comment data from the 2016 Pregnancy Risk Assessment Monitoring System survey. *Substance abuse*, 1-8.
- ⁵⁹ Radel, L., Baldwin, M., Crouse, G., Ghertner, R., & Waters, A. (2018). Substance use, the opioid epidemic, and the child welfare system: Key findings from a mixed methods study. *Washington, DC: Office of the Assistant Secretary for Planning and Evaluation*.
- ⁶⁰ Jones HE, O'Grady KE, Malfi D, Tuten M. Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. *Am J Addict*. 2008 Sep-Oct;17(5):372-86
- ⁶¹ Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In: *Medication-assisted treatment for opioid addiction in opioid treatment programs*. Treatment Improvement Protocol (TIP) Series, No. 43 . Rockville (MD): Substance Abuse and Mental Health Services Administration; 2005. p. 211–24
- ⁶² Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. *J Pharmacol Exp Ther*. 1985;233:1–6
- ⁶³ Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL J (1985) Altered methadone pharmacokinetics in methadone-maintained pregnant women. *Pharmacol Exp Ther*. 1985 Apr; 233(1):1-6.
- ⁶⁴ Caritis, et al (2017). An evidence-based recommendation to increase the dosing frequency of buprenorphine during pregnancy. *American journal of obstetrics and gynecology*, 217(4), 459-e1.
- ⁶⁵ Wong, J. S., Nikoo, M., Westenberg, J. N., Suen, J. G., Wong, J. Y., Krausz, R. M., ... & Azar, P. (2021). Comparing rapid micro-induction and standard induction of buprenorphine/naloxone for treatment of opioid use disorder: protocol for an open-label, parallel-group, superiority, randomized controlled trial. *Addiction Science & Clinical Practice*, 16(1), 1-10.

- ⁶⁶ Moe, J et al. (2020). Microdosing and standard-dosing take-home buprenorphine from the emergency department: a feasibility study. *Journal of the American College of Emergency Physicians Open*, 1(6), 1712-1722.
- ⁶⁷ Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010 Dec 9; 363(24):2320-31.
- ⁶⁸ J. Kakko et al. Buprenorphine and methadone treatment of opiate dependence during pregnancy: Comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug and Alcohol Dependence*. 96 (2008) 69–78
- ⁶⁹ Thomas CP, Fullerton CA, Kim M, Montejano L, Lyman DR, Dougherty RH, Daniels AS, Ghose SS, Delphin-Rittmon ME Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatr Serv*. 2014 Feb 1; 65(2):158-70.
- ⁷⁰ Holbrook, A. M. (2015). Methadone versus buprenorphine for the treatment of opioid abuse in pregnancy: science and stigma. *The American journal of drug and alcohol abuse*, 41(5), 371-373.
- ⁷¹ Minozzi S, Amato L, Bellisario C, et al. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev*. 2013; 94: CD006318
- ⁷² Ahmed, S., Bhivandkar, S., Lonergan, B. B., & Suzuki, J. (2021). Microinduction of buprenorphine/naloxone: a review of the literature. *The American Journal on Addictions*, 30(4), 305-315.
- ⁷³ Irwin, M., Petersen, K. S., & Smith, M. A. (2021). Rapid buprenorphine induction for cancer pain in pregnancy. *Journal of Palliative Medicine*, 24(8), 1257-1262.
- ⁷⁴ Kelly, J. , Raghuraman, N. ,et al (2021). Home Induction of Buprenorphine for Treatment of Opioid Use Disorder in Pregnancy. *Obstetrics & Gynecology*, 138 (4)
- ⁷⁵ Rosenfeld, C. S. (2022). *The placenta as a target of opioid drugs*. *Biology of reproduction*.
- ⁷⁶ Sastry, B. V. (1991). Placental toxicology: tobacco smoke, abused drugs, multiple chemical interactions, and placental function. *Reproduction, Fertility and Development*, 3(4), 355-372.
- ⁷⁷ Pan, J. et al. Oxidative stress in heroin administered mice and natural antioxidants protection. *Life Sci*. 77, 183–193 (2005)
- ⁷⁸ Hamdy, M. M., Elbadr, M. M. & Barakat, A. Bupropion attenuates morphine tolerance and dependence: Possible role of glutamate, norepinephrine, inflammation, and oxidative stress. *Pharmacol Rep*. 70, 955–62. (2018)
- ⁷⁹ McCarthy JJ, Leamon MH, Finnegan LP, Fassbender C: Opioid dependence and pregnancy: Minimizing stress on the fetal brain. *Am J Obstet Gynecol* 2017;216:226–231.
- ⁸⁰ McCarthy JJ: Intrauterine abstinence syndrome (IAS) during buprenorphine inductions and methadone tapers: Can we assure the safety of the fetus? *J Matern Neonatal Med*. 2012;25:109–112

- ⁸¹ Terplan, M., Laird, H. J., Hand, D. J., Wright, T. E., Premkumar, A., Martin, C. E., ... & Krans, E. E. (2018). Opioid detoxification during pregnancy: a systematic review. *Obstetrics and gynecology*, 131(5), 803.
- ⁸² Wong S, Kahan M, Ordean A. *Substance use in pregnancy*. Ottawa, ON: SOGC 2011
- ⁸³ Opioid use and opioid use disorder in pregnancy. Committee Opinion No. 711. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2017;130:e81–94
- ⁸⁴ Caritis, S. N., & Panigrahy, A. (2019). Opioids affect the fetal brain: reframing the detoxification debate. *American journal of obstetrics and gynecology*, 221(6), 602-608.
- ⁸⁵ Bailey, B. A., Shah, D. S., Boynewicz, K. L., Justice, N. A., & Wood, D. L. (2022). Impact of in utero opioid exposure on newborn outcomes: beyond neonatal opioid withdrawal syndrome. *The Journal of Maternal-Fetal & Neonatal Medicine*, 1-8.
- ⁸⁶ Wang, M et al. Opioid Detoxification during Pregnancy: Systematic Review and Meta-Analysis of Maternal and Neonatal Outcomes [11R]. *Obstetrics & Gynecology*. 131 (2018): 197S.
- ⁸⁷ Bailey, B. A., Shah, D. S., Boynewicz, K. L., Justice, N. A., & Wood, D. L. (2022). Impact of in utero opioid exposure on newborn outcomes: beyond neonatal opioid withdrawal syndrome. *The Journal of Maternal-Fetal & Neonatal Medicine*, 1-8.
- ⁸⁸ Terplan, M., Laird, H. J., Hand, D. J., Wright, T. E., Premkumar, A., Martin, C. E., ... & Krans, E. E. (2018). Opioid detoxification during pregnancy: a systematic review. *Obstetrics and gynecology*, 131(5), 803.
- ⁸⁹ Saia KA, Schiff D, Wachman EM, Mehta P, Vilkins A, Sia M, et al. Caring for pregnant women with opioid use disorder in the USA: expanding and improving treatment. *Curr Obstet Gynecol Rep*. 2016;5:257–63 .
- ⁹⁰ (1) Committee on Obstetric Practice. Committee Opinion No. 711: Opioid Use and Opioid Use Disorder in Pregnancy. *Obstet Gynecol* 2017 Aug;130(2):e81-e94; (2) Rodriguez CE, Klie KA. Pharmacological treatment of opioid use disorder in pregnancy. *Semin Perinatol*. 2019; (3) Klamon S, Isaacs K, Leopold A, Perpich J, Hayashi S, Vender J, et al. Treating Women Who Are Pregnant and Parenting for Opioid Use Disorder and the Concurrent Care of Their Infants and Children: Literature Review to Support National Guidance. *J Addict Med* 2017;11(3):178-190
- ⁹¹ LePreau, F. J., GARVEY, B., PAULL, N., & STEIN, M. D. (1995). Opiate detoxification of pregnant women using clonidine: an observational cohort study. *Journal of Women's Health*, 4(4), 381-386.
- ⁹² Terplan, M., et al. (2018). Opioid detoxification during pregnancy: a systematic review. *Obstetrics and gynecology*, 131(5), 803.
- ⁹³ Jones HE, Deppen K et al Clinical care for opioid-using pregnant and postpartum women: the role of obstetric providers. *Am J Obstet Gynecol*. 2014 Apr; 210(4):302-310
- ⁹⁴ Fischer G, Jagsch R, Eder H, et al. Comparison of methadone and slow-release morphine maintenance in pregnant addicts. *Addiction*. 1999;94:231-9

- ⁹⁵ Dooley, R., Dooley, J., Antone, I., Guilfoyle, J., Gerber-Finn, L., Kakekagumick, K., ... & Kelly, L. (2015). Narcotic tapering in pregnancy using long-acting morphine: an 18-month prospective cohort study in northwestern Ontario. *Canadian Family Physician*. 61(2), e88-e95.
- ⁹⁶ Roberts S, Pies C. Complex calculations: how drug use during pregnancy becomes a barrier to prenatal care. *Matern Child Health J* 2011;15:333
- ⁹⁷ Elms, N., Link, K., Newman, A., & Brogly, S. B. (2018). Need for women-centered treatment for substance use disorders: results from focus group discussions. *Harm reduction journal*, 15(1), 1-8.
- ⁹⁸ Elms, N., Link, K., Newman, A., & Brogly, S. B. (2018). Need for women-centered treatment for substance use disorders: results from focus group discussions. *Harm reduction journal*, 15(1), 1-8.
- ⁹⁹ Kuo C, Schonbrun YC, Zlotnick C, Bates N, Todorova R, Kao JC, et al. A qualitative study of treatment needs among pregnant and postpartum women with substance use and depression. *Subst Use Misuse*. 2013;48(14):1498–508
- ¹⁰⁰ Peacock-Chambers, E., Paterno, M. T., Kiely, D., Fioroni, T., Byatt, N., & Friedmann, P. D. (2021). Engagement in perinatal outpatient services among women in recovery from opioid use disorders. *Substance abuse*, 42(4), 1022-1029.
- ¹⁰¹ Holbrook BD. The effects of nicotine on human fetal development. *Birth Defects Res C Embryo Today*. 2016;108(2):181–192. doi: 10.1002/bdrc.21128
- ¹⁰² Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: A systematic review based on 173 687 malformed cases and 11.7 million controls. *Hum Reprod Update*. 2011;17(5):589–604
- ¹⁰³ Jones HE, Heil SH, Tuten M, et al. Cigarette smoking in opioid-dependent pregnant women: Neonatal and maternal outcomes. *Drug and Alcohol Dependence*. 2013;131(3):271–277
- ¹⁰⁴ Mendelsohn CP, Gould GS, Oncken C. Management of smoking in pregnant women. *Aust Fam Physician*. 2014;43(1)
- ¹⁰⁵ Kandall SR, Akbin RS, Gartner LM, Lee KS, Eidelman A, Lowinson J, et al. The narcotic dependent mother: fetal and neonatal consequences. *Early Hum Develop*. 1977;1:159–169
- ¹⁰⁶ Dietz PM, England LJ, Shapiro-Mendoza CK, et al. Infant Morbidity and Mortality Attributable to Prenatal Smoking in the US. *Am J Prev Med*. 2010;39(1):45–52
- ¹⁰⁷ Pollack HA. Sudden infant death syndrome, maternal smoking during pregnancy, and the cost-effectiveness of smoking cessation intervention. *American journal of public health*. 2001;91(3):432–436
- ¹⁰⁸ Bowker K, Lewis S, Coleman T, Cooper S. Changes in the rate of nicotine metabolism across pregnancy: A longitudinal study. *Addiction*. 2015;110(11):1827–1832
- ¹⁰⁹ Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. 2018

- ¹¹⁰ Diamanti, A., Papadakis, S., Schoretsani, S., Rovina, N., Vivilaki, V., Gratziou, C., & Katsaounou, P. A. (2019). Smoking cessation in pregnancy: An update for maternity care practitioners. *Tobacco induced diseases*, 17.
- ¹¹¹ Stotts AL, Northrup TF, Cinciripini PM, et al. Randomized, controlled pilot trial of bupropion for pregnant smokers: challenges and future directions. *Am J Perinatol*. 2015;32(4):351–356
- ¹¹² Richardson JL, Stephens S, Yates LM, et al. Pregnancy outcomes after maternal varenicline use; analysis of surveillance data collected by the European Network of Teratology Information Services. *Reprod Toxicol*. 2017;67:26–34
- ¹¹³ Harter, K. (2019). Opioid use disorder in pregnancy. *Mental Health Clinician*, 9(6), 359-372
- ¹¹⁴ Tsakiridis, I., Mamopoulos, A., Athanasiadis, A., & Dagklis, T. (2019). The management of nausea and vomiting of pregnancy: synthesis of national guidelines. *Obstetrical & Gynecological Survey*, 74(3), 161-169
- ¹¹⁵ El Marroun H, et al. (2009) Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. *J Am Acad Child Adolesc Psychiatry*.;48(12):1173-1181. and (2018) An epidemiological, developmental and clinical overview of cannabis use during pregnancy. *Prev Med*.;116:1-5
- ¹¹⁶ Richardson KA, Hester AK, McLemore GL. Prenatal cannabis exposure - The “first hit” to the endocannabinoid system. *Neurotoxicol Teratol*. 2016;58:5-14. doi:10.1016/j.ntt.2016.08.003
- ¹¹⁷ Sorensen, C. J., DeSanto, K., Borgelt, L., Phillips, K. T., & Monte, A. A. (2017). Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment—a systematic review. *Journal of Medical Toxicology*, 13(1), 71-87.
- ¹¹⁸ Wallace, E. A., Andrews, S. E., Garmany, C. L., & Jelley, M. J. (2011). Cannabinoid hyperemesis syndrome: literature review and proposed diagnosis and treatment algorithm. *South Med J*, 104(9), 659-664
- ¹¹⁹ Hutton, J. (2021). Distinguishing Cannabinoid Hyperemesis from Hyperemesis Gravidarum. *EC Gynaecology*, 10, 102-105.
- ¹²⁰ London, V et al. (2017). Hyperemesis gravidarum: a review of recent literature. *Pharmacology*, 100(3-4), 161-171.
- ¹²¹ Soens MA, He J, Bateman BT. Anesthesia considerations and post- operative pain management in pregnant women with chronic opi- oid use. *Semin Perinatol*. 2019;43(3):149-161
- ¹²² Sen, S., Arulkumar, S., Cornett, E. M., Gayle, J. A., Flower, R. R., Fox, C. J., & Kaye, A. D. (2016). New pain management options for the surgical patient on methadone and buprenorphine. *Current pain and headache reports*, 20(3), 1-8.
- ¹²³ Sunilkumar, M. M., & Lockman, K. (2018). Practical pharmacology of methadone: A long-acting opioid. *Indian Journal of Palliative Care*, 24(Suppl 1), S10.

- ¹²⁴ Jones, H. E., O'Grady, K., Dahne, J., Johnson, R., Lemoine, L., Milio, L., ... & Selby, P. (2009). Management of acute postpartum pain in patients maintained on methadone or buprenorphine during pregnancy. *The American journal of drug and alcohol abuse*, 35(3), 151-156.
- ¹²⁵ Meyer M, Wagner K, Benvenuto A, Plante D, Howard D Intrapartum and postpartum analgesia for women maintained on methadone during pregnancy. *Obstet Gynecol*. 2007 Aug; 110(2 Pt 1):261-6
- ¹²⁶ Dryden C, Young D, Hepburn M, et al. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *BJOG : an international journal of obstetrics and gynaecology*. 2009;116(5):665–671
- ¹²⁷ McQueen KA, et al. The impact of infant feeding method on neonatal abstinence scores of methadone-exposed infants. *Advances in neonatal care : official journal of the National Association of Neonatal Nurses*. 2011;11(4):282–290
- ¹²⁸ O'Connor AB, Collett A, Alto WA, et al. Breastfeeding Rates and the Relationship Between Breastfeeding and Neonatal Abstinence Syndrome in Women Maintained on Buprenorphine During Pregnancy. *J Midwifery Wom Heal*. 2013;58(4):383–388
- ¹²⁹ Academy of Breastfeeding Medicine Protocol C. Jansson LM. ABM clinical protocol #21: Guidelines for breastfeeding and the drug-dependent woman. *Breastfeeding medicine: the official journal of the Academy of Breastfeeding Medicine*. 2009;4(4):225–228
- ¹³⁰ Schwarz, E.B., Ray, R.M., Stuebe, A.M., Allison, M.A., Ness, R.B., Freiberg, M.S., et al. (2009). Duration of lactation and risk factors for maternal cardiovascular disease. *Obstetrics & Gynecology*; 113(5): 974-982.
- ¹³¹ American College of Obstetricians and Gynecologists. (2013). Committee Opinion No. 570: Breastfeeding in Underserved Women: Increasing Initiation and Continuation of Breastfeeding.
- ¹³² Ray, J. G., Park, A. L., Dzakpasu, S., Dayan, N., Deb-Rinker, P., Luo, W., & Joseph, K. S. (2018). Prevalence of severe maternal morbidity and factors associated with maternal mortality in Ontario, Canada. *JAMA network open*, 1(7), e184571-e184571.
- ¹³³ Dzakpasu, et al (2019). Severe maternal morbidity in Canada: temporal trends and regional variations, 2003-2016. *Journal of Obstetrics and Gynaecology Canada*, 41(11), 1589-1598
- ¹³⁴ Lisonkova, S., Richter, L. L., Ting, J., Muraca, G. M., Wen, Q., Mehrabadi, A., ... & Lyons, J. (2019). Neonatal abstinence syndrome and associated neonatal and maternal mortality and morbidity. *Pediatrics*, 144(2)
- ¹³⁵ Murray L, Fiori-Cowley A, Hooper R, Cooper P The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. *Child Dev*. 1996 Oct; 67(5):2512-26.
- ¹³⁶ Klinger G, Selective serotonin reuptake inhibitor induced neonatal abstinence syndrome. *Isr J Psych Relat Sci*. 2008; 45(2):107-13.

- ¹³⁷ Stephansson O, et al Selective serotonin reuptake inhibitors during pregnancy and risk of stillbirth and infant mortality. *JAMA*. 2013 Jan 2; 309(1):48-54
- ¹³⁸ Peranathan V, Buckley NA. Opioids and antidepressants: which combinations to avoid. *Aust Prescr* 2021;44:41-4.
- ¹³⁹ Daoud, N et al (2019). Postpartum depression prevalence and risk factors among Indigenous, non-Indigenous and immigrant women in Canada. *Canadian Journal of Public Health*, 110(4), 440-452.
- ¹⁴⁰ Benningfield MM, Arria AM, Kaltenbach K, et al. Co-occurring psychiatric symptoms are associated with increased psychological, social, and medical impairment in opioid dependent pregnant women. *Am J Addict*. 2010;19(5):416–421
- ¹⁴¹ Gressier, F., Guillard, V., Cazas, O., Falissard, B., Glangeaud-Freudenthal, N. M., & Sutter-Dallay, A. L. (2017). Risk factors for suicide attempt in pregnancy and the post-partum period in women with serious mental illnesses. *Journal of Psychiatric Research*, 84, 284-291
- ¹⁴² Campbell, J., Matoff-Stepp, S., Velez, M. L., Cox, H. H., & Laughon, K. (2021). Pregnancy-associated deaths from homicide, suicide, and drug overdose: Review of research and the intersection with intimate partner violence. *Journal of Women's Health*, 30(2), 236-244
- ¹⁴³ Nielsen, T., Bernson, D., Terplan, M., Wakeman, S. E., Yule, A. M., Mehta, P. K., ... & Schiff, D. M. (2020). Maternal and infant characteristics associated with maternal opioid overdose in the year following delivery. *Addiction*, 115(2), 291-301.
- ¹⁴⁴ Alhusen, J. L., Ray, E., Sharps, P., & Bullock, L. (2015). Intimate partner violence during pregnancy: maternal and neonatal outcomes. *Journal of women's health*, 24(1), 100-106.
- ¹⁴⁵ Stone, R., & Rothman, E. F. (2019). Opioid use and intimate partner violence: A systematic review. *Current Epidemiology Reports*, 6(2), 215-230.
- ¹⁴⁶ Garbarino, J. (2001). Lost boys: Why our sons turn violent and how we can save them. *Smith College Studies in Social Work*, 71(2), 167-181.
- ¹⁴⁷ Campbell, J et al. (2021). Pregnancy-associated deaths from homicide, suicide, and drug overdose: Review of research and the intersection with intimate partner violence. *Journal of Women's Health*, 30(2), 236-244
- ¹⁴⁸ Campbell, J et al. (2021). Pregnancy-associated deaths from homicide, suicide, and drug overdose: review of research and the intersection with intimate partner violence. *Journal of Women's Health*, 30(2), 236-244.
- ¹⁴⁹ Chen PH, Rovi S, Washington J, Jacobs A, Vega M, Pan KY, Johnson MS. Randomized comparison of 3 methods to screen for domestic violence in family practice. *Ann Fam Med*. 2007;Sep-Oct; 5(5):430-5.
- ¹⁵⁰ Bjork, J. M., & Grant, S. J. (2009). Does traumatic brain injury increase risk for substance abuse? *Journal of neurotrauma*, 26(7), 1077-1082.

- ¹⁵¹ Jeremy RJ, Bernstein VJ. Dyads at risk: Methadone-maintained women and their four-month-old infants. *Child Development*. 1984;55:1141–1154.
- ¹⁵² Hans LL, Bernstein VJ, Henson LG. The role of psychopathology in the parenting of drug-dependent women. *Development and Psychopathology*. 1999;11:957–977.
- ¹⁵³ Hofkosh D, Pringle JL, Wald HP, Switala J, Hinderliter SA, Hamel SC. Early interactions between drug-involved mothers and infants: Within-group differences. *Archives of Pediatrics and Adolescent Medicine*. 1995;149:665–672
- ¹⁵⁴ Capen K (1997) Mother's Rights Can't be Infringed to protect fetus, Supreme Court's landmark ruling states. *Can Med Assoc J*;157:1586-7.
- ¹⁵⁵ Boyd, S. C., & Marcellus, L. (2007). *With Child: Substance use during pregnancy, A woman-centred approach*.
- ¹⁵⁶ Derkas, E. (2012). " Don't let your pregnancy get in the way of your drug addiction": CRACK and the ideological construction of addicted women. *Social Justice*, 38(3 (125), 125-144.
- ¹⁵⁷ Paltrow, Lynn M. (Winter 2003). ""Why Caring Communities Must Oppose C.R.A.C.K./Project Prevention: How C.R.A.C.K. Promotes Dangerous Propaganda". (505 KB). *The Journal of Law in Society* (Wayne State University) 5 (11): 11–117.
- ¹⁵⁸ Krieg, B. (2016). Understanding the role of cultural continuity in reclaiming the identity of young Indigenous women. *Girlhood Studies*, 9(2), 28-45.
- ¹⁵⁹ Dawe S, Harnett PH, Staiger P, Dadds MR Parent training skills and methadone maintenance: clinical opportunities and challenges. *Drug Alcohol Depend*. 2000 Jul 1; 60(1):1-11.
- ¹⁶⁰ Torresani S, Favaretto E, Zimmermann C Parental representations in drug-dependent patients and their parents. *Compr Psychiatry*. 2000 Mar-Apr; 41(2):123-9
- ¹⁶¹ Cidro, J., Doenmez, C., Sinclair, S. et al. (2021). Putting them on a strong spiritual path: Indigenous doulas responding to the needs of Indigenous mothers and communities. *International journal for equity in health*, 20(1), 1-11.
- ¹⁶² Wiechelt, S. A., & Sales, E. (2001). The role of shame in women's recovery from alcoholism: The impact of childhood sexual abuse. *Journal of Social Work Practice in the Addictions*, 1(4), 101-116.
- ¹⁶³ Sperlich, M., Seng, J. S., Li, Y., Taylor, J., & Bradbury-Jones, C. (2017). Integrating trauma-informed care into maternity care practice: conceptual and practical issues. *Journal of midwifery & women's health*, 62(6), 661-672.
- ¹⁶⁴ Sanders, A. N., Vance, D. E., Dudding, K. M., Shorten, A., & Rice, M. (2022, January). Maternal-infant bonding for the opioid exposed dyad: A rodgers' evolutionary concept analysis. In *Nursing Forum* (Vol. 57, No. 1, pp. 165-170).

- ¹⁶⁵ Blackstock, C., Clarke, S., Cullen, J., D'Hondt, J., & Formsma, J. *Keeping the promise: The convention on the rights of the child and the lived experiences of first nations youth*. First Nations Child and Family Caring Society of Canada. 2004. <https://fncaringsociety.com/sites/default/files/docs/KeepingThePromise.pdf>
- ¹⁶⁶ Kenny, K. S., Barrington, C., & Green, S. L. (2015). I felt for a long time like everything beautiful in me had been taken out: Women's suffering, remembering, and survival following the loss of child custody. *Int. J. Drug Policy*, 26, 1158–1166.
- ¹⁶⁷ Marsh, W., & Leamon, J. (2019). Babies Removed at Birth: What Professionals Can Learn From 'Women Like Me'. *Child Abuse Review*, 28(1), 82–86
- ¹⁶⁸ Wall-Wieler, E et al (2018). Postpartum depression and anxiety among mothers whose child was placed in care of child protection services at birth: a retrospective cohort study. *Maternal and Child Health Journal*, 22(10), 1393-1399.
- ¹⁶⁹ Thumath, M. et al. (2021). Overdose among mothers: The association between child removal and unintentional drug overdose in a longitudinal cohort of marginalised women in Canada. *International Journal of Drug Policy*, 91, 102977.
- ¹⁷⁰ Malone KG. *Change to Manitoba's child apprehension laws ensures kids can't be taken solely because of poverty*. CBC News. Available from: <https://www.cbc.ca/news/canada/manitoba/manitoba-cfs-child-apprehension-changes-1.4894953>. 2019
- ¹⁷¹ Blackstock, C. et al. (2006). *Reconciliation in child welfare: Touchstones of hope for indigenous children, youth, and families*. Ottawa, ON, Canada: First Nations Child & Family Caring Society of Canada/Portland OR: National Child Welfare Association.
- ¹⁷² Larrieu, J. A. et al (2008). Predictors of permanent loss of custody for mothers of infants and toddlers in foster care. *Infant Mental Health Journal: Official Publication of The World Association for Infant Mental Health*, 29(1), 48-60.
- ¹⁷³ Mackay, L., Ickowicz, S., Hayashi, K., & Abrahams, R. (2020). Rooming-in and loss of child custody: key factors in maternal overdose risk. *Addiction (Abingdon, England)*, 115(9), 1786.
- ¹⁷⁴ Schiff DM, Nielsen T, Terplan M, et al. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. *Obstet Gynecol*. 2018;132:466–74
- ¹⁷⁵ Wright, T. G., Liu, W., Heideman, E., Kendle, A., Delgado, A., & Louis, J. (2022). The association between traumatic birth events and opioid relapse after delivery. *American Journal of Obstetrics & Gynecology*, 226(1), S404-S405.
- ¹⁷⁶ Chapman SLC, Wu L-T. Postpartum substance use and depressive symptoms: a review. *Women Health*. 2013;53(5):479–503
- ¹⁷⁷ Schauburger, C. W., Borgert, A. J., & Bearwald, B. (2020). Continuation in treatment and maintenance of custody of newborns after delivery in women with opioid use disorder. *Journal of Addiction Medicine*, 14(2), 119-125.

- ¹⁷⁸ Thumath M et al. Overdose among mothers: The association between child removal and unintentional drug overdose in a longitudinal cohort of marginalised women in Canada. *Int J Drug Policy*. 2020 Oct 28:102977.
- ¹⁷⁹ Gorski T, Miller M. *Staying Sober: A Guide for Relapse Prevention*. Independence, MO: Independence Press; 1986.
- ¹⁸⁰ Melemis, S. M. (2015). Focus: addiction: relapse prevention and the five rules of recovery. *The Yale journal of biology and medicine*, 88(3), 325.
- ¹⁸¹ Covington, E. C., et al. (2020, October). Ensuring patient protections when tapering opioids: consensus panel recommendations. In *Mayo Clinic Proceedings* (Vol. 95, No. 10, pp. 2155-2171). Elsevier.
- ¹⁷³ Boyd, S. C., & Marcellus, L. *With Child: Substance use during pregnancy, A woman-centred approach*. Fernwood Publishing. 2007.
- ¹⁸² Ferri, M., Minozzi, S., Bo, A., & Amato, L. (2013). Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database of Systematic Reviews*, (6).
- ¹⁸³ Schneider C, Fischer G, Diamant K, et al. Pregnancy and Drug Dependence. *Wien Klin Wochenschr* 1996;108:611-4. 31. Etzersdorfer P, Fischer G, Eder H, et al. Comparison of morphine and methadone maintenance in pregnant opiate addicts. *NIDA Res Monogr*. 1997;178:343.
- ¹⁸⁴ Minozzi S, Amato L, Vecchi S, and Davoli M. Maintenance agonist treatments for opiate dependent pregnant women (Review). *The Cochrane Collaboration*. 2009; Issue 1: i-24.
- ¹⁸⁵ Towers, C. V., & Deisher, H. (2020). Subcutaneous extended-release buprenorphine use in pregnancy. *Case Reports in Obstetrics and Gynecology*, 2020.
- ¹⁸⁶ Cleary, E. M., Byron, R. K., Hinely, K. A., Talley, A. W., Costantine, M. M., & Rood, K. M. (2020). Subcutaneous buprenorphine extended-release use among pregnant and postpartum women. *Obstetrics & Gynecology*, 136(5), 902-903.
- ¹⁸⁷ Winhusen, T., Lofwall, M., Jones, H. E., Wilder, C., Lindblad, R., Schiff, D. M., ... & Rosa, C. (2020). Medication treatment for opioid use disorder in expectant mothers (MOMs): Design considerations for a pragmatic randomized trial comparing extended-release and daily buprenorphine formulations. *Contemporary Clinical Trials*, 93, 106014.
- ¹⁸⁸ Bernstein, S. N., Peckham, A. M., Schiff, D. M., & Gray, J. R. (2021). Subcutaneous buprenorphine extended-release use among pregnant and postpartum women. *Obstetrics & Gynecology*, 137(2), 377-378.
- ¹⁸⁹ Cleary, E. M., Byron, R. K., Hinely, K. A., Talley, A. W., Costantine, M. M., & Rood, K. M. (2020). Subcutaneous buprenorphine extended-release use among pregnant and postpartum women. *Obstetrics & Gynecology*, 136(5), 902-903.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.10 Managing Acute, Chronic, & Perioperative Pain in the Context of Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Pain management in patients receiving opioid agonist therapy (OAT) presents a unique set of challenges to the practitioner. The practitioner must consider appropriate management of the patient's pain, a largely subjective condition, in the context of an opioid use disorder (OUD). They must also consider the impact of additional medications that are prescribed concurrently with the patient's OAT.

To compound the situation further, there is often a history of mistrust of the medical system. It is not uncommon for patients with a substance use disorder to present late in the course of their illness, due to fear of having their pain inadequately managed, or of being told they are "just drug seeking". When treating pain in a patient with OUD, healthcare professionals need to be aware of their own biases and recognize the impact those biases may have on the management of the patient's pain.

Pain is a complex condition to treat, for numerous reasons. The International Association for the Study of Pain defines pain as, "**an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage**"¹. Pain cannot be objectively measured, and two patients experiencing the same degree of tissue damage can have very different pain experiences. Understanding the complex interactions that can drive or enhance *the pain experience* can be helpful in managing pain.

SPECIFIC CONSIDERATIONS

Principles of Pain Management in the Context of OAT

Pain management should begin with a comprehensive pain assessment. While such an assessment can be time consuming, it is important to understand the type of pain that is being treated. This allows therapy to be tailored to the specific type/cause of pain.

The pain assessment should elucidate:

- The cause and type of pain (neuropathic vs nociceptive vs nociplastic),
- The temporal nature of the pain (acute or chronic), and
- The functional limitations caused by the pain.

Understanding the patient's experience with previous similar pain, and the management of that pain, can also be helpful in guiding treatment. There are several guidelines available, as well as primary literature, that can assist in the management of specific types/causes of pain.

Setting Mutually Agreed Upon Expectations

Establishing realistic expectations, through discussion with the patient and their support system, is important for successful pain management. In most cases it is not achievable to completely eliminate pain, at least not in the short term. It is thus important that patients have realistic expectations of their treatment outcomes. Having a mutual understanding of safety parameters should be a part of this discussion. The patient should be made aware that there are limits around the prescribing of both opioid and non-opioid medications for them to be used safely.

If additional opioids are being prescribed to the patient already on OAT, highlighting the importance of a naloxone kit can be helpful to increase the patient's understanding of the risks of using additional opioids. If the patient does not already have a kit, **providing a naloxone kit and education is strongly recommended.**

It may be more successful to work toward functional goals that allow the patient to directly observe and report the impact of their pain management. This also has the benefit of shifting the focus away from the negative perception of pain, toward goal-oriented functional improvement. Helping the patient understand what is achievable will contribute to successful patient interactions.

ACUTE PAIN MANAGEMENT IN PATIENTS ON OAT

In general, acute pain in a patient on OAT should be managed similarly to someone who is not on OAT. The initial management should take into consideration the type/source of pain and

the evidence for managing that particular pain. Often non-opioid analgesics (e.g., NSAIDs, acetaminophen, gabapentinoids) are recommended as first-line treatment and the approach should be the same for someone on OAT.

However, it is important to note that gabapentinoids have significant abuse potential. If they are prescribed as part of an overall acute pain management strategy, it is important to discuss this risk with the patient and have a plan for monitoring and discontinuation after an agreed upon period of time. **In the interest of patient safety, gabapentinoids should generally be dispensed at the same interval as OAT.**

A multimodal approach to the management of acute pain is recommended and should be tailored to the patient's clinical circumstances and injury/surgical procedure. In hospitalized patients, regional anesthesia or other advanced pain management techniques may be an option in consultation with acute pain services and/or anesthesia.

Opioid Analgesia

For the most part, if the acute pain management would normally require the use of opioid analgesics (e.g., hip arthroplasty), it would also be appropriate for the patient on OAT. **Given the baseline tolerance of patients on OAT to opioids, doses may need to be escalated to achieve an adequate response.** The practitioner should start at doses similar to those used in a patient not on OAT and reassess early in order to provide adequate pain management. Additionally, it is important for the practitioner to discuss the short-term nature of the opioid analgesic. The plan to taper and discontinue the opioid analgesic should be part of the initial discussions.

Controlled Dispensing

Additional opioids prescribed in the community setting, or continued post hospital discharge, **must be dispensed at the same interval as OAT.** If short-term additional pain management is required (opioids and/or gabapentinoids) and the patient cannot attend the pharmacy regularly due to their pain/injury, regular pharmacy deliveries, if available, can also enhance the safety of the overall pain management plan.

The request to deliver OAT doses must be made by the OAT prescriber and discussed with the pharmacy directly. This request must only be made in *exceptional circumstances* and for the shortest period of time, to accommodate recovery from acute injury/pain that immobilizes the patient and thus makes pharmacy attendance impossible.

Further to the above, delivery of OAT doses typically implies that the dose is not witnessed. This is not acceptable practice in most circumstances. Deliveries must only be considered for mandatory infectious isolation periods and significant acute injury/pain that makes pharmacy attendance impossible for a limited time.

CHRONIC PAIN MANAGEMENT IN PATIENTS ON OAT

Additional use of opioids for the management of chronic non-cancer pain is not recommended in most cases². Chronic pain does not have the same protective biologic benefit as acute pain. In general, chronic pain is also much harder to treat.

A multidisciplinary approach with emphasis on non-drug related modalities and non-opioid analgesics should be exhausted first. If these treatments are unsuccessful, it may be appropriate to consider a trial of opioids. The opioid trial should have clear functional goals and timelines for reassessment. There should be a clear plan for discontinuation if benefit is not shown. **Additional opioids must be dispensed at the same intervals as OAT.**

ADDITIONAL CONSIDERATIONS FOR PAIN & OAT

Continue the OAT Medication

It is important to recognize that the maintenance opioid (e.g., methadone or buprenorphine) the patient is taking for OUD is the baseline for preventing withdrawal and does not provide significant pain relief. If possible, the OAT should be continued at the current dose.

This recommendation to continue OAT applies to the perioperative period as well, where it should similarly be considered baseline for withdrawal management and not a significant contributor to analgesia³. Holding methadone or buprenorphine on the day of surgery can lead to the additional complication of withdrawal at the time of surgery. Any decision to hold methadone or buprenorphine on the day of surgery must be discussed and coordinated between the OAT prescriber and the anesthesiology team.

Depending on the surgery, consideration can be given to regional anaesthesia and/or nerve blocks. A pre-operative assessment is recommended for elective surgical procedures where it is anticipated that the patient will experience significant post-operative pain.

Split Dosing for Analgesic Benefit

Some patients will experience analgesia from their OAT medication in the hours immediately post-dose. In this case split dosing of the OAT medication can be considered to help manage acute pain. This option should only be considered as an adjunct if all other non-opioid modalities of treatment are not effective or appropriate. This may be easier to facilitate in the inpatient setting than in the community setting.

Patients who are clinically unstable and who do not have routine take-home doses (carries), may not be appropriate candidates for split dosing in the community. Prescriptions with split dosing for these patients would require multiple trips per day to the pharmacy, which may be impossible or impractical.

In determining if a trial of split dosing is appropriate in the community setting, the OAT prescriber should consider:

- The overall stability of the patient,
- The number of regular take-home doses,
- The nature and duration of the pain condition,
- The patient's overall mobility, and
- Public safety.

A transitional plan back to once daily dosing at the earliest opportunity should be included in the care plan.

Similarly, split dosing for the management of chronic pain in the context of OAT should only be explored if all other non-opioid modalities of treatment are not effective or appropriate. A multidisciplinary approach is strongly recommended, where available. Long-term split dosing for the management of chronic pain must be reviewed with a provider experienced in managing pain in the OAT population, or an Addiction Medicine Specialist.

Avoid Drug of Choice

If the decision is made to use an additional opioid, the opioid(s) identified by the patient as their drug(s) of choice associated with their OUD should be avoided if possible. For example, if fentanyl is their drug of choice, morphine or hydromorphone may be better options.

Shared Decision Making

The patient should be included in the decision about how to manage pain, especially when considering the use of an additional opioid. Some patients stabilized on OAT will refuse treatment with opioid analgesics out of fear of relapse.

In the interest of keeping the patient safe, it is important to set initial boundaries around dose escalation, quantities, and the expected duration of analgesic need. This is not to say that the dose cannot be increased, or the duration extended if the clinical situation warrants it. However, this should not happen without reassessment and intentional consideration of risks and benefits by both the practitioner and the patient.

PRESCRIPTION CONSIDERATIONS FOR OPIOID ANALGESIA

Communication is Paramount

Ideally the patient has one prescriber, or identified group of prescribers, responsible for all their controlled medications. This includes their OAT, additional opioids used for pain

management, and all other sedating/psychoactive medications. Similarly, best practice is to utilize one community pharmacy for all medications dispensed. See [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use](#) for further recommendations.

If the decision is made to prescribe opioid analgesia in addition to the patient's OAT, this opioid should be prescribed by their OAT provider and dispensed from their regular community pharmacy. If this is not possible, the OAT prescriber must be consulted and made aware of the treatment plan. Similarly, the patient's regular community pharmacy must be made aware of the treatment plan. The prescription for the additional opioid should include a note that it is to be used in conjunction with the patient's OAT, to avoid any interruptions to care at the receiving pharmacy, especially if a different pharmacy is used.

Ensuring that this information is clearly communicated to the community provider and pharmacy at the time of discharge from hospital is extremely important. **A “warm handoff” where all parties are involved (including the patient) can ensure a common understanding of the care plan, identify potential issues, and set timelines for follow up.**

NIHB Client Safety Program

Patients on OAT whose medications are covered by Non-Insured Health Benefits (NIHB) for First Nations and Inuit are enrolled in the NIHB Client Safety Program. These patients are required to have a *sole prescriber* (or identified group of prescribers) as a provision for coverage of opioids, benzodiazepines, stimulants, gabapentinoids, and/or nabilone (i.e., restricted medications).

When patients are initiated in a community pharmacy on buprenorphine/naloxone, methadone, or SROM to treat OUD, they are automatically enrolled. Often the sole prescriber will be their regular OAT prescriber (or group of prescribers), and this should be considered when developing the discharge plan. If any of these restricted medications are prescribed by a clinician not listed as the sole prescriber, prescription costs will not be covered.

Mitigating Risk of Misuse

As noted previously, additional opioids prescribed in the community setting **must be dispensed at the same interval as OAT**. Limiting the medication supply dispensed at one time can help mitigate potential misuse of the opioid analgesic.

For example, if the patient is on daily dispensed OAT, the new opioid analgesic should also be dispensed daily. If significant concern for misuse exists, *witnessed* daily dosing may be implemented, depending on the formulation of the opioid. For patients with routine take-home doses (carries) of OAT, the number of days' supply of the new opioid analgesic should not exceed the number of carry days dispensed. If the patient has weekly carries (i.e., OAT is witnessed once weekly), it may be prudent to initially dispense the opioid analgesic at shorter intervals to mitigate risk of misuse.

SPECIAL CONSIDERATIONS FOR PATIENTS ON BUPRENORPHINE

Continuing Buprenorphine

Buprenorphine binds very tightly to the mu-opioid receptor, however, as a partial agonist, it has low intrinsic activity. This can make acute pain management for patients maintained on buprenorphine challenging. **In most circumstances, buprenorphine should be continued when treating acute and perioperative pain.** Discontinuing buprenorphine can result in delayed surgeries and put the patient at risk for relapse if not restarted quickly.

Additionally, restarting buprenorphine while receiving a full mu opioid agonist can pose logistical challenges (e.g., the risk of precipitated withdrawal) or take a significant amount of time if a micro-dosing approach is utilized. In many cases, acute pain can be managed with non-opioid analgesics.

Adjusting Buprenorphine

Splitting the daily buprenorphine dose into 3-4 divided daily doses may also be considered. If the person is maintained on a lower daily dose of buprenorphine (e.g., 8-16 mg) a *temporary increase* in the total daily dose may provide the additional analgesia needed. If additional opioid analgesics are required, a full mu opioid agonist may be used in addition to the patient's baseline buprenorphine dose.

In some cases, where adequate analgesia has not been achieved with the above strategies, or where a significant amount of post-operative pain is anticipated (e.g., spinal surgery), a *temporary reduction* in the buprenorphine dose to 8-16 mg per day may improve the analgesic efficacy of a full mu opioid agonist, by increasing the proportion of available opioid receptors that are not occupied by buprenorphine⁴. When considering this approach, there should be careful assessment of the risk/benefits of decreasing the dose and the patient should be included in this decision.

If the buprenorphine dose is lowered, this should be done only for the shortest time required. If the patient is in hospital, the buprenorphine dose should be increased back to the maintenance dose prior to discharge, to minimize the risk of relapse. If this is not possible, a plan should be created, prior to discharge, in conjunction with the patient's OAT prescriber, to return to their baseline buprenorphine dose. This plan must also be communicated to the patient's regular OAT community pharmacy.

Depot Buprenorphine Formulations

Patients who are using the depot formulation of buprenorphine will need to be managed with adjunctive therapy, with non-opioids and/or additional opioids. Additional monitoring for adverse effects, in particular respiratory depression, may be prudent given the high doses of opioids that may be required.

IN SUMMARY

Pain management can be complex in patients on OAT. In general, patients should be managed like any other patient who presents similarly but that does not have OUD. However, **additional considerations apply to ensure adequate analgesia and patient safety.** Both undertreated pain and the inappropriate use of additional opioids can precipitate relapse or serious adverse outcomes.

While the patient's OAT medication may not supply sufficient analgesia on its own, is it paramount to continue as it provides a baseline for withdrawal prevention, and is integral to minimizing the risk of relapse and to avoiding additional withdrawal-mediated pain. If an opioid is prescribed for acute pain, the short-term nature of this management should be discussed at the outset. Communication between all parties involved (including the patient) can ensure a common understanding of the care plan, identify potential issues, and set timelines for follow up.

Buprenorphine, as a partial agonist with a very high affinity for the mu-opioid receptor, can make management of severe acute pain more challenging and may require special consideration.

OAT prescribers who are inexperienced in managing acute, perioperative, and chronic pain, are strongly encouraged to consult with an experienced colleague, an Addiction Medicine Specialist, or the HSC Addiction Medicine Consult Team on-call physician.

References & Resources

1. International Association for the Study of Pain. Terminology. 2021. <https://www.iasp-pain.org/resources/terminology/#pain>. Accessed February 2022.
2. Busse J, Craigie S, Jurrlink D, et al. The 2017 Canadian guideline for opioids for chronic non-cancer pain. *CMAJ*. 2017; 189(18):4-5
3. American Society of Addiction Medicine. National Practice Guideline For the Treatment of Opioid Use Disorder: 2020 Focused Update. *J Addict Med*. 2020; 14(2S):1-91
4. Kohan L, Potru S, Barreveld A, et al. Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. *Reg Anesth Pain Med*. 2021; 46(10): 840-859.
5. Kohan L, Potru S, Barreveld A, et al. Guidelines for the use of buprenorphine for opioid use disorder in the perioperative setting. *Reg Anesth Pain Med*. 2021; 46(10): 860-861.
6. Anderson TA, Quaye AN, Ward EN, Wilens TE, Hillard PE, Brummett CM. To stop or not, that is the question: acute pain management for the patient on chronic buprenorphine. *Anesthesiology*. 2017; 126(6):1180-1186.

7. Quaye AN, Zhang Y. Perioperative management of buprenorphine: solving the conundrum. *Pain Med.* 2019; 20(7):1395-1408.
8. Goel A, Azargive S, Lamba W, et al. The perioperative patient on buprenorphine: a systematic review of the perioperative management strategies and patient outcomes. *Can J Anesth.* 2019; 66(2):201-217.
9. Goel A, Azargive S, Weissman J, et al. Perioperative Pain and Addiction Interdisciplinary Network (PAIN) clinical practice advisory for perioperative management of buprenorphine: results of a modified Delphi process. *Br J Anaesth.* 2019; 123(2):e333-e342.
10. Lembke A, Ottestad E, Schmiesing C. Patients maintained on buprenorphine for opioid use disorder should continue buprenorphine through the perioperative period. *Pain Med.* 2019; 20(3):425-428.
11. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med.* 2010;152(2):85-92.
12. Krebs E, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain". *JAMA.* 2018; 319(9):872-882.
13. Martin Y, Deljou A, Weingarten T, Schroeder D, Sprung J, et al. Perioperative opioid requirements of patients receiving sublingual buprenorphine-naloxone: a case series. *BMC Anesthesiol.* 2019; 19(1):68
14. Veazie S, Mackey K, Peterson K, Bourne D. Managing acute pain in patients taking medication for opioid use disorder: a rapid review. *J Gen Intern Med.* 2020; 35(Suppl 3):945-953.
15. Macintyre P, Russell R, Usher K, Gaughwin M, Hustable A. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. *Anaesth Intensive Care.* 2013; 41(2): 222-230.
16. Namiranian K, Siglin J, Sorkin J, Norris E, Aghevli M, Covington E. Postoperative opioid misuse in patients with opioid use disorders maintained on opioid agonist treatment. *J Subst Abuse Treat.* 2020; 109:8-13.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.11 Prevention, Screening, & Management of HIV & Hepatitis C in Individuals with Opioid Use Disorder

GENERAL CONSIDERATIONS

Screening for All STBBIs

While this chapter will focus on the prevention, screening, and treatment of HIV and hepatitis C infection, it is important to note that opioid agonist therapy (OAT) providers **MUST** offer comprehensive screening for Sexually Transmitted and Blood Borne Infections (STBBIs) to all patients with Opioid Use Disorder (OUD). This can occur around intake for OAT and periodically thereafter based on ongoing risk assessment.

Patients at significant and ongoing risk of infection should be offered STBBI screening every 6 to 12 months. Initial screening should include testing for HIV, hepatitis A, B, and C, as well as syphilis, chlamydia, and gonorrhea, including throat and rectal swabs if indicated. Repeat testing may be customized based on individual risk factors.

Testing for hepatitis A and B antibodies serves to assess a patient's immune status against these infections. If susceptible to these infections, patients on OAT should be offered immunization against hepatitis A and B to offer protection, as they may have additional risks for hepatic illness and impairment due to hepatitis C infection, alcohol, other substance use disorders, or another cause.

See the [Treatment of OUD in Pregnancy](#) chapter for further recommendations around STBBIs, risk reduction, and preconception counselling for patients on OAT of reproductive age.

An Approach to STBBI Screening & Testing

It is important for OAT providers to normalize STBBI screening in the context of OAT care, and medical care in general. Explaining that this testing is **routinely offered to all patients** as part of a [comprehensive OAT intake assessment](#), or periodic health examination, can decrease (perceived) stigma and increase patient engagement.

Many strategies can be used to increase patient uptake of STBBI testing:

- Include STBBI testing when other routine or clinically indicated lab work is ordered.
- Discuss the benefits of knowing one's status, including the fact that many infections can be cured, and that HIV can be treated.
- If testing is initially declined, OAT providers should explore with the patient why they are declining testing, including any fears, misinformation, or beliefs that may represent a barrier to testing.
- Non-judgmental and compassionate education, along with practical support around testing, can go a long way to increase uptake of testing.
- If testing is initially declined, revisit the issue with the patient after 3-6 months in treatment. The patient may be more open to STBBI screening once a stronger therapeutic relationship has been established with clinic staff, and the benefits of treatment are better established. Include a support person(s) in the discussion, if requested or desired by the patient.
- It is important to note that a patient declining STBBI testing once does not mean that the issue should not be revisited periodically. The OAT provider must document each time STBBI screening is offered, including the outcome of the conversation.
- If testing is accepted, provide the patient with the requisition and a list of laboratory locations and their hours. If testing can be offered at the OAT treatment site that is ideal, but not always possible. Explore barriers to accessing lab work, such as transport, ID, health card requirements, and provide practical support if possible.
- Remind patients who did not attend the lab for testing at follow-up appointments and replace lost requisitions whenever needed.
- Discuss when results will be available and offer an in-person or virtual appointment to discuss results as soon as possible, especially if the patient is anxious about results.
- Reassure the patient that a positive result will be addressed in a timely manner and that the OAT treatment team will support the patient by providing treatment, or a treatment referral, in a confidential manner.
- Offer assistance with lab work or other special investigations required by consultants and treatment services.

Providers are strongly encouraged to develop a tracking system for STBBI results for all patients on OAT. This will help ensure that an initial refusal of testing or delay in attending the lab does not result in unidentified or untreated HIV or hepatitis C in the longer term. Tracking systems can also be useful for patients with diagnosed HIV/hepatitis C who require regular blood work.

SPECIFIC CONSIDERATIONS

This manual section offers expertise and recommendations for the care of patients with OUD within the following contexts:

- Screening for HIV and hepatitis C infections
- Management of diagnosed HIV and hepatitis C
- Prevention of HIV and hepatitis C
- Special considerations for OAT, including buprenorphine and methadone.

Helpful resources are linked throughout and listed in **Appendix K**.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

HIV is a retrovirus that spreads through blood, genital or rectal fluids, and breast milk. The main modes of transmission are through sexual intercourse, sharing needles or drug use equipment, and perinatal transmission. Untreated HIV can weaken the immune system and lead to opportunistic infections and death. However, early detection and treatment can prevent transmission and lead to a life expectancy close to that of the general population.

Screening for HIV

It is important that healthcare providers know the HIV status of all patients under their care. Detailed recommendations regarding appropriate intervals for initial and repeat HIV testing are outlined below.

RECOMMENDATION: WHEN TO OFFER AN HIV TEST

To all patients who present for OAT intake.

Every year to all patients aged 12-70 years who have additional risks for HIV acquisition, including gay, bisexual, and other men who have sex with men (gbMSM), people who inject drugs (PWID), and people who have unprotected sex with multiple partners, as well as those who belong to populations with a higher burden of HIV infection.

Every five years to all patients aged 12-70 years.

Once for patients older than 70 years of age, if HIV status is not known¹.

Please see the Manitoba HIV Program [HIV Testing Recommendations](#) for more detailed information on screening, including their specific program [HIV Testing Guidelines](#).

Management of HIV

If HIV testing is positive, the OAT provider or another skilled member of the treatment team must notify the patient and provide counselling regarding the natural history of HIV infection, the importance of treatment, and the prevention of HIV transmission. The provider should also review with the patient the potential legal implications of non-disclosure of HIV status to sexual partners².

Patients who test positive for HIV must be offered referral to the Manitoba HIV Program for ongoing care. Visit the [MB HIV Program Healthcare Provider](#) site for details and referral information.

The initial workup for new diagnoses of HIV may be done by the diagnosing clinician or will be done by the HIV care provider. The British Columbia Centre for Excellence in HIV/AIDS provides detailed [Therapeutic Guidelines](#) for the baseline evaluation, monitoring, and ongoing care recommendations for people living with HIV.

HIV & Opioid Use Disorder

OAT increases retention in HIV care, antiretroviral uptake and adherence, and viral suppression in those with OUD and HIV^{3,4}.

OAT with buprenorphine or methadone should be offered to eligible individuals with OUD who have HIV.

Drug interactions between antiretroviral medications and OAT should be considered prior to initiating therapy or adjusting doses. Useful resources to help navigate drug interactions include:

- [Liverpool HIV Drug Interaction Checker](#) (free online).
- MB HIV Program pharmacists are available for consultation for persons living with HIV in MB by calling 204-787-4005 for Health Sciences Centre (HSC), or 204-940-6022 for Nine Circles.

HIV & Patients on OAT

Patients who are newly diagnosed with HIV may benefit from more frequent visits for emotional and practical support around living with chronic illness, including their OUD and the HIV infection. OAT providers are in an excellent position to support patients while they adjust to their diagnosis, the burden of treatment, and the impact it has on their lives and significant relationships.

Where patients with HIV experience barriers to accessing specialty care for the management of HIV, the relationship with the OAT provider should also be leveraged to facilitate access to care and treatment. For patients not connecting to HIV care, OAT providers should consider connecting with the Manitoba HIV Program to reach a provider who can assist in creating a management plan (call 204-940-6089 or 1-866-449-0165).

Manitoba HIV specialists and pharmacists are also available for non-urgent management advice through eConsult MB: email to register at servicedesk@sharedhealthmb.ca or call 204-940-8500 or 1-866-999-9698. Or contact HSC paging for urgent concerns (call 204-787-2071).

Immunizations for People Living with HIV

Individuals living with HIV have additional immunization recommendations which can be found in the Canadian Immunization Guide: [Part 3, Vaccination of Specific Populations](#). See the [HIV Infection](#) section and [Table 5: Vaccination of HIV-Infected Persons](#).

Prevention of HIV

Providers should counsel at-risk patients regarding prevention of HIV, this includes:

- Routine testing for HIV, HCV, and other STBBIs. This is a vital component of prevention. **Early detection and treatment can prevent transmission.** Regular screening and treatment of STBBIs is essential, as **untreated STBBIs are associated with increased risk of acquisition or transmission of HIV.**
- Consistent and correct use of internal and external condoms.
- Harm reduction for PWID, including access to new needles, syringes, and other drug use equipment, as well as OAT, if indicated.
- Pre-exposure prophylaxis (PrEP), which is the use of medications for the prevention of HIV in HIV-negative individuals who are at high-risk of acquiring HIV.
- Post exposure prophylaxis (PEP), which is the use of antiretroviral medications in an HIV-negative individual who has had a potential exposure to HIV. PEP must be initiated within 72 hours of potential HIV exposure. Patients should be referred to urgent care or emergency if they meet the criteria for PEP.
- Antiretroviral therapy for HIV-positive patients to prevent transmission of the virus.
- Prevention of mother to child transmission including contraception counselling, routine HIV testing for individuals who are of childbearing years and HIV negative, and antiretroviral therapy for pregnant individuals who are HIV positive⁵. See [Treatment of OUD in Pregnancy](#) for further recommendations on contraception and preconception counselling.

The Manitoba HIV Program [HIV Guidelines](#) page provides further information regarding prevention, including their [HIV Prevention Guidelines](#) and other Canadian resources.

HEPATITIS C VIRUS (HCV)

Hepatitis C is an RNA flavivirus that infects the liver. It is spread when the blood of a person with hepatitis C comes in contact with the blood of another person. The main mode of transmission in Canada is through sharing needles, drug use equipment, and tattoo or body piercing equipment⁶. Hepatitis C can be transmitted through sharing of razors, toothbrushes, or unsterilized medical equipment, condomless sex, blood transfusions in a country where the blood supply is not routinely screened for HCV, and through perinatal transmission.

About one quarter of people who become infected will clear hepatitis C, while three quarters will develop a chronic infection⁷. Chronic hepatitis C infection can lead to cirrhosis, liver failure, or hepatocellular carcinoma if left untreated. **However, current treatments are available for the treatment of hepatitis C, and these are highly effective and well tolerated.**

Screening for Hepatitis C

Hepatitis C screening is recommended for all individuals born between 1945 - 1975, as well as additional risk-based screening in individuals at increased risk of infection, as outlined below.

RECOMMENDATION: WHEN TO SCREEN FOR HEPATITIS C

Commonly encountered risk factors that should prompt screening in the context of OAT include:

- Present or past injection drug use
- History of incarceration
- History of sexual contact or sharing personal care items with someone who has a hepatitis C infection
- Those with a HIV infection
- Those with an elevated alanine aminotransferase (ALT)

Additional risk factors that are an indication for screening include:

- Chronic hemodialysis
- Having received healthcare or personal services where there is a lack of infection prevention and control practices
- Originating or living in a region with a hepatitis C prevalence > 3%
- Having received blood products or organ transplantation before 1992 in Canada
- Infants born to a mother who has hepatitis C⁸

Re-screening for hepatitis C should be guided by risk activity. Re-screening should be done at least annually in those who have ongoing risk factors for acquisition of hepatitis C⁸. Screening for hepatitis C should involve testing for HCV antibodies for those with no past history of infection. If HCV antibodies are positive, a HCV RNA should be ordered to differentiate an active infection from a resolved infection. For those with a history of resolved hepatitis C, HCV RNA should be the initial screening test.

Management of Hepatitis C

If hepatitis C testing is positive the provider should notify the patient, counsel regarding the natural history, the availability of treatment, and prevention of transmission. It is important to emphasize that current hepatitis C treatment is effective and typically very well tolerated.

Patients may have had past experience with interferon/ribavirin treatment or know someone who was treated with an interferon/ribavirin regimen. These older treatments were poorly tolerated and less effective in curing hepatitis C. It is worthwhile to highlight that these medications are not routinely used in hepatitis C treatment anymore.

After diagnosis, an initial assessment may include:

- A documented history and physical examination to assess for signs and symptoms of advanced liver disease.
- A documented assessment of factors that influence disease progression such as alcohol intake, obesity, and co-infections.
- Baseline laboratory testing (liver enzymes, liver function, CBC, creatinine, testing for other STBBIs, HCV genotype and RNA)
- A liver ultrasound.
- An assessment of the stage of fibrosis.

For further information on the baseline assessment and management of hepatitis C, see Canadian Medical Association Journal article, [The management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the Liver](#).

Treatment for Hepatitis C

All individuals with chronic hepatitis C should be considered for treatment. Neither active injection drug use nor OAT are contraindications to treatment of hepatitis C. Adherence to treatment and efficacy of treatment have been demonstrated among those who inject drugs, with low rates of reinfection^{9, 10, 11}.

The ideal treatment setting for this population is multidisciplinary, with access to management of social and psychiatric comorbidities, and access to harm reduction services to reduce the risk of reinfection.

OAT and supply distribution in concert with hepatitis C treatment has significant potential to reduce the prevalence of hepatitis C among PWID^{12, 13, 14, 15}.

Patients may be referred for hepatitis C treatment in Manitoba through:

- The Viral Hepatitis Investigative Unit, Health Sciences Centre, call 204-787-3630, and/or fax 204-787-7086.
- Mount Carmel Clinic, call 204-589-9428 and/or fax: 204-582-6006.
- eConsult MB Hepatology – Hepatitis C Treatment advice: email to register at servicedesk@sharedhealthmb.ca or call 204-940-8500 or 1-866-999-9698.

Hepatitis C & Patients on OAT

OAT providers often have a unique relationship with their patients that can be leveraged to assist with the monitoring of hepatitis C and facilitate access to treatment.

OAT providers should consider having material available in the office to help inform patients regarding prevention, testing, monitoring, and treatment of hepatitis C. For example, the [CATIE](#) website contains valuable resources for patient education and support, available at [Hepatitis C Basics](#).

Where patients with hepatitis C experience barriers to accessing specialty care for the management of hepatitis C, OAT providers should:

- Offer routine monitoring of liver enzymes, liver function tests, a complete blood count, and
- Calculate APRI and FIB-4 scores to assess the degree of fibrosis, which is necessary to establish an appropriate management plan. Visit Hepatitis C Online to access an [AST to Platelet Ratio Index \(APRI\)](#) calculator and [Fibrosis-4 \(FIB-4\)](#) calculator.

Hepatitis C management advice outside of an in-person consultation may be accessed through eConsult MB's hepatology service, as listed above.

Drug-drug interactions with hepatitis C medications should be considered. A useful resource for checking drug interactions is the [Liverpool Hepatitis Drug Interaction Checker](#) available online.

Immunizations for People Living with Hepatitis C

Individuals with hepatitis C who are susceptible to hepatitis A and B should be offered immunization for hepatitis A and B.

Prevention of Hepatitis C

Providers should counsel at-risk patients regarding prevention of hepatitis C, which includes:

- Harm reduction for PWID, including access to new needles, syringes, and other drug use equipment, as well as OAT, if indicated.
- Providing education to patients regarding safer sex practices, not sharing personal items such as razors or toothbrushes, and ensuring single-use needles and proper sterilization for procedures such as tattoos and piercings.
- Routine testing for HIV, HCV, and other STBBIs. This is an important component of prevention. **Early detection and treatment can prevent transmission.** Regular screening for STBBIs is recommended as risk of transmission of HCV could be increased in the setting of untreated STBBIs^{16, 17}.

IN SUMMARY

The OAT provider and treatment team, including pharmacists, can play a key role in the prevention, screening, and management of both HIV and hepatitis C. The unique relationship and comprehensive care of OAT can be an effective avenue to educate patients about the risks of transmission, to offer timely screening, to provide harm reduction supplies, and to support patients through new diagnoses and treatment, in collaboration with experts.

References

1. Manitoba HIV Program. *Manitoba HIV Program HIV Testing Guidelines*. 2021. <https://mbhiv.ca/wp-content/uploads/2021/11/MB-HIV-Pgm-Testing-Guidelines-FINAL-1.pdf>
2. Government of Canada. *Justice Canada's Report on the Criminal Justice System's Response to HIV Non-Disclosure*. 2017. https://www.canada.ca/en/departement-justice/news/2017/12/fact_sheet_hiv_non-disclosureandthecriminallaw.html. Accessed March 26, 2022.
3. Kamarulzaman A, Altice FL. Challenges in managing HIV in people who use drugs. *Curr Opin Infect Dis*. 2015;28(1):10-16. doi:10.1097/QCO.000000000000125
4. Low AJ, Mburu G, Welton NJ, et al. Impact of Opioid Substitution Therapy on Antiretroviral Therapy Outcomes: A Systematic Review and Meta-Analysis. *Clin Infect Dis*. 2016;63(8):1094-1104. doi:10.1093/cid/ciw416
5. Manitoba HIV Program. *Manitoba HIV Program HIV Prevention Guidelines*. 2021. <https://mbhiv.ca/healthcare-providers/guidelines/>
6. CATIE. *The epidemiology of hepatitis C in Canada*. 2019. https://www.catie.ca/the-epidemiology-of-hepatitis-c-in-canada-0?utm_source=grant&utm_medium=ad&utm_campaign=cpc&utm_content=en. Accessed March 11, 2022.
7. CATIE. *Intro to hepatitis C*. 2019. <https://www.catie.ca/hepatitis-c-an-in-depth-guide/intro-to-hepatitis-c>. Accessed March 11, 2022.

8. Shah H, Bilodeau M, Burak KW, Cooper C, Klein M, Ramji A, Smyth D, Feld JJ. The management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the Liver. *CMAJ*. 2018;190(22): E677-E687. doi: <https://doi.org/10.1503/cmaj.170453>
9. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clin Infect Dis*. 2013;57 Suppl 2:S80-S89. doi:10.1093/cid/cit306
10. Grebely J, Matthews GV, Hellard M, et al. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. *J Hepatol*. 2011;55(1):76-85. doi:10.1016/j.jhep.2010.10.033
11. Dore GJ, Altice F, Litwin AH, et al. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. *Ann Intern Med*. 2016;165(9):625-634. doi:10.7326/M16-0816
12. Martin NK, Vickerman P, Grebely J, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology*. 2013;58(5):1598-1609. doi:10.1002/hep.26431
13. Barbosa C, Fraser H, Hoerger TJ, et al. Cost-effectiveness of scaling-up HCV prevention and treatment in the United States for people who inject drugs. *Addiction*. 2019;114(12):2267-2278. doi:10.1111/add.14731
14. Fraser H, Zibbell J, Hoerger T, et al. Scaling-up HCV prevention and treatment interventions in rural United States-model projections for tackling an increasing epidemic. *Addiction*. 2018;113(1):173-182. doi:10.1111/add.13948
15. Falade-Nwulia O, Irvin R, Merkow A, et al. Barriers and facilitators of hepatitis C treatment uptake among people who inject drugs enrolled in opioid treatment programs in Baltimore. *J Subst Abuse Treat*. 2019;100:45-51. doi:10.1016/j.jsat.2019.01.021
16. Lissen E, Alter HJ, Abad MA, et al. Hepatitis C virus infection among sexually promiscuous groups and the heterosexual partners of hepatitis C virus infected index cases. *Eur J Clin Microbiol Infect Dis*. 1993;12(11):827-831. doi:10.1007/BF02000402
17. Tohme RA, Holmberg SD. Is sexual contact a major mode of hepatitis C virus transmission? *Hepatology*. 2010;52(4):1497-1505. doi:10.1002/hep.23808

Appendix K

ADDITIONAL RESOURCES FOR HIV & HEPATITIS C

Manitoba HIV Program

Homepage	https://mbhiv.ca/
For Healthcare Providers	https://mbhiv.ca/healthcare-providers/
HIV Testing Guidelines	https://mbhiv.ca/healthcare-providers/guidelines/
HIV Prevention Guidelines	https://mbhiv.ca/healthcare-providers/guidelines/

Manitoba Health, Seniors and Active Living | Public Health Branch

Post-exposure Prophylaxis for HIV, HBV and HCV: Integrated protocol for managing exposures to blood and body fluids in Manitoba.

https://www.gov.mb.ca/health/publichealth/cdc/protocol/hiv_postexp.pdf

British Columbia Centre for Excellence in HIV/AIDS

Therapeutic Guidelines	http://bccfe.ca/therapeutic-guidelines
------------------------	---

University of Liverpool

HIV Drug Interaction Checker	https://www.hiv-druginteractions.org/
Hepatitis Drug Interaction Checker	https://www.hep-druginteractions.org/checker

Canadian Medical Association Journal

The management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the Liver <https://www.cmaj.ca/content/190/22/E677>

CATIE

Homepage	https://www.catie.ca/
HIV Basics	https://www.catie.ca/essentials/hiv-basics
Hepatitis C Basics	https://www.catie.ca/essentials/hepatitis-c-basics

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.12 Managing Co-Occurring Psychiatric Disorders in the Context of Opioid Use Disorder

GENERAL CONSIDERATIONS

In prescribing opioid agonist therapy (OAT) for patients with opioid use disorder, providers are certain to see some individuals presenting with psychiatric symptoms of a mental health disorder. Patients can present with symptoms of anxiety, depression, and/or psychosis. It is often very difficult to tell if these symptoms are a natural part of the recovery process, induced by substances, a normal reaction to a stressful life, or rather indicative of a psychiatric disorder requiring specific medication or psychotherapy .

This chapter will cover basic principles of psychiatric assessment of patients being treated for opioid use disorder (OUD) and provide recommendations for management of mental health symptoms. Assessment and treatment of some specific psychiatric symptoms will also be discussed, along with a brief review of issues related to personality disorders, in the context of managing opioid use disorder.

General Principles of Mental Health in Addiction

The OAT prescriber must recognize that that it is impossible to make a definitive psychiatric diagnosis and formulate a successful treatment plan when substance use is out of control. Generally*, stabilizing substance use and harm reduction measures should take priority over prescribing psychiatric medications in the initial stages of treatment.

*Acute psychosis or mania may be an exception and will be discussed in more detail later in this chapter.

Negative emotions are extremely common in early recovery. In fact, people are unlikely to make changes until they have experienced negative consequences because of their addiction. These consequences are often associated with uncomfortable feelings and emotions.

Substance use disorders can mimic primary psychiatric disorders by different pathways:

- **Intoxication:** For example, intoxication with stimulants can cause psychotic symptoms.
- **Withdrawal:** Commonly, mild withdrawal from benzodiazepines or alcohol often presents with increased anxiety, even without physiological signs of sedative withdrawal. Anxiety, poor sleep, loss of appetite, low motivation, and loss of interest can all be associated with opioid use, particularly in withdrawal.
- **Chaotic & dangerous lifestyle:** This is often required to maintain the addiction and pattern of use. The daily need to get money to buy opioids/other drugs, to safely purchase supplies, to find a safe place to use, and to prevent troublesome circumstances (e.g., being robbed, “ripped off”, injured, or arrested), along with the cycle of intoxication and withdrawal, will inevitably lead to disturbances in mood, behaviour, and cognition.
- **Regular long-term use of substances:** This can lead to symptoms identical to primary psychiatric disorders. The best evidence of this is with long-term use of alcohol causing major depressive features, but long-term use of cannabis, benzodiazepines, and opioids can also be associated with depression. The best treatment is usually abstinence along with lifestyle changes and supportive therapy with cognitive behavioural therapy (CBT) elements. The value of 12-step/peer-support groups cannot be understated for many individuals in recovery.

SPECIFIC CONSIDERATIONS

This manual section offers expertise and recommendations for the care of patients with OUD under the following headings:

- Separating a primary psychiatric disorder from substance-induced disorder
- Key principles when considering psychiatric medications
- Depression & anxiety
- Post-traumatic stress disorder
- Psychosis & schizophrenia
- Attention-deficit/hyperactivity disorder
- Personality disorders
- Sleep disorders

Helpful resources are linked throughout and listed in **Appendix L**.

SEPARATING A PRIMARY PSYCHIATRIC DISORDER FROM SUBSTANCE-INDUCED DISORDER

Step 1 – A proper psychiatric history

A psychiatric history and assessment, taken when patients are seen prior to initiating OAT, is recommended. However, it can be difficult to get a complete history while the patient is experiencing acute symptoms. Providers may need to complete a more thorough psychiatric review as patients stabilize on OAT, or as new symptoms present.

Essential parts of the psychiatric history include:

- **Review of past psychiatric hospitalizations/emergency visits.** If there is a history of these, get consent to obtain the medical records of the encounters. Gathering collateral information from family may also be helpful.
- **Review of prescribed psychiatric medications.** If there is past or current use of prescribed psychiatric medications, obtain consent for relevant records and review E-chart and/or DPIN as able.

If the patient is presently prescribed **psychoactive/sedating medications, particularly benzodiazepines**, it is strongly recommended the OAT provider take over prescribing and limit the amount dispensed. Ideally, if ongoing prescribing is indicated and effective, the dispensing frequency should mirror the OAT dispensing schedule. Communication with the patient's primary care provider, pharmacy, and/or specialist(s) is also required to review the plan and rationale for the OAT prescriber to take over prescribing these medications. It is important to emphasize that the primary care provider and/or specialist(s)'s care is still essential to the patient's other medical needs, while highlighting that **some changes to the medication regimen may be required for safe OAT induction and ongoing care**. Likewise, good communication with the pharmacy promotes interprofessional collaboration, patient safety, and consistent messaging around medication management. The chapter, [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#), provides detailed recommendations for managing psychoactive/sedating medications and benzodiazepines.

Briefly, the concurrent prescribing of OAT and benzodiazepines is associated with increased mortality and should generally be avoided. Please see the polypharmacy chapter section, "Managing Prescribed and Illicit Benzodiazepines & Z-Drug use" for detailed guidance on this important topic.

- **Review of past psychiatric treatment or consultation.** Again, ask for consent to obtain these medical records. Discuss openly with the patient the importance of communicating with their circle-of-care providers as needed (e.g., family physician, pharmacist, psychiatrist, counsellors, and other professionals involved). This requirement for transparency facilitates patient safety for OAT induction and ongoing care, and is typically outlined in treatment agreements with patients (see the Comprehensive Assessment chapter for more details).

Step 2 – Chicken or the egg

Which came first? Psychiatric symptoms or substance use? If substance use preceded the appearance of psychiatric symptoms, this increases the likelihood that the symptoms are substance induced.

Step 3 – Ask about past abstinence

What happened during their longest period of abstinence? How did they feel – what happened with their symptoms? The DSM-5 states that if the symptoms are still prominent after a month, a primary disorder is likely. Review past instances of abstinence, associated life events, and the patient's experiences. For example, events that can be associated with longer periods of abstinence can include incarceration, work where urine drug testing is common (such as an isolated work camp), or pregnancy/perinatally (if the patient chose to remain mostly abstinent during this time). Note: These examples are generalizations only and are mentioned as a possible suggestion to gathering information in the interview.

Step 4 – Get a family history

Is there a family history of mental health issues? The more specific the history, the better. For example, a family history of bipolar disorder with several hospitalizations and successful treatment with Lithium is more useful information than "...everyone in my family is crazy, they just don't know it". Encourage patients to elaborate and seek details.

Step 5 – What are they using?

Are the symptoms consistent with the substance(s) they are using? For example, psychotic symptoms are very commonly seen with use of psychostimulants such as cocaine or amphetamines. However, if a patient reports psychotic symptoms with alcohol use, this is more suggestive of a primary psychotic disorder.

Step 6 – Objective observation

How does the patient look objectively when they are not aware you are observing them? This is much easier to assess when a patient is in a supervised environment such as a psychiatric ward, medical withdrawal-management unit, or a residential treatment facility. If they are observed to be outgoing and boisterous on the unit, but when you meet, they report marked anxiety symptoms and a need for prescribed benzodiazepines, this may be suggestive of "drug-seeking" behavior. For out-patient clinics, you may see incongruity in the patient's behavior in the waiting room compared to their presentation during the visit, which may also suggest drug-seeking behaviour.

It is not uncommon for patients to struggle with difficult thoughts and feelings, particularly in early recovery, when the numbing and sedating effects of regular drug use have lifted. They

may still seek prescribed or over-the-counter medications (other than their drug of choice) to alleviate this discomfort. **Learning coping skills and distress tolerance in recovery takes time.** Remind and encourage patients that navigating difficult states of mind, and the associated physiological and psychological symptoms, is part of recovery. The OAT provider can help differentiate between behaviours and symptoms that stem from a need to sooth unwanted thoughts and feelings, compared to symptoms of a primary psychiatric disorder.

Step 7 – Give it time

Given much of the above, a short period of observation is helpful before prescribing psychiatric medication. Generally, it is advised to optimize OAT first before adding psychiatric medication.

Step 8 – Explore the symptoms

Get a very clear idea of the patient’s symptoms. A statement of “I’m depressed” does not necessarily mean a diagnosis of major depression. For example, some patients will report “anxiety” (and a need for benzodiazepine prescribing), but on further assessment they more accurately struggle with serious anger management difficulties.

Step 9 – Don’t rush diagnosis

Be aware that individuals may have various reasons or “hidden agendas” in their complaints (e.g., looking for drugs, hospitalization, reasons not to work, etc.). Taking the time to gather collateral and medical records, and not rushing to make a diagnosis of a psychiatric disorder or decide on a clinical treatment plan, is often in both yours and the patient’s best interest.

KEY PRINCIPLES WHEN CONSIDERING PSYCHIATRIC MEDICATIONS

There are at least four possible prescribing scenarios for patients on OAT and psychiatric medications. Some providers may prescribe all the patient’s medications, including the OAT, psychiatric, and primary care medications (e.g., for high blood pressure, thyroid issues, diabetes, etc.). Some may prescribe the OAT and primary care medications, while the psychiatric medications are left to the psychiatrist to manage. Conversely, some may prescribe the OAT and all psychoactive/sedating medications, while primary care providers manage the other medications. And some prescribe only OAT, although this is **not recommended** (unless in the context of a RAAM clinic or emergency/urgent care, where OAT may be initiated and even titrated short term, with appropriate and timely communication back to any primary care or specialist providers and pharmacies involved).

It is **strongly recommended** that the community-based OAT provider take over prescribing of any psychoactive and/or sedating medications to mitigate risk of overdose or misuse, by implementing the medication management strategies recommended in this manual. Please refer to above mentioned chapter regarding [polypharmacy and benzodiazepines](#) for detailed recommendations about the OAT provider’s role in managing psychoactive/sedating medications.

If there is more than one prescriber involved, **all prescribers must communicate with each other to minimize the chance of dangerous drug interactions and accidental medication overdose.** If the psychiatrist wishes to continue managing the psychoactive/sedating medications, collaboration and communication is key, and the dispensing schedule for these medications should mirror the OAT dispensing schedule in most circumstances.

Communication must also occur with the pharmacy about the plan for managing these medications. Controlled dispensing instructions, such as “dispense as per OAT schedule”, must be written on all relevant prescriptions. If there is more than one prescriber involved, ideally all medications should be dispensed through one pharmacy. This will minimize the chances of adverse drug interactions.

There may be occasional circumstances when the prescriber’s risk assessment, considering all medications and psychosocial factors, would safely allow for less controlled dispensing of psychoactive/sedating medications. Clinical judgment can be applied; for example, if a patient is paying out of pocket for medications and there are no high-risk behaviours identified, the additional cost of daily dispensing may not be justifiable. **The prescriber must document their risk assessment and rationale for dispensing intervals that diverge from the OAT schedule.**

PRESCRIBING ESSENTIALS: PATIENTS ON OAT & PSYCHIATRIC MEDICATIONS

- 1) Communicate with other prescribers, pharmacists, and other professionals within the circle of care. Be transparent with patients that consenting to this communication is important for safety (often outlined in treatment agreements when initiating care and revisited as needed).
- 2) Patients with substance use disorders are accustomed to taking substances as they see necessary to alleviate mood or anxiety symptoms. As a result, emphasize the need to take psychiatric medication exactly as prescribed, and not to change the dose or timing unless they have spoken with the prescriber.
- 3) Avoid polypharmacy or doses higher than recommended. As a rule, it is advisable to ensure one medication is at an optimal dose before prescribing a second.
- 4) Minimize the use of “prn” medications. This may lead to overuse, or the failure to use healthy coping strategies before reaching for medication or a “chemical fix.”
- 5) Set realistic expectations with the patient. It is very unlikely that a medication will alleviate all symptoms completely – a modest reduction in symptoms is the most likely outcome.
- 6) Be cautious of the amounts dispensed to minimize the risk of overdose or diversion – dispensing should mirror the OAT witness and carry schedule in most circumstances.
- 7) Monitor compliance by checking DPIN, ordering occasional comprehensive urine drug screens (UDS) in addition to point-of care testing, and conducting pill counts as needed. See other chapters of this manual for detail guidance around UDS use.

The information presented here is consistent with the [latest Substance Abuse and Mental Health Service Administration recommendations](#) (see [TIP 42](#))¹. Free resources are available at samhsa.gov.

DEPRESSION & ANXIETY

Generally, symptoms of anxiety and depression will show substantial improvement within two to four weeks of abstinence. **Pharmacological treatment is usually not recommended until OAT is optimized.** However, telling the patient they are “not really depressed” may come across as invalidating to them and may negatively impact engagement in care. Most patients will accept that there are different subtypes of depression/anxiety (e.g., substance-induced vs bipolar vs major depression), each with its own recommended treatment. Offer support and encouragement, while noting that it is impossible to know the best treatment without a period of abstinence and assessment.

If depressive symptoms continue despite optimizing OAT, further assessment should include:

- Review the course of depressive symptoms, specific symptoms of depression, and psychosocial stressors.
- Review recent substance use with the patient. A comprehensive UDS can be informative; but note that generally urine screening does not detect alcohol. Point-of-care UDS does not detect alcohol and possibly some benzodiazepines – negative UDS results do not rule out ongoing substance use. See other manual sections for more guidance on urine drug testing.
- If not recently done, send the patient for lab work including CBC, TSH/T4, kidney function, liver function, glucose, Beta-HCG, and any other investigations suggested by a review of systems. Rule out if any physical health conditions may be contributing to symptoms.
- Review prior psychiatric system contact and treatment, as per *Step 1* above.

Management of Depression

If considering specific psychiatric treatment following assessment, several options are available:

- 1) For mild to moderate depression, some patients benefit from supportive therapy, behavioral activation including regular exercise (the best evidence is for aerobic exercise), and healthy lifestyle advice.
- 2) Specific psychotherapy for depression, especially CBT, can be effective. Some multidisciplinary clinics have counsellors that can provide this individually or in a group setting. Resources are also included in **Appendix L** and the patient handout, [Emotions, Anxiety, and Addiction](#).
- 3) If prescribing antidepressant medication, an antidepressant with a low propensity for interactions or side-effects is generally the best initial choice. Additionally, a history of any prior antidepressant trials should be obtained.
- 4) Consultation with an addiction aware psychiatrist can be considered. There should be agreement between the OAT prescriber and the primary care provider about who will

request a consultation and who will prescribe any medication recommended. Preferentially the OAT provider should prescribe any psychoactive/sedation medications, as above.

Practical examples of the assessment and management of other mood and anxiety issues are outlined in the **VIGNETTES** for **BARB** and **CHERYL**, respectively.

VIGNETTE: BARB STRUGGLES WITH DEPRESSED MOOD

Barb is a 35-year-old woman in the clinic that has been stable on 75 mg of methadone for several years. The nurses all find her quite likeable; she has weekly dispensing and usually stops in to chat when she picks up her weekly doses and always treats the staff to her homemade baking. The staff book her into clinic on an urgent basis, as she has reported being increasingly sad, with no interest in previously enjoyed activities, poor sleep, loss of appetite and concentration, loss of energy, and thoughts of dying with no active suicidal plan.

When seen, she is close to tears for most of the interview and definitely not her usual energetic and bubbly self. A review of psychosocial stressors is unremarkable, there are no new physical symptoms, and she denies any substance use other than cannabis which she has been using regularly for years.

She reports being hospitalized for approximately 3 months on a psychiatric ward at age 23, but really cannot remember any details, other than she had follow-up for a couple of months and had to take some red and white capsules, which she discontinued long ago.

There are no acute safety issues; she is agreeable to meeting with the staff on Wednesday and Friday and seeing you again on Monday. She is sent for blood work to see if there is any physical contribution to her symptoms and she signs a consent for release of information to obtain her medical records.

The discharge summary from her past admission arrives later that week. It indicates she had a severe manic episode which required a lengthy psychiatric hospitalization – she was stabilized on Lithium and eventually discharged.

When seen the next week, she was started back on Lithium, agreed to more frequent meetings with her nurse, and her depression improved substantially over the next few weeks.

Teaching Points

- If an antidepressant had been started without knowing that Barb had a history of bipolar mood disorder, it may have precipitated a manic episode.
- Patients often do not have a perfect recollection of why they were in hospital or what the treatment was. This is probably because they are under a great deal of stress at the time.
- Additionally, patients are often prescribed relatively large doses of benzodiazepines and/or other sedatives to treat acute psychiatric symptoms when admitted to inpatient wards – this can interfere with the formation of new memories.
- Gathering collateral outside of patient report is essential.

VIGNETTE: CHERYL STRUGGLES WITH ANXIETY

Cheryl is a 22-year-old woman, recently started on OAT, presently at buprenorphine/naloxone 12 mg daily and titrating. At her initial assessment she reported regular use of IV hydromorphone, methamphetamine, benzodiazepines (non-prescribed), cannabis, and alcohol. She has witnessed dispensing 7 days a week. The nurses report she adheres to clinic expectations, but is quite emotional and labile. Her recent UDS was positive for fentanyl and cannabis. Cheryl states, “The guy must have laced the marijuana”. She informs the nurses she wants to talk about anxiety at her next appointment.

Cheryl reports a very chaotic early life and upbringing. She was in a series of foster homes and has never had a period of stability. She has had several psychiatric assessments throughout her childhood and early adulthood, but no sustained follow up. She has been prescribed several different antidepressants, mostly of the SSRI class. She reports many side effects from these, and at no time have antidepressants been taken regularly for longer than two weeks.

A review of her psychiatric symptoms is positive for nearly *all criteria of all anxiety disorders*. She is increasingly irritable when you ask her to elaborate or give examples of symptoms. She mentions on more than one occasion that she has used her friend’s Xanax – it was effective for all her symptoms and all she needs is for you to prescribe this for her. It is difficult to redirect her to discuss other treatment options. She leaves your office in a huff when she realizes you will not prescribe alprazolam.

Teaching Points

- The buprenorphine dose can likely be increased, based on clinical assessment and ongoing withdrawal. (See chapter on buprenorphine induction for details.)
- It is very unusual for illicit suppliers to lace cannabis with fentanyl. The most likely explanation is the continued use of fentanyl – hence the need for further OAT titration.
- CBT is the recommended first-line treatment for anxiety, regardless of the subtype. The handout [Emotions, Anxiety, and Addiction](#) lists community resources and recommended reading for the treatment of anxiety disorders.
- Benzodiazepines *are not* recommended as a first-line treatment for anxiety disorders. They are easy to start, but very difficult to stop, particularly for patients that have a pre-existing substance use disorder (SUD). At best, benzodiazepines are a third-line treatment for severe and acute issues in patients who do not have SUD and should only be considered when all other treatments have failed – they are *not recommended for individuals with OUD*. If benzodiazepines are used, dispensed amounts should be limited (mirroring the OAT schedule as described above), closely monitored and, ideally, short-term.
- Alprazolam seems to be the most requested benzodiazepine. This may be due to the rapid onset of action and short half-life; even patients without a substance use disorder can find themselves taking it more frequently than prescribed. **CPSM standards of practice indicate alprazolam prescribing should be avoided, due to the risk of abuse and diversion.**
- Non-benzodiazepine medications for anxiety are not necessarily benign. Quetiapine can be associated with serious metabolic effects including weight gain and diabetes. Some antidepressants have interactions with OAT (particularly methadone). If these options are chosen, they must be monitored carefully with limited dispensing.

POST-TRAUMATIC STRESS DISORDER (PTSD)

Many patients with substance use disorder have experienced traumatic events in their lifetime. This does not necessarily mean that they have post-traumatic stress disorder, even though they may report that they have PTSD.

PTSD is associated with a triad of symptoms including:

- 1) Re-experiencing the traumatic event through flashbacks or nightmares.
- 2) Avoidance of activities that remind them of the traumatic event.
- 3) Heightened arousal including symptoms such as being easily startled, disturbed sleep, and increased irritability or outbursts of anger.

Managing PTSD

Treatment generally begins with stabilizing the substance use disorder, along with initial cognitive behavioral recommendations, and learning *grounding techniques* that orient patients to the *here and now* and to utilize coping strategies. **This requires regular and consistent practice and rehearsal, when not acutely distressed, in order to successfully utilize these techniques in times of distress or when triggered.** Reliving the initial trauma is not recommended until stabilization and coping techniques have been achieved.

Occasionally, patients will indicate they have been diagnosed with complex PTSD. This refers to someone who has suffered numerous traumatic or abusive events during childhood and has developed symptoms that are consistent with a cluster B personality disorder, particularly borderline personality disorder.

Treatment recommendations for complex PTSD are similar to those with more classic PTSD. There are two programs in Winnipeg that have particular expertise in its treatment. The [Short Term Assessment & Treatment \(STAT\) Program](#), a multidisciplinary day hospital at the Health Sciences Centre, can be a helpful resource. They offer courses in dialectical behavioral therapy (DBT), a specialized type of psychotherapy that has shown to be quite beneficial in patients with symptoms consistent with borderline personality and frequent suicidal ideation. The [Co-Occurring Disorders Initiative \(CODI\)](#) also offers DBT and specializes in consultation and management of concurrent mental health and substance use disorders, particularly for patients whose rehabilitation needs are not well met by less intensive programming. Both STAT and CODI require referral from a medical care provider who follows the patient longitudinally, to incorporate consultative recommendations into their care. Again, there should be agreement between the OAT prescriber and the primary care provider about who will initiate the referral and follow through on recommendations. Preferentially the OAT provider should prescribe any psychoactive/sedation medications.

Another program that may be helpful is the [Heartwood Healing Centre](#) which accepts self-referral and offers specialized treatment for individuals who have suffered abuse.

Medications & PTSD

The SSRI class of antidepressants has the most evidence for PTSD treatment. Benzodiazepines are *not recommended*. There is also some evidence to suggest the use of the antihypertensive medication prazosin can be helpful for treating nightmares related to PTSD. Before starting this medication, a baseline blood pressure and heart rate should be obtained, and blood pressure monitored during the initial stages of treatment.

Although there is a strong lobby for the use of “medical marijuana”, the evidence for the successful use of cannabis in PTSD treatment is limited. Cannabis is not a benign substance and has effects on cognition and mood. Regular use, particularly of smoked cannabis, can lead to increased anxiety symptoms as the effects quickly wear off. This can exacerbate baseline anxiety already associated with PTSD.

If patients ask for specific recommendations on the use of cannabis, edible cannabis with a low THC content and high CBD content may be an option. Some case studies have suggested it may be particularly helpful for symptoms of nightmares. Please see the [polypharmacy and polysubstance use](#) chapter noted above regarding cannabis use. Additional information can be also found in the CPSM [Standard of Practice for Authorizing Cannabis for Medical Purposes](#), which came into effect November 1, 2020.

PSYCHOSIS & SCHIZOPHRENIA

Symptoms of psychosis include hallucinations (usually auditory), delusions, and markedly disorganized thinking or behavior. Psychosis can be associated with several psychiatric disorders including schizophrenia, mania, psychotic depression, and substance use.

Patients with psychosis often require an urgent psychiatric assessment and possible psychiatric hospitalization. In Winnipeg, two resources that can provide rapid assessment are the Crisis Response Centre (817 Bannatyne Ave) and the Mobile Crisis Team which can be reached at 204-940-1781. If a patient does not wish to access these or other crisis resources, and you believe they are an imminent threat to themselves or others, or will suffer substantial physical or mental deterioration, any physician in Manitoba can complete a **Form 4 of the Mental Health Act**. This is an application for Involuntary Psychiatric Assessment which authorizes that a person can be taken to a facility for assessment by a psychiatrist. More information is available in the WRHA Mental Health Practice Guideline [Appendix D Guide to Complete Form 4](#).

Substance-Induced Psychosis

Substance-induced psychosis will likely be the most common cause of psychosis seen in OAT practice. Schizophrenia is generally associated with disorganization of thinking and behavior, and frequently a lack of motivation, which can make it very difficult to execute the behaviours required to sustain daily opioid use.

Substance-induced psychosis is being seen more frequently in Winnipeg largely due to the increased community use of methamphetamine. Methamphetamine can cause a long-acting psychosis that is very difficult to differentiate from schizophrenia.

The psychosis that is caused by cocaine is generally short-lived (less than 24 hours) and often the psychotic symptoms are not bizarre in nature, but rather could have some basis in reality. For example, some common symptoms of cocaine-induced psychosis could be the patient believing that the police are hiding outside their residence, or are listening in on their telephone conversations. Conversely, methamphetamine-induced psychosis can be associated with more implausible delusions such as secret devices being implanted under the skin.

Patients with psychosis of any type generally require assessment in an emergency ward. If the psychosis resolves overnight, perhaps with the use of a sedative along with antipsychotic medication, it is generally assumed to be substance induced. The treatment recommendation is to stop using psychostimulants. Once a person has experienced psychotic symptoms because of psychostimulant use, the symptoms are far more likely to return in a more pronounced fashion and to last longer with continued use, due to a neurological phenomenon known as kindling.

If the symptoms do not resolve in the emergency ward, the patient is often admitted to psychiatry and treated with antipsychotic medications. If methamphetamine was being used, it becomes close to impossible to tell whether this was a primary psychotic disorder such as schizophrenia or induced solely by methamphetamine use. If the symptoms resolve in hospital, they are generally discharged with a prescription for antipsychotic medication.

Cannabis & Psychosis

The regular use of cannabis has also been associated with psychotic symptoms and a diagnosis of schizophrenia. One Swedish study indicated the prevalence of schizophrenia was six times higher than the normal population for patients that had used cannabis more than 50 times in their lifetime².

There is some debate in the literature as to whether cannabis causes schizophrenia, or causes the symptoms to appear earlier in one's life. In either case, it is **strongly recommended that patients with a psychotic disorder do not use cannabis, as it has a negative effect on prognosis**. If patients are insistent on using cannabis, they should be strongly encouraged to use a strain with a low percentage of THC. A benefit of legal suppliers and commercial storefronts for cannabis is that consumers can choose the strain that they use, including the THC/CBD content. Again, see the [polypharmacy and polysubstance use](#) chapter regarding cannabis use and OAT.

Investigations

If your patient presents with psychotic symptoms, some websites and advocacy agencies recommend a complete medical workup including a CT scan or MRI of the brain, and an EEG.

Generally, these investigations are not fruitful, however there are some red flags in the history that would suggest such tests be done on an urgent basis. Indicators of a potential medical cause of psychosis include:

- A history of seizures,
- Focal neurological signs, and
- Disorientation or delirium.

Treatment for Psychosis

Treatment recommendations for psychosis include stopping the use of those substances that may be contributing to the symptoms. If the physician believes that the psychosis is a primary disorder, first-line treatment is an antipsychotic medication.

There is some debate about the advantages of one antipsychotic over another. When choosing an antipsychotic, consider the potential for side effects. Many antipsychotics have marked metabolic side effects, including weight gain and diabetes, and caution should be used in prescribing these. Another consideration is whether the antipsychotic medication is available in a long-acting injectable form. There is substantial evidence that patients treated with a long-acting formulation of an antipsychotic are less likely to be hospitalized, will have more improvement in symptoms, and achieve greater functional improvement. **These decisions may be best made in consultation with a psychiatrist.** Collaboration and communication remain essential to build safety into the medication management plan – again the dispensing of any psychoactive medications should mirror the OAT dispensing schedule in most circumstances.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

There has been an explosion in the diagnosis of ADHD and prescription of psychostimulant medication in both children and adults over the past 20 years. Some experts have suggested that the increase in diagnosis is due, in part, to sociological factors and technological innovations that cause constant interruptions in our day-to-day life.

ADHD has also been associated with an *increased* rate of substance use disorder, while proper treatment of ADHD, at least in children, has been associated with a *decreased* rate of substance use disorder.

There are many self-assessment forms available online that people can complete, and frankly, many people that complete these forms will test positive for ADHD and then assume that they have a diagnosis and need treatment, particularly with prescribed psychostimulants. **It is advisable that patients who report having ADHD symptoms, and who are requesting treatment, have an assessment by a psychiatrist or psychologist.** If the diagnosis is confirmed by a specialist who is well versed in ADHD assessment, there are some considerations before treatment is initiated.

Managing ADHD

There are many non-pharmacological measures that can be utilized before prescription medication is considered. There are several websites or self-help books available to learn self-regulation and coping skills. One resource that many patients have found helpful is “Driven to Distraction: Recognizing and Coping with Attention Deficit Disorder from Childhood through Adulthood” by Hallowell and Ratey³. There is also evidence that regular aerobic exercise can be a useful treatment.

Prescribing Considerations for ADHD

If pharmacological treatment is considered, there are some non-stimulant medications that have a very low risk of addiction. These include atomoxetine and bupropion (Wellbutrin®).

If psychostimulant medication is considered, it is *not recommended* to prescribe an immediate release formulation such as methylphenidate (Ritalin®) or dextroamphetamine (Dexedrine®). These have a higher rate of addiction, and can be crushed and used by insufflation or intravenously. There are newer longer-acting and tamper-resistant formulations available that have a relatively low risk of developing a substance use disorder. Even though the risk for misuse/diversion of these newer formulations is lower than immediate release formulations, patients should be dispensed limited amounts at a time, ideally, mirroring the OAT dispensing schedule in most circumstances.

Compliance with psychostimulant medications must be monitored through comprehensive UDS, DPIN checks and, if indicated, pill counts. A comprehensive UDS is required to detect these specific medications. Of note, a comprehensive UDS can be used to not only check for the use of illicit substances such as cocaine or non-prescribed opioids, but also to check if prescribed medication is being taken.

Again, please see the [polypharmacy and polysubstance use management chapter](#) for further guidance around UDS use, particularly “[KNOW YOUR TOOL: INTERPRETING COMPREHENSIVE UDS RESULTS](#)” to understand the limitations of this test. If prescribers need a specific medication identified that is not included on the [list of 80 substances tested](#) for in Manitoba (often to monitor compliance with a prescribed medication), they may request Diagnostic Services test for that medication, by adding a written request on the comprehensive UDS requisition. The clinical rationale for needing this information should also be documented on the requisition.

PERSONALITY DISORDERS

Personality disorders are long-term patterns of behavior and inner experiences that differ significantly from what is expected. The pattern of experience and behavior begins by late adolescence or early adulthood and causes distress or problems in functioning.

Improvement is Gradual

Patients with personality disorders can be very disruptive to the clinic and lead to staff burn-out. However, psychiatric treatment is not fruitless for these individuals and gradual improvement is often seen, over the course of months and years. Some patients presenting with personality disorder symptoms markedly improve as OAT is optimized, but it is impossible to predict which patients will improve.

The [STAT](#) and the [CODI](#) programs outlined above may be helpful resources for some individuals with personality disorder, once substance use is stabilized. These programs will accept referrals for patients that are stable on OAT. Keeping local crisis numbers and resources handy for patients is also essential for times of increased distress or instability.

See **Appendix L** for more information on personality disorders. There is much information online and books published to better understand the experience of individuals with personality disorders. The Centre for Addiction and Mental Health patient booklet, [Borderline Personality Disorder: An information guide for families](#)⁴ is a helpful resources for patients and clinicians.

Compassion combined with clear boundaries is often needed to support patients with OUD, particularly if the patient is struggling with personality disorder symptoms. It is important that all patients and prescribers understand their respective expectations and responsibilities when it comes to participating in OAT care. Mutual respect is essential and worth the investment of time and effort. **Reviewing and signing a Treatment Agreement that includes behavioral expectations is a useful tool to assist in clarifying roles and expectations.** A clear discussion of boundaries around behavior may be needed so that patients understand that threats or aggression to staff, pharmacists, or co-patients, will not be tolerated and may result in discontinuation of care. Treatment agreements can be revisited in early treatment when patients are stabilizing on OAT, ideally when they are clear-headed and able to retain more information, to ensure mutual understanding of expectations.

SLEEP DISTURBANCES

It is worth noting that sleep problems are a common experience for patients with substance use disorders and/or psychiatric disorders. Sleep problems also occur in healthy individuals as part of everyday day life. Likewise, this is a very frequent complaint of patients on OAT, particularly in early recovery.

The chemical roller-coaster of intoxication and withdrawal that accompanies regular substance use can greatly disturb the natural sleep-wake cycle and dismantle circadian rhythms. This warrants discussion, as a good night's sleep is essential to early recovery – to learn new skills, to emotionally regulate, and to manage triggers and cravings. Sleep is an important part of self-care to sustain sobriety.

Some patients will benefit from simple encouragement, teaching around sleep hygiene, and reassurance that sleep will improve as their recovery progresses. Often sleep improves naturally once patients stabilize on OAT and establish a healthier diurnal sleep-awake cycle, but this may also take several weeks.

Tips for a Good Night's Sleep

While quite common, discussing sleep problems in early recovery is essential. When sleep is jeopardized, particularly if patients are accustomed to chemical sedation for sleep, they may seek non-prescribed (illicit) or over-the-counter medications to induce sleep. This can increase their risk of accidental overdose.

Most patients will benefit from education on [Sleep Hygiene](#) practices. There is also good evidence for the effectiveness of CBT for insomnia as first-line treatment for sleep disturbances. Referral to the WRHA Psychology Services [Sleep Disorders Online Treatment Program](#) may be useful. Some patients can also navigate online and practice CBT for insomnia skills themselves, and there are several useful sites and apps available to promote sleep (see **Appendix L**).

Nighttime Sedation

If medications are considered for nighttime sedation, ideally these should be short-term and with limited dispensing for safety. Benzodiazepines and Z-drugs are *not recommended*. Discuss collaboratively with the patient that sleep aids may be used short-term to help reset the sleep cycle in early recovery. Highlight that they should be used alongside behavioral strategies that promote sleep as part of overall wellness.

Quetiapine and trazodone are commonly prescribed in lower doses to manage insomnia and/or acute anxiety in early treatment. This strategy is often used while waiting for a SSRI, SNRI and/or CBT interventions to take effect. It is important to note that given their sedating and psychoactive properties, quetiapine and trazodone can also increase the overall risk of overdose when combined with other sedatives. Again, dispensing of these should be limited to the OAT dispensing schedule in most cases.

IN SUMMARY

Many patients on OAT report psychiatric symptoms. A mental health history must be taken prior to the initiation of OAT for all patients, and a thorough psychiatric assessment completed if they report psychiatric symptoms – if not prior to starting OAT, then as they stabilize. In some patients, psychiatric symptoms may not present until later in treatment, necessitating a complete psychiatric review and collection of collateral information relevant to the concerns at that time.

If a psychiatrist, primary care provider, and/or mental health professional are treating the patient, consent to communicate with them should be obtained for safety and planning, as outlined in the treatment agreement signed with the patient during OAT induction.

Communication and collaboration, between all those involved in the patient's care, are key to ensure safe medication management. Clarify who is prescribing what medication and ensure the dispensing is limited to the OAT dispensing schedule for any sedating and/or psychoactive medications, in most cases.

Many patients with psychiatric symptoms improve with OAT. If symptoms persist, psychiatric medication can be prescribed, but caution and close monitoring is advised.

OAT is most effective when combined with psychosocial interventions. Ideally these interventions are available and reasonably accessible for patients, but this is not always the case. The OAT team can advocate for access to appropriate interventions and coach patients to explore self-help and peer-based supports. A list of community resources can be found at the Canadian Mental Health Association site (mbwpg.cmha.ca) and in their local [Resource Guide](#).

References

1. Substance Abuse and Mental Health Service Administration. *Treatment Improvement Protocol (TIP) 42: Substance Use Disorder Treatment for People With Co-Occurring Disorders*. SAMSAH. 2020. Available at: https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP20-02-01-004_Final_508.pdf
2. Andréasson S, Engström A, Allebeck P, Rydberg U. Cannabis and Schizophrenia: A longitudinal study of Swedish conscripts. *The Lancet*. 1987 Dec 26; 330(8574):1483-1486. doi: 10.1016/s0140-6736(87)92620-1.
3. Hallowell EM, Ratey JJ. *Driven to Distraction: Recognizing and Coping with Attention Deficit Disorder from Childhood through Adulthood*. Anchor Books, division of Random House; 1994.
4. Centre for Addiction and Mental Health. *Borderline Personality Disorder: An information guide for families*. CAMH; 2009. Available at: <https://www.camh.ca/-/media/files/guides-and-publications/borderline-guide-en.pdf>

Appendix L

ADDITIONAL MENTAL HEALTH RESOURCES

Anxiety & Depression

ADAM Homepage	https://www.adam.mb.ca/
MDAM Homepage	http://www.mooddordersmanitoba.ca/
CBT with Mindfulness	https://cbtm.ca/
CBT Institute Manitoba Resources	https://cbtmanitoba.com/resources/

Canadian Mental Health Association

CMHA Manitoba & Winnipeg	https://mbwpg.cmha.ca/
CMHA Resources Guide	https://mbwpg.cmha.ca/wp-content/uploads/2017/11/MHRG_ALL_2020.pdf

Substance Abuse and Mental Health Service Administration

SAMHSA Homepage	https://www.samhsa.gov/
TIP 42: Substance Use Disorder Treatment for People with Co-Occurring Disorders	https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP20-02-01-004_Final_508.pdf

Canadian Centre for Addiction and Mental Health

Professional Resources	https://www.camh.ca/en/professionals
Patient Resources	https://www.camh.ca/en/your-care
Guides & Handouts	https://www.camh.ca/en/health-info/guides-and-publications

Psychosis & Schizophrenia

Peer Connections Manitoba	https://peerconnectionsmb.ca/
---------------------------	---

WRHA Primary Care/Shared Care Mental Health Practice Guidelines

Guide to Complete Form 4 Application by Physician for Involuntary Psychiatric Assessment

<https://professionals.wrha.mb.ca/old/professionals/primary-care-providers/files/APPENDIXDGuide.pdf>

Trauma & Personality Disorder

Heartwood Healing Centre <https://heartwoodcentre.ca/>

PTSD Handout <https://www.camh.ca/-/media/files/guides-and-publications/posttraumatic-stress.pdf>

Co-occurring Disorders Outreach <https://sharedhealthmb.ca/services/mental-health/codi/>

Short Term Assessment & Treatment (STAT) Program

<https://umanitoba.ca/medicine/departments/psychiatry> (Community and Partners dropdown menu)

Borderline Personality Disorder: An information guide for families

<https://www.camh.ca/-/media/files/guides-and-publications/borderline-guide-en.pdf>

Zero Shades of Grey: Living with BPD

<https://www.pennmedicine.org/news/news-blog/2018/may/zero-shades-of-grey-living-with-bpd>

Sleep Problems & Insomnia

Sink Into Sleep <https://sinkintosleep.com/>

WRHA Sleep Disorders <https://wrha.mb.ca/psychology/services/sleep-disorders/>

Sleep Hygiene Handouts

<https://www.anxietycanada.com/sites/default/files/SleepHygiene.pdf>

https://www.cci.health.wa.gov.au/~/_media/CCI/Mental-Health-Professionals/Sleep/Sleep---Information-Sheets/Sleep-Information-Sheet---04---Sleep-Hygiene.pdf

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.13 Recommendations for Adolescents & Opioid Agonist Therapy

GENERAL CONSIDERATIONS

The treatment of choice for adults with opioid use disorder (OUD) is opioid agonist therapy (OAT), ideally in combination with psychosocial interventions such as counseling, contingency management, and/or peer support.

Similarly, while the evidence for treating youth is less robust compared to adults³, the general consensus among experienced providers is that OAT is *also effective* in adolescents*. **Those who meet criteria for OUD should be offered timely OAT induction.** Careful assessment is needed to assure the adolescent meets OUD criteria before prescribing⁴ and, in some cases, consultation with experienced colleagues may be warranted. Despite the limited evidence for treating adolescents with OAT, the vast evidence demonstrating the risks of untreated OUD would far outweigh the risks of treatment³.

Ideally, adolescents should be treated in OAT programs with case management capacity and wrap-around care supports, such as low-barrier counselling, harm-reduction interventions, and connection to primary and/or specialist care as needed. However, given the risks of untreated OUD, timely induction should be pursued even if this level of care is not readily available. Connection and collaboration with additional supports can be established once the patient is medically stable and able to participate in further psychosocial treatment planning.

*For the purpose of this manual, **Adolescence is defined as “the phase of life between childhood and adulthood, from ages 10 to 19. It is a unique stage of human development and an important time for laying the foundations of good health”¹.** However, for healthcare purposes in Manitoba, and medicine in general, patients are considered and treated as adults by age 18. The authors also acknowledge that Adolescent & Youth Medicine is a subspecialty that focuses on the healthcare and well-being of patients who are between the *ages of 10 and 25 years*, and that this transitional period is a critical time for addiction medicine intervention^{1,2}.

SPECIFIC CONSIDERATIONS

Patients under the age of 18 who seek assessment and treatment for OUD represent a very small percentage of all patients on OAT. Inexperienced providers and providers who have never treated adolescents are strongly encouraged to reach out to experienced OAT colleagues for guidance as needed.

Occasionally, providers may also wish to obtain a second opinion from a colleague as to the appropriateness of OAT in an adolescent patient. However, seeking a second opinion should not delay induction and thereby potentially expose the patient to further preventable harms associated with OUD.

The approach to induction and dose titration for youth is similar to the approach for adults. Induction and titration recommendations for [Buprenorphine/naloxone](#) and [Methadone](#) are reviewed in those respective chapters. It is important to titrate the dose to therapeutic effect to establish a stable dose as soon as practically possible. This promotes the adolescent's ongoing engagement in care to optimize treatment retention and progress toward therapeutic goals.

Buprenorphine First-line Treatment

Due to its comparable effectiveness and enhanced safety and side-effect profile, buprenorphine/naloxone is the preferred first-line treatment for OUD. For the majority of patients with OUD, including adolescents, it should be used preferentially.

Consideration for methadone as an alternative agent may be appropriate if there is a contraindication to buprenorphine/naloxone, if there are intolerable side-effects on buprenorphine/naloxone, or if preferred by the patient. Treatment should not be withheld if the adolescent patient specifically requests methadone. If the patient has received adequate education about the benefits of buprenorphine, methadone is a reasonable second-line treatment option, but again, further consultation with an experienced colleague may be warranted.

Capacity to Consent

Like in other areas of medical care, it is important for the OAT prescriber to assess and document whether or not the **adolescent patient is capable of giving informed consent to treatment**.

It is also important to consider that adolescents may be dependent on their parent(s) or guardian(s) for medication coverage/financial support. Parental involvement may need to be explored if the patient requires access to medication coverage/funds to pay for OAT medications. An exception is youth with medication coverage through Non-Insured Health Benefits (NIHB), as parental involvement is not required to facilitate this coverage.

LOCKED BOXES & NIHB

For patients whose medications are covered by Non-Insured Health Benefits (NIHB), the cost of a lockbox may be covered once per patient, per lifetime (up to \$35), for the safe storage of take-home doses of OAT. If indicated, this coverage extends to safe storage of other high-risk medications, including other opioids, benzodiazepines, stimulants, or sedating/psychoactive drugs, where a lockbox can improve safety for NIHB clients and communities.

Access to Care & Provincial Resources

Youth under 18 years of age *cannot* be assessed or treated for substance use disorders at the Rapid Access to Addiction Medicine (RAAM) clinic located at the Crisis Response Centre (CRC) in Winnipeg, due to a facility restriction (CRC does not see any patients under age 18).

However, there are no restrictions to youth being assessed and treated with OAT in the other [RAAM clinics](#) across Manitoba, including at the River Point Centre in Winnipeg.

It may be beneficial to connect adolescents to **Youth Addiction Centralized Intake (YACI)** after OAT induction, as they may benefit from the additional supports/services available through YACI, or the **Youth Addictions Stabilization Unit (YASU)**. It is important to note that there are unfortunately no OAT providers associated with YACI or YASU.

In general, publicly funded youth addiction and mental health services in Manitoba do not include OAT access. Community prescribers who are willing and comfortable treating youth on OAT are a valuable resource for adolescents with OUD. Effective collaboration between OAT prescribers and existing youth addiction and mental health services has the potential to optimize outcomes and fill gaps in care for vulnerable patients.

“Detox” NOT Recommended

It is not uncommon for young patients and their parents/guardians to request “detox” towards cessation of opioid use and abstinence-based treatment. In adults with OUD, withdrawal management or “detox” without transition to OAT and long-term treatment is specifically *not recommended* as it has been associated with increased morbidity, such as HIV transmission, and mortality secondary to overdose.

Likewise, “detox” towards abstinence is not recommended for adolescents with OUD due to the same substantial risk of serious harms. These potential harms include death by overdose given the lost tolerance created by an abstinence-based detoxification admission. However, home “detox” may be an alternative option for some individuals. Home “detox” is defined as a self-guided process of tapering a low to moderate dose of opioids, or abstinence from opioids over a predetermined period, outside of an established clinical or institutional setting. **It is important to consider that this approach has limited evidence and carries significant risk⁵.**

If adolescents decline OAT despite the risks, a slow outpatient taper of opioids is a safer approach than admission to a hospital or residential detox setting. Please refer to [Alternative Treatment Approaches for OUD](#) for further considerations around home-based withdrawal management. Again, consultation with an experienced colleague may be warranted.

Parental Involvement

Overall, it can be beneficial for parents or guardians to receive education about OAT and to be involved in exploring solutions to potential barriers to treatment. Parental support can facilitate medication funding, transport, housing and/or other practical support that aligns with the treatment plan.

However, the adolescent's relationship with their parent(s) or guardian(s) may be non-existent, strained, or a source of instability and/or trauma. These issues can be complex and must be explored in a sensitive and culturally safe manner during the initial assessment.

Insisting on parental involvement or consent to treatment may be harmful in some cases and can cause the adolescent to disengage and become lost to care. OAT prescribers must use their professional judgement, on a case-by-case basis, to determine if seeking parental consent/involvement in treatment is prudent. Most importantly, if parental involvement is not possible or desirable for the adolescent, **treatment can still proceed if capacity to consent has been established and funding for medication is in place.**

Duty to Report

Suffering from OUD is not reportable. Nor is engaging in OAT care. However, when caring for patients under the age of 18, OAT providers can encounter issues/circumstances that may require reporting to the relevant authorities. Reporting requirements may differ by profession, and it is important for OAT team members to discuss these issues in a frank and collaborative manner.

The CPSM [Standard of Practice for the Duty to Report Self, Colleagues, or Patients](#) outlines the expectations, ethics, and legalities of reporting. This Standard came into effect in 2021 and all physicians holding a CPSM Certificate of Practice must comply. Physicians must also document all relevant information in the medical record, including a decision to report. The Standard highlights that honesty and compassion are fundamental to the patient-physician relationship. It encourages communication with patients around reporting duties and potential breaches as appropriate, to foster a trusting relationship between patient and provider⁶. Please see the Standard for more information about mandatory reporting with patients.

There may be times when a prescriber, after carefully considering all available information together with the treatment team, believes that reporting a particular issue will cause serious harm to the therapeutic alliance with a young patient. This harm may include damage to the therapeutic relationship, the patient disengaging from care, and potentially returning to

unregulated opioid use with the associated harms of relapse. In such situations, the physician must carefully weigh their duty to report against the real and/or perceived harms of making a report. Prescribers must document their rationale for the decision made, including the patient's response to this information in the medical record.

STANDARD OF PRACTICE: DUTY TO REPORT⁶

This Standard of Practice, specifically **Part 3 Duty to Report the Medical Condition or Knowledge of Patient Information**, emphasizes:

- 3.1. Registrants must comply with any duty to report the medical condition or knowledge of patient information as prescribed by Provincial and Federal Legislation (see Contextual Information and Resources for list of legislation).
- 3.2. Honesty and compassion are virtues fundamental to the patient-physician relationship. To ensure a trusting physician-patient relationship, registrants should communicate with their patients about their reporting duties and breach of confidentiality except in rare instances when notifying the patient is not appropriate, such as where the registrant is concerned about the safety of the patient or another person.

The Manitoba Government provides information on [Reporting for Child Protection and Child Abuse](#), along with resources for services providers. Additionally, the *Contextual Information and Resources* in the above-mentioned Standard of Practice lists legislation that involves mandatory reporting, and outlines further considerations in reporting and patient/public safety.

References

1. World Health Organization. *Adolescent Health*. WHO 2023. Available at: https://www.who.int/health-topics/adolescent-health#tab=tab_1
2. Moreno M, MD, Thompson L. What Is Adolescent and Young Adult Medicine? *JAMA Pediatr*. 2020;174(5):512. doi:10.1001/jamapediatrics.2020.0311
3. Camenga D, Colon-Rivera H, Muvvala S. Medications for maintenance treatment of opioid use disorder in adolescents: A narrative review and assessment of clinical benefits and potential risks. *Journal of Studies on Alcohol and Drugs*. 2019;80:393-402. doi:10.15288/jsad.2019.80.393
4. Vest N, Humphreys K. Do We Know Enough to Prescribe Opioid-Agonist Therapies to Adolescents With Problematic Opioid Use? A Commentary on Camenga et al. (2019). *J Stud Alcohol Drugs*. 2019; 80(4): 406–407. doi: 10.15288/jsad.2019.80.406
5. Dunlap B, Cifu AS. Clinical management of opioid use disorder. *JAMA*. 2016; 316(3):338-339. doi: 10.1001/jama.2016.9795.
6. College of Physicians & Surgeons of Manitoba. *Standard of Practice: Duty to Report Self, Colleagues, or Patients, Contextual Information and Resources*. CPSM; 2021.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.14 Recommendations for Older Patients & Patients with Disabilities on Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Many providers of opioid agonist therapy (OAT) are treating an increasing number of older patients, some of whom may have medical co-morbidities or may develop other disabilities. The number of patients on OAT who are age 65 or older is rising, and this is related to:

- OAT being an effective long-term treatment option that has been available for over 40 years, and many patients have been aging while in treatment.
- A growing number of patients accessing OAT at an older age for treatment of an opioid use disorder (OUD) that developed from taking prescribed opioids for chronic pain, often for a prolonged period prior to seeking addiction treatment.

OAT providers must be mindful of extra safety considerations when treating the aging patient. Likewise, adult patients of any age with physical, mental, cognitive, learning, or sensory disabilities will access treatment for OUD, and may require adaptations to the treatment approach and plan for safe and effective OAT care.

This chapter will highlight key considerations for safety and support while engaging older patients and patients with disabilities in care. The care of other specialty populations is addressed elsewhere in this manual. Specifically, recommendations for patients with [Acute, Chronic, & Perioperative Pain](#), [HIV & Hepatitis C](#), [Pregnancy](#), and [Psychiatric Disorders](#) can be found in those respective chapters.

SPECIFIC RECOMMENDATIONS

There are several important issues to consider when caring for older patients and patients with disabilities on OAT, as outlined below.

Co-Occurring Conditions & Medication Interactions

Older patients are more likely to have co-occurring physical and/or mental health issues (e.g., cardiovascular issues, COPD, osteoarthritis, renal disease, dementia, depression).

Pharmacotherapy for these conditions may interact with OAT medications and altered age-related metabolism must be considered. Careful assessment of comorbidities and thoughtful medication planning is key to optimizing quality of life and avoiding polypharmacy, and the associated harms.

Similarly, pharmacotherapy for management of some disabilities may also interact with OAT medications. Careful medication planning is also key for these patients to optimize quality of life and manage polypharmacy.

The chapters on [Managing Polypharmacy](#) and [Co-Occurring Psychiatric Disorders](#) in patients with OUD provide detailed recommendations for overall medication management and considerations specific to mental health issues.

STRONG RECOMMENDATION: REMINDER TO DISPENSE WITH OAT

Typically, all psychoactive/sedating medications should be dispensed with OAT, i.e., on the same schedule as OAT. Communicating with the patient's pharmacy about the plan for managing these medications is essential. Controlled dispensing instructions, such as "dispense as per OAT schedule", must be written on all relevant prescriptions. Please see the [Managing Polypharmacy in OAT](#) chapter for further medication safety recommendations.

Caution with Induction & Titration

Generally, older age is associated with increased blood concentrations of drugs and altered metabolism, reduced effectiveness, and increased risk of adverse reactions for many medications, including OAT. Therefore, lower induction doses, slower titration, and more frequent reassessment are important for safety when titrating OAT in older patients.

Similar caution should also be exercised for any patients with co-occurring diagnoses or disorders that would impact metabolic, cardiovascular, or central nervous system function, to prevent overdose during induction and titration of OAT.

Small Dose Reductions with Age

In patients who have been on OAT for many years or even decades, it is important to consider a small OAT dose reduction periodically as the patient ages.

This consideration also applies to other medications that contribute to cognitive impairment and/or sedation. Benzodiazepines/Z-drugs are particularly problematic in older adults, and renewed efforts should be made to taper and/or discontinue these medications as patients age. See [Managing Polypharmacy in OAT](#), specifically **MANAGING PRESCRIBED AND ILLICIT BENZODIAZEPINES & Z-DRUG USE** for further guidance.

Accommodating Patient Needs

Older patients and patients with disabilities may have mobility, cognitive, or sensory limitations that can impact their ability to attend traditional/in-person clinic appointments. Similarly, attending the pharmacy regularly for witnessed dosing may be problematic.

In establishing the medication management plan, a thoroughly documented risk-benefit analysis is important to support a witnessed versus take-home (carry) dosing schedule that takes into consideration the patient's physical, geographical, and transport challenges, while balancing safety and treatment retention. The patient's overall clinical stability, living situation, and public safety issues must be considered and documented in these situations, particularly when clinical discretion is used to grant take-home doses outside of the typical recommendations for awarding carries. Please see the respective chapters on take-home dosing for [Buprenorphine/naloxone](#) and [Methadone](#) for further guidance.

Effective communication is vital to assessment, treatment, and therapeutic alliance with any patient. It is important to ask patients about disabilities upon intake and after a new diagnosis, especially since some disabilities are not obvious or visible to treatment providers. Some cognitive, learning, and sensory disabilities will require the OAT treatment team, including pharmacy staff, to adapt their practice to decrease barriers to communication. Given the opportunity to provide honest feedback about their care, patients can often identify helpful adjustments to the treatment approach. A blended model of in-person and virtual care, the use of an appropriate interpreter, and printed materials in large font are just a few examples of how providers can address access barriers. The treatment team must also remain flexible in navigating the role of substitute decision makers, caregivers, supports, and/or aides that are critical to the patient's health and wellness.

Take-Home Dosing & Cognitive Impairment

Cognitive impairment, more common with advancing age, can impact the risk/benefit analysis of having carry doses at home. This concern also extends to other sedating and/or psychoactive medications dispensed along with OAT.

Occasionally, home care support (where available) or other designated personnel/family members may need to be involved in the safe storage of medication and the supervision of self-administration in the home.

Continuity of Care for Hospital & Personal Care Homes

With multiple comorbidities there exists an increased likelihood of hospitalizations. Coordination of care between hospital staff and the community prescriber/clinic staff and pharmacy is essential. The [In-Hospital Care](#) chapter provides detailed recommendations for continuity of care.

Elderly patients on OAT may also be transferred to Personal Care Homes (PCH). The PCH attending physician can continue an existing OAT prescription at the same (stable) dose or a reduced dose, if needed, without an OAT prescribing approval. However, consultation with an approved OAT prescriber (ideally the primary OAT prescriber) is required if a dose increase is considered necessary, or to initiate or restart OAT.

If a patient has an existing relationship with an OAT prescriber when they enter PCH, it is recommended that a care plan be established between the OAT provider and the PCH prescriber and/or medical staff. This will ensure that the OAT dose is regularly reviewed, at least quarterly, or at any point of significant change in the patient's health status or medications, or at the request of the patient or their family/caregivers.

IN SUMMARY

OAT providers are encouraged to be watchful for changes in cognitive, mental, sensory, and physical abilities in their patients, especially as they age. Adapting practice to support patients with disabilities to effectively engage in OAT care is important for safety and equity.

Providers with experience in caring for older patients or patients with disabilities on OAT can be a valuable resource when questions or concerns arise. Importantly, the patients themselves and/or caregivers are the experts in navigating their needs, barriers, and problem solving what works best for them; ask questions and collaborate with patients for effective care and treatment retention.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.15 Recommendations for Continuity of Care in Opioid Agonist Therapy: Residential Treatment, Travelling, Incarceration & RAAM Clinics

GENERAL CONSIDERATIONS

This chapter summarizes recommendations to promote continuity of care for patients on opioid agonist therapy (OAT). As a long-term treatment, it is not uncommon for patients on OAT to transfer between care providers and pharmacies, as housing and life circumstances change, nor is it uncommon for patients to move between community and institutional settings.

Specifically, this section addresses continuity of care for patients participating in residential treatment, as well patients on OAT who are travelling in Manitoba, out-of-province, and internationally. Key considerations are also addressed for the care of incarcerated patients. Lastly, the role of Rapid Access to Addiction Medicine (RAAM) clinics in Manitoba is reviewed, along with the importance of transfer of care of patients from this interim service to long-term OAT providers.

Further recommendations for continuity of care are also addressed in the [In-Hospital Care](#) chapter, particularly considerations for discharge planning and medication management.

Communication and collaboration remain paramount to ensure patient safety on OAT, along the entire continuum of care. A “warm handoff” where all parties are involved (including the patient) can ensure a common understanding of the care plan, identify potential issues, and set timelines for follow up as needed.

SPECIFIC CONSIDERATIONS: RESIDENTIAL TREATMENT

Residential treatment programs offer a valuable period of treatment intensification for patients on OAT. This can be beneficial for patients who are struggling with ongoing substance use and/or those who wish to further develop coping and relapse-prevention skills. The recommendations discussed below should be considered for patients who express interest in attending residential treatment while on OAT.

Stable OAT Dose Continued

It is important for a patient's stable OAT dose to be continued while in residential treatment.

This promotes the patient's ongoing medical stability and enables them to optimally participate in the psychosocial components of residential treatment.

It is thus important to ensure that a treatment agency/center is supportive of the patient's choice to participate in OAT, prior to engaging that agency/center in further planning. It is also important to consider the program's geographic location, proximity of the closest pharmacy that offers OAT services, and the need for witnessed dosing when making these arrangements.

Pharmacy Considerations

Like any other patient, patients on OAT have the right to work with a pharmacy of their choice. However, certain residential treatment centers have established relationships and processes with specific pharmacies that will provide all medications for the patients in their program.

These arrangements may be in place due to proximity of the particular pharmacy for the purpose of witnessed dosing of OAT, or simply to standardize processes upon patient intake for medication dispensing, delivery, and administration.

It is often more practical for patients entering residential treatment to receive their medication from the program's designated pharmacy for the duration of their stay. **Communication between the patient's usual community pharmacy, the pharmacy serving the treatment center, OAT clinic staff, and residential program staff is therefore essential.** This communication can facilitate a smooth transition into treatment and back to the usual community pharmacy once the program is completed.

Maintain Witnessed Dosing & Medication Standards

When a residential treatment center relies on a particular pharmacy to deliver medications for patients in their program, all the usual standards for witnessed dosing and safe medication transport, delivery, storage, and record keeping must be maintained.

Participation in residential treatment *does not exempt patients on OAT from the typical witnessed dosing schedule* as prescribed by their OAT provider. They will still need to attend a local pharmacy for witnessed dosing while in treatment.

Patients who would normally receive take-home (carry) doses of OAT may be eligible to have their carries securely stored in the treatment center and then handed to them for self-administration, as part of the routine medication administration at the facility. If carry doses will be stored in the facility, the provider and pharmacy must be confident that the facility is able and willing to provide secure storage of OAT doses. This may include confirming that there are policies in place to ensure a secure lockup system exists, that is only accessible to authorized staff. Many treatment centers simply prefer for patients on OAT to attend a local pharmacy for witnessed dosing seven days a week (regardless of the patient's carry status).

Residential treatment centers may on rare occasions have staff on site who are able to witness OAT doses. Eligible staff include pharmacists, authorized prescribers, RNs, RN(NP)s, LPNs, and RPNs with the necessary knowledge and skill to appropriately witness OAT doses. If such staff are available, witnessed dosing may be handled on site by the qualified staff. As above, the provider and pharmacist must be confident that the facility will be able and willing to store OAT doses securely. Additionally, prescribers may need to provide authorization and/or a new prescription to the applicable pharmacy to allow doses to be supplied and witnessed at the facility. All residential treatment centers are encouraged to have a formal medication management policy/procedure manual in place that addresses the needs of all patients, including those on OAT.

Communication for Prescription Coordination

Treatment centers must notify the patient's community pharmacy and community-based prescriber/treatment team of a planned admission into residential treatment. This should ideally occur prior to the planned admission date or, if that is not possible, on the first day of admission. This communication can help coordinate the OAT prescription for the duration of the treatment program.

The treatment center must also notify the community pharmacy and prescriber/treatment team when the patient leaves the program, to coordinate a new OAT prescription for the patient's preferred pharmacy, ideally prior to completion and *before* the patient departs. If the patient decides to leave or is discharged from the treatment centre prematurely, the community pharmacy and OAT prescriber/treatment team must be notified *right away*.

Dose & Medication Changes

Clear and timely communication between the treatment center staff and the community pharmacy/treatment team is especially important when changes occur to the OAT dose or other medications while the patient is in treatment. **If an OAT dose change occurs during admission, the treatment center staff must notify the patient's community pharmacy and prescriber of the dose change *as soon as possible* after it occurs.** This allows for the pharmacy to proactively acquire a new OAT prescription for discharge in case the patient presents to the pharmacy unexpectedly (i.e., they leave the program prematurely).

SPECIFIC CONSIDERATIONS: CARING FOR TRAVELLING PATIENTS

At times patients on OAT may travel within Manitoba, elsewhere in Canada, or even internationally. Travel may be required for essential reasons such as medical appointments, work opportunities, and important life events such as funerals, weddings, etc. Conversely, travel may also be for non-essential reasons, such as vacation. Both stable and unstable patients will request accommodation of their travel plans. **Supporting these plans, as long as it is safe and practically possible, is an important component of long-term treatment retention.**

OAT treatment teams, in collaboration with the patient's community pharmacy, are encouraged to accommodate travel requests whenever possible. Occasionally creative planning, such as arranging guest dosing, may be required to balance the needs of the patient with considerations for patient and community safety.

All patients on OAT should be counselled about their clinic's travel request policy. Depending on the hours and availability of case management resources, it may be reasonable to require patients on OAT to provide a period of advance notice regarding planned travel. However, occasionally patients will travel without advance notice and the OAT provider may be contacted when the patient is already enroute. This section will provide recommendations on how to best manage the most common scenarios involving travel and OAT.

CLINICALLY STABLE PATIENTS & EXTRA CARRIES

Patients who are clinically stable and who have participated in OAT treatment for extended periods may be eligible for take-home (carry) doses to accommodate their travel plans. Providers may consider this option when patients already have several regular take-home doses as part of their routine treatment plan. Extra carry doses, in addition to their usual carry schedule, may be authorized to facilitate travel at the prescriber's discretion.

Authorizing Travel Carries

Clinical judgement must be used regarding how many additional carry doses can be authorized based on:

- The patient's overall stability,
- Record of UDT results in recent weeks/months,
- History of responsible medication use/storage,
- The travel plan,
- Where the patient will be staying and who else is residing in that location, and
- The patient's ability to store carry doses safely while travelling.

This risk-benefit assessment must be documented when authorizing travel carries in addition to the patient's normal dosing schedule.

CLINICALLY UNSTABLE PATIENTS

When a patient is generally unstable and does not have routine take-home doses, it may also occasionally be appropriate to authorize a limited number of travel carries. For example, this could be considered with a patient who must travel to a medical appointment and who (due to the transportation schedule) will not be able to reasonably attend the pharmacy on the travel day. One travel carry, stored in a locked box, may be appropriate to support the patient's overall medical care.

However, should an extended stay away from home be required for any reason, unstable patients **should not** typically be provided with multiple carry doses. Instead, OAT providers are encouraged to explore *Guest Dosing* options.

Guest Dosing

Guest dosing involves providing a pharmacy, other than the patient's regular community pharmacy, with an OAT prescription so that the patient may attend the interim *host* pharmacy for witnessed *guest* dosing for a limited time to facilitate travel. The guest dosing pharmacy may also be asked to provide the patient with a carry dose for travel home, as needed.

There should be a discussion with the potential guest dosing pharmacy prior to faxing the prescription to ensure the pharmacy can provide OAT services and is able to accommodate a new patient and the specific medications they are taking. The prescriber/treatment team should also explore the following in advance of the patient's departure date to prevent treatment delays at the receiving pharmacy:

- If the pharmacy is outside of Manitoba, it may have special requirements, such as a copy of the prescriber's Certificate of Practice or other verification procedures.
- It is also important for the prescriber to ensure that the guest dosing pharmacist understands the witnessed dosing expectations, especially if OAT dosing guidelines in that location/jurisdiction vary from those in Manitoba. For instance, pharmacist expectations for the buprenorphine witnessing process can vary significantly from province to province (e.g., some may not need to confirm tablets have been self-administered and/or sufficiently dissolved). Verbal collaboration with the out-of-province pharmacist can be useful to ensure that everyone understands what is expected.
- Include all witnessed dose instructions on the prescription, along with carry dose authorizations.

- Prescription writing requirements may also vary from province to province. Some provinces require that prescriptions be written on a special form, or may have different requirements surrounding the legitimacy of faxed OAT prescriptions. Additionally, some provinces may use different units of measure to describe OAT doses (e.g., mL vs mg for methadone). **It is imperative to be very clear on the units of measure when providing prescriptions to out-of-province pharmacies to prevent significant dosing errors.**

When prescribers provide a new prescription for guest dosing temporarily at a different pharmacy, it must be remembered that *any new prescription cancels the old prescription* (see [Relationship with Pharmacy & Prescriptions for OAT](#)). Accordingly, the old prescription at the previous pharmacy will be canceled.

It is also important for prescribers to coordinate with the pharmacy that the patient will attend upon their return from travel (i.e., the regular community pharmacy). This could mean proactively sending another prescription to the regular pharmacy to be initiated upon return from travel, and/or requiring the patient to contact the prescriber/clinic staff after their return to arrange for a new prescription.

Communication between the prescriber/treatment team, the patient's regular pharmacy, and the guest dosing pharmacy is essential for medication safety, to prevent double dosing, and to ensure continuity of care.

The plan must also be documented in the patient's medical record, including the clinical rationale for the number of travel carries and the guest dosing arrangements.

Travel carries must always be stored in a locked box and patients must understand that they are responsible for the safety and security of their travel carries. Patients must also be aware that lost or stolen medication will not be replaced.

Patients Travelling Outside of Manitoba

For patients travelling outside of Manitoba, all the above-mentioned recommendations still apply. However, providers also need to be mindful of legal and liability issues surrounding the location of the medical care to be provided. This alters the approach to care when patients travel out of the province or internationally.

The legal interpretation of the Regulated Health Professions Act, Regulations, and common law concludes that the **location of medical care in Manitoba is the location of the patient**. The CPSM Standard of Practice for [Virtual Medicine](#) reinforces this¹. The onus is on the care provider to determine the patient's location if providing care virtually.

Likewise, the CRNM resources on [Telepractice](#) and [Guidance on Telepractice](#) also put limitations on cross-border care^{2,3}.

A Manitoba prescriber cannot provide care to a Manitoba patient in *another country* by virtual care/phone call to renew or adjust a prescription while the patient is travelling. This applies not only to OAT but to all prescriptions. CPSM registration does not extend to the provision of medical care in that country. Likewise, medical liability insurance may not cover a Manitoba physician or RN(Nurse Practitioner) who provides care to a patient while in another country.

Similarly, CPSM registration does not extend to the provision of medical care in *another province*. Manitoba-registered physicians wanting to provide care in another province will need to be aware of and comply with licensing and liability requirements in that Canadian jurisdiction. RN(NP)s are expected to contact the regulatory body in the province/territory where the patient resides to determine if they need to be registered in that jurisdiction before providing healthcare services in that location.

It is important for OAT providers to make their patients aware of these limitations before they travel. **The patient should be informed that once they have left the province, they will need to seek care locally if their travel plans change and/or if other medical care is needed** (e.g., to extend prescriptions or for dose adjustments). Hence, pre-planning for guest dosing is important if this is to be pursued. The Manitoba provider can advise a local OAT prescriber and share collateral information, but they cannot actively provide the medical care.

Pharmacists should also notify the OAT prescriber if a patient asks about interprovincial or international travel, so that the patient can be made aware of the importance of planning ahead. The [Information Sheet on Virtual Medicine Across Provincial and International Borders](#) may be a helpful resource for physicians and pharmacists providing care to travelling patients⁴.

Additional Recommendations for International Travel

For patients travelling internationally, the following is also recommended:

- Consider providing the patient with a travel letter for their prescriptions. This letter can state that the patient is carrying medication for their own personal use, especially when crossing international borders. This can be presented to customs officials if they are questioned about the medication they are carrying. Contact information for the prescriber/clinic team should be included in this letter.
- Medication should be transported in the original labelled containers and packed in carry-on luggage, in case checked baggage is lost.
- For patients on methadone, consideration can be given to prescribing methadone tablets for the duration of travel, if appropriate, to avoid patients carrying multiple vials of diluted liquid methadone (most airports have fluid restrictions, and this avoids the possibility of leakage). A separate prescription is required to prescribe methadone tablets for travel, and the regular community pharmacy may require a new prescription

for liquid methadone upon return from travel. Additionally, it may be beneficial to forewarn patients that methadone tablets may not be covered (for OAT) by provincial and federal drug coverage programs.

TRANSFER OF CARE FOR PATIENTS RELOCATING

Moving Within Manitoba

All patients should be encouraged to advise their OAT provider and pharmacy regarding any plans to relocate. The OAT team can then facilitate transfer of care, as needed. This could involve simply transferring to a new pharmacy closer to the patient's new home, or to a new OAT provider and pharmacy if moving a great distance between cities, towns, or regions. As with any transfer of care, communicating in advance and sharing the patient's history, status, and treatment plan is critical to a safe and smooth transition between providers. One or more carry doses may be appropriate to facilitate travel and relocation, based on clinical stability (similar to the outlined approach for interim travel carries).

If the patient is relocating to a region without any OAT providers, the treatment team may have to problem solve providing care over a distance in collaboration with the patient. The provider should be prepared to be flexible and employ novel approaches to providing OAT, to promote equity in access to care. **This can include a blended model of virtual appointments and in-person assessment.** Occasionally, partnerships with local healthcare providers who are willing to assist with in-person assessment may also be a useful strategy. See [FREQUENCY OF ASSESSMENTS](#) in the [Ongoing Care](#) chapter for further guidance.

Moving Out of Province

Patients should be also encouraged to advise their OAT provider and pharmacy *as soon as possible* regarding any plans to move out of province. This will allow the OAT team to facilitate transfer of care by actively supporting the patient to find a new OAT provider. Such facilitation can be a formal referral to an identified program that is accepting new patients, or simply practical information on how to access OAT care in a new community, if that community offers same-day resources.

For planned departures, a bridging prescription for guest dosing may be appropriate for up to one month. Again, one or more carry doses may be appropriate to facilitate travel and relocation, based on clinical stability (similar to the outlined approach for interim travel carries).

It is important to clearly communicate with the patient about the maximum duration of a bridging prescription for out-of-province travel or relocation, as well as the limitations of ongoing care given the [Virtual Medicine Standard](#) and the legal/liability considerations for cross-border care. These conversations should be clearly documented in the medical record.

SPECIFIC CONSIDERATIONS: CARING FOR INCARCERATED PATIENTS

This section discusses unique considerations for the care of patients on OAT in correctional settings. This includes the importance of continuity of care when patients transition from corrections facilities to the community, and vice versa.

Opioid use, withdrawal, and associated high-risk behaviours occur commonly in correctional settings. Opioid-related deaths are also increasing among incarcerated people⁵. In the two weeks after release, an individual's risk of overdose is further increased (up to fifty times), compared to that of the general population⁶.

OUD in the correctional setting should be managed with evidence-based care and OAT is the recommended therapy, with buprenorphine/naloxone as first-line treatment.

Resources Vary Between Facilities

The availability of OAT varies dramatically between different corrections facilities in Manitoba, particularly between federal and provincial settings. OAT diversion is also known to be problematic within corrections facilities, including issues of intimidation, with patients on OAT being targeted for their medication. As a result, institutions have various protocols in place aimed at protecting patients and preventing diversion.

It is also known that the spread of HIV and viral hepatitis (hepatitis C) is problematic in correctional settings. Substance use in prisons and the lack of harm reduction measures increase risk for hepatitis C and HIV, particularly through riskier injection practices such as reusing equipment. Access to harm reduction supplies, along with timely diagnosis and treatment, varies between institutions and remains an urgent priority.

PROVINCIAL CORRECTIONS

Provincial corrections facilities in Manitoba typically do not offer access to medical assessment of OUD and OAT induction onsite. It is also customary practice in the provincial correctional system in Manitoba to *not* permit increases in OAT dosing while a patient is incarcerated.

Providers should thus consider the following:

- When an individual has a known OUD, it is ideal to stabilize them on OAT prior to incarceration, as dose changes may be more difficult once incarcerated.
- Ideally, OAT dosing should still be titrated to an optimal dose even during a period of incarceration if possible. Clinical assessment could be arranged to occur in-person (the patient is typically escorted to the prescriber's practice location) or virtually (video assessment is preferred). Collaboration with the medical unit staff at the facility is typically required to make such arrangements.

- If patients already on OAT do not have access to onsite OAT care while incarcerated, the **community prescriber is responsible to ensure access to a continued OAT prescription throughout the period of incarceration.** Communication with the facility's medical staff is imperative. If no dose changes are requested/required, the community provider may not see the patient for extended periods. It is acceptable to continue the OAT prescription at the same dose regardless, if no concerning information is received from medical staff at the facility. A call to check in with medical staff, upon faxing refill prescriptions every 3-6 months, is good practice to ensure lines of communication remain open.
- It is not unusual for undesirable prescriptions such as benzodiazepines/Z-drugs to be tapered/discontinued by medical staff in corrections facilities. If a patient is clinically stable upon release from such a facility, benzodiazepines/Z-drugs should not be restarted, unless critical for patient safety (these medications are typically contraindicated with OAT).
- Most institutions use a specific pharmacy to supply and deliver all inmate medications to the facility's medical unit. These pharmacies are typically proficient in dispensing OAT. However, if that is not the case, the prescriber may need to liaise with the facility to ensure OAT is continued. A new prescription will need to be provided to the pharmacy contracted to supply and deliver OAT to that facility for witnessed self-administration by nursing staff on site.
- Pre-trial detention centres (e.g., Winnipeg Remand Centre) may not use a specific pharmacy to provide OAT to their facility. As such, the OAT prescriber may need to authorize delivery of OAT doses from the *regular* community pharmacy to the pre-trial detention centre for witnessed self-administration by nursing staff at the facility.
- **With release from the provincial system, communication with the OAT provider around the release date is critical so that a prescription can be sent to a community pharmacy for continued care.** Planning for transition into the community in anticipation of release is key to prevent missed doses and relapse upon release. Should an individual be released unexpectedly, for instance after a court appearance, it remains the community prescriber's responsibility to provide a discharge prescription to the patient's pharmacy of choice upon learning of the release. These occurrences are another reason why OAT prescribers must maintain an on-call system to respond to urgent calls from pharmacies and other healthcare providers, including after hours.

FEDERAL CORRECTIONS

In federal institutions there is capacity for the onsite assessment and treatment of OUD, including OAT. OAT can be initiated and continued with appropriate dose adjustments directed by the onsite prescriber(s).

However, there can be a significant waiting period before inmates are seen for assessment and induction, given limited resources/significant waitlists. Therefore, starting OAT in the community as soon as possible is still indicated, even if arrest and potential federal incarceration is imminent, so that OAT can be ideally continued in the federal facility.

Other considerations for federal institutions include:

- If patients already on OAT are incarcerated in a federal facility, their OAT will likely be continued. Prescribers employed by Correctional Service Canada provide ongoing care prescriptions for inmates on OAT, along with financial coverage of same by Correctional Service Canada.
- When individuals are released or paroled from the federal system into the community, coverage and prescriptions from Correctional Services Canada may continue for up to 28 days from date of release. Prior to COVID-19, this period was 14 days but was increased given pandemic-related limitations in timely access to community care, including OAT providers. Corrections staff must attempt to arrange community follow-up prior to day 28. This may include finding an OAT provider who can take over the individual's care if OAT was started in prison or started in another province prior to incarceration.

During this 28-day period of coverage, the inmate and their personal/professional supports must be encouraged to maintain communication with the new OAT provider to schedule/confirm an intake appointment and to arrange medication coverage, if this was not possible or confirmed prior to release.

- **If an inmate is being transferred from a federal to provincial facility, a community provider must be found.** This is a known system challenge and therefore bridging prescriptions from community OAT providers are occasionally requested prior to the provider being able to assess the individual. If such a prescription can be provided with reasonable safety, based on reliable collateral information and subject to daily dispensing, then a time-limited prescription is recommended to bridge the patient until they can be seen for assessment and ongoing care with the new community provider.

MEDICATION & SUBSTANCE USE REVIEW FOR INCARCERATION TRANSITIONS

At any point of transition (between corrections facilities or into the community) it is strongly recommended that the patient's medication record (e.g., DPIN or E-Chart) be reviewed and/or verified with the community pharmacy or facility medical staff. This will help ensure dosing accuracy of OAT and other medications as applicable during the transition.

Some transitions may require more urgent clinical assessment of the patient to assess/observe for sedation or withdrawal and review recent substance use, as they may have missed OAT doses and/or they may have been supplementing with other opioids.

Likewise, assessment of other substance use is also important upon incarceration or release. Patients using alcohol or benzodiazepines/Z-drugs (either in the community or illicitly while incarcerated) may require further medical management and collaboration with the facility medical unit staff. Patients have also reported illicit use of bupropion and gabapentin while incarcerated, and may present to intake or follow-up appointments seeking these medications. Careful assessment and medication planning is key to mitigating the risks of polypharmacy. See [Managing Polypharmacy & Polysubstance Use](#) for more detailed recommendations.

STRONG RECOMMENDATION: REMINDER TO DISPENSE WITH OAT

Typically, all psychoactive/sedating medications should be dispensed with OAT, i.e., on the same schedule as OAT. Communicating with the patient’s pharmacy about the plan for managing these medications is essential. Controlled dispensing instructions, such as “dispense as per OAT schedule”, must be written on all relevant prescriptions. Please see the [Managing Polypharmacy in OAT](#) chapter for further medication safety recommendations.

SPECIALTY POPULATIONS & INCARCERATION

Pregnancy

For female inmates with OUD, pregnancy is a time of utmost importance to ensure seamless OAT care. If not already on OAT, pregnant individuals with a suspected OUD should be urgently assessed (and/or referred) for initiation of treatment.

If already on OAT, regular reassessments are recommended as ongoing dose adjustments may be required, particularly during the third trimester. See the [Treatment of OUD in Pregnancy](#) chapter for detailed recommendations around pregnancy.

STBBI Testing

It is highly recommended to offer Sexually Transmitted and Blood Borne Infection (STBBI) testing to all patients upon release from incarceration, and at appropriate clinical intervals thereafter. Initial screening should include testing for HIV, hepatitis A, B, and C, as well as syphilis, chlamydia, and gonorrhea, including throat and rectal swabs if indicated.

Patients at significant and ongoing risk of infection should be offered STBBI screening every 6 to 12 months. Repeat testing may be customized based on individual risk factors. Please see the chapter [Prevention, Screening, & Management of HIV & Hepatitis C in Individuals with OUD](#) for further guidance.

RAPID ACCESS TO ADDICTION MEDICINE CLINICS

As in other parts of Canada, the landscape of addiction medicine in Manitoba has evolved rapidly over the last few years. These changes have been driven primarily by the escalating opioid crisis and public demand for accessible addiction treatment services.

Low-Barrier Access to Addiction Care

Federal and provincial reports have all outlined a chronic state of underfunding of mental health and addiction services, along with the need for increased access to evidence-based addiction treatments. Initiatives are now underway to improve awareness and training for healthcare providers, to enable earlier recognition and treatment of substance use disorders within a standardized and evidence-based treatment framework. This goes hand-in-hand with community advocacy to improve access to a wide variety of harm reduction strategies, both embedded within treatment services and in a variety of public spaces.

Regrettably, there remains much stigma around accessing care for individuals with substance use disorders. For individuals and families, it can be very difficult to accept that substance use is problematic, and the experience is often associated with feelings of shame, guilt, fear, and/or anger. This translates into poor and often delayed access to care and complications of untreated disease.

The rollout of [Rapid Access to Addiction Medicine \(RAAM\)](#) clinics in Manitoba began in the fall of 2018. With subsequent expansions, there are now six RAAM clinics located across all five Regional Health Authorities. **These clinics represent a significant increase in the availability of low-barrier addiction assessment and treatment for Manitobans.**

The RAAM clinic model was established by the Mentoring, Education, and clinical Tools for Addiction: Partners in Health Integration (META:PHI) group. It is a low-barrier, walk-in style clinic that adults (ages 18+) can attend to get help for substance use disorders, including OUD. **No appointment or formal referral is required.**

The RAAM Clinic Role in the Healthcare System

RAAM clinics provide time-limited medical addiction care, including pharmacotherapy such as OAT, brief counselling, and referrals to community services. The RAAM model plays a key role in reducing overall harms and improving general health outcomes. Ultimately, this reduces the risk of serious complications such as overdose or contracting STBBIs.

Individuals who access RAAM services are typically stabilized with evidence-based substance use disorder treatments. Patients are then transferred to longer-term services for ongoing care that is typically provided by primary care providers or specialists. **It is essential for RAAM clinics to build collaborative connections with both acute and chronic care services, to support**

patients along the continuum of disease and recovery. This ensures continuity and safety of care plans developed at RAAM.

In the context of OUD, RAAM clinics may be utilized to initiate OAT, stabilize complex patients, assist with crisis management, offer consultation, and to support case management where appropriate. RAAM also provides an on-call service in Manitoba as a resource for other professionals who are managing individuals connected with RAAM, to collaborate on care.

RAAM clinics do not provide emergency services for people needing urgent medical attention for serious physical or mental health illnesses such as overdose, psychosis (e.g., paranoia, delusions, hallucinations), agitation, suicidal or homicidal ideations, or who require police and/or security involvement.

Capacity Building & Transfer of Care

RAAM clinics are meant to function within the health system as a whole, providing an intermediary bridge (i.e., intervention and stabilization) along the care continuum. RAAM typically follows an individual for up to six months before the transfer to ongoing care occurs. However, as with the rollout of RAAM in other provinces, a major hurdle has been capacity building within the system to allow timely transition of patients to longer-term care providers.

RAAM clinic team members include nurses, counsellors, physician assistants, nurse practitioners, and physicians, all of whom are valuable resources to other care providers and patients. Prescribers are encouraged to be aware of local RAAM resources to support patients along the continuum of care. **OAT providers are also encouraged to collaborate with RAAM on transfers of care, as able, to support patient flow within the system and to ensure ongoing capacity for rapid access and stabilization.** OAT providers who are open to accepting transfers of care from RAAM are strongly encouraged to provide their contact information and preferred method of referral to the RAAM clinic coordinators/medical directors.

References

1. College of Physicians & Surgeons of Manitoba. *Standard of Practice: Virtual Medicine*. CPSM; 2021.
2. College of Registered Nurses of Manitoba. *Telepractice*. CRNM; 2021.
3. College of Registered Nurses of Manitoba. *Guidance on Telepractice*. CRNM; 2020.
4. College of Physicians & Surgeons of Manitoba. *Information Sheet on Virtual Medicine Across Provincial and International Borders*. CPSM; 2021.
5. Correctional Service Canada. *Overdose incidents in federal custody, 2012/2013 – 2016/2017*. Government of Canada. 2018. <https://www.csc-scc.gc.ca/research/sr-18-02-en.shtml>
6. Kouyoumdjian F, Kiefer L, Wobeser W, Gonzalez A, Hwang S. Mortality over 12 years of follow-up in people admitted to provincial custody in Ontario: a retrospective cohort study. *CMAJ Open*. 2016;4(2):E153-E161. doi: <https://doi.org/10.9778/cmajo.20150098>

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.16 Discontinuing Treatment: Voluntary & Involuntary Withdrawal from Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Opioid agonist therapy (OAT) is an effective and evidence-based treatment for opioid use disorder. OUD is a chronic medical condition that requires long-term treatment, and no recommendations exist to indicate a specific optimal treatment duration. However, it is encouraged and recommended that treatment continue for as long as desired by the patient to provide stability, functionality, and reduce harms.

During the course of treatment, OAT doses should be tapered and/or titrated up as needed and clinically indicated, to meet the needs of the individual in the context of their overall stability, other health conditions, and life circumstances. Where OAT doses higher than the typical range have been necessary for initial stabilization, it is encouraged to periodically trial a gradual small dose reduction to evaluate if stability can be maintained, while minimizing the side-effects and long-term medical complications of treatment.

For many individuals, the overall duration of treatment is an important question. Since OAT programs can be very intensive and demand a large commitment of time and resources from the patient, it is not uncommon for them to request withdrawal of treatment during their lifetime.

While withdrawal of treatment may occur for many reasons, it can typically be categorized as:

- **Voluntary and clinically reasonable.** A taper is requested and directed by a stable patient, in collaboration with the treatment team. In this context, the patient and provider agree that many treatment goals, including clinical stability, have been achieved and that a trial of tapering is a reasonable option.
- **Voluntary with clinical concerns.** A taper is requested by the patient before many important treatment goals are achieved, and/or before clinical stability is reached. The patient thus wishes to taper off of OAT but remains at high risk of relapse to non-prescribed opioid use and other harms.
- **Involuntary.** The patient is not requesting withdrawal from treatment, but given significant safety concerns (for the patient, treatment team, or the community), the treatment team determines that continuing OAT is either unsafe or inappropriate.

Whether voluntary or involuntary, it is important for OAT providers to have a good understanding of the benefits and risks of withdrawal of treatment and to develop practical strategies to support the patient and other members of the team throughout this process.

SPECIFIC CONSIDERATIONS

OAT is a long-term indefinite treatment. Patients who continue to benefit from OAT and do not wish to taper should not be pressured to do so.

When a taper is deemed appropriate, gradual tapering (over months to years) is preferred for safety and stability reasons. Often patients request more rapid tapering, and it is important that prescribers explain the dangers of rapid tapers to patients in language that is clear, yet compassionate and non-judgemental. Recognizing the overall burden of treatment is an important component of a balanced risk-benefit discussion. **Additionally, OAT providers must also recognize that the principle of patient autonomy dictates that prescribers cannot refuse to reduce a patient's OAT dose.**

Tapering the OAT dosage should ideally be undertaken as a *trial of weaning*. It is strongly recommended that the approach to tapering remain flexible to accommodate the patient's physical and psychosocial needs. This flexibility often serves to strengthen the therapeutic alliance, especially when the prescriber has concerns about the patient's readiness. Harm reduction strategies, including naloxone kits, should be revisited more regularly. **During or following a trial of tapering, patients who relapse to opioid use or who decompensate psychosocially or functionally should be encouraged to titrate back up to a stable dose.** These patients should be offered expedited access to resume and restabilize on OAT to prevent further serious adverse outcomes. Patients must never be penalized in any way for unsuccessful weaning.

VOLUNTARY TAPERING: WHEN CLINICALLY REASONABLE FOR A STABLE PATIENT

As with the treatment of other chronic diseases, the optimum benefits from OAT are not realized immediately and are often not seen for at least a year in treatment. Depending on the patient's pre-treatment circumstances, overall health, and severity of OUD, some patients may take longer to optimally benefit from treatment. In general, patients who have been on OAT for at least two to three years will have better outcomes when tapered than those who elect to taper after shorter durations in treatment. Therefore, to reduce the risk of relapse and other harms, patients should be encouraged to participate in OAT until stability is reached and important patient- and provider-driven treatment goals are achieved.

Evaluating a Request for Withdrawal of Treatment

A request to taper should be discussed collaboratively with the patient. The patient's motivation for the request and the **KEY CONSIDERATIONS** below should be explored.

KEY CONSIDERATIONS: QUESTIONS TO EVALUATE A TAPER REQUEST

- 1) How long has the patient been abstinent from non-prescribed opioids and/or other mood-altering substances, as per the patient's treatment goals around abstinence? The longer the period of stability, the higher the likelihood of success with a taper.
- 2) How stable is the patient's mental and physical health?
- 3) Does the patient have stable housing?
- 4) Does the patient have a stable source of income?
- 5) Has the patient developed healthy and non-chemical coping skills?
- 6) Has the patient developed supportive relationships (particularly with others who do not use drugs)? Do they still have contact/inappropriate involvement with dealers or criminal organizations? Do they still associate or live with others who use drugs regularly?
- 7) Does the patient have a concurrent chronic pain condition that may complicate withdrawal of treatment? Should other pain management strategies be explored or optimized prior to initiating withdrawal of treatment?
- 8) Has the patient attempted withdrawal of treatment in the past? What did they learn from that experience that could help them in this attempt?
- 9) Is the patient able and willing to attend more frequent follow-up appointments during the tapering process, to facilitate appropriate monitoring and dose adjustment?

It is important to understand what is driving the desire to stop treatment. Some of the patient's concerns may be amenable to medical management (e.g., side-effects, re-evaluating take-home dosing schedules), education, and/or reassurance. Providers may want to ask about finances, difficulties with transport, family responsibilities, and work schedules.

Explore any misconceptions about the need to withdraw, for example, due to a pending incarceration. Patients may also be subject to stigma and judgements from family or friends, employers, or even other care providers. These concerns must be explored in a sensitive manner.

Preparing for Withdrawal of Treatment

Once the decision is made to start an OAT taper, the initial tapering plan should be discussed with the patient. This plan must include relapse prevention strategies, including practical instructions on how the patient can access a dose increase in between follow-up appointments.

Providers should also incorporate the following into the tapering plan:

- **Individualize the tapering plan for each patient.** The plan may include a dose reduction schedule for patients with previous tapering experience, who can anticipate what to expect over time. For patients tapering for the first time, in-person assessment is often a good idea after an initial small dose reduction. Discuss how the change felt for the patient. This discussion will inform decisions about the size and intervals of future dose reductions, as needed.
- **Inform the pharmacy about the plan to taper.** The pharmacist can be another source of support for tapering patients. They can also notify prescribers of any concerns and can offer feedback on how the patient is coping with the change.
- **Include more frequent reassessment appointments in the plan.** Patients who are ready to taper are often seeing their provider every three months, given their long-term stability. It is important to advise the patient that a taper will likely require more frequent appointments to evaluate progress and the need to modify the tapering plan.
- **Prepare the patient for potential difficulties associated with tapering,** namely anxiety, craving, withdrawal symptoms, and decreased overall distress tolerance. The risk of relapse must be discussed. Discuss strategies to proactively manage these challenges. Ideally, patients should be guided to taper at a pace that minimizes these symptoms. Patients should be able to perform all their previous activities of daily living while tapering slowly over time, to decrease the risk of decompensation.
- **Reassure the patient that flexibility with dose adjustments during the taper is standard care,** i.e., it is reasonable to return to the previous dosage or to hold the taper at a certain dose for an extended period, as needed, if tapering becomes too challenging. Encourage the patient to proactively discuss life issues that may require their taper to be adjusted or paused to maintain stability.
- **Offer supportive resources during the process** and discuss if engaging in additional counselling or support groups would be helpful, especially if the patient benefitted from such supports in early treatment.

General Tapering Recommendations

In general, it is recommended that the OAT dose be lowered by no more than 5-10% of the total remaining dosage per month, to minimize cravings and reduce the risk of destabilization.

When low doses of OAT have been achieved (i.e., ≤ 10 mg buprenorphine and ≤ 30 mg methadone), the rate of taper may be slowed even further to optimize successful weaning.

Voluntary withdrawal can be suspended at any time with the option of titration back to a stable dosage.

For patients who are unsuccessful tapering off OAT, or dissatisfied with their quality of life while tapering, other ways of simplifying treatment without stopping OAT should be discussed. These options may include alternate day dosing, buprenorphine extended-release subcutaneous injections (Sublocade[®]) or the buprenorphine subdermal implant (Probuphine[®]).

Taper Considerations for Buprenorphine/naloxone

Given that the buprenorphine/naloxone lowest dosage in tablets and film is 2 mg/0.5 mg, many patients on buprenorphine may find the step-downs towards the end of tapering difficult, especially below 10 mg daily.

Many patients tolerate a buprenorphine/naloxone taper better when reducing by 1 mg at a time, particularly below 10 mg daily. Consider splitting a 2 mg tab or cutting a 2 mg film in half (i.e., taking approximately 1 mg of the 2 mg tablet/film daily). When splitting a 2 mg tablet or film, the remaining half should be stored in an enclosed container and protected from moisture until it is used at the next scheduled dosing time. Avoid splitting tablets or film in advance. These measures will help protect the integrity of the tablet or film used for splitting. Off-label utilization of a buprenorphine transdermal patch (Butrans[®]) is also an option for stable patients who struggle with further tapering once they reach 2 mg or 1 mg of buprenorphine/naloxone daily.

It is important to discuss such tapering strategies with the pharmacy in advance of sending a prescription requiring tablet or film splitting. This will ensure everyone is on the same page and consistent instructions and support are given to the patient by all members of the team.

Taper Considerations for Sublocade

Currently, no clear evidence exists to guide clinical decision making for patients who are stable on Sublocade[®] when they request to stop treatment. The injectable depot version of buprenorphine has a half-life of 43 to 60 days. Considering the long half-life, withdrawal symptoms and signs may be delayed. Furthermore, “model simulations indicate that steady state buprenorphine plasma concentrations decrease slowly over time following the last injection and could remain at therapeutic levels for up to 2 to 5 months, depending on the dosage administered (100 or 300 mg, respectively)”¹.

Practical experience, however, indicates that some patients may experience withdrawal symptoms much sooner after stopping treatment, especially if they were prone to early withdrawal symptoms when they presented late for routinely scheduled monthly injections or if they never felt entirely stable on their routine Sublocade® regimen. These patients may have been receiving Sublocade® at more frequent intervals, or at higher doses than indicated by the product monograph to facilitate clinical stability.

Patients who elect to discontinue treatment with Sublocade® should thus be monitored for symptoms and signs of withdrawal for several months. If acceptable and accessible to the patient, providers may consider low dose transmucosal buprenorphine, if needed, to treat withdrawal after discontinuing Sublocade®.

Frequent Assessment of Stability & Safety

During the taper, reassess stability more frequently to ensure patient and community safety by:

- Re-evaluating take-home dose schedules more often,
- Adjusting follow-up appointment frequency as appropriate, and in partnership with the patient,
- Screening for relapse at each appointment and in between as needed, including urine drug testing (UDT), and
- Continually reviewing and adjusting the tapering plan and other treatment goals.

In some cases, it may be useful to collaborate with the community pharmacy if the provider has specific concerns about instability during the taper. The pharmacist is in a unique position to report any behavior or activity that could warrant attention at the next reassessment.

Importantly, **documentation of these issues is critical** to support clinical decision making and to facilitate appropriate episodic care by other OAT team members or other healthcare providers.

VOLUNTARY TAPERING: WHERE CLINICAL CONCERNS OR INSTABILITY EXIST

Some patients choose to taper OAT despite its benefits. Patients may also request a taper early in treatment or before meaningful clinical stability is reached, and/or major treatment goals are achieved.

When the potential harms of a taper outweigh the potential benefits, the tapering process may put the patient at high risk of relapse and other serious harms. The OAT prescriber must explore the patient's motivation for tapering, educate them about the potential harms, and clarify any misconceptions. The prescriber may recommend the continuation of OAT using the same medication or by exploring simplifications of treatment. Details of this discussion and education should be documented in the patient record.

However, if despite this discussion the patient still insists on withdrawing from OAT, the patient and prescriber should prepare a plan for a *trial of weaning*, taking into consideration the relevant risks.

Harm reduction strategies should be offered proactively throughout the process, and especially if relapse occurs. Education on safer use techniques, sterile drug consumption equipment, and take-home naloxone kits should be offered regularly. Patients who relapse to opioids and become unstable, or who change their decision to wean at any point, should be encouraged to continue OAT in some form and ideally return to a stable dose.

INVOLUNTARY WITHDRAWAL OF OAT TREATMENT

Clinical decision making while providing OAT can be challenging at times. Deciding to involuntarily withdraw a patient from treatment is an example of a potentially difficult treatment decision. It is thus important to have a thorough understanding of the issues that may make ongoing treatment unsafe or inappropriate, and to have a practical approach to involuntary withdrawal of treatment.

Treatment agreements can be revisited with patients to review behavioural and safety expectations throughout the course of treatment and particularly as concerns arise that may warrant withdrawal of treatment. See the [Comprehensive Assessment](#) chapter for more information on treatment agreements.

In general, involuntary withdrawal of treatment is indicated when the OAT prescriber, in collaboration with the treatment team, determines that **ongoing treatment poses a serious risk to the patient, a member of the treatment team (including pharmacy staff), or the community.**

Once a decision is made to withdraw treatment on an involuntary basis, alternative treatment options, including a referral to another OAT treatment program/provider must be considered and offered to the patient, if available.

Concerns That May Warrant Involuntary Withdrawal

Examples of behavior or circumstances that may warrant involuntary withdrawal of treatment include:

- **Evidence of repeated failure to ingest dispensed OAT doses.** This includes witnessed and/or take-home doses. This may constitute sufficient grounds for immediate dose reduction or cessation of OAT. Dose reduction is appropriate if the patient is not consuming their full dose or if they are potentially diverting one or more doses. Such a **dose reduction is intended to protect against overdose** when take-home doses are converted to witnessed doses and/or when the patient resumes consuming their full witnessed dose on a daily basis.

Discussion around these behaviors is always warranted to ensure that legitimate patient concerns are addressed. Explore the patient's potential reason for this behaviour.

For example, were they feeling unwell, sedated, or experiencing side effects on their prescribed dose? Are they wanting to taper, are they being pressured to divert doses, or selling doses for extra income? This should be discussed sensitively and non-judgementally with patients, while explaining the risks in clear language. This includes the risk of being discharged from care via involuntary withdrawal, especially if the issue is medication diversion.

Again, it may be useful to review the OAT treatment agreement with the patient and increase supervision during administration. The pharmacy team must be included in the clinical discussion and plan moving forward, as they are on the front lines of dosing safety and can help observe for clinical sedation.

- **Conclusive evidence of diversion of prescribed OAT doses.** This constitutes sufficient grounds for an involuntary taper to zero or immediate cessation of OAT. Alternatively, increased supervision and strict witnessed dosing seven days per week, with no option for take-home dosing (for any reason) may be considered, if deemed appropriate by the treatment team. If the latter option is chosen but the behavior continues, OAT must be discontinued. Instituting a dose reduction (as above) can again protect against overdose while the treatment team considers the situation and decides on a longer-term plan.

Evidence of methadone and/or slow-release oral morphine (SROM) diversion is typically considered a much greater safety risk to the public, and thus results in involuntary withdrawal of treatment more often.

Diversion of buprenorphine/naloxone still constitutes a concern, and may be grounds for a written request from the prescriber to the pharmacist to crush all buprenorphine doses prior to witnessed self-administration. This practice is not routinely recommended and should be reserved for exceptional circumstances. If there are ongoing concerns despite this measure, treatment should be discontinued.

- **Physical or verbal threats to any member of the OAT care team, including pharmacy staff.** Such behavior constitutes sufficient grounds for immediate cessation of OAT. In some cases, an involuntary taper to zero may be attempted, along with a more intensive behaviour agreement, prior to opting for immediate cessation of treatment.
- **Ongoing disruptive behaviour in clinic or at the pharmacy.** This may also constitute sufficient grounds for cessation of OAT. In some cases, a trial of weaning or a more intensive behavioural treatment agreement may be an interim measure.

- **Continued, heavy use of non-prescribed, sedative/hypnotic medications, including benzodiazepines/Z-drugs, OTC medications and/or alcohol**, may constitute a serious enough safety concern to justify cessation of OAT. A careful risk-benefit assessment, including the patient's response to options for treatment intensification, should help determine whether treatment should be continued or stopped.

Patients who repeatedly seek sedating prescription medications from prescribers other than their designated treatment providers (as also outlined in the treatment agreement) may also be at sufficient risk to warrant involuntary withdrawal of treatment.

- **Repeated failure to attend appointments**, including the minimum requirement for in-person assessment as deemed appropriate by the treatment team, may constitute sufficient grounds for involuntary withdrawal of treatment. Appropriate initial responses to repeated missed appointments should include the 1) removal of any take-home doses, 2) slow involuntary tapers of undesirable sedating prescription medications, and eventually 3) a taper of the OAT medication to zero.

Process for Involuntary Withdrawal

During the involuntary withdrawal of treatment process, the following steps should be considered:

- 1) **The decision to involuntarily withdraw treatment should be discussed as a treatment team.** These discussions are crucial to build consensus and maintain team morale, as different team members may have different thresholds for what constitutes unacceptable behavior. When strong therapeutic relationships exist between the patient and certain members of the team, it is important to keep in mind that all team members have a right to be heard and feel safe at work.
- 2) **Ensure that pharmacy staff are notified about the clinical decision to involuntarily withdraw treatment.** Provide the pharmacy with enough information to determine if they wish to be involved in the involuntary withdrawal process. This is especially relevant if the behavior occurred in the pharmacy or within the immediate vicinity of the pharmacy. It may be necessary to switch the patient to an alternative pharmacy if the plan involves an involuntary taper over time.
- 3) **Inform the patient of the decision to involuntarily withdraw treatment using clear language.** Set clear expectations and boundaries around what is expected of the patient moving forward (in terms of clinic/pharmacy attendance, consequences of further inappropriate behavior, etc.). Discuss details of the tapering schedule and provide the patient with a written copy if requested. Document the team's decision, rationale for the decision, the plan moving forward, and the discussion with the patient, including the patient's response to the plan, in the medical record.

- 4) **Provide the patient an option to transfer to another OAT prescriber or program**, if appropriate and possible. Provide appropriate collateral information to the new prescriber or program regarding the circumstances around the transfer of care.
- 5) **Reinforce that safety is key for all involved**. Patients exhibiting verbally abusive or threatening behaviour may have their OAT rapidly tapered or simply discontinued if the prescriber has concerns regarding the safety of clinic staff, pharmacy staff, other patients, or the public (for instance individuals accessing the same area/building where the pharmacy or clinic is located).
- 6) **Consider safety in aspects of dispensing and witnessed dosing**. If the patient was not regularly ingesting their prescribed dose, there may be a need to lower the dose and observe the patient for a period after dosing (i.e., in clinic or in pharmacy) to monitor for sedation or opioid toxicity.
- 7) **A typical schedule for involuntary tapering is generally quicker than a voluntary taper** and may involve a 5-10% reduction of the remaining daily dose per day, or per week, depending on the patient's level of cooperation and the severity of the perceived risk.
- 8) **During involuntary tapering all doses must be daily witnessed doses with no take-home doses permitted**. This means that if the patient has no pharmacy access on a given day, that dose will not be dispensed to the patient.

Returning to OAT After Involuntary Withdrawal

Patients who are involuntarily withdrawn from treatment may be considered for return to treatment at a future date, especially in regions where other OAT prescribers/clinics are not available. This is a decision that the prescriber must make case by case, along with the treatment team, considering the circumstances at the time of involuntary withdrawal and the circumstances when the patient wishes to resume treatment.

A minimum waiting period of three to six months should be considered before resuming treatment in the same program. **This reinforces the message that unacceptable behavior will not be tolerated and that the safety of clinic and pharmacy staff is non-negotiable.** During the second half of the waiting period, it may be beneficial for the patient to meet with program counselling staff, if available and deemed safe, to discuss what went wrong leading up to the involuntary withdrawal and to assess the patient's insight and readiness to commit to behavioral expectations upon their return. Prescribers are not obligated to resume treating patients who have been involuntarily withdrawn if significant safety concerns or behavioural problems persist, or if the program is no longer accepting new patients (e.g., the program has reached capacity).

References

- ^{1.} INDIVIOR. *Prescribing Information: Sublocade® (buprenorphine extended-release) injection, for subcutaneous use.* <https://www.sublocade.com/Content/pdf/prescribing-information.pdf>. Accessed January 10, 2023.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.1 Introduction: The Pharmacology of Buprenorphine, Precipitated Withdrawal & Management of Adverse Effects

PHARMACOLOGY

Buprenorphine is a long-acting semi-synthetic opioid that is a partial agonist and has a high affinity at the mu-opioid receptor. This unique pharmacology allows it to be utilized as an effective tool in the treatment of opioid use disorder.

Buprenorphine – The Partial Agonist

The partial agonist activity of buprenorphine at the mu-opioid receptor helps reduce cravings and alleviate opioid withdrawal, in a patient experiencing withdrawal. Buprenorphine has a relatively high affinity for the mu-opioid receptor and will displace and block most of the full agonist effects of other opioids (e.g., morphine, oxycodone, or heroin). A long duration of action allows buprenorphine to be dosed once daily, providing a convenient method for health professionals to witness and monitor ingestion. Since buprenorphine is a partial agonist, the intrinsic activity (e.g., respiratory depression effect) plateaus when the dose increases, essentially producing a “ceiling effect” at higher doses¹. This differs from the response produced by a full agonist (e.g., methadone) in that the intrinsic activity continues to increase linearly with the dose (see [FIGURE 1](#)). The partial agonist property of buprenorphine may reduce its potential for abuse and makes it a safer choice in terms of overdose risk, especially when compared to methadone.

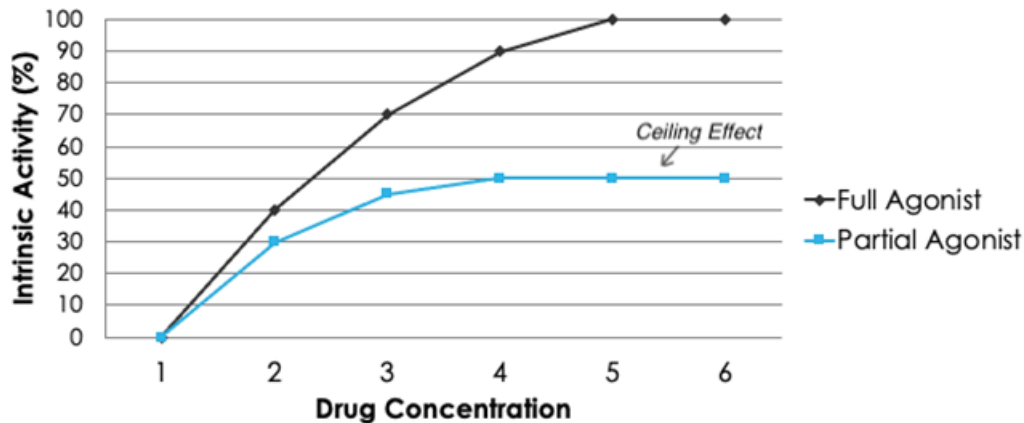


FIGURE 1: FULL AGONIST VS. PARTIAL AGONIST

Sublingual Administration

Buprenorphine has poor oral bioavailability due to a high first-pass hepatic metabolism and generally requires alternative routes of administration to be effective. Sublingual administration of buprenorphine produces an efficacious bioavailability of approximately 30%². Other effective methods of administration include subcutaneous (e.g., Sublocade®) and subdermal implant (e.g., Probuphine®) methods. Sublingual administration produces an onset of action in 30 to 60 minutes, and the peak effects occur between 1 and 4 hours. The mean elimination half-life is 37 hours, and most of the dose is excreted in the feces with approximately 10-30% excreted in the urine¹.

Naloxone – The Antagonist

The sublingual formulation of buprenorphine used most commonly in opioid agonist therapy (OAT) contains naloxone in a ratio of 4:1 (buprenorphine:naloxone). Naloxone, an antagonist at the mu-opioid receptor, has poor oral and sublingual bioavailability. In the doses used in the sublingual formulation this component has not been found to affect the pharmacokinetics of buprenorphine when used sublingually¹. **The naloxone component is helpful in discouraging intravenous and intranasal use of the sublingual tablet since the resultant plasma levels can precipitate opioid withdrawal³.**

ADVERSE EFFECTS & MANAGEMENT

A patient may experience adverse effects immediately after switching to buprenorphine which are most consistent with opioid withdrawal symptoms (precipitated withdrawal). This is fortunately a rare occurrence and is discussed in greater detail later in this document.

If precipitated withdrawal is successfully avoided, then the patient may still experience mild to moderate opioid withdrawal symptoms until they reach a therapeutic dose.

Comparatively, opioid agonist effects are more common. These adverse effects are generally milder than full agonists (e.g., methadone) due to the partial agonist activity of buprenorphine. Some adverse effects will dissipate with continued use, such as nausea, sedation, headache, and insomnia. Other adverse effects may persist and require some management, such as constipation, hyperhidrosis, and sexual dysfunction.

Constipation

Constipation is a common persistent adverse effect that has been found to be prevalent in 8-12% of individuals, compared to 3% in placebo, after 4 weeks of treatment with buprenorphine⁴.

An effective treatment regimen for opioid-induced constipation can include:

- Daily administration of an osmotic laxative (e.g., polyethylene glycol 3350),
- Use of a stimulant laxative, as needed (e.g., senna or bisacodyl),
- The above can be used with or without a stool softener (e.g., docusate), and
- Non-pharmacological methods such as increased fiber intake and fluid consumption should always be endorsed for the prevention of opioid-induced constipation⁵.
- While most laxatives can be helpful, bulk-forming laxatives (e.g., psyllium) are typically not effective for opioid-induced constipation and should be avoided.

Constipation often goes unrecognized in this patient population and may adversely affect quality of life. OAT prescribers are encouraged to ask about and treat constipation aggressively. This approach may improve long-term adherence to agonist therapy.

Hyperhidrosis

Hyperhidrosis has been shown to occur in approximately 15% of patients taking buprenorphine/naloxone¹. While most cases of hyperhidrosis are mild and do not require pharmacological intervention, there are instances where the severity can be enough to affect the patient's quality of life. Clonidine, an inhibitor of sympathetic stimulation, has been used off-label with some success to treat excessive sweating⁶, although it should be noted that research analyzing its use in this patient population is lacking. Misuse of clonidine has been reported⁷, and consideration should be made to control the dispensing frequency. **Clonidine should, in most patients, be dispensed on the same schedule as buprenorphine.** Oxybutynin has been shown to have some success off-label as well⁸, however the evidence is very limited.

Most patients with hyperhidrosis, who benefit from treatment with clonidine, will experience effective relief with no more than clonidine 0.1 mg po BID.

In cases where a trial of clonidine is not effective in reducing sweating, it should be discontinued to avoid unwanted side-effects and prevent diversion. Clonidine has sedating properties and may cause fatigue that not all patients tolerate. Clonidine is also centrally acting and reduces blood pressure. A baseline blood pressure check, repeated after starting clonidine, may be warranted. The use of clonidine can also exacerbate postural hypotension, especially in older patients. Educating patients about this risk is important, especially if they are already at risk of falls.

Sexual Dysfunction

There is some research showing that buprenorphine/naloxone may cause sexual dysfunction in some patients. Hypoactive sexual desire, intercourse dissatisfaction, and erectile dysfunction (ED) were shown to be the most common sexual dysfunctions in men⁹. There is robust evidence to suggest that chronic opioid use can lead to decreased testosterone levels in men, and it is speculated that this may be a contributing factor to sexual dysfunction¹⁰. The research on sexual dysfunction in women is much more limited. It is speculated that interference with the production of LH and FSH subsequently interferes with certain sex hormones, which can lead to a depressed libido and oligomenorrhea or amenorrhea¹⁰.

Sexual dysfunction may have a major impact on treatment adherence, so addressing this adverse effect may improve patient outcomes. Treating the specific symptoms, for example, by using PDE-5 inhibitors for ED, or managing low testosterone levels in men, can be a suitable approach to managing this condition.

PRECIPITATED WITHDRAWAL

The unique pharmacology of buprenorphine can lead to a risk of precipitated withdrawal during the induction phase. Precipitated withdrawal can occur when a partial agonist with a higher affinity for the mu-opioid receptor (e.g., buprenorphine) replaces a full agonist with a lesser affinity for the receptor (e.g., morphine, heroin, fentanyl). If precipitated withdrawal occurs, withdrawal symptoms will appear as early as 15 to 60 minutes after taking buprenorphine and can sometimes be very distressing. This may discourage a patient who is new to buprenorphine from continuing with treatment. It is imperative to take preventative measures to avoid this situation when switching from a full agonist to buprenorphine. If precipitated withdrawal does occur, supportive therapy is indicated. This is discussed in more detail in the [Conventional Buprenorphine Induction](#) and initial monitoring section of this manual (see *Management of Precipitated Withdrawal*).

To avoid precipitated withdrawal, ensure that the patient is in adequate withdrawal before initiating treatment. The timing of the last reported use of opioids can be useful in determining whether it is safe to proceed. Initiation of treatment can usually be considered 6 to 12 hours after the last use of a short-acting opioid (e.g., heroin, oxycodone, fentanyl), at least 24 hours after a long-acting opioid (e.g., oxycodone or morphine controlled-release), or at least 72 hours after the last use of methadone¹¹. Additional strategies to avoid the risk of precipitated withdrawal are discussed elsewhere in this manual. See [Ongoing Care](#) for further guidance on rotating between OAT medications, specifically, *Patients Transitioning from Methadone to Buprenorphine*.

References

1. Pharmascience. *Product Monograph: Pms-Buprenorphine-Naloxone, Sublingual Tablets 2mg/0.5mg and 8mg/2mg*. Pharmascience Inc; 2017. https://pdf.hres.ca/dpd_pm/00041002.PDF. Accessed May 17, 2021.
2. Mendelson J, Upton RA, Everhart ET, Jacob P, Jones RT. Bioavailability of sublingual buprenorphine. *Journal of Clinical Pharmacology*. 1997;37(1):31–7.
3. Jones JD, Sullivan MA, Vosburg SK, et al. Abuse potential of intranasal buprenorphine versus buprenorphine/naloxone in buprenorphine-maintained heroin users. *Addict Biol*. 2015;20(4):784-798. doi:10.1111/adb.12163
4. Webster LR, Camilleri M, Finn A. Opioid-induced constipation: rationale for the role of norbuprenorphine in buprenorphine-treated individuals. *Subst Abuse Rehabil*. 2016;7:81-86. doi:10.2147/SAR.S100998
5. Sizar O, Genova R, Gupta M. *Opioid Induced Constipation*. [Updated 2020 Nov 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK493184/>
6. del Boz J. Systemic Treatment of Hyperhidrosis. *Actas Dermo-Sifiliográficas* (English Edition). 2015; 16(4): 271-277. <https://doi.org/10.1016/j.adengl.2015.03.003>
7. Beuger M, Tommasello A, Schwartz R, Clinton M. Clonidine use and abuse among methadone program applicants and patients. *J Subst Abuse Treat*. 1998;15(6):589-93. doi: 10.1016/s0740-5472(97)00309-7. PMID: 9845872.
8. McCormack L, Ponce J, Chatterjee A, Tan JK. Oxybutynin treatment for buprenorphine-naloxone-induced hyperhidrosis. *JAAD Case Rep*. 2021;10:22-24. doi:10.1016/j.jocr.2020.12.031
9. Mattoo SK, Ghosh A, Subodh BN, et al. Sexual dysfunction in men on buprenorphine/naloxone-based substitution therapy. *Indian J Psychiatry*. 2020;62(1):66-72. doi:10.4103/psychiatry.IndianJPsychiatry_195_19
10. Brown RT, Zueldorff M. Opioid substitution with methadone and buprenorphine: sexual dysfunction as a side effect of therapy. *Heroin Addict Relat Clin Probl* 2007; 9(1):33-44.
11. Kumar R, Viswanath O, Saadabadi A. *Buprenorphine*. [Updated 2020 Oct 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK459126/>

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.2 Recommendations for Conventional Buprenorphine/naloxone Induction for Opioid Use Disorder

GENERAL CONSIDERATIONS

This chapter will outline recommendations regarding the general approach to a conventional buprenorphine/naloxone induction for the treatment of opioid use disorder (OUD).

Buprenorphine is considered first-line therapy for the treatment of OUD, and a conventional induction should be considered for most patients starting buprenorphine/naloxone.

As a partial agonist with high affinity for the *mu*-opioid receptor, buprenorphine has the potential to displace other full agonists at the receptor level, and precipitate clinically significant opioid withdrawal symptoms. This occurs when an initial dose of buprenorphine/naloxone is taken by a patient who has recently consumed other opioids. This phenomenon of precipitated withdrawal can be very distressing to the patient and may negatively impact treatment retention. Please see [The Pharmacology of Buprenorphine, Precipitated Withdrawal & Management of Adverse Effects](#) for further details. **Therefore, the conventional buprenorphine induction takes place after a planned period of abstinence from other opioids and requires clinical evidence of opioid withdrawal.** The initial dose(s) are administered under the direct supervision of a pharmacist, approved prescriber, or nurse.

For select patients who face specific barriers to in-office assessment of withdrawal and witnessed dosing, an unwitnessed (“home”) induction may be considered. Alternatively, these patients, and those who are unlikely to tolerate the prerequisite interval of opioid abstinence, may benefit from a micro-dosing induction. Please see the respective chapters, [Recommendations for Unwitnessed Induction with Buprenorphine/naloxone](#) and [Recommendations for Buprenorphine/naloxone Micro-dosing Induction](#) for details on these approaches.

SPECIFIC CONSIDERATIONS

INITIATING OPIOID AGONIST THERAPY

Urgency of OAT Induction

Following the decision to initiate opioid agonist therapy (OAT), induction should be arranged urgently, ideally the same day or within 2-3 days of presentation. When access to OAT induction within this timeframe is not feasible due to patient, prescriber, geographic, or systemic factors, other interventions should be considered in the interim, including harm reduction strategies (e.g., clean supplies, naloxone), patient safety education, wound care, psychosocial support, and access to primary care and other forms of addiction treatment.

Providers involved in addiction treatment are encouraged to advocate for improved access to OAT in their region of practice.

Initial Assessment & Patient Education

Patients must undergo a comprehensive assessment including history and focused physical examination to establish the diagnosis of OUD before initiating OAT. Please see [Initiating OAT: Comprehensive Assessment, Diagnosis, Informed Consent & Investigations](#) for detailed guidance on the assessment process.

Where immediately available, point-of-care urine drug screening should be performed. This is a useful clinical tool in the context of the initial assessment. Relevant lab work, including an STBBI screening, should also be ordered and completed as soon as practically feasible. **While urine drug testing and other investigations are ideal on initial assessment or in early treatment, they should not delay access to timely treatment if OAT is indicated.**

Due to its lower potential for respiratory depression and lethal overdose, buprenorphine is strongly preferred over full agonists (e.g., methadone) for the treatment of OUD among patients with risk factors for opioid toxicity. These include:

- Patients with concurrent use of alcohol, benzodiazepines, and other sedatives. In general, prescribers should avoid prescribing new sedating medications during induction. Patients should be counselled to avoid the use of sedating drugs, including over-the-counter medications, if possible. See [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#) for further recommendations.
- Older patients (age > 60).
- Patients with acute or chronic respiratory disease (e.g., COPD, pneumonia).
- Patients with low opioid tolerance (e.g., codeine use only, low-dose or low-potency opioid use, intermittent opioid use, or a recent period of abstinence due to incarceration or residential treatment).

Patients should be educated about the symptoms and signs of opioid toxicity, overdose, and should be offered access to a naloxone kit at the time of induction.

Prescribers should obtain and document informed consent for buprenorphine/naloxone treatment. The use of a written **Treatment Agreement** is strongly recommended. Informed consent and treatment agreements are also discussed in the above-mentioned [Comprehensive Assessment](#) chapter.

IMPORTANT NOTE: PATIENTS WITH SEVERE LIVER IMPAIRMENT

Patients with severe liver impairment may not stabilize on buprenorphine/naloxone as expected.

Buprenorphine is absorbed sublingually but naloxone is not. Therefore, during sublingual administration, naloxone in the saliva is eventually swallowed and some of it is absorbed from the gastrointestinal tract. Normally, this naloxone is almost completely inactivated by the liver (i.e., first pass effect) prior to reaching the systemic circulation (about 3% bioavailability). In patients with severe liver dysfunction the first pass effect might be diminished, and a much higher amount of naloxone (approximately ten times as much) can reach the systemic circulation, potentially resulting in ongoing withdrawal symptoms. In such patients, a trial of methadone may be beneficial.

Clinical Stability & Treatment Goals

Prescribers should discuss and document the goals of treatment prior to induction and at regular intervals during follow-up. Both provider and patient-driven goals should be used to inform treatment decisions and support continued buprenorphine/naloxone prescribing.

In most patients, buprenorphine/naloxone allows for rapid dose titration to address opioid withdrawal quickly and effectively. This promotes engagement in further treatment. The patient's dose should be titrated, based on regular clinical assessment, until initial dose stability is reached. A stable dose is achieved when opioid withdrawal is eliminated or adequately suppressed to allow patients to further engage in ongoing medical and psychosocial treatment. **The ultimate goal is to work toward clinical stability**, which is characterized by, but not limited to:

- Absence of opioid withdrawal symptoms and significantly reduced cravings
- Absence or significant reduction in illicit substance use (self-reported and supported by urine drug testing)
- Financial and/or employment stability
- Housing stability
- Improvements in self-care and wellness practices
- Strengthening of supportive relationships (and/or navigating difficult relationships)
- Improvements in mental and physical health

PREPARATION FOR INDUCTION

In most cases, patients should be instructed to abstain from opioid use for 12-24 hours prior to their planned induction or intake appointment, to minimize the risk of precipitated withdrawal. The suggested interval of abstinence may be informed by a thorough clinical history of recent opioid use and knowledge of the pharmacokinetics of various opioids.

Prescribers in community settings may consider scheduling the induction in the morning and on a weekday to facilitate in-person reassessment.

Collaboration with Pharmacy

Collaboration with the pharmacist is strongly encouraged prior to induction and should include:

- **Verify the pharmacy provides OAT.** It is important to note that not all pharmacies in Manitoba dispense OAT, as specialized training is required. Thus, it is important to confirm that a pharmacy does dispense the specific OAT medication selected for treatment (i.e., buprenorphine/naloxone or methadone), prior to faxing a prescription to that pharmacy.
- **Communicate the plan.** Sharing the titration plans and communicating an action plan for any missed doses during the induction phase is helpful for all those involved.
- **Share special instructions.** Specifying any special instructions for the induction schedule is also helpful. Writing the approximate time of day for induction doses on the M3P prescription is very useful to prevent dosing errors and confusion. This is especially true if multiple doses are to be witnessed/dispensed on the same day.
- **Provide comprehensive prescriber contact info.** Supplying the pharmacy with method(s) to contact the prescriber/office outside of regular clinic hours is vital to ensuring that urgent clinical matters can be addressed quickly.

Patients Transitioning from Methadone

For patients using methadone, the methadone dose should ideally be gradually tapered to ≤ 30 mg/day, and the patient should be advised to abstain from methadone for 48-72 hours prior to buprenorphine/naloxone induction. Alternatively, in patients transitioning from methadone to buprenorphine/naloxone, prescribers may consider a micro-dosing induction, or switching from methadone to slow-release oral morphine (SROM/Kadian®, the 24-hour formulation) for five days prior to transitioning to buprenorphine.

Regardless of the clinical approach taken, this can be a challenging process for patients. Patients therefore need to be carefully selected and all appropriate options discussed.

The risk of relapse must be discussed with the patient and the discussion documented. Prescribers who are inexperienced with transitioning patients from methadone to buprenorphine/naloxone are strongly advised to seek expert guidance.

INDUCTION DAY 1

See **Appendix M** for a detailed buprenorphine/naloxone induction flow diagram.

Assess the Severity of Opioid Withdrawal

Prescribers should make use of the Clinical Opiate Withdrawal Scale (COWS) to assess and document the severity of opioid withdrawal prior to administration of the initial buprenorphine dose(s) (see **Appendix N**). Induction typically proceeds when the COWS score is 12 or greater to minimize the risk of precipitated withdrawal.

At the prescriber's discretion, a COWS score *less than* 12 may be considered when supported by a thorough history including knowledge of the specific opioids consumed, their potency and duration of action, the time elapsed since last use, and urine drug screen results. For example:

- An experienced prescriber may feel that the COWS assessment underestimates the degree of withdrawal for a particular patient who reliably reports abstinence from opioids for a sufficient interval.
- A patient presenting after a longer period of abstinence (e.g., weeks) may be appropriate for buprenorphine/naloxone induction with a COWS score less than 12, provided the available history is sufficiently reliable and the diagnosis of OUD is certain (e.g., patients previously on OAT, or following discharge from abstinence-based treatment programs).
- An experienced prescriber may determine that the potential for harm in delaying induction to the next available clinic day (e.g., overdose) exceeds the risk of precipitated withdrawal for a particular patient.
- An experienced prescriber may suspect that a patient who uses lower dose opioids, or non-potent opioids only, may never reach a COWS of 12, and therefore elect to proceed with induction after a sufficient amount of time has passed since last reported opioid use.

In other cases, a prescriber may require a *higher* minimum COWS score. For example:

- Some illicit opioids (e.g., “down”) contain an unpredictable mixture of short- and long-acting opioids. They may also contain fentanyl analogues which may increase the risk of precipitated withdrawal, due to their high lipophilicity resulting in prolonged clearance among frequent users. A higher COWS score, expert consultation, and/or a micro-dosing induction may be considered in these cases (see [Recommendations for Buprenorphine/naloxone Micro-dosing Induction](#) for details).
- Patients may be consuming or withdrawing from other substances that may impact a COWS assessment (e.g., stimulants or benzodiazepines), warranting additional caution to avoid toxicity and/or precipitated withdrawal.

It is strongly encouraged to instruct the pharmacist to communicate any concerns that the patient may have used opioids between the clinic assessment and the induction dose, prior to administering the Day 1 induction dose.

At all times, the prescriber must carefully consider the risk of precipitated withdrawal, as well as the potential harms of delaying the buprenorphine/naloxone induction. In challenging scenarios, a benefit-risk assessment must be documented in the medical record. Prescribers are also encouraged to seek expert guidance in these situations.

Determine the Initial Dose

The initial dose of buprenorphine on Day 1 should be 2-4 mg and should be witnessed by the prescriber, pharmacist, or nurse. In most cases, a 4 mg initial dose is appropriate.

An initial dose of 2 mg may be considered for patients deemed to be at high risk of precipitated withdrawal (e.g., those consuming long-acting opioids) and those with low opioid tolerance (e.g., lower-dose use or recent abstinence).

An initial dose of 6 mg may be considered in *exceptional circumstances* for patients presenting in severe withdrawal (COWS \geq 25); however, this may increase the risk of toxicity and precipitated withdrawal and may warrant increased monitoring or expert consultation.

Reassess Withdrawal

Reassess the severity of opioid withdrawal 1-2 hours after the initial dose:

- **If withdrawal severity/COWS score has worsened significantly after the initial dose**, the prescriber should consider the possibility of precipitated withdrawal (see below, *Management of Precipitated Withdrawal*). If the patient reports feeling better or “a little worse”, the induction may proceed. Precipitated withdrawal typically involves the patient feeling *much worse* than before.
- **If withdrawal symptoms have completely resolved after the initial dose**, document the Day 1 total dose, and arrange clinical follow-up on Day 2.
- **If withdrawal symptoms have not completely resolved**, an additional 2-4 mg witnessed dose may be prescribed. Reassessment should occur 1-2 hours after the second dose, at which time a third 2-4 mg witnessed dose may be considered if withdrawal symptoms persist, to a **maximum Day 1 dose of 12 mg**. Where resources permit repeated patient reassessment (e.g., monitored settings), experienced providers may consider a fourth 2-4 mg dose 1-2 hours after the third, for a maximum Day 1 dose of 16 mg.

If withdrawal symptoms persist after reaching the Day 1 maximum dose, consider prescribing non-opioid medications for symptomatic management (see **Appendix O**). Typically, regularly scheduled acetaminophen and ibuprofen is sufficient. Use caution when prescribing symptomatic management medications with sedating properties.

Take-home Dose(s) on Day 1 of Induction

When repeated in-office reassessment after the initial Day 1 dose(s) is not feasible and continued withdrawal is anticipated, prescribers may consider prescribing one or two 2 mg tablets (maximum of 4 mg) for the patient to take home to complete the induction, up to a maximum Day 1 dose of 12 mg. **The patient should be counselled regarding recognition of withdrawal and the appropriate timing of take-home doses** (e.g., “2 mg SL q 2h PRN for withdrawal symptoms”). Please see [Recommendations for Unwitnessed Induction with Buprenorphine/naloxone](#) for details.

The prescription must have clear instructions as to which doses are to be witnessed or released as take-home doses. Storage of Day 1 take-home doses in a locked box is strongly recommended.

Management of Precipitated Withdrawal

If withdrawal symptoms worsen significantly *shortly* after the initial buprenorphine dose (within 15-60 minutes), the prescriber must decide whether to continue or terminate the induction.

There is currently limited evidence to guide this decision, which should consider the patient’s preferences and an informed discussion of the risks and benefits of each approach:

- If the induction is terminated, the patient can be rescheduled for another attempt at induction (e.g., the next clinic day). Non-opioid medications to manage withdrawal symptoms (**Appendix O**) may be considered. In inpatient settings, experienced prescribers may consider administering short-acting opioids to relieve withdrawal symptoms.
- Alternatively, the prescriber may continue the induction with frequent reassessment and administration of 2 mg doses every 1-2 hours until withdrawal symptoms have resolved (to a maximum 12 mg on Day 1).

When discussing the treatment plan and obtaining informed consent it is important to discuss a plan for potential precipitated withdrawal management with the patient *prior* to induction.

INDUCTION DAY 2

Reassess the Severity of Withdrawal

Reassess the severity of opioid withdrawal prior to Day 2 dosing:

- **If no withdrawal symptoms have emerged prior to Day 2 dosing**, prescribe the total Day 1 dose for witnessed administration on Day 2 and subsequent days.
- **If withdrawal symptoms have emerged prior to Day 2 dosing**, increase the Day 2 dose by 2-4 mg. If possible, reassess the patient 2-4 hours after administration, and consider an additional top-up dose of 2-4 mg at that time if withdrawal persists.

STABILIZATION - DAY 3 ONWARDS

Frequent Reassessment In the Beginning

The patient should ideally be reassessed frequently (e.g., daily) until they achieve relief of withdrawal symptoms and cravings, in the absence of sedation or toxicity, for a complete 24-hour period following their dose. During this time, prescribers may titrate the dose in 2-4 mg increments each day to a maximum of 24 mg daily (usual dose 8-24 mg). A more gradual titration should be considered for those at high risk of opioid toxicity, including those concurrently taking other sedative medications.

In exceptional cases, doses greater than 24 mg may be considered (up to 32 mg/day). In such cases, the clinical rationale should be clearly documented, and inexperienced prescribers should consider expert consultation.

Additionally, after the first week of treatment, prescribers should consider allowing 3-7 days between further dose increases, especially if increasing the dose beyond 24 mg to allow the patient to experience the full benefit of each increase.

After an initial stable dose has been achieved (typically 3-7 days), continue to reassess the patient every 1-2 weeks. The frequency of follow-up can be reduced as the patient on a stable dose begins to demonstrate evidence of clinical stability.

MAINTENANCE

Ongoing Follow Up

At each follow-up visit, review and document the patient's dosage, withdrawal symptoms and cravings if present, ongoing substance use, missed doses, adverse effects, and relevant markers of clinical stability. Please see [Initiating OAT: Comprehensive Assessment, Diagnosis, Informed Consent & Investigations](#) for a detailed list of items to address upon routine follow up, as applicable.

Periodically discuss the patient- and prescriber-driven goals of treatment and discuss adjuncts such as harm reduction strategies and psychosocial supports.

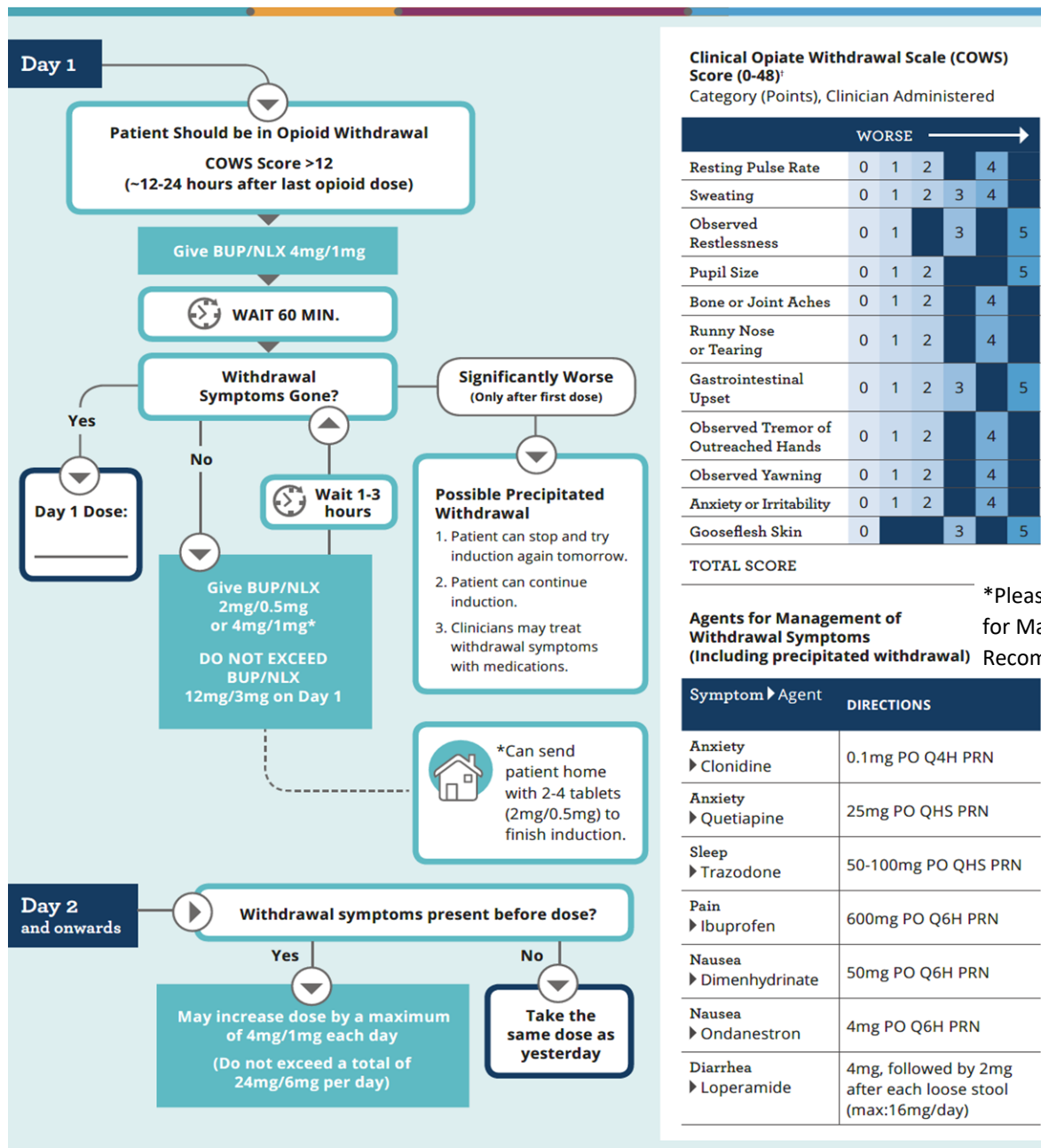
When indicators of clinical stability do not improve as expected during OAT treatment, consider whether continued prescribing is appropriate and aligns with the patient's and prescriber's goals (see other manual sections for guidance on extremely unstable patients).

Criteria for provision of take-home doses are discussed elsewhere in this manual (see [Take-home \(Carry\) Dosing Recommendations](#) and [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#) for details), along with a detailed review of other issues often encountered during the maintenance phase of treatment.

Appendix M¹



Buprenorphine/Naloxone (BUP/NLX) Induction Flow Diagram



[†] Full COWS Scoring Available at: <https://www.drugabuse.gov/sites/default/files/files/ClinicalOpiateWithdrawalScale.pdf>
 For home induction, use patient administered Subjective Opiate Withdrawal Scale (SOWS) scoring available at: <http://www.bccsu.ca/wp-content/uploads/2017/08/SOWS.pdf>



¹ From Korownyk C, Perry D, Ton J, et al. Managing opioid use disorder in primary care: PEER simplified guideline. *Canadian Family Physician*. 2019; 65(5): 321-330. Available at <https://acfp.ca/tools-resources/tools-resources-opioid-response/simplified-guideline-for-opioid-use-disorder-in-primary-care/>

Appendix N²



CLINICAL OPIATE WITHDRAWAL SCALE¹

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient's name: _____ Date and Time: ____/____/____:____

Reason for assessment: _____

<p>Resting Pulse Rate _____ beats/minute <i>Measured after patient is sitting or lying for one minute</i></p> <p>0 pulse rate 80 or below 1 pulse rate 81–100 2 pulse rate 101–120 4 pulse rate greater than 120</p>	<p>GI Upset over last ½ hour</p> <p>0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting</p>
<p>Sweating over past ½ hour not accounted for by room temperature or patient activity</p> <p>0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face</p>	<p>Tremor observation of outstretched hands</p> <p>0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching</p>
<p>Restlessness observation during assessment</p> <p>0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds</p>	<p>Yawning observation during assessment</p> <p>0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute</p>
<p>Pupil Size</p> <p>0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible</p>	<p>Anxiety or Irritability</p> <p>0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult</p>
<p>Bone or Joint Aches <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i></p> <p>0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort</p>	<p>Gooseflesh Skin</p> <p>0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection</p>
<p>Runny Nose or Tearing <i>Not accounted for by cold symptoms or allergies</i></p> <p>0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks</p>	<p>Total Score _____ <i>The total score is the sum of all 11 items.</i></p> <p>Initials of person completing assessment: _____</p>

Score: 5–12 = mild; 13–24: moderate; 25–36 = moderately severe; more than 36 = severe withdrawal

Reference:

1. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35(2):253–259.

More information:
www.bccsu.ca



BRITISH COLUMBIA
CENTRE for EXCELLENCE
in HIV/AIDS



- ² From <https://www.bccsu.ca/wp-content/uploads/2017/08/Clinical-Opiate-Withdrawal-Scale.pdf>

Appendix O

NON-OPIOID MEDICATION FOR SYMPTOMATIC MANAGEMENT OF OPIOID WITHDRAWAL

The following non-opioid medications may be useful to treat symptoms of opioid withdrawal.

Prescribers should exercise caution with all sedating medications during OAT induction, as they may interfere with the assessment of withdrawal severity and increase the risk of fatal overdose. In the absence of precipitated withdrawal, many prescribers prefer to avoid these medications entirely during induction.

- Acetaminophen 500-1000 mg PO Q4-6h PRN for muscle pain (to a maximum dose of 4000 mg in 24 hours, or as appropriate based on known liver function/impairment).
- Ibuprofen 400 mg PO Q6-8H PRN for muscle pain.
- Ondansetron 4 mg PO Q6H PRN for nausea.
- Loperamide 4 mg PO PRN for diarrhea, then 2 mg PO after each loose stool, up to a maximum of 16 mg in 24 hrs.
- Trazodone 50-100 mg PO QHS PRN for insomnia.
- Quetiapine 25-50 mg PO QHS PRN for anxiety/insomnia.
- Clonidine 0.1 mg PO QHS PRN for opioid withdrawal symptoms and insomnia. Clonidine can be titrated up to 0.2 mg PO BID for severe withdrawal, but caution is advised due to the potential risks of sedation, hypotension, and diversion.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.3 Recommendations for Buprenorphine Take-home (Carry) Dosing in Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Take-home dosing can help make opioid agonist therapy (OAT) more acceptable to patients by reducing the burden of treatment. It can reduce the time commitment and cost associated with daily pharmacy attendance, enhance patient autonomy, and integrate OAT with other social, employment, and recreational life goals. This, in turn, can have a positive impact on treatment retention and reinforcement of abstinence.

These benefits must be weighed against the patient and public health risks associated with take-home dosing. Diversion of buprenorphine certainly poses a risk to public health. However, buprenorphine/naloxone has a superior safety profile when compared to methadone, slow-release oral morphine (SROM), and other commonly prescribed opioids, and deaths due to buprenorphine/naloxone are very rare. Therefore, the risks associated with take-home dosing of buprenorphine may be considered limited. In contrast, if a patient discontinues OAT due to excessively restrictive take-home dose policies, they will be subject to an increased risk of fatal overdose and the ongoing impacts of untreated opioid use disorder (OUD).

It is the responsibility of the OAT prescriber to determine a patient's eligibility for take-home dosing and to continually reassess the patient's stability/take-home dosing status. Prescribers should consult with treatment team members and other providers involved in the patient's care, including the pharmacy team, to ensure that all relevant safety information is taken into consideration.

It is recommended that patients and providers complete a Take-home (Carry) Dosing Agreement (see **Appendix P**) prior to authorizing carries. A copy of this agreement should be incorporated into with the medical record and a copy should be provided to the patient.

SPECIFIC CONSIDERATIONS

In general, buprenorphine/naloxone doses should be dispensed as daily witnessed doses. Daily witnessed doses are self-administered under the direct supervision of a pharmacist, approved prescriber, or a nurse, until the patient has demonstrated sufficient clinical stability to be considered for take-home doses.

INDUCTION: THE FIRST 3 DAYS OF TREATMENT

In most cases, with [Conventional Buprenorphine Induction](#), **the first buprenorphine/naloxone dose given during induction should be witnessed. Ideally, all additional doses given during the first 3 days of treatment should also be witnessed.** Conversely, see [Recommendations for Unwitnessed Induction with Buprenorphine/naloxone](#) for further guidance on home inductions.

When repeated reassessment after the initial day 1 dose(s) is not feasible due to travel barriers or clinic/pharmacy hours, and continued withdrawal is anticipated, prescribers may consider providing take-home doses during induction.

Specifically, take-home doses of buprenorphine/naloxone may be prescribed in combination with witnessed doses to facilitate induction, **provided that the patient can safely store the medication** in a locked box or a locked cabinet at home. The patient also needs to be provided with detailed instructions and phone number(s) to access support if needed, prior to returning to the clinic or pharmacy for further assessment and witnessed dosing the following day.

For example, the prescriber may prescribe one or two 2 mg tablets (maximum of 4 mg) for the patient to take home to complete the induction, up to a maximum day 1 dose of 12 mg. The patient should be counselled regarding recognition of withdrawal and the appropriate timing of take-home doses (e.g., “2 (two) mg SL q 2h PRN for withdrawal symptoms”). The prescription must have clear instructions as to which doses are to be witnessed, and which doses are to be released as take-home doses.

As above, the **criteria for home inductions** (wherein the first and possibly additional doses of buprenorphine/naloxone are given as take-home doses) are discussed in [Recommendations for Unwitnessed Induction](#). Take-home doses for induction are not recommended unless home induction criteria are met and there are no alternative witnessed dosing options available to engage the patient in care.

TAKE-HOME DOSING AFTER THE FIRST 3 DAYS OF TREATMENT

Recommendations for take-home dosing are discussed under the following categories:

- 1) Routine recommendations for take-home dosing.

- 2) Recommendations for take-home dosing for patients who achieve significant, early clinical stability.
- 3) Recommendations for patients who present with compelling reasons for early take-home doses, who do not achieve significant early stability.
- 4) Recommendations for patients who should NOT receive take-home dosing.
- 5) Recommendations for occasional take-home doses in patients who do not otherwise meet criteria for take-home dosing.

1) Routine recommendations for take-home dosing.

All patients treated with buprenorphine/naloxone should receive **daily witnessed dosing for the first two weeks of treatment**. Take-home doses are permitted for pharmacy or clinic closures.

After the first two weeks of treatment, patients may receive **a gradually increasing number of take-home doses** if they meet the following criteria:

- They are on a stable dose of buprenorphine/naloxone.
- Missed doses are an infrequent occurrence (< 2 per month) or are specifically related to access barriers (e.g., transportation, work, or finances) that would be remedied by authorizing take-home doses.
- No evidence of ongoing use of illicit opioids, alcohol, benzodiazepines/Z-drugs, stimulants (e.g., cocaine or methamphetamines), and/or illicit sedating/psychoactive prescription or over-the-counter medications, as evidenced by regular clinical assessment and urine drug testing (UDT) results, collected at the minimum frequency recommended in this manual. (See Recommendations for UDT for further guidance, specifically **RECOMMENDATIONS FOR FREQUENCY OF UDT**).
- The patient's physical health, mental health, and social situation are sufficiently stable to support the safe consumption and storage of take-home doses in a locked box or a locked cabinet at home.
- The patient is generally compliant with the treatment agreement, including the minimum recommended UDT and pill counting requirements of treatment as outlined in this manual.

After an **initial two weeks of daily witnessed dosing**, patients who continuously meet the above criteria may receive **one weekly take-home dose for every two weeks of demonstrated stability**. After twelve weeks, a clinically stable patient will thereby attend the pharmacy for witnessed dosing once weekly (i.e., a maximum of six take-home doses).

If a patient with six regular take-home doses demonstrates a **further three months of clinical stability**, they may transition to witnessed dosing once every two weeks (i.e., a maximum of 13 take-home doses).

After **one year of documented clinical stability**, a patient may transition to witnessed dosing once per month, receiving the rest of the month's medication supply as take-home doses (i.e., a maximum of 29 take-home doses).

If a period of instability occurs, the prescriber should determine if the frequency of take-home doses needs to be reduced while treatment is intensified. If treatment intensification results in improved stability, the prescriber, in consultation with other members of the treatment team, may elect to reinstate take-home dosing more rapidly than outlined above.

2) Recommendations for take-home dosing for patients who achieve significant, early stability.

In some cases (see more detailed criteria below), sufficient clinical stability could be evident shortly after buprenorphine/naloxone induction (as early as 1-3 days), according to the prescriber's best judgement.

After the first 1-3 days of treatment, early take-home dosing (i.e., take-home dosing for up to 6 days per week) may be considered in patients who meet the following criteria:

- The patient's OUD is not complicated by other significant substance use issues (alcohol, benzodiazepines/Z-drugs, stimulants such as cocaine or methamphetamines, and/or illicit sedating/psychoactive prescription or over-the-counter medications).
- The patient has no major unstable physical or mental health conditions.
- The patient can store take-home doses safely in a locked box or locked cabinet at home.
- The patient rapidly achieves satisfactory physical and emotional stability during the induction phase, including a stable dose of buprenorphine/naloxone that eliminates significant opioid withdrawal and the need for illicit opioid use.

Once a patient with 6 weekly take-home doses demonstrates a **further 3 months of clinical stability**, providers may follow the same recommendations for take home doses as outlined above under ¹⁾ *Routine recommendations for take-home dosing*.

LOCKED BOXES & NIHB

For patients whose medications are covered by Non-Insured Health Benefits (NIHB), the cost of a lockbox may be covered once per patient, per lifetime (up to \$35), for the safe storage of take-home doses of OAT. If indicated, this coverage extends to safe storage of other high-risk medications, including other opioids, benzodiazepines, stimulants, or sedating/psychoactive drugs, where a lockbox can improve safety for NIHB clients and communities.

3) *Recommendations for patients who present with compelling reasons for early take-home doses, who do not achieve significant early stability.*

Patients who do not meet the above criteria for early clinical stability and take-home dosing may nonetheless present with other compelling reasons to consider early take-home dosing. These reasons may include:

- Meaningful work opportunities that make daily attendance at a clinic or pharmacy for witnessed ingestion impossible or impractical. Such work opportunities should be verified by clinic staff, as is possible and reasonable.
- Childcare or other family responsibilities that make daily witnessed ingestion impossible or impractical.
- Physical disability that makes daily witnessed ingestion impossible or impractical.
- Advanced pregnancy or significant medical complications associated with pregnancy that make daily witnessed ingestion impossible or impractical.
- The patient lives in a remote community with no reasonable access to daily witnessed ingestion at a clinic or pharmacy.
- The patient is unable to start treatment due to an immediate lack of funding or coverage for daily witnessed ingestion and the associated travel.

In such cases, early take-home doses for up to 6 days per week may be considered at the discretion of the OAT prescriber, provided the patient can store take-home doses safely in a locked box or a locked cabinet at home.

4) *Recommendations for patients who should NOT receive take-home dosing.*

Take-home doses *should not* be given under the following circumstances:

- The patient is unable to store take-home doses safely (e.g., unstable housing, no fixed address, recurrent history of lost or stolen medication, etc.)
- Evidence of diversion.
- Significant, unstable substance use issues (especially other opioids, alcohol, stimulants, benzodiazepines/Z-drugs, and other sedating medications, including over-the-counters).
- Significant prescribed polypharmacy involving sedating/psychoactive medications where there is notable risk of accidental or intentional overdose. In these cases, polypharmacy needs to be carefully addressed prior to considering take-home dosing. See [Managing Polypharmacy, Benzodiazepines, Alcohol & Polysubstance Use](#) for discussion of these issues, specifically **AN APPROACH TO POLYPHARMACY IN THE CONTEXT OF OAT**.

- Significant, unstable physical or mental health conditions that may impact the patient's ability to manage take-home doses safely and responsibly.
- Significant cognitive impairment.
- The patient is not attending the minimum acceptable number of clinic appointments required by the treatment team to provide care safely. These expectations need to be explicitly discussed and documented in the treatment agreement and/or patient chart.
- Abusive, intimidating, or harassing behavior directed toward staff, including pharmacy staff, or other patients in the clinic and pharmacy. Behavior expectations need to be explicitly discussed and documented in the treatment agreement and/or patient chart.
- The patient's preference is to attend the pharmacy daily or more frequently for witnessed ingestion.

Pharmacy closures over weekends and statutory holidays may require occasional take-home doses regardless of the above-mentioned contraindications. However, the prescriber may elect to withhold take-home doses altogether if the risks to the patient and/or public outweigh the potential benefits, and there is no other pharmacy available to access on these days.

5) Recommendations for occasional take-home doses in patients who do not otherwise meet criteria for take-home dosing.

Occasional take-home doses may be appropriate under certain circumstances for patients who do not otherwise meet criteria for take-home doses. Examples may include:

- Travel for verified medical appointments.
- Significant family events such as weddings and funerals.
- Significant family illness or other responsibilities requiring travel.
- Other non-specified circumstances deemed reasonable by the OAT provider.

Before authorizing take-home doses for travel purposes, clinicians should consider whether guest dosing at a pharmacy near the patient's travel destination may more appropriate.

Authorization of Take-home Doses & Communication with Pharmacy

Additions, changes, and exceptions to the take-home dosing schedule must be clearly documented in the medical record, and clearly communicated with the pharmacy.

The schedule of take-home doses can be communicated to the pharmacy by either writing the instructions for witnessed and take-home doses directly on the prescription, or by sending it to the pharmacy as a separate note or letter (see Relationship with Pharmacy for an example).

The latter is especially useful when the current prescription is still valid and the treatment team wishes to authorize changes to take-home doses, such as a new permanent carry or one-time carries for travel or another reason.

Take-home doses must be authorized by the prescriber or a member of the clinical team. The pharmacist cannot authorize take-home doses, and the prescriber/clinic staff should clearly explain this to the patient to avoid misunderstanding. Pharmacists can often provide valuable input on the appropriateness of take-home doses. Discussion is encouraged, especially when the prescriber/clinic staff are questioning the safety of providing carries in certain situations.

MONITORING FOR CLINICAL INSTABILITY & DIVERSION OF PRESCRIBED MEDICATION

It is the responsibility of the OAT prescriber and the treatment team to monitor clinical stability on an ongoing basis. All members of the treatment team must be vigilant when it comes to detecting diversion of prescribed medication. This is especially relevant when it comes to decisions regarding take-home dosing. See [Discontinuing Treatment](#) for guidance on managing potential diversion and considerations for involuntary withdrawal of treatment.

UDT & Medication Monitoring

In practice, monitoring for stability and diversion involves periodic UDT and/or pill counts for patients with take-home doses. If feasible, random UDT and/or random pill counts are an effective method for detecting diversion and illicit substance use. Due to the inherent logistical challenges associated with *random* testing and pill counts, it is recognized that most clinicians perform *periodic* testing and pill counts at scheduled patient visits.

Prescribers may consider asking the pharmacist to bubble pack take home doses to improve compliance and facilitate monitoring (pill counts). Bubble packed medications are not child proof and therefore may not be a safe option in some patient settings. Patients must secure bubble packs in a locked box or cabinet.

It should be noted that at this time the only reliable method of detecting buprenorphine in urine is by using point-of-care UDT kits that include a buprenorphine detection strip. The current street urine drug screen does not detect buprenorphine and the comprehensive urine drug screen only detects buprenorphine at supratherapeutic levels (as well as two metabolites).

See the Use of UDT in the Management of OUD chapter for a general approach to drug testing, including the recommended frequency and important issues to consider when interpreting results. Determination of clinical stability is never based on UDT results alone. Clinicians should rely on patient history, collateral information, and direct observation/clinical examination, which is augmented by UDT results, to formulate treatment plans in partnership with the patient. The chapters on Ongoing Care and [Managing Polypharmacy, Benzodiazepines, Alcohol & Polysubstance Use](#) also provide further guidance on assessing clinical stability.

Appendix P

TAKE-HOME (CARRY) DOSING AGREEMENT

I, _____, agree to the following conditions to receive take-home (or “carry”) doses of my medication.

- I am aware that the ingestion of even a small amount of my medication by a child or other person who is not accustomed to opioids could result in overdose or death.
- I will store my medication in a safe, locked box, or locked cabinet that cannot be accessed by other people or by pets.
- I will not sell or share my medication with another person. I understand that doing so is dangerous and may lead to loss of access to take-home doses or removal from the program.
- I will assume responsibility for my take-home doses, and I understand that take-home doses cannot be replaced if they are lost, stolen, spilled, or vomited.
- I will provide a urine sample when asked to do so by program staff. If I do not provide a sample as requested, or non-prescribed drugs are found in my sample, I may lose access to one or more take-home doses.
- I will bring my medication to my clinic or pharmacy if asked to do so. If I do not, I may lose access to one or more take-home doses including return to daily witnessed ingestion.

Patient Name: _____ Date: _____

Signature: _____

Witness Name: _____ Date: _____

Signature: _____

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.4 Recommendations for Unwitnessed Induction with Buprenorphine/naloxone

GENERAL CONSIDERATIONS

An unwitnessed induction of buprenorphine/ naloxone, otherwise known as a home induction, is an approach that does not require the patient to take the first dose(s) of buprenorphine under the direct supervision of a pharmacist, approved prescriber, or nurse.

This approach is particularly useful to engage patients in care who are unable to appear for a [Conventional Buprenorphine Induction](#) schedule at a pharmacy, or with an approved prescriber, due to a variety of patient characteristics or systemic barriers. The logistics involved with planning a conventional induction may be challenging for both patients and providers. Presenting for induction in moderate withdrawal requires careful planning, as well as some flexibility in the patient and prescriber's availability for assessment and dose titration. This may lead to overall lower utilization of buprenorphine/naloxone despite the superior safety profile.

It is important to note that *unwitnessed induction is not suggested here as an equally evidence-based* alternative to the [Conventional Induction](#) described in this manual. A limited number of studies that compare unobserved versus observed induction protocols have not shown differing rates of adverse or serious adverse events. These events include precipitated or protracted opioid withdrawal, pediatric exposure, or diversion-related emergency department visits. However, it is important to note that to date there are no high-quality randomized controlled trials with adequate power to model the equivalence or noninferiority of the two approaches with respect to infrequent safety events.

Providers must weigh the benefits and risks of witnessed versus unwitnessed induction in each case, based on individual circumstances. Only experienced prescribers who are competent and comfortable with witnessed buprenorphine/naloxone inductions should consider or utilize an unwitnessed induction approach, for select patients who face barriers to repeat in-office assessment of withdrawal and witnessed dosing. Some patients may also meet criteria for micro-dosing, as described in [Recommendations for Buprenorphine Micro-Dosing Induction](#).

SPECIFIC CONSIDERATIONS

It is the responsibility of the prescriber to educate a patient being considered for unwitnessed induction about the risks of this approach, including but not limited to precipitated withdrawal.

The prescriber must ensure that the patient can adequately understand these risks and that they know where to seek help if concerns arise. This includes providing afterhours contact number(s) for support.

See the [Conventional Buprenorphine Induction](#) chapter for guidance on *Management of Precipitated Withdrawal*, and [The Pharmacology of Buprenorphine, Precipitated Withdrawal & Management of Adverse Effects](#) for further details.

Patients Appropriate for Unwitnessed Induction

Unwitnessed induction may be considered in the following patients:

- Patients who have difficulty tolerating moderate withdrawal in the clinic/waiting room environment. (A conventional witnessed induction in the clinic setting requires a patient to be in moderate opioid withdrawal before initiating buprenorphine/naloxone, to avoid precipitated withdrawal. This can take 8-24 hours for short-acting and slow-release opioids, and 48-72 hours for long-acting opioids such as methadone.)
- Patients who have difficulty timing moderate withdrawal with the time of an assigned induction appointment in a clinic.
- Patients with significant psychosocial instability that makes attending a scheduled clinic appointment for induction challenging (examples may include no access to reliable transport, a lack of financial resources for transport, significant mobility limitations, chaotic lifestyle, lack of social supports, etc.)
- Work, school, or child/family care commitments that make attending a clinic appointment difficult or impossible.
- Patients who do not have reasonable access to a pharmacy for witnessed induction due to geographic limitations (distance to pharmacy and/or clinic), especially when dosing multiple times per day during the induction phase.

Good Candidates for Unwitnessed Induction

Patients who may be particularly good candidates for unwitnessed induction include:

- Patients who have previously completed a successful witnessed induction with buprenorphine/naloxone.
- Patients who have previously demonstrated responsible use of prescribed medications, including previous opioid agonist therapy (OAT) medications.
- Patients who can adequately understand the risks of unwitnessed inductions, including but not limited to precipitated withdrawal.
- No regular or heavy use of alcohol, benzodiazepines, or other sedative-hypnotics (including over-the-counter medications).
- No polypharmacy, especially multiple prescribed, sedating medications.
- Patients who express willingness to come into the office or attend an emergency department if problems arise during the induction process.
- Patients with stable housing.
- Patients with stable and supportive friends or family (as defined by the patient) who may assist in supporting and monitoring the home induction process.
- Individuals who present to the emergency department or other episodic care facilities with serious complications of opioid use disorder (OUD) such as overdose, infectious complications or a mental health crisis.
 - These patients may not be in enough withdrawal for a buprenorphine/naloxone induction in the emergency department. Discharging these individuals with a limited medication supply and home induction instructions may be an effective way to engage this high-risk population in timely care, as long as infrastructure for follow-up OAT care exists. The earliest possible follow-up at a local [Rapid Access to Addiction Medicine](#) (RAAM) clinic or an alternative clinic is recommended, ideally within 24-48 hours after discharge from the emergency department.
 - Patients being offered a witnessed or unwitnessed buprenorphine/naloxone induction in the emergency department must be provided with written information on where they can reasonably access follow-up care as part of the induction plan. (See [In Hospital Care](#), specifically the section **EMERGENCY DEPARTMENT/URGENT CARE OF INDIVIDUALS WITH OUD** for detailed recommendations).

Contraindications for Unwitnessed Induction

Some patients are more likely to experience adverse effects during unwitnessed induction. In general, it is not recommended for the following patient populations:

Relative contraindications include:

- Patients who are being switched from methadone to buprenorphine/naloxone. This is a much more difficult induction process. Prolonged opioid withdrawal persisting over several days after buprenorphine/naloxone induction is much more likely in patients being transitioned from methadone.
- Patients who express significant fear of opioid withdrawal. These patients may be more likely to start buprenorphine/naloxone too early and cause precipitated withdrawal.
- Patients who have experienced precipitated withdrawal in the past and who express reluctance to risk such an outcome again.

Absolute contraindications include:

- Patients with concurrent, heavy, problematic use of alcohol or sedative-hypnotics.
- Prescribed polypharmacy of other sedative/psychoactive medications. (See [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use](#) for details.)
- Acute significant medical illness such as pneumonia, sepsis, or recovery from physical injury requiring opioids for analgesia.
- Patients with significant active mental health concerns in the absence of a reliable support person at home who can assist in monitoring the home induction process.
- Patients with acute psychosis.
- Patients with active suicidal ideation or recent suicide attempts.
- Severe respiratory disease requiring careful monitoring during induction.
- Elderly, frail individuals, especially if they have multiple medical comorbidities.
- Significant cognitive impairment in the absence of a reliable support person at home who can assist in monitoring the home induction process.
- No safe place to stay during the induction.
- No ability to safely store medication where the patient is staying.

Patient Education & Support

A robust patient education strategy is necessary when preparing for home inductions. A well-documented conversation and written material, reviewed with the patient and their support person (if permitted by the patient), should be used to support this process.

Patients should be provided with written instructions regarding:

- The subjective and objective assessment of opioid withdrawal (see *Supporting Documents* below),
- The timing and dosing of buprenorphine/naloxone, and
- The phone numbers or other established processes for patient assistance in the event of patient or support-person questions, concerns, or adverse events. This should include contact information for the prescriber (and/or experienced clinic staff) and the pharmacy involved.

Simply advising the patient to “go to the nearest emergency department” is *not* an adequate support strategy. If a patient does not have access to a phone, or clinic hours do not permit in-person assessment after hours, attending an emergency department may be used as an additional strategy to support patients during the unwitnessed induction process.

It is important that the prescriber or representative of a prescriber group be available for contact by the pharmacy or emergency room staff to discuss issues that may arise during the induction process.

Patients must receive clear instructions on safe storage of buprenorphine (ideally in locked box or cabinet) as well as what to do with any unused medication (e.g., return to pharmacy for disposal at next pharmacy visit).

Witnessed Dosing Requirements & Reassessment

Generally, with conventional induction, buprenorphine/naloxone dose should be dispensed as witnessed doses.

Daily witnessed doses are self-administered under the direct supervision of a pharmacist, approved prescriber, or a nurse, until the patient has demonstrated sufficient clinical stability to be considered for take-home (carry) doses.

Comparatively, the following is recommended unwitnessed inductions:

- In most cases, buprenorphine/naloxone doses should be witnessed at the pharmacy starting **no later than Day 2**. Should an evening top-up dose be required on day 2, this dose may be given as a take-home dose.

- Under exceptional circumstances (e.g., geographic isolation from the pharmacy, with phone support and reassessment from prescriber or experienced clinic staff), patients may be given more than a one-day supply of medication for home induction. The rationale for this approach must be clearly documented and communicated to the pharmacy.
- The patient should be reassessed by the prescriber or experienced clinic staff, in person, **no later than Day 3** after initiating buprenorphine/naloxone at home. If this is not possible for any reason, a phone assessment must be completed with in-person follow-up as soon as possible thereafter.

All interactions with clinic staff (by phone or in person) during the home induction should be documented in the patient’s medical record.

Criteria for the provision of take-home doses are discussed elsewhere in this manual. See [Take-home \(Carry\) Dosing Recommendations](#) and [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#) for take-home guidance, and [Ongoing Care](#) for a detailed review of other issues often encountered during the maintenance phase of treatment.

Pharmacy Communication

Clear communication with the pharmacy is essential to facilitate a smooth home induction process. Even if the patient is provided with a medication starter pack from clinic or hospital stock, the community pharmacy that the patient attends for continued treatment must be contacted and made aware of the plan, as the patient may seek support from the pharmacy at any time during the unwitnessed induction process.

If possible, the induction doses should be dispensed by the pharmacy, and not given as a starter pack from clinic or hospital stock, to ensure that the medication is entered into the patient’s medication record (DPIN).

In addition to the M3P prescription, the community pharmacy must also be provided with the following information (see **Appendix Q** for suggested template):

- A copy of the unwitnessed induction protocol/instructions provided to the patient (see **Appendix R** for an example).
- The induction start date.
- When the patient is expected to attend the pharmacy to commence witnessed dosing.
- Clinic contact information.
- After-hours prescriber contact information.

Supporting Documents

An example of an unwitnessed induction protocol for patients with moderate- to high-dose opioid use is included as **Appendix R**. These induction instructions, or a similar customized protocol, should be provided to the patient and the pharmacy.

This induction protocol, or a similar customized protocol, should be provided to the patient along with a copy of the [Subjective Opiate Withdrawal Scale](#) (SOWS) or the [Clinical Opiate Withdrawal Scale](#) (COWS) score sheet. SOWS is a useful tool for a support person to utilize when assisting the patient in managing a home induction.

For patients with low-dose opioid use, or other risk factors for over-sedation or toxicity, lower overall induction doses will need to be used. See the [Conventional Buprenorphine Induction](#) chapter for further induction and titration dosing guidance, and the [Ongoing Care](#) chapter for recommendations around overall dosing stability.

The patient must also be provided with an **unwitnessed induction wallet card**. This is especially important when a patient is given an unwitnessed induction starter pack from hospital or clinic stock and the medication has not been entered into the DPIN system. The wallet card serves as a notification to EMS/ER staff that the patient was prescribed an unwitnessed induction protocol. See **Appendix S** for an unwitnessed induction wallet card template.

Appendix Q

PHARMACY UNWITNESSED INDUCTION NOTIFICATION

Date: _____

Pharmacy: _____

Phone: _____

Fax: _____

Dear Pharmacist,

RE: _____

DOB: _____

PHIN: _____

Clinic Phone: _____

Fax: _____

I have assessed the above-named patient and they are a candidate for unwitnessed induction of buprenorphine/naloxone. I have provided instructions to the patient regarding their unwitnessed induction. A copy of the induction protocol is included. **Please note the following:**

- The patient has been provided with a **starter pack of buprenorphine/naloxone from clinic/hospital stock** to start home induction. They will present to pharmacy on _____ (DATE) to commence witnessed dosing. An M3P prescription is included.

OR

- An M3P prescription is included, and the patient will present to pharmacy on _____ (DATE) to obtain the unwitnessed (home) induction medication supply.

The patient will present to pharmacy again on _____ (DATE) to commence witnessed dosing.

Please notify my clinic at _____ (PHONE NUMBER) of any missed doses, in case the induction schedule needs to be adjusted. I have advised my patient as follows regarding missed doses at home: _____.

After hours I can be reached at _____ (PHONE NUMBER) or call _____ to speak to our on-call prescriber.

Sincerely,

Prescriber Name, signature, & credentials

Appendix R

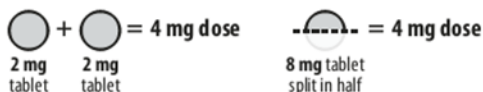
STARTING BUPRENORPHINE/NALOXONE (SUBOXONE®) AT HOME*

Before starting buprenorphine/naloxone (Suboxone®) at home, you need to wait until you feel very sick from withdrawal (“dope sick”).

Your prescriber will tell you how long you should wait after using opioids before following these steps.

Use the SOWS withdrawal scale on the next page before you start the medication. **When your SOWS score is 17 or higher, you are ready to begin.**

Prescriber Name: _____
 Prescriber Phone: _____
 Next Appointment: _____
 Pharmacy Name: _____
 Pharmacy Phone: _____



DAY 1 8-12 mg of buprenorphine

4 mg **STEP 1: Take your first 4 mg dose when your SOWS score is 17 or higher.**

- Keep the medication under your tongue until it has dissolved completely (15 minutes).
- Do NOT eat, drink or swallow while it's dissolving, or it will not work.
- If you feel a lot worse, STOP and contact your provider or pharmacy. This can happen if you start the medication before your withdrawal symptoms are bad enough.

Wait 1 hour

4 mg **STEP 2 (after 1 hour): If you still feel sick, take a second 4 mg dose.**

- Many people feel better after two doses (8 mg total).

Wait 6 hours

4 mg **STEP 3 (after 6 hours): If you still feel sick, take a third 4 mg dose.**

- STOP after this dose. Don't take more than 12 mg total on Day 1.

DAY 2 12-16 mg of buprenorphine

12 mg **STEP 1: Take your Day 2 morning dose (usually 12 mg).**

- Your morning dose will usually be taken at your pharmacy. You'll also receive a dose to take home for later.

Wait 6 hours

4 mg **STEP 2 (after 6 hours): If you still feel sick, take an additional 4 mg dose.**

- Don't take more than 16 mg total on Day 2.

DAY 3 16 mg of buprenorphine

16 mg **STEP 1: Take your Day 3 morning dose (usually 16 mg).**

- This dose will usually be taken at your pharmacy.
- Repeat this dose each day until you see your provider in clinic (usually by Day 3).

*This induction protocol is an example only. Prescribers should adjust dosages to reflect factors such as low opioid tolerance.

Appendix S

SAMPLE WALLET UNWITNESSED INDUCTION NOTIFICATION CARD

FRONT

UNWITNESSED INDUCTION NOTIFICATION CARD
For buprenorphine/naloxone (Suboxone®)

I, _____ (NAME)
and _____ (DOB) am undergoing
an unwitnessed (home) induction with Suboxone®

Pharmacy Name: _____

Pharmacy Address: _____

Pharmacy Phone: _____

Start date: _____

BACK

PRESCRIBER/HOSPITAL INFORMATION
(could be copy of business card)

Suboxone® starter pack provided?
 Yes No

Provided by: _____
(Prescriber/Hospital Name)

Address: _____

Phone: _____

After Hours Ph: _____

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.5 Recommendations for Buprenorphine/naloxone Micro-Dosing Induction for Opioid Use Disorder

GENERAL CONSIDERATIONS

As a partial agonist with high affinity for the *mu*-opioid receptor, buprenorphine has the potential to displace other full agonists at the receptor level, and precipitate clinically significant opioid withdrawal symptoms. This occurs when an initial dose of buprenorphine/naloxone is taken by a patient who has recently consumed other opioids. Therefore, the [Conventional Buprenorphine Induction](#) requires a patient to be in moderate opioid withdrawal before initiating buprenorphine/naloxone. This can take 8-24 hours for short-acting and slow-release opioids, and 48-72 hours for long-acting opioids such as methadone.

The opioid withdrawal symptoms experienced during this waiting period may be intolerable or impractical for some patients for a variety of reasons. Additionally, the logistics involved with planning a conventional buprenorphine/naloxone induction may be challenging for both patients and providers. Presenting for induction in moderate withdrawal requires careful planning, as well as some flexibility in the patient and prescriber's availability for assessment and dose titration. This may lead to overall lower utilization of buprenorphine/naloxone despite the superior safety profile.

Comparatively, micro-dosing of buprenorphine/naloxone (commonly referred to as the "Bernese method") involves a buprenorphine induction overlapping with the continued use of a full opioid agonist by the patient, and does not require a patient to reach moderate withdrawal. It is based on the hypothesis that *small repetitive dosing of buprenorphine* with adequate dosing intervals should not precipitate withdrawal. Due to its high receptor affinity and long binding time, buprenorphine will *gradually* replace the full opioid agonist at the mu receptor, as it slowly accumulates at the receptor sites.

It is important to note that *micro-dosing is not suggested here as an equally evidence-based alternative to the [Conventional Buprenorphine Induction](#) method described in this manual. The evidence supporting the micro-dosing approach is lacking and consists mainly of case descriptions. However, there is a substantial amount of practical experience with this method in Canada and it has gained acceptance as a viable alternative when the conventional induction method is not practical or possible.*

Micro-dosing induction may be considered for select patients who are unlikely to tolerate the prerequisite interval of opioid abstinence, and when barriers exist to repeat in-office assessment of withdrawal and witnessed dosing. Some patients may also meet criteria for unwitnessed (“home”) induction, as described in [Recommendations for Unwitnessed Induction with Buprenorphine/naloxone](#).

SPECIFIC CONSIDERATIONS

It is the responsibility of the prescriber to educate a patient being considered for micro-dosing induction about the risks of this approach, including but not limited to precipitated withdrawal.

The prescriber must ensure that the patient can adequately understand these risks and that they know where to seek help if concerns arise. This includes providing afterhours contact number(s) for support.

See the [Conventional Buprenorphine Induction](#) chapter for guidance on *Management of Precipitated Withdrawal*, and [The Pharmacology of Buprenorphine, Precipitated Withdrawal & Management of Adverse Effects](#) for further details.

Patients Appropriate for Micro-Dosing

Micro-dosing induction may be considered in the following patients:

- Patients who fear withdrawal or experience severe withdrawal symptoms during conventional induction (as above, moderate withdrawal is required to begin a conventional induction).
- Patients who have failed a conventional induction due to inability to tolerate moderate withdrawal.
- Patients with significant psychosocial instability that makes attending a scheduled clinic appointment for induction challenging (examples may include no access to reliable transport, a lack of financial resources for transport, significant mobility limitations, chaotic lifestyle, lack of social supports, etc.)

Good Candidates for Micro-Dosing

Patients who may be particularly good candidates for micro-dosing include:

- Patients who are being switched from methadone or other high-dose long-acting opioids to buprenorphine/naloxone. Due to the complexity and case-by-case variability of these medication transitions, specialist guidance must be sought to ensure appropriate customization of the micro-dosing schedule, including appropriate cross-titration of methadone, or the other high-dose long-acting opioid being discontinued. See [Ongoing Care](#) for further guidance on the **ROTATION OF OAT MEDICATIONS**.
- Patients who are using illicit fentanyl and/or fentanyl analogues (due to the uncertain risk of precipitated withdrawal).
- Patients who may be unable to tolerate moderate withdrawal due to a comorbid physical or mental health condition.
- Pregnant persons who are not currently in withdrawal and for whom methadone is contraindicated, who refuse treatment with methadone, or who do not have access to methadone treatment in their home community. An inpatient admission for induction may also be reasonable under these circumstances. See [Treatment of OUD in Pregnancy](#) and [In-Hospital Care](#) for detailed recommendations.

Witnessed Dosing Requirements & Reassessment

Generally, with conventional induction, buprenorphine/naloxone should be dispensed as daily witnessed doses. Daily witnessed doses are self-administered under the direct supervision of a pharmacist, approved prescriber, or a nurse, until the patient has demonstrated sufficient clinical stability to be considered for take-home (carry) doses.

Comparatively, the following is recommended for micro-dosing inductions:

- In most cases, buprenorphine/naloxone doses should be witnessed at the pharmacy starting **no later than Day 4**, with evening doses being provided as carries.
- Under exceptional circumstances (e.g., geographic isolation from the pharmacy, with phone support and reassessment from prescriber or experienced clinic staff), patients may be given more than a 3-day supply of medication for a micro-dosing induction. The rationale for this approach must be clearly documented and communicated to the pharmacy.
- After initiating a buprenorphine micro-dosing protocol, the patient should be **reassessed no later than Day 7, in person, by the prescriber or experienced clinic staff**. If this is not possible for any reason, a phone assessment should be completed, with in-person follow-up as soon as possible thereafter.

All interactions with clinic staff (by phone or in person) during the micro-dosing induction should be documented in the patient’s medical record.

Criteria for the provision of take-home doses are discussed elsewhere in this manual. See [Take-home \(Carry\) Dosing Recommendations](#) and [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#) for take-home guidance, and [Ongoing Care](#) for a detailed review of other issues often encountered during the maintenance phase of treatment.

Pharmacy Communication

Clear communication with the pharmacy is essential to facilitate a smooth micro-dosing induction process. Even if the patient is provided with a medication starter pack from clinic or hospital stock, the community pharmacy that the patient attends for continued treatment must be contacted and made aware of the plan, as the patient may seek support from the pharmacy at any time during the micro-dosing induction process.

If possible, the induction doses should be dispensed by the pharmacy, and not given as a starter pack from clinic or hospital stock, to ensure that the medication is entered into the patient’s medication record (DPIN).

If the patient is given a medication starter pack from clinic or hospital stock, the community pharmacy that receives the follow-up M3P prescription must also be provided with the following information (see **Appendix T** for suggested template):

- A copy of the micro-dosing induction protocol/instructions provided to the patient (see **Appendix U** for an example).
- The micro-dosing induction start date.
- Advice to be given to the patient if one or more doses are missed. This is at the prescriber’s discretion – no clear evidence exists to guide approach.
- When the patient is expected to attend the pharmacy to commence witnessed dosing.
- Clinic contact information.
- After-hours prescriber contact information.

Due to the small starting doses, tablets need to be split. Pharmacists should dispense or administer split buprenorphine/naloxone tablets to the same patient in consecutive doses since splitting tablets can result in uneven doses and may hasten the degradation of the tablet.

As micro-dosing induction approaches are still under development and not entirely evidence-based, prescribers must ask pharmacists to share treatment outcomes for data collection and quality improvement purposes.

Supporting Documents

An example of a micro-dosing induction protocol for patients with moderate- to high-dose opioid use is included as **Appendix U**. These induction instructions, or a similar customized protocol, should be provided to the patient and the pharmacy.

For patients with low-dose opioid use, or other risk factors for over-sedation or toxicity, lower overall induction doses will need to be used. See the [Conventional Buprenorphine Induction](#) chapter for further induction and titration dosing guidance, and the [Ongoing Care](#) chapter for recommendations around overall dosing stability.

The patient must also be provided with a **micro-dosing induction wallet card**. This is especially important when a patient is given a micro-dosing starter pack from hospital or clinic stock and the medication has not been entered into the DPIN system. The wallet card serves as a notification to EMS/ER staff that the patient was prescribed a micro-dosing induction protocol. See **Appendix V** for a micro-dosing induction wallet card template.

Appendix T

PHARMACY MICRO-DOSING INDUCTION NOTIFICATION

Date:

Pharmacy:

Phone:

Fax:

Dear Pharmacist,

RE:

DOB:

PHIN:

Clinic Phone:

Fax:

I have assessed the above-named patient and they are a candidate for micro-dosing induction of buprenorphine/naloxone. I have provided instructions to the patient regarding their micro-dosing induction. A copy of the induction protocol is included. **Please note the following:**

- The patient has been provided with a **starter pack of buprenorphine/naloxone from clinic/hospital stock** to start micro-dosing. They will present to pharmacy on _____ (DATE) to commence witnessed dosing. An M3P prescription is included.

OR

- An M3P prescription is included, and the patient will present to pharmacy on _____ (DATE) to obtain the micro-dosing induction medication supply. **Please supply the first 3 days of medication in blister packaging with tablets already split as required by the dosing regimen.** Unless otherwise indicated, these first 3 days do not require witnessed dosing.

The patient will present to pharmacy again on _____ (DATE) to commence witnessed dosing.

Please notify my clinic at _____ (PHONE NUMBER) of any missed doses, in case the induction schedule needs to be adjusted. I have advised my patient as follows regarding missed doses at home: _____.

After hours I can be reached at _____ (PHONE NUMBER) or call _____ to speak to our on-call prescriber.

Sincerely,

Prescriber Name, signature, & credentials

Appendix U

BUPRENORPHINE/NALOXONE (SUBOXONE®) MICRO-DOSING INSTRUCTIONS

Micro-dosing Suboxone® is one way to start opioid agonist treatment (OAT) when you aren't able to stop your opioid use.

Your pharmacy will give you 3 days of medication to take at home in gradually increasing doses, reducing the risk of experiencing sudden severe withdrawal symptoms (“precipitated withdrawal”). On Day 4, you’ll start going to your pharmacy daily to continue the micro-dosing process. During this time, you can continue using opioids, but will gradually decrease the amount of opioids you use.

Prescriber Name: _____

Prescriber Phone: _____

Next Appointment: _____

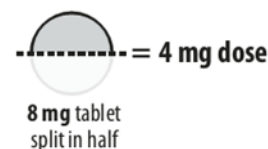
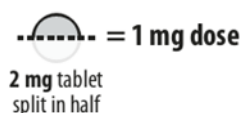
Pharmacy Name: _____

Pharmacy Phone: _____

	BUPRENORPHINE/NALOXONE*	OTHER OPIOIDS
Day 1	0.5 mg, twice per day	
Day 2	1 mg, twice per day	Start gradually reducing your opioid use
Day 3	2 mg, twice per day	↓
Day 4	3 mg, twice per day	
Day 5	4 mg, twice per day	
Day 6	4 mg, three times per day	Last day of other opioids
Day 7	12 mg, once per day	No other opioids

Day 8 & onwards

Your doctor may continue to adjust your medication to relieve withdrawal symptoms until a stable dose is achieved.



*This induction protocol is an example only. Prescribers should adjust dosages to reflect factors such as low opioid tolerance.

Appendix V

SAMPLE WALLET MICRO-DOSING INDUCTION NOTIFICATION CARD

FRONT

MICRO-DOSING INDUCTION NOTIFICATION CARD
For buprenorphine/naloxone (Suboxone®)

I, _____ (NAME)
and _____ (DOB) am undergoing
a micro-dosing induction with Suboxone®

Pharmacy Name: _____

Pharmacy Address: _____

Pharmacy Phone: _____

Start date: _____

BACK

PRESCRIBER/HOSPITAL INFORMATION
(could be copy of business card)

Suboxone® starter pack provided?
 Yes No

Provided by: _____
(Prescriber/Hospital Name)

Address: _____

Phone: _____

After Hours Ph: _____

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

2.6 Recommendations for Sublocade® & Considerations for Informed Consent

GENERAL CONSIDERATIONS

Buprenorphine extended-release injection (Sublocade®) is a partial opioid agonist for the management of moderate to severe opioid use disorder (OUD). As a subcutaneous monthly depot injection, it is an alternative treatment option that essentially replaces daily dosing with sublingual buprenorphine/naloxone.

It is important to note that thus far in clinical trials Sublocade® has only been evaluated for clinical effectiveness in the treatment of OUD against placebo. The effectiveness of Sublocade® has yet to be definitively compared to sublingual buprenorphine/naloxone¹. Results of a true non-inferiority study are not yet available. The intent of this chapter is *not* to promote Sublocade® use over daily buprenorphine/naloxone treatment, but to discuss considerations for its use and associated recommendations.

To be considered for Sublocade® a patient must tolerate a sublingual buprenorphine/naloxone dose of 8 to 24 mg daily. Presently, there is no injectable dose equivalency for patients requiring less than 8 mg of buprenorphine. While patients treated with 26 to 32 mg of buprenorphine/naloxone daily may be considered for Sublocade®, this option may be less effective at adequately treating withdrawal than buprenorphine/naloxone in this population.

Sublocade® must be administered by subcutaneous injection in the abdominal region by a trained physician, nurse, or pharmacist. For effective treatment, it is administered once per month. This may reduce the patient burden of treatment when compared to daily administration of buprenorphine/naloxone¹. Sublocade® can be helpful for patients who wish to simplify treatment, who have barriers to regular pharmacy attendance, and/or who have no practical pharmacy access due to geographic limitations. Monthly administration can offer patients more flexibility with treatment, particularly when clinical instability does not warrant take-home dosing of sublingual buprenorphine.

Other potential benefits may include more predictable steady-state concentrations and lower peak-to-trough fluctuations than with daily dosing², potentially providing superior overdose protection, especially in patients who frequently miss doses on a daily regimen. Sublocade® may also be associated with reduced stigma (associated with regular pharmacy visits) and reduced risk for theft/diversion of sublingual tablets. The monthly administration can also support extended travel and employment opportunities without the added effort of arranging daily medication availability.

Importantly, Sublocade® has created treatment access for northern/remote patients who do not have pharmacy access in their home communities and where daily witnessed self-administration of OAT medications (under the direct supervision of a pharmacist, approved prescriber, or a nurse) cannot be feasibly arranged.

SPECIFIC CONSIDERATIONS

Sublocade® can be explored with both clinically stable patients and those struggling with instability and/or regular pharmacy attendance. As above, it can enhance convenience for some patients who may find less frequent medication administration preferable. It can also enhance medication adherence, particularly when patients are frequently missing doses of sublingual buprenorphine/naloxone.

Sublocade® for Patients Missing Doses

Missed doses of OAT (due to patients not attending the pharmacy for witnessed self-administration and possible take-home doses) can indicate a variety of problems that warrant exploration. The prescriber should review reasons for missed doses and make every effort to problem solve with the patient (see [Ongoing Care](#) for details, specifically **MISSED OAT DOSES**).

If the patient is on buprenorphine/naloxone and sufficiently stable, but struggling to attend the pharmacy due to work or family responsibilities, consider accelerating the provision of take-home doses as outlined in [Buprenorphine Take-home Dosing Recommendations](#).

Alternatively, if the patient is not a candidate for accelerated take-home doses, consider switching to Sublocade® to facilitate fewer pharmacy visits. An open-label randomized clinical trial in Australia found that treatment satisfaction was higher in patients receiving depot buprenorphine (a different formulation, brand name Brixadi®) compared to sublingual buprenorphine/naloxone, after 24 weeks³. Providers should assess and discuss with the patient if switching to Sublocade® would be suitable and preferable, based on their patient-specific circumstances.

Sublocade® therapy can be considered in patients stabilized on 8 to 24 mg sublingual buprenorphine/naloxone daily, for at least 3 (based on local experience) to 7 days. The depot injection does not require abstinence from other opioids before initiation, but it is preferable.

Importantly, if a patient switches to depot buprenorphine therapy, the prescriber must also consider the overall medication management plan for patients on other sedating/psychoactive medications to determine a safe and reasonable dispensing schedule for these medications.

Training Requirements

To prescribe other formulations of buprenorphine, including Sublocade® or Probuphine® (subdermal implant), prescribers must hold a buprenorphine/naloxone prescribing approval/authorization from their respective regulatory body and pursue additional training as required by Health Canada and outlined in the box below. Additionally, see **A NOTE ON PROBUPHINE®** at the end of this chapter.

Prescribers must also ensure they have the requisite knowledge, skills, and clinical competence to administer Sublocade®, and for the proper insertion and removal of the Probuphine® implant, before prescribing.

Pharmacists should review the joint [Guidance on the Administration of Sublocade by a Pharmacist](#) and contact the College of Pharmacists of Manitoba (CPhM) for more information on training requirements for dispensing the buprenorphine injectable depot and subdermal implant formulations.

INFORMATION ON SUBLOCADE® TRAINING

More information on Sublocade® use and administration is available **for prescribers and pharmacists** in this document: [Joint Guidance on Sublocade® Administration](#).

- Prescribers must hold a current, active buprenorphine/naloxone prescribing approval/authorization from CPSM/CRNM to prescribe Sublocade®.
- Currently, approved/authorized prescribers wanting to prescribe Sublocade® must complete the non-accredited certification program, **a Health Canada requirement**, available at www.sublocadecertification.ca. The completed program certificate must be faxed to the pharmacy along with the M3P prescription when prescribers first order Sublocade® from a particular pharmacy.

INFORMATION ON PROBUPHINE® TRAINING

More information on Probuphine® (buprenorphine implant) is available **for prescribers and pharmacists** by contacting the CPSM's Prescribing Practices Program directly.

- Please note that prescribers must hold a current, active buprenorphine/naloxone prescribing approval/authorization from CPSM/CRNM to prescribe/implant Probuphine®.
- Because of the risks associated with insertion and removal, Probuphine® must be prescribed, implanted, and removed only by trained prescribers who have successfully completed a training program on the insertion and removal of Probuphine®.

Medication Coverage

Sublocade® is covered for patients whose medications are covered by Non-Insured Health Benefits (NIHB) for First Nations and Inuit. Additionally, to qualify for coverage, patients are **no longer required** to be on a stable dose of buprenorphine/naloxone for a minimum of 7 days prior to starting Sublocade®. Prior approval for Sublocade® is also no longer required.

Otherwise, Sublocade® is an eligible benefit under Part 2 of the Manitoba Drug Benefits Formulary for the management of moderate to severe OUD, in adult patients who have been inducted and clinically stabilized on a transmucosal buprenorphine-containing product, if the following criteria and conditions are met:

Criteria:

- Patients must be induced and stabilized on an equivalent of 8 to 24 mg per day of transmucosal buprenorphine for a minimum of 7 days.

Conditions:

- Patients are under the care of a healthcare provider with experience in the diagnosis and management of OUD and who has been trained to administer the buprenorphine extended-release injection.
- Buprenorphine extended-release injection should be used as part of a complete treatment plan that includes counselling and psychosocial support.
- Buprenorphine extended-release injection must be administered subcutaneously in the abdominal region by a healthcare provider.

CONSIDERATIONS FOR INFORMED CONSENT

When starting any OAT medication, prescribers must counsel patients about the benefits and risks of treatment to obtain informed consent. Starting Sublocade® is no different. The Centre for Addiction and Mental Health (CAMH) guideline, [*Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*](#), notes that there is not yet evidence about the long-term safety and effectiveness of depot (or implant) buprenorphine therapy and encourages prescribers to review the existing evidence to counsel patients accordingly for informed consent⁴. Other considerations include the patient's comfort with an invasive procedure and available medication coverage options.

Patients of Reproductive Age & Informed Consent

Unique considerations for informed consent with Sublocade® include discussion about pregnancy and reliable contraception. **Presently, it is not known if Sublocade is safe in pregnancy.**

While there is limited evidence surrounding its use in pregnancy, providers must weigh the risks and benefits of treatment with Sublocade® collaboratively with the patient and be frank about what is not yet known from a medical perspective. (see *Sublocade® In Pregnancy* below).

Prescribers must ensure that female patients of reproductive age are counselled to use a reliable form of birth control (such as an intrauterine device (IUD) or Depo Provera) prior to receiving a Sublocade® injection, and for the duration of treatment with Sublocade®. Two forms of less reliable birth control (such as an oral contraceptive pill combined with a barrier method) may be an alternative.

Due diligence is also needed to ensure patients understand the potential implications of not using reliable birth control. While medicine is not aware of any teratogenicity with Sublocade® use in pregnant women to date, it is not yet known if Sublocade® is safe in pregnancy as one of its excipients, *N*-methyl-pyrrolidone (NMP), has been identified as potentially teratogenic in animal studies.

If a patient who understands this information indicates that they do not require birth control for some reason or indicates that they find the use of birth control unacceptable, OAT providers are to use their clinical judgement in **weighing the potential benefits of treatment with Sublocade® (including treatment access and retention) against the risks of an unplanned pregnancy while on Sublocade®**. This conversation and any decisions made, should be carefully documented in the patient record.

Regardless of the patient's choice around the use of reliable birth control, if the provider and patient agree to proceed with Sublocade® treatment, the use of a **written consent form is strongly recommended** to facilitate further documentation of the patient's informed consent to treatment with Sublocade® (see **Appendix W** and **X** for an example).

In addition to the above, in patients of reproductive age, an in-office pregnancy test is strongly recommended before every injection and regardless of the contraceptive option selected by the patient.

When Sublocade® is administered in pharmacy and a pregnancy test is not available, periodic pregnancy tests in clinic are recommended when the patient presents for follow-up care and other reasons.

Other Considerations for Consent

Another important aspect of informed consent is ensuring that patients understand the implications of missing their monthly Sublocade® injection. If patients are more than two weeks late for a scheduled administration, this may necessitate restarting on daily witnessed buprenorphine/naloxone at a pharmacy, for a period, before transitioning to Sublocade® again. See *Approach to Missed Injections* for details.

CARING FOR PATIENTS ON SUBLOCADE®

OAT treatment teams are encouraged to actively track the intervals between Sublocade® injection appointments. If a patient misses an injection appointment, a member of the team should contact the patient to remind them their injection is due and to proactively reschedule the appointment or offer drop-in times when they could be accommodated, considering prescriber/nurse and patient availability, and travel/transportation issues. Missed monthly administration can have a substantial negative impact on patients' lives and responsibilities, and carries a risk of relapse, especially if the patient is prone to breakthrough withdrawal if the injection is delayed (see *Breakthrough Withdrawal* and other considerations below).

Approach to Missed Injections

A patient who misses a Sublocade® injection should receive the dose as soon as possible, with the following dose given no less than 26 days later. Unavoidable occasional delays in dosing up to two weeks are not expected to have a clinically significant impact on treatment effect for patients stable on Sublocade®.

Occasionally patients may present for the next Sublocade® injection past the six-week mark. The following is recommended in these situations:

- The prescriber, or a member of the treatment team, should assess the patient in-person or, if not possible, virtually (ideally on-camera) to inform the next steps.
- During assessment, ask about recent opioid use including the pattern of use and when the patient last used opioids.
- Assess the patient for opioid withdrawal. A [Clinical Opiate Withdrawal Scale \(COWS\)](#) score may be useful.
- Conduct a urine drug test (UDT) to verify the patient history. A point-of-care UDT is preferred, if available, due to immediate availability of results.
 - **Consider Sublocade® injection** if the patient has not used opioids and this is confirmed by UDT, and they look well or are experiencing mild opioid withdrawal. Clinical discretion can be used at this point to determine if the Sublocade® injection is advisable. The patient must be made aware of the limited risk of precipitated withdrawal in this scenario.
 - **A restart on buprenorphine/naloxone with transition to Sublocade®** is indicated if the patient confirms opioid use and/or this is confirmed on UDT, and/or if the patient is in moderate to severe opioid withdrawal, and/or if the patient presents well past the six-week mark. The patient should also be educated about the increased risk of precipitated withdrawal under these circumstances.

If point-of-care UDT is not readily available and lab results will be delayed, and the patient report is deemed reliable, the absence of UDT results *should not* significantly impact clinical decision making.

Sublocade® Dosing Intervals

According to the product monograph, Sublocade® is to be administered monthly only by subcutaneous injection in the abdominal region, and the recommended dose is 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly. The maintenance dose may be increased to 300 mg monthly for patients who tolerate the 100 mg dose, but do not demonstrate a satisfactory clinical response, and where the benefits outweigh the risks⁵.

Breakthrough Withdrawal

With the conventional monthly dosing regimen, practical experience indicates that about two-thirds of patients treated with Sublocade® achieve clinical stability early on, with elimination of opioid withdrawal for 24 hours. In one-third of patients, opioid withdrawal often returns several days before the second injection of 300 mg is due. In select patients, withdrawal may return as soon as two weeks before the second dose is due and intensify until the second dose is administered. OAT treatment teams are encouraged to make patients aware of this possibility from the first discussion about transitioning to Sublocade®. Reassure patients that they will not be left to suffer if they report breakthrough withdrawal symptoms before the next injection is due.

The experience of breakthrough withdrawal will gradually improve and eventually resolve in a subset of patients, as Sublocade® accumulates and reaches steady state after multiple monthly injections (it can take 4-6 months to achieve steady state⁵). While this happens, it is important to support the patient by treating breakthrough withdrawal, as this promotes adherence and treatment retention over time. This is especially important in patients who do not have practical pharmacy access and who cannot to return to daily buprenorphine/naloxone dosing.

Top-Up Dosing

Top-up dosing with sublingual buprenorphine/naloxone can address breakthrough withdrawal on Sublocade®. This is typically done by prescribing a low dose of buprenorphine/naloxone for daily use, in addition to scheduled Sublocade® injections. The buprenorphine/naloxone dose may be titrated to effect. As the Sublocade® serum level accumulates over time, top-up dosing should be tapered accordingly and eventually discontinued.

In communities with no pharmacy access, top-up dosing often implies take-home (carry) doses, and the benefits of this approach must be weighed against the potential patient and community risks associated with buprenorphine take-home dosing. A low dose of

buprenorphine/naloxone prescribed as a top-up is often reasonable in communities without pharmacy access, provided the patient has a lockbox and can store the medication safely.

Adjusted Dosing Intervals

A second potential strategy to address breakthrough withdrawal on Sublocade® is to schedule injections closer together. The product monograph states that Sublocade® injections should not be administered less than 26 days apart. However, practical experience dictates that patients who experience *significant* breakthrough withdrawal can benefit from administering Sublocade® within a shorter interval.

OAT prescribers/treatment teams must assess the patient frequently and use their clinical discretion in scheduling Sublocade® injections less than 26 days apart. This strategy can be particularly useful when sublingual buprenorphine/naloxone is not a practical/safe option. As the Sublocade® serum level accumulates, injections may be scheduled further apart, and providers should rely on regular clinical assessment to guide adjustments in the dosing schedule.

Concurrent Chronic Pain & OUD

Occasionally, a patient with an active chronic pain condition and OUD may require Sublocade® to facilitate engagement in OAT care. If the chronic pain condition is not adequately addressed with the traditional Sublocade® dosing regimen, and with adjunctive pharmacological and non-pharmacological pain therapies, consideration may be given to continuing with the 300 mg Sublocade® dosage beyond two months and potentially long-term. Once again, the patient should be assessed regularly to ensure that they are tolerating the sustained higher dose and that the burden of treatment (side effects) does not outweigh the benefits of the adjusted dosing regimen.

Patients with Severe & Persistent Breakthrough Withdrawal

OAT providers may occasionally encounter a patient who experiences *early* and *persistent* severe withdrawal with a traditional Sublocade® dosing regimen, that does not resolve in time and is not associated with chronic pain. While top-up dosing may be utilized in early treatment, this is not always a desirable or practical long-term option. Patient safety and stability, community safety, and potential diversion of top-up doses, may dictate that alternatives must be explored when breakthrough withdrawal does not resolve after 4-6 months on Sublocade®.

In such rare cases, consideration may be given to continuing with 300 mg doses indefinitely AND scheduling these doses closer together on an ongoing basis. **Inexperienced prescribers are encouraged to reach out for advice/mentorship support from prescribers with robust Sublocade® experience to navigate these complex patients.**

Extended Intervals Between Injections

A subset of patients who are transitioned to Sublocade® may report that their withdrawal is immediately and effectively addressed for more than one month following their first injection. If Sublocade® injections are adequately controlling withdrawal for more than 30 days and this pattern persists, such patients may elect to present for their injections at extended intervals. Prescribers/treatment teams are encouraged to accommodate these requests based on the absence of withdrawal throughout the dosing interval and to further reduce the burden of treatment. These patients should be encouraged to present for Sublocade® injections no more than six weeks apart, even if they are not experiencing breakthrough withdrawal.

Opaskwayak Health Authority (OHA) OAT Program

The OHA OAT Program is a northern remote program serving individuals with OUD from Opaskwayak Cree Nation, The Pas, Moose Lake, Easterville, Grand Rapids, and surrounding areas. Many patients from these areas do not have pharmacy access in their home communities, making daily dispensing of OAT especially challenging.

The availability of Sublocade® has created treatment access for many patients in this region who previously did not have practical access to OAT. The program's clinical experience with Sublocade® has highlighted key aspects of patient care and consent that require careful navigation. The program has developed consent forms to manage these special considerations in clinic and offered to share their forms as a resource for other programs. See **Appendix W** and **X** for the following templates:

- Treatment with Sublocade® Consent Form: [General Version](#)
- Treatment with Sublocade® Consent Form: [Reproductive Age Version](#)

Respectfully, please retain the acknowledgment that this work is the intellectual property of the OHA OAT program staff when adapting them for clinical use. Prescribers/nurses from this program are also available to provide advice/guidance to other prescribers regarding the use of Sublocade® as challenges or clinical questions arise.

Sublocade® In Pregnancy

As outlined in [Treatment of OUD in Pregnancy](#), there is limited evidence surrounding the use of Sublocade® in pregnancy. As data emerges, these recommendations will be revised accordingly, however, reliable data is not expected to be imminently available:

- **Consideration of RISK:** In general, pregnancy and breastfeeding have been viewed as relative contraindications to Sublocade®, as one of its excipients, *N*-methyl-pyrrolidone (NMP), has been identified as potentially teratogenic in animal studies. Human data is extremely limited: two cases of undiagnosed pregnancy treated with Sublocade®, up to 18 weeks gestation, had normal obstetrical and pediatric outcomes⁶.

- **Anticipation of BENEFIT:** The motivation to explore Sublocade® in pregnancy is not only for the perceived benefits that apply to non-pregnant patients (more stable steady-state than daily dosing, fewer pharmacy visits and associated stigma, and reduced risk for theft/diversion of sublingual tablets)⁷. The pharmacokinetics are also theorized to result in decreased neonatal withdrawal severity. Clinical trials of a novel formulation without NMP are underway at the time of writing. CAM2038 has a weekly depot formulation that replaces NMP with ethanol at a clinically irrelevant concentration; the maximum fetal exposure over 9 months gestation is one tablespoon⁸. This is being studied in a randomized control trial compared with daily sublingual buprenorphine/naloxone.
- As above, it is not uncommon to have breakthrough withdrawal during the first month of Sublocade® treatment, requiring supplementation with sublingual buprenorphine/naloxone⁹. For some patients, breakthrough withdrawal may even last longer than the first month of treatment. This may obviate some of the improved convenience of Sublocade® during pregnancy.

STRONG RECOMMENDATION: USE OF SUBLOCADE® IN PREGNANCY

Given the paucity of data for antepartum efficacy, maternal tolerance, and fetal safety, introduction to **Sublocade® during pregnancy should be deferred to the postpartum interval.**

Continuation of Sublocade® may be considered when pregnancy is identified after treatment is well-established with Sublocade®, if alternative therapy is not available, and gestation is already greater than 12 weeks (beyond embryogenesis). Patients who are breastfeeding are encouraged to further defer until 6 months postpartum when breastfeeding is no longer exclusive nutrition.

PRESCRIBING, DISPENSING, & ADMINISTRATION OF SUBLOCADE®

As above, Sublocade® can only be prescribed by an approved/authorized prescriber who has completed the Health Canada required [Sublocade® Certification](#). The certificate generated by this program must be faxed to the pharmacy along with the M3P prescription when the prescriber first orders Sublocade® from a particular pharmacy.

Of note, Sublocade® must be ordered by a pharmacist via a closed-distribution system. Prescribers should contact pharmacists prior to sending a prescription to ensure the patient can access Sublocade® in a timely manner, to account for expected shipping times, as well as delivery of the product to the healthcare professional for administration. Pharmacists who need to set up an account with the manufacturer for the first time will require additional time. Pharmacists and prescribers/treatment teams who need further information about this process may contact CPhM or the Prescribing Practices Program at CPSM.

The following requirements must also be met:

- Ideally, the first two Sublocade® injections should be administered by the approved prescriber or a nurse who works in the clinic the patient attends for OAT care.
- The subcutaneous injection of Sublocade® must be within the scope of practice of the nurse or physician doing the injection. Additionally, if a patient that a physician or nurse cares for requires access to Sublocade® injections, they are encouraged to seek the appropriate training to become competent in performing this procedure.
- Sublocade® must only be injected by a trained physician or nurse **with the knowledge and authorization of the approved prescriber** (i.e., if a physician who is not an approved buprenorphine prescriber wishes to inject Sublocade® they require authorization from the prescriber who wrote the Sublocade® prescription).
- A pharmacist can administer further doses if they meet the requirements outlined in [Guidance on the Administration of Sublocade by a Pharmacist](#) and are authorized to do so by the Sublocade® prescriber. A pharmacist should only administer the first dose of Sublocade® if the prescriber or a nurse is not able to administer the medication in a timely manner and the pharmacist is comfortable and competent in doing so. Prescriber obligations in terms of counselling, ruling out pregnancy, discussing/offering reliable fertility control, informed consent, and all standards of care would still apply.
- Communication and collaboration between the pharmacist and prescriber, throughout the patient's treatment, are of utmost importance to ensure that the patient receives safe and optimal care:
 - Prescribers must actively collaborate and communicate with pharmacists when circumstances indicate that Sublocade® administration by a pharmacist would facilitate access to care for the patient and support the patient's ability to participate in their care plan.
 - A pharmacist must receive authorization from the prescriber to administer the medication, to ensure that the patient has been assessed and will receive the appropriate follow up from the prescriber. **The pharmacist must also notify the prescriber when the medication has been administered or if a patient misses their injection.**
- Pharmacy managers must ensure that all pharmacists, including new or casual staff, are aware of the requirements around the administration of Sublocade®. Information must be included in the pharmacy policy and procedures manual.
- It is recommended that Sublocade® be administered to patients in the supine position, in both clinic and pharmacy settings. To ensure appropriate administration, a prescriber, nurse, or pharmacist should administer the injection where the patient is able to lie

down, face up. **A private area with an exam table is required.** Occasionally, in patients who are very slim with minimal subcutaneous fat, it may be beneficial for the patient to sit in a chair during administration, as this may help to manipulate the site to gather enough subcutaneous fat for appropriate injection. This must still occur in a private area.

Other Practical Considerations for Sublocade®

- Patients are not permitted to pick up their Sublocade® injection from the pharmacy or self-administer (inject) their dose. Therefore, the logistics of this treatment option warrant discussion and collaborative planning between the pharmacy team and the prescriber/clinic team.
- Once the pharmacy notifies the clinic team that a Sublocade® dose is ready, a member of the clinic team will need to pick up the dose from the pharmacy. Alternatively, if practically possible, the prescriber may request that the Sublocade® dose be delivered to the clinic by the pharmacy.
- Specific federal and provincial narcotic transport, delivery, storage, and record-keeping requirements must be adhered to by the pharmacy and clinic teams for pick-up and delivery procedures. Templates for record keeping can be helpful for quality control.
- Importantly, the cold chain must be preserved. In clinic, Sublocade® doses must be stored in a locked temperature-controlled fridge with an alarm to alert staff if the temperature fluctuates outside of the recommended range.
- In clinic, two nurses/physicians are required to sign the medication log when adding or removing Sublocade® doses to/from the locked storage fridge. The use of a separate medication administration record (MAR) is also strongly recommended when administering Sublocade® doses in clinic.
- Once the patient has arrived in clinic for their Sublocade® injection appointment, the package containing the Sublocade® pre-filled syringe should be removed from the fridge 15-20 minutes prior to administration to warm to room temperature.
- A private room with exam table is required for the administration, as above.
- Offering the patient an ice pack during administration is a useful strategy to address the burning sensation that may occur with the injection. This burning sensation is often more intense with the 300 mg dose due to the larger volume injected. It usually improves after 3-5 minutes. Some patients may also prefer to apply the ice pack to the abdominal skin for a few minutes prior to the prescriber/nurse disinfecting the area and injecting the dose.

- It is important to remind patients not to manipulate the injection site for the first couple of days after injection and to watch for injection site reactions that may need to be assessed by clinic staff.
- Some patients report feeling “high” (e.g., dizzy, nauseous) following the first 300 mg Sublocade® injection. It is important to remind patients not to drive or operate heavy machinery during this brief period. Reassure them that this feeling usually subsides after a few hours, and in rare cases it may persist up to two days.

A NOTE ON PROBUPHINE®

Probuphine® is a buprenorphine subdermal implant used for the treatment of OUD that allows for continuous blood levels of buprenorphine for up to six months following implantation¹.

The ability of this subdermal implant to release continuous, non-fluctuating levels of buprenorphine may also enhance medication adherence and convenience for some patients and can be explored with both clinically stable patients and those struggling with stability and/or regular pharmacy attendance. Probuphine® can be considered in patients stabilized on ≤ 8 mg of sublingual buprenorphine/naloxone daily, noting the implant requires a period of abstinence from opioids before initiation⁴.

The subdermal implant is currently not recommended for use beyond two treatment cycles of six months¹.

Additional Information & Recommendations for Probuphine®

- The Probuphine® subdermal implant must be inserted and removed by a prescriber who have successfully completed a live training program, the PROBUPHINE Education Program.
- Ongoing, prescribers must also ensure they have the requisite knowledge, skills, and clinical competence for the proper insertion and removal of the Probuphine® implant. Support, including in-person procedural support, is available to new and existing prescribers from the manufacturer.
- Patients must be adequately counselled regarding the potential risks and benefits of transitioning to Probuphine®, including what is not known at this time. It is important that patients are adequately informed regarding the potential risks of the implant and explant procedures, as these are invasive in nature.
- Each Probuphine® is a sterile, single, off-white, soft, flexible, rod-shaped ethylene vinyl acetate (EVA) implant, 26 mm in length and 2.5 mm in diameter, containing 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride)¹⁰.

- Each dose consists of four Probuphine® implants inserted subdermally in the inner side of the upper arm¹⁰.
- The implant must be removed by the end of the six-month period¹⁰.

Practical Considerations for Probuphine®

Given that local practical experience with Probuphine® is still growing, the following recommendations rely predominantly on the product monograph:

- Once prescribers have completed the training program, the manufacturer will provide prescribers with the forms that essentially act as the prescription and order form for the implant kit. The manufacturer will work collaboratively with the patient and insurance plans/agencies to facilitate coverage.
- Once coverage is confirmed, the manufacturer will ship one dose (four rods) of Probuphine®, along with the sterile implant kit directly to the prescriber's office address ahead of the insertion date. Probuphine® can only be acquired through this closed distribution system (one pharmacy only).
- Prescribers should arrange to have a second healthcare professional present during the implant procedure. This individual can assist in the sterile procedure and serve as an emotional support person for the patient. The procedure is usually completed with local anaesthetic only. Before going home, patients must be educated about appropriate wound care and to watch for any symptoms or signs of an insertion site infection.
- After completing an implant, the provider must notify the manufacturer and confirm the implant date. The manufacturer will then ship the explant kit to the prescriber's office six months after the implant date.
- Should the patient elect to continue with Probuphine® treatment, the explant procedure of the existing Probuphine® and the implant of the new Probuphine® can be completed during the same office visit. The second device is implanted in the other arm to allow the first site to heal¹⁰.
- If new implants are not inserted on the same day as the removal, patients should be switched back to their previous dose of transmucosal buprenorphine (i.e., the dose from which they were transferred to Probuphine® treatment) prior to additional Probuphine® treatment, if so desired by the patient¹⁰.
- After one insertion in each arm, most patients should be transitioned back to their previous sublingual buprenorphine dose (i.e., the dose from which they were transferred to Probuphine® treatment) for continued treatment. At this time, there is no experience with inserting new implants into a previously-used site or using another site of a previously used arm¹⁰.

- The following procedures should only be considered if the potential benefits of continuing Probuphine® outweigh the potential risks of additional insertion and removal procedures and the clinical need of the patient for ongoing treatment with subdermal medication. If continued treatment is desired at the completion of two six-month treatment periods, new Probuphine® implants may be inserted into a previously unused area of the opposite arm. It is important to avoid previously-implanted sites because the effect of scarring and fibrosis in previously-used insertion sites on either the effectiveness of Probuphine®, or the safety of insertion, have not been evaluated. Dosing beyond 24 months (fifth implantation) cannot be recommended at this time¹⁰.
- Finally, although some patients may require occasional supplemental dosing with buprenorphine/naloxone, patients should not be provided with ongoing prescriptions for transmucosal buprenorphine-containing products for as-needed use. Patients who feel the need for supplemental dosing should be seen and evaluated promptly. Ongoing use of supplemental dosing with transmucosal buprenorphine indicates that the amount of buprenorphine delivered by Probuphine® is not adequate for patient stability. Consider use of alternate buprenorphine products for continuing treatment¹⁰.

References

1. British Columbia Centre on Substance Use (BCCSU). *Opioid Use Disorder Practice Update*. BCCSU and BC Ministry of Health; 2022. Available at: <https://www.bccsu.ca/wp-content/uploads/2022/02/Opioid-Use-Disorder-Practice-Update-February-2022.pdf>
2. Jones AK, Ngaimisi E, Gopalakrishnan M, Young MA, Laffont CM. Population pharmacokinetics of a monthly buprenorphine depot injection for the treatment of opioid use disorder: A combined analysis of phase II and phase III trials. *Clin Pharmacokinet*. 2021;60: 527–540. doi.org/10.1007/s40262-020-00957-0
3. Lintzeris N, Dunlop AJ, Haber PS, et al. Patient-reported outcomes of treatment of opioid dependence with weekly and monthly subcutaneous depot vs daily sublingual buprenorphine: A randomized clinical trial. *JAMA Netw Open*. 2021;4(5):e219041. doi:10.1001/jamanetworkopen.2021.9041
4. Centre for Addiction and Mental Health (CAMH). *Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*. CAMH; 2021. Available at: <https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf>
5. Indivior. *Product Monograph: SUBLOCADE® (buprenorphine extended-release injection)*. Indivior UK Limited; 2022. <https://www.sublocade.com/Content/pdf/prescribing-information.pdf> Accessed May 11, 2023

6. Towers CV, Deisher H. Subcutaneous extended-release buprenorphine use in pregnancy. *Case Reports in Obstetrics and Gynecology*. 2020;3127676. doi: 10.1155/2020/3127676.
7. Cleary EM, Byron RK, Hinely KA, Talley AW, Costantine MM, Rood KM. Subcutaneous buprenorphine extended-release use among pregnant and postpartum women. *Obstetrics & Gynecology*. 2020;136(5): 902-903. doi: 10.1097/AOG.0000000000004126.
8. Winhusen T, Lofwall M, Jones HE, et al. Medication treatment for opioid use disorder in expectant mothers (MOMs): Design considerations for a pragmatic randomized trial comparing extended-release and daily buprenorphine formulations. *Contemporary Clinical Trials*. 2020;93:106014. doi: 10.1016/j.cct.2020.106014.
9. Bernstein SN, Peckham AM, Schiff DM, Gray JR. Subcutaneous buprenorphine extended-release use among pregnant and postpartum women. *Obstetrics & Gynecology*. 2021;137(2):377-378. doi: 10.1097/AOG.0000000000004270.
10. Knight Therapeutics. *Product Monograph: PROBUPHINE (buprenorphine hydrochloride implant)*. Knight Therapeutics Inc; 2019. https://pdf.hres.ca/dpd_pm/00056235.PDF Accessed May 11, 2023

Appendix W

TREATMENT WITH SUBLOCADE® CONSENT FORM: GENERAL VERSION

Used with permission & acknowledgment of original author **Opaskwayak Health Authority OAT Program** (2021)



OAT PROGRAM

Address _____

Phone _____

Fax _____

I hereby acknowledge that I am a client of the _____ Opioid Agonist Therapy (OAT) Program. I have had an opportunity to discuss the next phase of my treatment with the clinic team and I have agreed to proceed with treatment with Sublocade. The common side-effects and potential for injection site reactions have been reviewed with me. I have had an opportunity to have my questions regarding this injectable treatment answered.

I understand that I must receive a Sublocade injection from an OAT program nurse or physician once per month, for treatment to be effective. I also understand that if I am more than two weeks late for my scheduled injection, I may have to restart on daily witnessed buprenorphine/naloxone (Suboxone) at my pharmacy, for a period, before I can be transitioned to Sublocade again. Having to restart on Suboxone may require an in-person assessment, which may result in a delay in returning to treatment. This delay carries a risk of relapse.

I acknowledge that Sublocade injections have NOT been studied in pregnant women. Therefore, it is NOT KNOWN if Sublocade is safe in pregnancy. The drug manufacturer states, in the written product information insert (product monograph): “Do NOT use Sublocade if you are:

- Pregnant. Your doctor will decide whether the benefit of giving you Sublocade outweighs the risk to your unborn baby.
- Or if you are of reproductive age and not using an effective and reliable method of birth control.
- Are pregnant or planning to become pregnant.”

By signing below, I acknowledge that this form has been reviewed with me and I have had an opportunity to have my questions answered.

Client’s Name: _____

Signature: _____ **Date:** _____

OAT Program RN or MD (name): _____

Signature: _____ **Date:** _____

Appendix X

TREATMENT WITH SUBLOCADE® CONSENT FORM: REPRODUCTIVE AGE VERSION

Used with permission & acknowledgment of original author **Opaskwayak Health Authority OAT Program** (2021)



OAT PROGRAM

Address

Phone

Fax

I hereby acknowledge that I am a client of the _____ Opioid Agonist Therapy (OAT) Program. I have had an opportunity to discuss the next phase of my treatment with the clinic team and I have agreed to proceed with treatment with Sublocade. The common side-effects and potential for injection site reactions have been reviewed with me. I have had an opportunity to have my questions regarding this injectable treatment answered.

I understand that I must receive a Sublocade injection from an OAT program nurse or physician once per month, for treatment to be effective. I also understand that if I am more than two weeks late for my scheduled injection, I may have to restart on daily witnessed buprenorphine/naloxone (Suboxone) at my pharmacy, for a period, before I can be transitioned to Sublocade again. Having to restart on Suboxone may require an in-person assessment, which may result in a delay in returning to treatment. This delay carries a risk of relapse.

I acknowledge that Sublocade injections have NOT been studied in pregnant women. Therefore, it is NOT KNOWN if Sublocade is safe in pregnancy. The drug manufacturer states, in the written product information insert (product monograph): “Do NOT use Sublocade if you are:

- Pregnant. Your doctor will decide whether the benefit of giving you Sublocade outweighs the risk to your unborn baby.
- Or if you are of reproductive age and not using an effective and reliable method of birth control.
- Are pregnant or planning to become pregnant.”

Being of reproductive age, I understand that it is important for me to use a reliable and effective birth control method while being treated with Sublocade. I have had an opportunity to discuss options for reliable birth control with my treatment team. **Both Depo Provera and an intra-uterine device were discussed with me as the two most reliable and effective forms of fertility control.**

Other methods such as the oral contraceptive pill, the pull-out method, and barrier methods such as male and female condoms or sex dams, are less effective at preventing pregnancy, especially in the context of a substance use disorder (addiction).

Therefore, if I choose to use one of these less reliable methods, I understand that it is strongly recommended that I use two different birth control methods at the same time, every time I have intercourse (e.g., an oral contraceptive pill plus condoms). **If I choose not to receive Depo Provera and I do not have an IUD in place, that also means that I will require a urine pregnancy test before every injection. This applies even if I use two less reliable methods of birth control.**

By signing below, I acknowledge that this form has been reviewed with me and I have had an opportunity to have my questions answered.

Client's Name: _____

Signature: _____ **Date:** _____

OAT Program RN or MD (name): _____

Signature: _____ **Date:** _____

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

3.1 Introduction: The Pharmacology of Methadone & Management of Adverse Effects

GENERAL CONSIDERATIONS

Methadone is a long-acting synthetic opioid. It is a full agonist, with actions predominantly at the mu-opioid receptor. The unique pharmacologic properties of methadone make it an effective medication for the treatment of opioid use disorder. However, it is this same unique pharmacology that poses a significant safety risk to patients when prescribed inappropriately. Therefore, a thorough understanding of the pharmacology of methadone is crucial for all team members involved in clinical decision making.

Providers and team members must ensure that patients receive adequate education regarding the risks involved with methadone treatment, as care plans are negotiated and adjusted over time. This education must be provided in a manner that is easy to understand and relevant to the patient's circumstances and literacy level. Handouts that patients can share with family, friends, and roommates, may be especially useful. See **Appendix Y**, "A Patient Guide: Avoiding Overdose in the First Two Weeks of Opioid Agonist Therapy (OAT)", as an example to facilitate this teaching.

PHARMACOLOGY

Methadone – The Full Agonist

The full agonist activity of methadone is predominantly at the mu-opioid receptor, with some additional agonist activity at the κ and σ opioid receptors¹. These pharmacologic actions produce effects common to all mu-opioid receptor *agonists*, which will reduce cravings and alleviate opioid withdrawal in a patient with an opioid use disorder.

Dissimilar to other opioids, methadone has also been shown to have some *antagonist* activity at the N-methyl-D-aspartate (NMDA) receptors. While these effects are not fully understood, this activity may make methadone more effective in treating neuropathic pain when compared to other opioids².

Peak plasma levels of methadone occur on average between 2.5 and 4 hours. Opioid agonist effects associated with this peak are sometimes noticed by the patient, particularly during the initiation phase and with sizable dose increases. Patients should be cautioned about sedative effects during this peak which will usually dissipate once the patient is on a stable dose. This is especially relevant to patients who drive or who engage in safety sensitive activities in their personal or professional lives.

Oral Administration & Metabolism

Methadone has a long duration of action and a high oral bioavailability which allows for once-daily oral dosing and a convenient method for health professionals to witness and monitor ingestion.

However, since methadone has a highly variable elimination half-life of 22 to 48 hours and time to reach steady state (i.e., 3 to 7 days) with a resultant variable response², the clinical response can be difficult to predict. Individuals who metabolize methadone slowly might experience a rapid accumulation of methadone blood levels, particularly during the induction phase and with dose increases. Since methadone is a full agonist and has **no ceiling effect** (see FIGURE 1), this accumulation may lead to toxicity and serious harm if the induction dose is too high, or the dose is increased too quickly. Figure 1 compares a full agonist, like methadone, to the partial agonist activity inherent to buprenorphine.

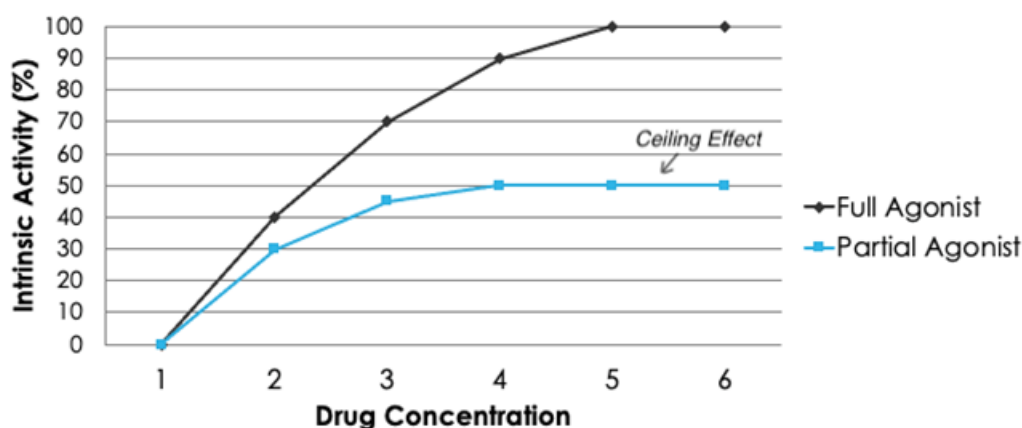


FIGURE 1: FULL AGONIST VS. PARTIAL AGONIST

Conversely, when metabolism of methadone occurs rapidly, once-daily dosing may elicit some withdrawal near the end of a 24-hour interval in a very small portion of patients who one would otherwise expect to be stabilized. While most patients may tolerate and adjust to this mild withdrawal, some cases may necessitate clinical intervention such as split dosing or switching to other treatments if suitable (e.g., buprenorphine). See [Ongoing Care](#) for further guidance around assessment of rapid metabolism and management of split dosing (specifically, *Rapid Metabolism & Serum Levels* and *Methadone Split Doses*).

Methadone Elimination

Methadone undergoes urinary and fecal excretion. The major metabolite of methadone is EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) which can be detected in the urine of patients who are metabolising methadone. EDDP is a useful marker to corroborate the authenticity of a urine sample. Patients who are on very low doses (e.g., below 5 mg/day) may not test positive for EDDP on a standard urine drug test, especially if they metabolize methadone quickly.

Drug Interactions – Hepatic Inhibitors & Inducers

Hepatic metabolism of methadone occurs principally at CYP3A4, and to a lesser extent CYP2B6, 2C19, 2D6, 2C9, and 2C8^{2,3}. Inhibitors and inducers of these enzymes may lead to clinically significant drug interactions.

Hepatic inhibitors will typically increase methadone levels noticeably in as little as one to two days². Studies have shown that pharmacodynamic outcomes with hepatic inhibitors have been associated with little to no reported adverse effects in stabilized patients³, however monitoring may still be warranted. Caution is advised in patients who would have an increased risk of additive central nervous system (CNS) depressant effects such as during the induction phase, after dose increases, in unstable patients, and/or patients taking other CNS depressants, such as benzodiazepines/Z-drugs.

Hepatic inducers typically cause effects to methadone plasma levels more slowly (i.e., one to two weeks²), and there have been reports of withdrawal effects from the reduction in methadone exposure. Some antiretroviral drugs, such as efavirenz and nevirapine, have led to significant reductions in C_{max} and AUC requiring methadone dose increases to treat resultant withdrawal effects³. Rifampin (commonly used for tuberculosis) and the anticonvulsants carbamazepine and phenytoin have also been shown to cause opioid withdrawal effects⁴.

Clinicians may need to increase and/or split the methadone dose because of the effects of a hepatic inducer. If this is the case, the original dose should be gradually resumed after the interacting medication is stopped. **If it is necessary to use a hepatic inducer for a patient on methadone, prescribers should consult with a specialist to manage this drug-drug interaction.**

Drug Interactions – CNS Depressants

Central nervous system depressants combined with methadone can produce additive CNS-depression effects, and this can lead to an increased risk of sedation and respiratory depression. Of note, benzodiazepines/Z-drugs have been associated with an increased risk of overdose and death in patients who are taking OAT⁵.

Starting methadone at low doses and titrating slowly is warranted in patients who are prescribed or suspected to be taking CNS depressants. This includes prescribed medications, prescription medications obtained from illicit sources, and over-the-counter medications with sedating properties. If such concerns are identified upon intake assessment or clinical suspicion is high, a comprehensive urine drug screen may be warranted to further evaluate this risk. The chapter [Methadone Induction, Titration, & Stabilization](#) provides detailed recommendations for different patient contexts, including induction and titration in higher-risk situations (see *Patients at Higher Risk for Methadone Toxicity*).

Combining medications that cause QTc interval prolongation with methadone, a well-established risk factor for QTc prolongation, increases the overall risk of developing torsade de pointes. Further discussion about this can be found in a subsequent section of this chapter under *QTc Interval Prolongation*.

Alcohol & Methadone

Patients on methadone who use alcohol can be difficult to manage due to the **dual effects of alcohol on hepatic metabolism and CNS depression**. *Acute* alcohol use has been shown to decrease methadone metabolism by competing for metabolic enzyme activity⁶. This may lead to accumulation of methadone levels, and when combined with the CNS depressant effects of alcohol can pose a serious risk of harm to the patient. Due to this heightened risk, it is imperative to assess the patient for intoxication prior to administering the dose.

Conversely, *chronic* alcohol use has been shown to induce hepatic metabolism of methadone⁶, which may lead to opioid withdrawal symptoms and can pose a challenge when trying to stabilize a patient on daily methadone. In the interest of optimizing safety, patients should be cautioned on the risks of both acute and chronic alcohol use when they are prescribed methadone.

Please refer to the chapter, [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#), for further recommendations around managing the risks of methadone treatment and other substances.

ADVERSE EFFECTS & MANAGEMENT

While methadone is typically well tolerated in most patients, it may cause adverse effects which are consistent with opioid agonist effects.

Due to the full agonist effect of methadone, adverse effects tend to be more pronounced than partial agonists used for OAT (e.g., buprenorphine).

With repeated use, patients usually develop tolerance to adverse effects caused by methadone. These transient adverse effects include sedation, nausea, vomiting, light-headedness, and dizziness^{1,2}. Methadone may also cause adverse effects that persist and require clinical management, such as constipation, sweating, and sexual dysfunction^{1,2}.

Constipation

Patients on methadone often endure constipation as an adverse effect with varying levels of severity. Approximately two-thirds of patients report some level of constipation, with approximately one-fifth of patients reporting severe to very severe constipation^{7,8}.

Methadone-induced constipation often goes unrecognized in this patient population and may adversely affect quality of life. OAT prescribers are encouraged to ask about and treat constipation aggressively. This approach may improve long-term adherence to agonist therapy.

The treatment regimen should include both pharmacological and non-pharmacological methods such as:

- Daily administration of an osmotic laxative (e.g., polyethylene glycol 3350),
- Use of a stimulant laxative, as needed (e.g., senna or bisacodyl),
- The above can be used with or without a stool softener (e.g., docusate), and
- Non-pharmacological methods such as increased fiber intake and fluid consumption should always be endorsed for the prevention of opioid-induced constipation⁹.
- While most laxatives can be helpful, bulk-forming laxatives (e.g., psyllium) are typically not effective for opioid-induced constipation and should be avoided.

Hyperhidrosis

Methadone-induced hyperhidrosis has been reported in up to 45% of patients, however this complaint is not often reported as patients may become accustomed to the side effect and prescribers may not inquire about this adverse effect¹⁰. It is important to differentiate excessive sweating as an adverse effect of methadone, since it may also be a symptom of opioid withdrawal which often presents at the end of the 24-hour dosing interval and will usually resolve independently as the patient approaches a stable dose.

Hyperhidrosis can often be tolerated without treatment, but medical intervention may be warranted in some cases. Clonidine, an inhibitor of sympathetic stimulation, has been used off-label with some success to treat excessive sweating¹¹, although it should be noted that research analyzing its use in this patient population is lacking. Misuse of clonidine has been reported¹², and consideration should be made to control the dispensing frequency.

Clonidine should, in most patients, be dispensed on the same schedule as methadone.

Oxybutynin and desloratadine have been shown to have some success off-label as well^{10,13}, however the evidence is very limited.

Most patients with hyperhidrosis, who benefit from treatment with clonidine, will experience effective relief with no more than clonidine 0.1 mg po BID. In severe cases, where sweating interferes with social function, up to clonidine 0.2 mg po BID may be trialled.

In cases where a trial of clonidine is not effective in reducing sweating, it should be discontinued to avoid unwanted side-effects and prevent diversion. Clonidine has sedating properties and may cause fatigue that not all patients tolerate. Clonidine is also centrally acting and reduces blood pressure. A baseline blood pressure check, repeated after starting clonidine, may be warranted. The use of clonidine can also exacerbate postural hypotension, especially in older patients. Educating patients about this risk is important, especially if they are already at risk of falls.

Sexual Dysfunction

The prevalence of sexual dysfunction has been reported to be as high as 52% in patients who take methadone and was significantly higher when compared to patients who take buprenorphine for opioid use disorder¹⁴. Men are more commonly affected and may experience a decrease in libido, erectile dysfunction (ED), and orgasm dysfunction, while reports show that women may experience decreases in libido and menstrual irregularity¹⁵.

Low testosterone levels, along with elevation of prolactin levels and interference with the normal production of LH, FSH, and GnRH, are suspected causes of sexual dysfunction in men, while interference of the normal cyclic production of LH and FSH are suspected to be the cause of sexual dysfunction in women¹⁵.

Sexual dysfunction can have a major impact on treatment adherence, so addressing this adverse effect may improve patient outcomes. Treating the specific symptoms, for example, by using PDE-5 inhibitors for ED, or managing low testosterone levels in men, can be a suitable approach to managing this condition. Bupropion has been shown in methadone patients to improve sexual desire, erectile function, and intercourse satisfaction, with more evidence in the male population¹⁶.

QTc Interval Prolongation

Methadone is known to cause QTc interval prolongation, a well-known risk factor to develop torsade de pointes which may lead to potentially fatal ventricular fibrillation. The prevalence of QT prolongation is not clearly established, but some reports showed that approximately 2% of methadone patients (all receiving doses over 100 mg/day) exhibited a QTc interval above 500ms, which is associated with a two-fold to three-fold increase in risk for torsade de pointes^{17,18}.

The effects of methadone on QTc prolongation are dose dependent. Doses above 100 mg/day are frequently reported in cases of torsade de pointes, and some case reports show that the QTc interval normalizes when methadone is discontinued or reduced in dose¹⁷.

The risk of torsade de pointes is often increased when other risk factors for QTc prolongation are present. In addition to a higher dose of methadone, other risk factors for QTc prolongation include:

- The presence of other drugs that prolong QTc interval,
- Hypokalemia,
- Female sex,
- Advancing age,
- Genetic predisposition,
- Hypomagnesemia,
- Heart failure, and
- Bradycardia¹⁹.

Whenever possible, modifiable risk factors like drug-drug interactions and hypokalemia should be rectified first. See [Ongoing Care](#) for further recommendations around clinical management of the QTc prolongation, specifically, **ECG MONITORING FOR PROLONGED QTc**.

Other Adverse Effects

Weight gain has been reported with methadone treatment; however, a causal link has not been firmly established. Some reports suggest that negative changes in diet habits and an increased preference for sweet foods when methadone is started may be contributory to weight gain, and for this reason education about nutritional habits may be beneficial²⁰. Documenting baseline weight at intake is a useful strategy and presents an opportunity to discuss healthy eating resources.

Patients on methadone tend to report poor dental health, including a high level of dental caries, however a direct causal link has not been established^{21,22}. It is thought that a variety of factors commonly affiliated with all opioid users might contribute to this issue, including dry mouth, poor dental hygiene, a higher intake of sweet foods, masking of dental pain, bruxism, and the high prevalence of alcohol and tobacco use in this population²². When treatment is initiated, it is recommended to inform patients about potential dental issues and encourage good dental hygiene, regular visits to the dentist, and limited intake of sugar-containing foods. Additional monitoring may be required in patients who experience a severe case of dry mouth (xerostomia), such as in patients who are taking antidepressants.

Peripheral edema in the extremities has been reported on rare occasions in patients on methadone and may occur even after three to six months of treatment²³.

Sometimes edema is self-limiting and will resolve on its own, but if edema persists, the only way to resolve it may be to taper off methadone and/or consider an alternative form of OAT (e.g., buprenorphine). However, the risk of reverting back to illicit opioid use must be considered and discussed with the patient if an adjustment to methadone treatment is considered².

References

1. Mallinckrodt Canada ULC *Product Monograph: Methadose™, Methadone Hydrochloride Oral Concentrate USP 10mg/mL*. Mallinckrodt Pharmaceuticals; 2018. Available at: https://pdf.hres.ca/dpd_pm/00047060.PDF. Accessed May 18, 2022.
2. Isaac P, Janecek E, Kalvik A, Zhang M. *Opioid Agonist Maintenance Treatment: A pharmacist's guide to methadone and buprenorphine for opioid use disorder*. 3rd ed. Centre for Addiction and Mental Health; 2015: p. 8, 12-17.
3. Volpe DA, Xu Y, Sahajwalla CG, Younis IR, Patel V. Methadone Metabolism and Drug-Drug Interactions: In Vitro and In Vivo Literature Review. *J Pharm Sci*. 2018 Dec;107(12):2983-2991. doi: 10.1016/j.xphs.2018.08.025. Epub 2018 Sep 8. PMID: 30205091.
4. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. *Am J Addict*. 2010;19(1):4-16. doi:10.1111/j.1521-0391.2009.00005.x
5. Franklyn AM, Eibl JK, Gauthier G, Pellegrini D, Lightfoot NE, & Marsh DC. The impact of benzodiazepine use in patients enrolled in opioid agonist therapy in Northern and rural Ontario. *Harm Reduction Journal*. 2017;14, Article 6. <https://doi.org/10.1186/s12954-017-0134-5>
6. Quinn DI, Wodak A, Day RO. Pharmacokinetic and pharmacodynamic principles of illicit drug use and treatment of illicit drug users. *Clin Pharmacokinet*. 1997 Nov;33(5):344-400. doi: 10.2165/00003088-199733050-00003. PMID: 9391747.
7. Gray D & Spence D. The prevalence of constipation in patients receiving methadone maintenance treatment for opioid dependency. *Journal of Substance Use*. 2005; 10(6): 397-401, DOI: 10.1080/14659890412331318912
8. Lugoboni F, Mirijello A, Zamboni L, Faccini M, Casari R, Cossari A, Gasbarrini A, Addolorato G & on behalf of GICS. High prevalence of constipation and reduced quality of life in opioid-dependent patients treated with opioid substitution treatments. *Expert Opinion on Pharmacotherapy*. 2016; 17(16): 2135-2141. doi: 10.1080/14656566.2016.1232391
9. Sizar O, Genova R, Gupta M. *Opioid Induced Constipation*. [Updated 2020 Nov 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK493184/>
10. Al-Adwani A & Basu N. Methadone and excessive sweating. *Addiction*. 2004 Feb;99(2):259. PMID: 14756718.
11. del Boz J. Systemic Treatment of Hyperhidrosis, *Actas Dermo-Sifiliográficas* (English Edition). 2015; 16(4): 271-277. ISSN 1578-2190, <https://doi.org/10.1016/j.adengl.2015.03.003>

12. Beuger M, Tommasello A, Schwartz R, Clinton M. Clonidine use and abuse among methadone program applicants and patients. *J Subst Abuse Treat*. 1998 Nov-Dec;15(6):589-93. doi: 10.1016/s0740-5472(97)00309-7. PMID: 9845872.
13. McCormack L, Ponce J, Chatterjee A, Tan JK. Oxybutynin treatment for buprenorphine-naloxone-induced hyperhidrosis. *JAAD Case Rep*. 2021 Jan;10:22-24. doi:10.1016/j.jdc.2020.12.031
14. Yee A, Loh HS, Hashim HM, Ng CG. The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: A meta-analysis study. *J Sex Med*. 2014;11:22-32.
15. Brown RT & Zuendorf M. Opioid Substitution with Methadone and Buprenorphine: Sexual Dysfunction as a Side Effect of Therapy. *Heroin Addict Relat Clin Probl* 2007; 9(1):33-44.
16. Ramli FF, Azizi MH, Syed Hashim SA. Treatments of Sexual Dysfunction in Opioid Substitution Therapy Patients: A Systematic Review and Meta-Analysis. *Int J Med Sci*. 2021 Apr;18(11):2372-2380. doi:10.7150/ijms.57641
17. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med*. 2009 Mar; 150(6):387-95. doi: 10.7326/0003-4819-150-6-200903170-00103. Epub 2009 Jan 19. PMID: 19153406.
18. Cohagan B, Brandis D. *Torsade de Pointes*. [Updated 2021 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK459388/>
19. Trinkley KE, Page RL 2nd, Lien H, Yamanouye K, Tisdale JE. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin*. 2013 Dec;29(12):1719-26. doi: 10.1185/03007995.2013.840568. Epub 2013 Sep 23. PMID: 24020938.
20. Peles E, Schreiber S, Sason A, Adelson M. Risk factors for weight gain during methadone maintenance treatment. *Subst Abuse*. 2016 Oct-Dec;37(4):613-618. doi: 10.1080/08897077.2016.1179705. Epub 2016 Apr 19. PMID: 27093441.
21. Tripathee S, Akbar T, Richards D, Themessl-Huber M, Freeman R. The relationship between sugar-containing methadone and dental caries: A systematic review. *Health Education Journal*. 2013;72(4), 469–485. <https://doi.org/10.1177/0017896912450247>
22. Gray A. *Systematic review of the safety of buprenorphine methadone and naltrexone*. Department of Therapeutics and Medicines Center for the AIDS Programme of Research in South Africa Congella; 2007. <https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.569.3254&rep=rep1&type=pdf>
23. Kharlamb V, Kourlas H. Edema in a patient receiving methadone for chronic low back pain. *Am J Health Syst Pharm*. 2007 Dec 15;64(24):2557-60. doi: 10.2146/ajhp060553. PMID: 18056943.

Appendix Y

A PATIENT GUIDE: AVOIDING OVERDOSE IN THE FIRST TWO WEEKS OF OPIOID AGONIST THERAPY

This clinic provides opioid agonist therapy (OAT) care *as safely as possible*, but accidental overdoses sometimes happen in the first two weeks of treatment. This is especially important when starting methadone treatment, but many of the same safety ideas should also be applied when starting buprenorphine/naloxone (Suboxone).

The questions and answers below will help you to get through this period safely. Share this information sheet with a friend or family member.

Why can't my doctor increase my dose more quickly?

When you first start taking methadone or buprenorphine/naloxone, you want to get on the right dose as soon as possible. With buprenorphine/naloxone your doctor may only need a few days to get you to the right dose while making sure you can safely tolerate the medication. With methadone, however, your doctor must increase your dose slowly over several weeks, because your body takes time to adjust to the methadone and (unlike other opiates), methadone builds up slowly in your bloodstream over several days. A dose that may feel like too little on a Monday could put you in hospital by Thursday.

What can I take to relieve withdrawal and help me sleep until the OAT medication begins to work?

Your doctor may discuss taking certain medications to assist with your symptoms. These medications may include plain Tylenol® (acetaminophen) and Advil® (ibuprofen). Drinking lots of water is important to stay hydrated. Occasionally, your doctor may prescribe other medications to help with specific symptoms – **only take medications that are approved by your OAT doctor**. If you're on a medication prescribed by another doctor, your OAT doctor needs to approve it because it could interact with the buprenorphine/naloxone or methadone.

Substances that make you relaxed or sleepy can be dangerous. This includes:

- Alcohol, opioids, and benzodiazepines (e.g., Ativan®, Valium®, Xanax®, Restoril®, etc.).
- Antihistamines, cold medications, and sleeping pills (such as, but not limited to, Gravol™, Benadryl®, Nyquil™, Benlyn®, or Tylenol® PM, zopiclone).
- Certain types of antidepressants and tranquilizers.

Even certain antibiotics can be dangerous as they block the breakdown of methadone in the body. **Make sure to check all your medications with your OAT doctor.**

What if I feel like I still need to use other opioids while starting OAT?

If you feel like you need to use other opioids in addition to the OAT medication, particularly while at a lower methadone dose, talk to your doctor about this honestly at every visit. Your doctor understands that your buprenorphine/naloxone or methadone dose may not last 24 hours in early treatment. Knowing that you are using other opioids and how much, will help your doctor to increase your OAT medication dose as needed, while being safe. Your doctor can also help you to determine the safest way to use additional opioids if this is needed. **However, if you can cope with your OAT dose only, that is the safest option.**

Isn't OAT, especially methadone, supposed to make you sleepy?

No. You are supposed to feel normal on your OAT medication, not high or sleepy. This applies to both buprenorphine/naloxone and methadone. When taken as prescribed by your doctor, OAT medications build up slowly in your system and should not make you feel drowsy. You should take the following precautions to help the clinic staff keep you safe:

- Take your OAT at the same time each day.
- See your doctor or case manager at least once a week for the first two weeks. (Many clinics will require visits that are more frequent.)
- Discuss your OAT treatment with a close friend or family member. If they see that you are drowsy, they must call your OAT doctor or 911.
- Discuss naloxone kits with your doctor and with a close friend or family member. Make sure you and your friend/family know how and when to use naloxone (your doctor or trained clinic staff can teach you this).

I'm starting methadone...What are some of the symptoms if my dose is too high?

- You may feel sleepy and nod off several times during the day.
- You may be forgetful.
- You may be difficult to wake up from your sleep.
- You may experience slurred speech, stumbling walk, or appear drunk.

If these things are occurring, you must call your doctor immediately and call 911 for help.

I've been offered a small amount of methadone by a methadone patient at the pharmacy. This can't hurt – I know I need 80 mg?

Above all, don't take any extra methadone! What is safe for your friend could be lethal for you. It may be true that you took 80 mg **once** and were okay. If you had taken 80 mg every day for three or four days, you might have overdosed. Remember, it takes *five or more days* for a certain dose to build up in your blood.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

3.2 Recommendations for Methadone Induction, Titration, & Stabilization in the Treatment of Opioid Use Disorder

GENERAL CONSIDERATIONS

This chapter will outline recommendations for methadone induction for the treatment of opioid use disorder (OUD). Dose titration and key considerations through early to later stages of stabilization will also be discussed. While buprenorphine/naloxone is considered first-line therapy for the treatment of OUD, methadone is an evidence-based and effective alternative for many individuals, as discussed in other sections of this manual. Please refer to [Recommendations for OUD](#) for further guidance on treatment approaches.

The most common reason for death or non-fatal overdose from methadone treatment is overly aggressive prescribing/dose-titration during the first two weeks of treatment. The combination of overestimated cross-tolerance and underestimated serum-level accumulation of methadone is the main cause. After stabilization, the most common reason for significant complications is drug-drug interactions, typically with sedative/hypnotic medications and/or substances. Appropriate dosing during each phase of methadone treatment is therefore vital for patient safety.

Methadone doses are self-administered under the direct supervision of a pharmacist, approved prescriber, or nurse, until candidacy for a take-home dosing schedule is established.

The Centre for Addiction and Mental Health (CAMH) recommends that methadone be prescribed “in a way that balances the risk of adverse effects to the patient and people in their environment while optimizing the benefits, including retention in treatment and decreased health and quality-of-life harms related to substance use”¹.

Patient and community safety must remain at the forefront of treatment decisions when providing opioid agonist therapy (OAT), particularly with methadone treatment. Providers must ensure that patients receive adequate education regarding the risks involved, as care plans are negotiated and adjusted over time. Please see the [Pharmacology of Methadone & Management of Adverse Effects](#) for further details.

SPECIFIC CONSIDERATIONS

INITIATING OPIOID AGONIST THERAPY

Urgency of OAT Induction

Following the decision to initiate OAT, induction should be arranged urgently, ideally the same day or within 2-3 days of presentation. When access to OAT induction within this timeframe is not feasible due to patient, prescriber, geographic, or systemic factors, other interventions should be considered in the interim, including harm reduction strategies (e.g., clean supplies, naloxone), patient safety education, wound care, psychosocial support, and access to primary care and other forms of addiction treatment.

Providers involved in addiction treatment are encouraged to advocate for improved access to OAT in their region of practice.

Initial Assessment & Patient Education

Patients must undergo a comprehensive assessment including history and focused physical examination to establish the diagnosis of OUD before initiating OAT. Please see [Initiating OAT: Comprehensive Assessment, Diagnosis, Informed Consent & Investigations](#) for detailed guidance on the assessment process.

Where immediately available, point-of-care urine drug screening should be performed. This is a useful clinical tool in the context of the initial assessment. Relevant lab work, including an STBBI screening, should also be ordered and completed as soon as practically feasible. **While urine drug testing and other investigations are ideal on initial assessment or in early treatment, they should not delay access to timely treatment if OAT is indicated².**

Consideration for methadone as an alternative to buprenorphine/naloxone may be appropriate in the presence of:

- Severe liver disease, such as advanced cirrhosis, that is causing problematic withdrawal symptoms (where activity of the naloxone component is enhanced due to reduced first pass effect).
- Previous failed treatment with buprenorphine/naloxone, severe side effects, or an allergy/intolerance to buprenorphine, naloxone, or to any ingredient in the formulation.

- Patient preference for methadone treatment, despite education regarding the enhanced safety and potential benefits of buprenorphine/naloxone.
- Very high opioid tolerance unlikely to stabilize on a partial opioid agonist.

Patients must be educated about the symptoms and signs of early opioid toxicity and overdose, and must be offered access to a naloxone kit at the time of induction.

Prescribers should also obtain and document informed consent for methadone treatment. The use of a written **Treatment Agreement** is strongly recommended. Informed consent and treatment agreements are also discussed in the [Comprehensive Assessment](#) chapter.

Clinical Stability & Treatment Goals

Prescribers should discuss and document the goals of treatment prior to induction and at regular intervals during follow-up. Both provider and patient-driven goals should be used to inform treatment decisions and support continued methadone prescribing.

While buprenorphine/naloxone often allows for rapid dose titration (see [Recommendations for Conventional Buprenorphine Induction](#)) **methadone induction and titration MUST be approached slowly and cautiously**. It may take several weeks to address opioid withdrawal effectively. It is important to be upfront with patients about this requirement and to discuss ways to cope with ongoing withdrawal and cravings, to maintain engagement in treatment.

However, unlike the conventional buprenorphine induction, methadone can be initiated without the prerequisite presence of opioid withdrawal. This may be preferential for some patients. The patient's dose should be titrated with a "start low and go slow" approach, based on regular clinical assessment, until initial dose stability is reached – see specific recommendations below.

A stable dose is achieved when opioid withdrawal is eliminated or adequately suppressed for 24 hours to allow patients to further engage in ongoing medical and psychosocial treatment. **The ultimate goal is to work toward clinical stability**, which is characterized by, but not limited to:

- Absence of opioid withdrawal symptoms and significantly reduced cravings
- Absence or significant reduction in illicit substance use (self-reported and supported by urine drug testing)
- Financial and/or employment stability
- Housing stability
- Improvements in self-care and wellness practices
- Strengthening of supportive relationships (and/or navigating difficult relationships)
- Improvements in mental and physical health

PREPARATION FOR INDUCTION

In most cases, methadone can be safely started in the community.

If concurrent use of sedative/hypnotic medications and/or substances are a concern, and/or if comorbid conditions could contribute to increased risk of respiratory depression or opioid toxicity during induction, further consultation with an addiction medicine specialist is recommended. Inpatient admission for induction and closer monitoring may be warranted, and further consideration of buprenorphine/naloxone may be required.

Collaboration with Pharmacy

Collaboration with the pharmacist is strongly encouraged prior to induction and should include the following:

- **Verify the pharmacy provides OAT (with methadone).** It is important to note that not all pharmacies in Manitoba dispense OAT, as specialized training is required. Thus, it is important to confirm that a pharmacy does dispense methadone prior to faxing an OAT prescription to that pharmacy.
- **Communicate the plan.** Sharing the plan for follow-up/titration and communicating an action plan if the patient misses any doses, appears intoxicated or unusually sedated, and/or receives sedating/psychoactive medication from a different prescriber during the induction phase is helpful for all those involved.
- **Share special instructions.** Specifying any special instructions for induction on the M3P prescription can be useful to prevent dosing errors and confusion.
- **Provide comprehensive prescriber contact info.** Supplying the pharmacy with method(s) to contact the prescriber/office outside of regular clinic hours is vital to ensuring that urgent clinical matters can be addressed quickly.

See [Relationship with Pharmacy & Prescriptions for OAT](#) for further recommendations.

THE EARLY STABILIZATION PHASE (0-2 WEEKS)

Methadone has a **significant risk of morbidity and mortality during the early stabilization phase.**

Since methadone has a highly variable elimination half-life of 22 to 48 hours and time to reach steady state can vary from 3 to 7 days, the clinical response can be difficult to predict. Additionally, methadone is a full agonist and has no ceiling effect. Thus, dose accumulation may lead to toxicity and serious harm if the induction dose is too high, or the dose is increased too quickly. A dose that is barely adequate on day one can be toxic after a few days at the same dose.

Clinical Assessment of Opioid Withdrawal

When clinically assessing opioid withdrawal, prescribers should consider using the Clinical Opiate Withdrawal Scale (COWS) to assess and document the severity of opioid withdrawal during methadone induction and titration (see **Appendix Z**). This helpful clinical tool utilizes objective and subjective measures of withdrawal and can assist in determining appropriate dosing during the early stabilization phase.

Of note, evidence of clinical opioid withdrawal is not necessarily required to start methadone if indicated, based on a thorough history including knowledge of the specific opioids (and other substances) consumed, their potency, duration of action, and urine drug screen results.

Conversely, if the patient appears sedated, somnolent, or intoxicated, methadone induction should be postponed until they can be reassessed to avoid opioid/multidrug toxicity or overdose.

Start Low & Go Slow

Methadone overdose can have an insidious onset. A patient appearing relatively alert during the day may succumb to an overdose during a nap or at night.

Early signs of toxicity include feeling tired or “nodding” during low stimulus activities, such as watching TV or attending a lecture in school. Ataxia, nausea/vomiting, slurred speech, euphoria, and slow or laboured breathing may be signs of progressive toxicity and require urgent medical attention. Careful prescribing, patient education, and intervention at the first sign of toxicity can reduce the risk of overdose. Again, patients must be offered access to a naloxone kit at the time of induction, and patients and their family/supports must be educated about the early signs of opioid toxicity. It is imperative that the dosing protocols below be followed to minimize the risks in early treatment.

The following dosing protocol is strongly recommended:

- The initial dose should be between 10-30 mg of methadone per day for at least the first three days. Patients at higher risk for methadone toxicity (see section below) should start on no more than 5-20 mg^{1,2}.
- During the early stabilization phase for patients new to methadone, doses may be increased by up to 5 mg every 3-5 days, or by 10 mg increments every 7 or more days.
- During the early stabilization phase for patients new to methadone, providers may elect to prescribe a single dose increase of 10 mg after 5 days, but all subsequent 10 mg dose increases should occur no sooner than 7 days apart. Alternatively, a 5 mg dose increase may be considered 5 days after a 10 mg dose increase. **Caution surrounding serial 10 mg dose increases is emphasized.**

Daily Witnessed Ingestion

Doses are to be self-administered under the direct supervision of a pharmacist, approved prescriber, or nurse, until candidacy for a take-home dosing schedule is established. Please see [Methadone Take-home \(Carry\) Dosing](#) for detailed recommendations.

Note that if methadone is not already in a formulation that deters misuse/injection (e.g., cherry-flavored), then all doses must be diluted in a vehicle (e.g., Tang/juice) that does not lend itself to misuse/injection.

No take-home doses (carries) should generally be granted during the first two months of treatment. An exception may be granted for Sunday carries due to pharmacy closures, if the provider determines the benefits of uninterrupted daily dosing outweigh the risks of the carry. This may be particularly useful for rural or remote patients with limited pharmacy options and/or where patients must travel longer distances to access a pharmacy or nursing station.

Some OAT programs give weekend carries in similar contexts **when there is no weekend pharmacy access** and the patient demonstrates sufficient early stability, reliable behaviour, and can store the medication safely. However, when patients are deemed unstable and the risks of earlier carry doses are significant, the patient may have to forgo one or two doses per week if no pharmacy access is available on Saturdays and/or Sundays. The prescriber must document their risk assessment and rationale for such decisions.

Patients at Higher Risk for Methadone Toxicity

An initial dose of 5-20 mg with careful titration is recommended for the higher-risk patients described below¹. Consultation with an experienced OAT provider may be warranted and further consideration of buprenorphine/naloxone over methadone may be required. Please refer to [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#) for detailed recommendations for managing some of these risks.

- **Patients using benzodiazepines/Z-drugs** are higher-risk. A thorough history of benzodiazepines/Z-drugs use is necessary. This includes use via prescribed and/or illicit sources. A strategy for benzodiazepine/Z-drug management (even for stable long-term prescriptions), including diagnosis of potential sedative-hypnotic use disorder, must be part of the overall treatment plan. See the polypharmacy chapter section **MANAGING PRESCRIBED AND ILLICIT BENZODIAZEPINES & Z-DRUG USE** for detailed guidance.
- **Patients using other sedating/psychoactive medications.** Patients using antipsychotic and sedating antidepressants are at higher risk, particularly if the sedating drug was started or increased within the last two months, or the dose is moderate or high.
- **Patients struggling with alcohol use or Alcohol Use Disorder.** Problematic alcohol use can be identified through an alcohol history and laboratory measures (GGT and MCV).

All patients should be advised to abstain from alcohol during early stabilization. If the patient is at significant risk for alcohol withdrawal, appropriate withdrawal management should be arranged. Consultation with an addiction medicine specialist may be helpful to review the treatment plan.

- **Patients who are older (> 60 years) and have a respiratory illness.** This includes patients with chronic illnesses such as COPD and acute illnesses such as pneumonia.
- **Patients who are on drugs that inhibit/promote methadone metabolism.** If a drug that inhibits metabolism is meant for short-term use only, the prescriber might recommend that the patient finish the course before prescribing methadone. Conversely, patients on medications that promote rapid methadone metabolism should avoid abrupt cessation of the medication.
- **Patients with lower opioid tolerance** (e.g., codeine use only, low-dose or low-potency opioid use, intermittent opioid use, or a recent period of abstinence due to incarceration or residential treatment). Tolerance is difficult to establish from history; therefore, if in doubt, it is safer to initiate methadone at a lower dose.

Urine drug testing (UDT) can be helpful in confirming the patient's self-reported use. Consideration must be given to select the type of UDT that will be most effective for the clinical context and history (e.g., point-of-care, street drug screen, or comprehensive).

Initiate methadone at 5-10 mg for the recently abstinent with initial negative urine screening.

- **Patients with low body mass (< 50 kg)** may also require lower induction doses.

STRONG RECOMMENDATION: REMINDER TO DISPENSE WITH OAT

Typically, all psychoactive/sedating medications should be dispensed with OAT, i.e., on the same schedule as OAT. Communicating with the patient's pharmacy about the plan for managing these medications is essential. Controlled dispensing instructions, such as "dispense as per OAT schedule", must be written on all relevant prescriptions. Please see the [Managing Polypharmacy in OAT](#) chapter for further medication safety recommendations.

Patients with High Tolerance of Potent Opioids

Specific guidance for methadone titration in patients with high tolerance of high-potency opioids (e.g., injecting or smoking primarily illicitly sourced fentanyl) is evolving. Please revisit this section for updates. While a more conservative approach to methadone titration is recommended for most patients, a subset of patients using primarily high-potency opioids may require more aggressive titration to stabilize effectively and for treatment retention, either alone or in combination with slow-release oral morphine (SRM).

See [Alternative Treatment Approaches for OUD Including SROM \(Kadian®\)](#) for detailed guidance. **Consultation with an addiction medicine specialist should be sought to best support these patients.**

CAMH guideline, [Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder](#), recommends the following approach¹:

- Conduct a risk-benefit assessment for patients with high tolerance of high potency opioids for whom slower titration could jeopardize retention in treatment.
- Prescribe an initial methadone dose of 5-30 mg. Then increase the dose by 5-15 mg every 3-5 days (as necessary) **for patients who both:**
 - a) Have high tolerance of high-potency opioids from daily use and have UDT confirmation of recent opioid use, and
 - b) Do not have risk factors for excessive CNS depression (i.e., patients who do not fall into one or more of the higher-risk patient categories listed above).
- Consider using a limited duration of SROM for outpatients, or immediate release oral morphine for inpatients, to manage emergent withdrawal while titrating the methadone dose to reach a clinically therapeutic outcome (i.e., 24 hours without any withdrawal or need for supplemental morphine).
- **Exercise extreme caution if you are considering rapid and high dose titration (increasing the methadone dose by more than 10 mg at a time in a period under 5 days).** Consult with a colleague who has experience with rapid and high dose titration.
- Monitor the patient closely, with direct assessment before each dose increase and assurance that they have a reliable family member/support person available for frequent contact and check-ins, for early detection of methadone toxicity.

It is paramount to reassess patients frequently during the first two weeks of treatment – they are at the highest risk of fatal overdose during this period. Discuss this risk and strategies to reduce it (e.g., use only small amounts of additional opioids, do not use alone, have a naloxone kit available). Document these discussions and reassess the patient with every subsequent dose increase.

Additional Resources – META-PHI Recommendations

It is important to note that these recommendations are more aggressive. Caution is advised.

- [Methadone treatment for people who use fentanyl: Recommendations](#)
- [Methadone treatment for patients who use fentanyl: Plain language summary](#)

Reducing Risk During the Early Stabilization Phase

The steps described below can help to reduce risk during the early stabilization phase.

- **No new prescriptions for sedative drugs.** Avoid prescribing any new sedating drugs during the early stabilization phase. Patients should also be advised to avoid alcohol and over-the-counter sedating drugs.

The risks and benefits of prescribing non-opioid medications for symptomatic withdrawal management must be carefully considered while methadone is being titrated (see **Appendix AA**). Regularly scheduled acetaminophen and ibuprofen may be sufficient. Use extra caution when prescribing symptomatic management medications with sedating properties in the context of methadone care.

- **Missed doses.** During the early stabilization phase, **patients should be on the same dose for three to four consecutive days with no missed doses before a dose increase.** If a patient misses three or more doses consecutively in this phase, they should resume at the initial dose (as per the dosing protocols above) for at least three consecutive days.
- **General advice to the patient and their family/supports.** Explain to the patient that it takes several weeks to reach the optimal dose of methadone, and that it is dangerous to try to relieve withdrawal symptoms with benzodiazepines, alcohol, opioids, illicit methadone, or other drugs. Advise the patient to limit their driving or use of machinery after a dose increase, particularly in the first few hours after dosing. Advise the patient to take their methadone dose in the morning, if possible, since the risk of overdose is increased at night.

During the early stabilization phase patients and their families/supports (with patient consent) should be educated about methadone toxicity, appropriate actions to take at the first signs of toxicity, and provided naloxone kits and training. A patient information guide may be used for this purpose (see [The Pharmacology of Methadone](#) **Appendix Y** for an example).

- **Explain the risks of diverted methadone.** Even a single dose of methadone can be fatal to both children and adults. Patients are responsible for the safe storage of their methadone. Prescribers must advise patients that it is dangerous and illegal to sell or give methadone to anyone, even in small doses or done with good intentions.

Treatment agreements are useful to clearly outline risks and delineate expectations.

UDT Negative for Opioids

Of note, if urine testing *does not* detect opioids upon intake, this does not preclude a patient from starting OAT if clinically indicated. There may be clinical reasons for this, such as recent abstinence, or failure of the test to reliably detect certain opioids.

However, if patients report recent abstinence and initial UDT results are negative for opioids – but OAT is indicated based on a reliable history – then buprenorphine/naloxone induction is strongly recommended over methadone. Methadone could be considered in some circumstances (e.g., patient choice, severe liver impairment), but titration must be approached with caution.

The initial methadone dose should be 5-10 mg, titrated upwards in increments of 5 mg or less, every five or more days, with careful assessment of withdrawal symptoms and sedation.

THE LATE STABILIZATION PHASE (2-6 WEEKS)

Frequent Reassessment Early in Treatment

Ideally, the patient should be reassessed frequently during the first few weeks/months of treatment, until they achieve reasonable relief of withdrawal symptoms and cravings, in the absence of sedation or toxicity, for a complete 24-hour period following their dose. The OAT prescriber, or a member of the treatment team who possesses the necessary knowledge, skills, and clinical judgement, should ideally see the patient weekly to assess and adjust their dose, in collaboration with the prescriber.

All dose adjustments require an assessment. These assessments can be completed using a combination of in-person and virtual visits. On-camera assessment is preferable with virtual visits, if available. Avoid automatic dosage adjustments on the prescription.

Ongoing Titration

Most patients in the late stabilization phase are taking between 50-80 mg of methadone.

Throughout the early to late stabilization phase, the patient may experience incomplete relief of withdrawal symptoms. They may continue to use other opioids. **Discuss the use of other opioids or non-prescribed substances candidly with patients, with a non-judgmental, non-punitive approach. Revisit harm-reduction strategies as needed.** The emphasis should be on using safely, if needed, while cutting back on amounts/frequency of use, as the methadone dose accumulates.

During this period, dose adjustments are usually in the **3-5 mg range every 3-7 days**, depending on the severity, onset, and duration of the patient's withdrawal symptoms. Careful assessment of withdrawal symptoms is essential, with continued use of the COWS (**Appendix Z**).

MAINTENANCE PHASE (6 WEEKS +)

By this time, most patients have substantially reduced opioid use, they are largely tolerant to methadone, and experience no withdrawal symptoms for most of the day. They may occasionally ask for dose increases because of episodic subjective withdrawal symptoms, opioid cravings, or a relapse to opioids. During the maintenance phase, or if the dose is 80 mg or higher, dose adjustments are **typically between 3-5 mg every 3-7 days**.

Stable Daily Dose

The optimal methadone dose will mostly eliminate withdrawal symptoms, block opioid-induced euphoria, and reduce cravings without sedation or other signs of toxicity. UDT should be negative for opioids most of the time (see [Recommendations for the Use of UDT](#) for further guidance).

With experience, prescribers can typically establish a stable dose for many patients within two to eight weeks of initiating methadone. The stable dosage range for most methadone patients is 50-120 mg, however the focus should be on clinical indicators of stability, not the dose.

Patients who use high-potency opioids (e.g., fentanyl) regularly, may require higher overall doses for stability.

Given the high degree of variability in methadone pharmacokinetics and metabolism, "the optimum methadone dose can vary significantly between patients, necessitating careful, individualized dose titration as opposed to standardized dosing regimens"².

See [Ongoing Care](#) for more detailed recommendations around methadone dosing, specifically the sections on *Higher Methadone Doses (Above 120 mg)*, *Methadone Split Doses*, *Rapid Metabolism & Serum Levels*, and ECG MONITORING FOR PROLONGED QTc.

Considerations for Low Maintenance Doses (Below 50 mg)

Some patients stabilize at lower than average doses. Low maintenance doses may be suitable for some patients, such as those with lower opioid tolerance (e.g., codeine use only, low-dose or low-potency opioid use, intermittent opioid use, or a recent period of abstinence) or those at higher risk for methadone toxicity. Again, buprenorphine/naloxone would be the preferential treatment for these patients and should be offered/discussed as appropriate.

Doses below 50 mg are generally less effective than higher doses at reducing high-potency opioid use and retaining patients in treatment². Again, the focus with patients should be on clinical indicators of stability, not the dose.

Ongoing Follow Up

At each follow-up visit, review as needed and document the patient's dosage, withdrawal symptoms and cravings if present, ongoing substance use, missed doses, adverse effects, and relevant markers of clinical stability.

See [Ongoing Care](#) for detailed guidance on **ASSESSING CLINICAL STABILITY** and issues commonly encountered during the course of treatment. See [Methadone Take-home \(Carry\) Dosing](#) for detailed guidance on the provision of carries.

Periodically discuss the goals of treatment and adjuncts such as harm reduction strategies and psychosocial supports.

If indicators of clinical stability do not improve as expected during OAT treatment, consider whether continued prescribing is appropriate and aligns with the patient's and prescriber's goals. See [Discontinuing Treatment](#) for guidance on managing safety concerns in unstable patients and recommendations around withdrawal of treatment.

References

1. Centre for Addiction and Mental Health (CAMH). *Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*. CAMH; 2021. Available at: <https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf>
2. Provincial Opioid Use Disorder Treatment Guideline Committee. *A Guideline for the Clinical Management of Opioid Use Disorder*. British Columbia Centre on Substance Use (BCCSU) and BC Ministry of Health; 2017. Available at: <https://www.bccsu.ca/care-guidance-publications/>

Appendix Z²



CLINICAL OPIATE WITHDRAWAL SCALE¹

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient's name: _____ Date and Time: ____/____/____:____

Reason for assessment: _____

<p>Resting Pulse Rate _____ beats/minute <i>Measured after patient is sitting or lying for one minute</i></p> <p>0 pulse rate 80 or below 1 pulse rate 81–100 2 pulse rate 101–120 4 pulse rate greater than 120</p>	<p>GI Upset over last ½ hour</p> <p>0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting</p>
<p>Sweating over past ½ hour not accounted for by room temperature or patient activity</p> <p>0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face</p>	<p>Tremor observation of outstretched hands</p> <p>0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching</p>
<p>Restlessness observation during assessment</p> <p>0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds</p>	<p>Yawning observation during assessment</p> <p>0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute</p>
<p>Pupil Size</p> <p>0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible</p>	<p>Anxiety or Irritability</p> <p>0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult</p>
<p>Bone or Joint Aches <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i></p> <p>0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort</p>	<p>Gooseflesh Skin</p> <p>0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection</p>
<p>Runny Nose or Tearing <i>Not accounted for by cold symptoms or allergies</i></p> <p>0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks</p>	<p>Total Score _____</p> <p><i>The total score is the sum of all 11 items.</i></p> <p>Initials of person completing assessment: _____</p>

Score: 5–12 = mild; 13–24: moderate; 25–36 = moderately severe; more than 36 = severe withdrawal

Reference:

1. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35(2):253–259.

More information:
www.bccsu.ca



BRITISH COLUMBIA
CENTRE for EXCELLENCE
in HIV/AIDS



2. From <https://www.bccsu.ca/wp-content/uploads/2017/08/Clinical-Opiate-Withdrawal-Scale.pdf>

Appendix AA

NON-OPIOID MEDICATION FOR SYMPTOMATIC MANAGEMENT OF OPIOID WITHDRAWAL

The following non-opioid medications may be useful to treat symptoms of opioid withdrawal.

Prescribers should exercise caution with all sedating medications during OAT induction, as they may interfere with the assessment of withdrawal severity and increase the risk of fatal overdose. In the absence of precipitated withdrawal (in the context of buprenorphine induction), many prescribers prefer to avoid these medications entirely during induction.

- Acetaminophen 500-1000 mg PO Q4-6h PRN for muscle pain (to a maximum dose of 4000 mg in 24 hours, or as appropriate based on known liver function/impairment).
- Ibuprofen 400 mg PO Q6-8H PRN for muscle pain.
- Ondansetron 4 mg PO Q6H PRN for nausea.
- Loperamide 4 mg PO PRN for diarrhea, then 2 mg PO after each loose stool, up to a maximum of 16 mg in 24 hrs.
- Trazodone 50-100 mg PO QHS PRN for insomnia.
- Quetiapine 25-50 mg PO QHS PRN for anxiety/insomnia.
- Clonidine 0.1 mg PO QHS PRN for opioid withdrawal symptoms and insomnia. Clonidine can be titrated up to 0.2 mg PO BID for severe withdrawal, but caution is advised due to the potential risks of sedation, hypotension, and diversion.

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

3.3 Recommendations for Methadone Take-home (Carry) Dosing in Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Take-home dosing can help make opioid agonist therapy (OAT) more acceptable to patients by reducing the burden of treatment. It can reduce the time commitment and cost associated with daily pharmacy attendance, enhance patient autonomy, and integrate OAT with other social, employment, and recreational life goals. This, in turn, can have a positive impact on treatment retention and reinforcement of abstinence.

As patients build clinical stability, the benefits of methadone take-home doses must be weighed against the associated patient and public health risks. Diversion of methadone poses significant risk of serious harms, including death, to the public. Methadone diversion also contributes to patient instability and often implies ongoing involvement with illicit drugs and related activities. As such, the recommendations for methadone are comparatively more conservative than those for [Buprenorphine/naloxone Take-Home Dosing](#), reflective of buprenorphine's superior safety profile and fewer associated public health risks.

However, if a patient discontinues methadone due to excessively restrictive take-home dose policies, they will be subject to the ongoing harms of untreated opioid use disorder (OUD). Providers must use a balanced approach to managing these risks and benefits, and ensure that patients receive regular education regarding risks as care plans are negotiated and adjusted over time. It is recommended that patients and providers complete a Take-home Dosing (Carry) Agreement (see **Appendix BB**) prior to authorizing carries. This agreement should be incorporated into the medical record and a copy should be provided to the patient.

It is the responsibility of the OAT prescriber to determine a patient's eligibility for take-home dosing and to continually reassess their stability and carry status. Prescribers should consult with team members and other providers involved in the patient's care, including the pharmacy team, to ensure that all relevant safety information is taken into consideration.

SPECIFIC CONSIDERATIONS

In general, methadone doses should be dispensed as daily witnessed doses. Daily witnessed doses are self-administered under the direct supervision of a pharmacist, approved prescriber, or a nurse, until the patient has demonstrated sufficient clinical stability to be considered for take-home doses.

INDUCTION & EARLY STABILIZATION

Daily Witnessed Ingestion

Generally, take-home doses (carries) should not be granted during the first two months of treatment. An exception may be granted for Sunday carries due to pharmacy closures, if the provider determines the benefits of uninterrupted daily dosing outweigh the risks of providing the carry. This may be particularly useful for rural or remote patients with limited pharmacy options and/or where patients must travel longer distances to access a pharmacy or nursing station.

Some OAT programs give weekend carries in similar contexts **when there is no weekend pharmacy access** and the patient demonstrates sufficient early stability, reliable behaviour, and can store the medication safely. However, when patients are deemed unstable and the risks of earlier carry doses are significant, patients may have to forgo one or two doses weekly if no pharmacy access is available on Saturdays and/or Sundays. The prescriber must document their risk assessment and rationale for such decisions.

LATER STABILIZATION & ONGOING CARE

The following criteria should be assessed prior to initiating take-home dosing of methadone and/or adjusting the number of take-home doses permitted:

- 1) Clinical Stability
- 2) The Length of Time on Methadone Treatment
- 3) Ability to Safely Store Methadone

STRONG RECOMMENDATION: INFORM PATIENTS OF THE RISKS TO THE OPIOID NAÏVE

Before initiating carries, OAT prescribers should advise patients of the potential danger to the opioid naïve, particularly children, of consuming methadone and the need to store the carries in a locked box or locked cabinet. Some patients may prefer or need to keep doses cold. Methadone doses stored in the fridge without being locked up is not acceptable. If patients prefer or need to keep methadone doses cold, an icepack can be added to the lockbox, and/or the lockbox stored in the fridge.

1) *Clinical Stability*

Patients are clinically stable when they demonstrate the social, cognitive, and emotional stability necessary to use methadone as prescribed, and assume responsibility for the care and safeguarding of methadone doses.

Clinical stability has been established when the following is demonstrated:

- The patient is on a stable dose of methadone.
- Missed doses are an infrequent occurrence (< 2 per month) or are specifically related to access barriers (e.g., transportation, work, or finances) that would be remedied by authorizing take-home doses.
- No evidence of ongoing use of illicit opioids, alcohol, benzodiazepines/Z-drugs, stimulants (e.g., cocaine or methamphetamines), and/or illicit sedating/psychoactive prescription or over-the-counter medications, as evidenced by regular clinical assessment and urine drug testing (UDT) results, collected at the minimum frequency recommended in this manual. (See Recommendations for UDT for further guidance, specifically **RECOMMENDATIONS FOR FREQUENCY OF UDT**).
- The patient's physical health, mental health, and social situation are sufficiently stable to support the safe consumption and storage of take-home doses in a locked box or a locked cabinet at home.
- The patient is generally compliant with the treatment agreement, including the minimum recommended UDT and pill count/methadone carry bottle count requirements of treatment as outlined in this manual.

2) *The Length of Time on Methadone Treatment*

As above, carries are not recommended during the first two months of treatment (except for Sundays, as applicable and appropriate). After two months of treatment, if a stable dose of methadone and clinical stability (as above) are established, a patient can receive **one additional take-home dose per month, each month, to a maximum of six carries per week** (i.e., one witnessed dose in the pharmacy, six take-home doses). As per **TABLE 1**, a clinically stable patient may attend the pharmacy for witnessed dosing once weekly within 6-7 months of starting treatment. Please see exceptions to this schedule further in this chapter.

Patients who have occasional non-problematic drug use while on methadone may be appropriate to receive carries, if the prescriber determines that they are clinically stable and able to store their medication safely. However, the number and progression of carries on their schedule would be reduced. Prescribers should clearly explain these expectations to patients and document these discussions in the medical record. Overall life stability and responsible attitudes are just as important to consider as UDT results.

TABLE 1: METHADONE TAKE-HOME DOSE SCHEDULE FOR CLINICALLY STABLE PATIENTS

TAKE-HOME DOSE CRITERIA	NUMBER OF CARRIES
Meets clinical stability criteria & on methadone for at least 2 months	1 (plus Sunday*)
Meets clinical stability criteria & on methadone for the past 3 months	2 (plus Sunday*)
Meets clinical stability criteria & on methadone for the past 4 months	3 (plus Sunday*)
Meets clinical stability criteria & on methadone for the past 5 months	4 (plus Sunday*)
Meets clinical stability criteria & on methadone for the past 6 months	5 (plus Sunday*)

*As applicable to the patient circumstances.

Again, the decision to give take-home doses must take into consideration both patient safety and public safety. If a period of instability recurs the prescriber must reassess the number and progression of carries (see *Reassessment & Reduction of Take-home Doses* and *Managing Relapse* below).

Some providers may choose to adopt a slower and more cautious rate of awarding carries. However, this should be balanced with managing the burden of treatment for patients, for treatment retention and re-engagement with meaningful life activities.

3) Ability to Safely Store Methadone

The patient must be instructed to store methadone take-home doses in a locked box and or locked cabinet. A pharmacist is required to observe and document evidence of a locked box or cabinet prior to releasing methadone take-home doses for the first time. A photograph of the patient with same would be sufficient proof in most circumstances. Additionally, evidence of this can be shown to the prescriber when carries are initiated. It is *not recommended* to ask patients to regularly carry locked boxes in and out of the clinic/pharmacy, as they may be targeted for theft.

LOCKED BOXES & NIHB

For patients whose medications are covered by Non-Insured Health Benefits (NIHB), the cost of a lockbox may be covered once per patient, per lifetime (up to \$35), for the safe storage of take-home doses of OAT. If indicated, this coverage extends to safe storage of other high-risk medications, including other opioids, benzodiazepines, stimulants, or sedating/psychoactive drugs, where a lockbox can improve safety for NIHB clients and communities.

The use of a locked box should be specified in the treatment agreement. The safe storage of medications should be assessed periodically by the OAT provider and pharmacist. Patients with unstable living arrangements, where medications cannot be safely stored, are not candidates for take-home doses, as below.

Patients Who Should NOT Receive Take-home Dosing

Take-home doses *should not* be given under the following circumstances:

- The patient is unable to store take-home doses safely (e.g., unstable housing, no fixed address, residing in shelters without locked storage, recurrent history of lost or stolen medication, or living with individuals with unstable mental health or substance use disorders).
- Evidence of diversion.
- Significant, unstable substance use issues (especially other opioids, alcohol, stimulants, benzodiazepines/Z-drugs, and other sedating medications, including over-the-counters).
- Significant prescribed polypharmacy involving sedating/psychoactive medications where there is notable risk of accidental or intentional overdose. In these cases, polypharmacy needs to be carefully addressed prior to considering take-home dosing. See [Managing Polypharmacy, Benzodiazepines, Alcohol & Polysubstance Use](#) for discussion of these issues, specifically [AN APPROACH TO POLYPHARMACY IN THE CONTEXT OF OAT](#).
- Significant, unstable physical or mental health conditions that may impact the patient's ability to manage take-home doses safely and responsibly.
- Significant cognitive impairment.
- The patient is not attending the minimum acceptable number of clinic appointments required by the treatment team to provide care safely. These expectations need to be explicitly discussed and documented in the treatment agreement and/or patient chart.
- Abusive, intimidating, or harassing behavior directed toward staff or other patients. Behavior expectations need to be explicitly discussed and documented in the treatment agreement and/or patient chart. This expectation also extends to the pharmacy and pharmacy staff.
- The patient's preference is to attend the pharmacy daily or more frequently for witnessed ingestion.

Pharmacy closures over weekends and statutory holidays may require occasional take-home doses regardless of the above-mentioned contraindications. However, the prescriber may elect to withhold take-home doses altogether if the risks to the patient and/or public outweigh the potential benefits, and there is no other pharmacy available to access on these days.

Occasional Take-home Doses for Exceptional Circumstances

Occasional take-home doses may be appropriate under certain circumstances for patients who do not otherwise meet criteria for regular carries. Examples may include:

- Travel for verified medical appointments.
- Significant family events such as weddings and funerals.
- Significant family illness or other responsibilities requiring travel.
- Other non-specified circumstances deemed reasonable by the OAT provider.

Before authorizing take-home doses for travel purposes, clinicians should consider whether **guest dosing at a pharmacy near the patient's travel destination may more appropriate**. It may, for instance, be appropriate to provide one carry for the day of travel, arrange for guest dosing during the stay away from home, and then request the guest dosing pharmacy provide a travel carry to the patient for the return trip home.

When prescribers provide a new prescription for guest dosing temporarily at a different pharmacy, it must be remembered that *any new prescription cancels the old prescription* (see Relationship with Pharmacy & Prescriptions chapter). Accordingly, **the old prescription at the previous/regular pharmacy must be canceled**. It is important for the OAT prescriber/clinic team to coordinate with the regular pharmacy that the patient will attend upon return from travel, to inform them of the arrangements and to provide a new prescription for when the patient returns. This could mean proactively sending another prescription to the previous/regular pharmacy to be initiated upon return from travel, and/or requiring the patient to contact the prescriber/clinic team after returning from travel to arrange a new prescription.

Extended Take-home Doses for Work or Travel

Patients who are eligible and have earned five to six methadone carries per week (thereby attending the pharmacy once or twice weekly), may be temporarily granted an increased number of carries for reasons such as travel and employment. Patients may be asked to provide the clinic with verification of their travel plans (e.g., plane ticket, letter from work).

Again, clinicians should consider whether guest dosing at a pharmacy near the patient's travel destination may be more appropriate. A **maximum of two to four weeks** of take-home dosing is recommended, if deemed appropriate in clinically stable patients. See the Continuity of Care chapter for further guidance regarding longer-term travel and guest dosing.

Authorization of Take-home Doses & Communication with Pharmacy

Additions, changes, and exceptions to the take-home dosing schedule must be clearly documented in the medical record, and clearly communicated with the pharmacy.

The schedule of take-home doses can be communicated to the pharmacy by either writing the instructions for witnessed and take-home doses directly on the prescription, or by sending it to the pharmacy as a separate note or letter (see the Relationship with Pharmacy chapter appendix for an example). The latter is especially useful when the current prescription is still valid and the treatment team wishes to authorize changes to take-home doses, such as a new permanent carry or one-time carries for travel or other reasons.

Take-home doses must be authorized by the prescriber or a member of the clinical team. The pharmacist cannot authorize take-home doses, and the prescriber/clinic staff should clearly explain this to the patient to avoid misunderstanding. Pharmacists can often provide valuable input on the appropriateness of take-home doses. Discussion is encouraged, especially when the prescriber/clinic staff are questioning the safety of providing carries in certain situations.

MONITORING FOR CLINICAL INSTABILITY & DIVERSION OF PRESCRIBED MEDICATION

It is the responsibility of the OAT prescriber and the treatment team to monitor clinical stability on an ongoing basis. All members of the treatment team must be vigilant when it comes to detecting diversion of prescribed medication. This is especially relevant when it comes to decisions regarding take-home dosing. See [Discontinuing Treatment](#) for guidance on managing potential diversion and considerations for involuntary withdrawal of treatment.

UDT & Medication Monitoring

In practice, monitoring for stability and diversion involves periodic UDT and/or pill or carry bottle counts for patients with take-home doses. Patients may be asked to routinely return labelled empty methadone bottles to the pharmacy, or they may be periodically asked to show unused carry bottles to the prescriber.

If feasible, random UDT and/or random pill/bottle counts are an effective method for detecting diversion and illicit substance use. Due to the inherent logistical challenges associated with *random* testing and counts, it is recognized that most clinicians perform *periodic* testing and pill/bottle counts at scheduled patient visits.

Prescribers may consider asking the pharmacist to bubble pack the patient's other medications to improve compliance and facilitate monitoring (pill counts). Bubble packed medications are not child proof and therefore may not be a safe option in some patient settings. Patients must be able to secure bubble packs in a locked box or cabinet.

See the Use of UDT in the Management of OUD chapter for a general approach to drug testing, including the recommended frequency and important issues to consider when interpreting results. Determination of clinical stability is never based on UDT results alone. Clinicians should rely on patient history, collateral information, and direct observation/clinical examination, which is augmented by UDT results, to formulate treatment plans in partnership with the

patient. The chapters on Ongoing Care and [Managing Polypharmacy, Benzodiazepines, Alcohol & Polysubstance Use](#) also provide further guidance on assessing clinical stability.

Reassessment & Reduction of Take-home Doses

If a period of instability occurs, the prescriber should determine if the frequency of take-home doses needs to be reduced while treatment is intensified. This could include instability in reliable or safe housing, mental health issues, relationship breakdown, and/or relapse to substance use. Patients who consume methadone carries early, report lost or stolen carries, or frequently vomit carries, should also have their number of take-home doses reduced, with possible return to daily witnessed ingestion (see *Complete Forfeit of Take-home Doses* below).

If treatment intensification results in improved stability, the prescriber, in consultation with the treatment team, may elect to reinstate take-home dosing more rapidly than outlined above.

Managing Relapse

A relapse is defined as a return to sustained problematic drug use, along with loss of clinical stability, and as such, the frequency of methadone carries should be reduced. Meanwhile, the frequency of clinical assessment and monitoring (UDT, pill/bottle counts) should increase until stability is re-established.

Prescribers may elect to *not* reduce the number of carries following a single episode of drug use (i.e., a slip or lapse), if the episode was short-lived and the patient does not demonstrate other signs of instability. The patient may instead be asked to present for one or more additional UDTs (7-10 days apart) and/or for additional clinical assessments with a member of the treatment team, to establish that the slip was indeed short-lived.

The following is recommended during a relapse for patients on methadone:

- Patients who demonstrate continued sustained substance use and/or clinical instability should have all take-home doses removed and return to daily witnessed ingestion.
- If the patient remains otherwise clinically stable, remove one carry dose per week for each positive urine sample (typically tested once per week).
- If the patient is otherwise stable and again meets take-home dosing criteria, carries can be gradually reinstated, but no faster than one carry per week for each negative urine sample (typically tested once per week).

Complete Forfeit of Take-home Doses

All take-home doses should be removed for the following reasons, if confirmed by sufficient collateral/evidence, and discussed collaboratively with the patient:

- Evidence of diverted methadone.

- Evidence of tampering with urine samples.
- Evidence of repeated failure to ingest dispensed methadone doses.
- Take-home doses are ingested early, and the patient runs out of methadone.

If the patient was not consuming their full dose or if they were skipping or diverting one or more doses, it may be necessary to reduce the methadone dose to 50% of the original dose (similar to recommendations for missed doses, as outline in the Ongoing Care chapter). Such a **dose reduction is intended to protect against overdose** when take-home doses are converted to witnessed doses and/or when the patient resumes consuming their full witnessed dose on a daily basis. Observing the patient for a period after dosing (i.e., in clinic or in collaboration with pharmacy) may be warranted to monitor for sedation/opioid toxicity.

If the methadone dose is reduced, the patient should also be assessed for signs and symptoms of opioid withdrawal, and appropriate dose increases should then be made to restabilize the patient, if the plan is to continue OAT.

Conversely, **if diversion is confirmed**, this constitutes sufficient grounds for an involuntary taper to zero or immediate cessation of OAT. See [Discontinuing Treatment](#) for guidance on the involuntary withdrawal process. Alternatively, increased supervision and strict witnessed dosing seven days per week, with no option for take-home doses (for any reason) may be considered, if deemed appropriate by the treatment team. If the latter option is chosen but the behavior continues, methadone must be discontinued. Evidence of methadone diversion is typically considered a much greater safety risk to the public, and thus results in involuntary withdrawal of treatment more often (compared to buprenorphine/naloxone).

Methadone Carries & Benzodiazepines/Z-Drugs

Patients are at greater risk of methadone toxicity if they are taking prescribed or illicitly acquired benzodiazepines/Z-drugs. See [Managing Polypharmacy in OAT](#), specifically **MANAGING PRESCRIBED AND ILLICIT BENZODIAZEPINES & Z-DRUG USE** for detailed guidance.

Patients using illicitly acquired benzodiazepines/Z-drugs are typically not candidates for take-home dosing. Patients who are *prescribed* benzodiazepines/Z-drugs and methadone may earn take-home doses if the following conditions are met, up to a **maximum of five carries a week**:

- The patient meets criteria for clinical stability.
- The prescribing physician has made a specific medical diagnosis that warrants the ongoing use of the benzodiazepines/Z-drug. This condition should be regularly reassessed.
- The dispensing interval of prescribed benzodiazepines/Z-drugs should mirror the OAT dispensing schedule, in most cases. **Communication and collaboration with any other prescribers and the pharmacy about this expectation is essential for patient safety.**

- Early refills should not be granted and lost stolen medication should generally not be replaced.
- If not medically essential, a taper of the benzodiazepine/Z-drug should periodically be attempted. Again, see [Managing Polypharmacy](#) for detailed guidance around tapering and managing problematic use of benzodiazepines/Z-drugs.

IMPORTANT NOTE: BENZODIAZEPINES/Z-DRUGS & CARRIES

In patients prescribed benzodiazepines/Z-drugs in the context of agonist therapy with methadone, the **maximum number of carries permitted per week is five**. If not medically essential, the patient should be encouraged to slowly taper off benzodiazepines over time. Once a taper to zero is complete, they may be awarded a sixth and final carry dose per week.

In the context of agonist therapy with buprenorphine and prescribed benzodiazepines/Z-drugs, the approach to carries is identical to the recommendations outlined in the [Buprenorphine/naloxone Take-home \(Carry\) Dosing Recommendations](#) section of this manual.

Medical Conditions Limiting Pharmacy Access

When a medical condition significantly interferes with the ability to attend the pharmacy, a prescriber may decide to initiate or increase take-home doses for a patient who otherwise would not qualify for carries, in collaboration with the treatment team.

Of note, the medical condition that necessitates take-home dosing may involve pain and/or other symptoms that could destabilize the patient and/or trigger relapse to substance use. A risk-benefit assessment that balances safety with treatment retention should be discussed and documented in the medical record.

For medical conditions of a temporary nature, the requirement for take-home doses should be reassessed once the patient's ability to attend the pharmacy is re-established.

Delivery of methadone to the patient's address is rarely indicated and should only be requested in exceptional medical/social circumstances. This would require collaboration with the pharmacist to evaluate a viable plan, dependent on the ability of the pharmacy to arrange for the delivery of methadone in an acceptable manner.

A witnessed self-administered dose can only be observed by a pharmacist, approved prescriber, or nurse in Manitoba. As such, delivered doses would be considered unwitnessed take-home doses (i.e., that the patient would self-administer in their own home) unless ingestion is actually witnessed by the pharmacist, and this is typically not feasible or realistic. **The prescriber should make it clear to the pharmacist that these delivered doses are intended to be unwitnessed, or take-home doses, in these circumstances.**

Arrangements to go without witnessed doses cannot be ongoing. Please refer to the [Advice for OAT Take-home Dosing in the context of COVID-19](#) for specific pandemic-related guidance.

CARE OF PATIENTS ON METHADONE WITH EXTENDED CLINICAL STABILITY

Some patients on long-term OAT may demonstrate extended clinical stability, including sustained remission of their OUD and successfully rehabilitated lives. This long-term stability may permit more flexibility with take-home dosing for quality-of-life reasons and to further decrease the burden of treatment.

The recommendations for [Buprenorphine/naloxone Take-Home Dosing](#) permit more flexibility for patients with long-term clinical stability. Patients on OAT with buprenorphine with one year of documented clinical stability may transition to witnessed dosing of buprenorphine once per month, receiving the rest of the month's medication supply as take-home doses.

Some patients on methadone with long-term clinical stability may similarly benefit from bi-weekly or eventually monthly witnessed dosing *if specific criteria are met*. This could also include temporary extended carries for personal or work-related travel.

To be considered for extended take-home dosing, patients must meet the following three criteria:

- 1) **Two consecutive years of documented clinical stability on OAT**, including:
 - Employment or other socially productive activity (e.g., school, parenting, volunteering/community involvement),
 - Absence of criminality or illicit activity, and
 - Sustained remission from problematic drug and alcohol use.
- 2) Reliability and honesty in keeping appointments and interaction with the OAT provider, treatment team, and pharmacy staff.
- 3) Ongoing ability to safely store medication.

As outlined in the Ongoing Care chapter, for stable patients with no significant changes in treatment, follow-up appointments every three months are appropriate. Clinical judgement should be applied to the frequency of appointments. Typically, at each visit, UDT should be completed, and the methadone prescription would be written for 3 months. If the above criteria are met, methadone may be dispensed every two weeks or, at the prescriber's discretion, monthly, with a witnessed dose at the time of dispensing (i.e., 13 take-home doses bi-weekly, or up to a maximum of 29 take-home doses for monthly dispensing). Tablets may be considered as an alternative to liquid methadone, especially for international travel purposes.

However, it is important to advise the patient that tablets are typically not covered for OUD. Providers must also document their risk-benefit assessment in this regard, as both diversion and injection use may be facilitated by prescribing tablets.

If *any* concern about stability arises, then the frequency of clinic visits and UDT should be increased, and the carry status should be reassessed. Any demonstrated instability should see the patient returned to *at most* weekly dispensing, and care should align with the recommendations for earlier treatment phases.

Signs of instability may include:

- Unexpected (confirmed) UDT results.
- Significant decompensation in mental or physical health.
- Loss of employment or other socially productive activity.
- Difficulty attending appointments or pharmacy.
- Signs of aberrant behaviour (e.g., criminal/illicit activity, concerns about diversion).

As outlined in the [Discontinuing Treatment](#) chapter, specifically **VOLUNTARY TAPERING**, some patients with long-term stability may choose to attempt a methadone taper. Voluntary tapering can be suspended at any time and patients who relapse to opioid use or who decompensate psychosocially or functionally should be encouraged to titrate back up to a stable dose. If these patients re-stabilize, they may be considered candidates for extended take-home dosing again after a further six months of sustained clinical stability.

Appendix BB

TAKE-HOME (CARRY) DOSING AGREEMENT

I, _____, agree to the following conditions to receive take-home (or “carry”) doses of my medication.

- I am aware that the ingestion of even a small amount of my medication by a child or other person who is not accustomed to opioids could result in overdose or death.
- I will store my medication in a safe, locked box, or locked cabinet that cannot be accessed by other people or by pets.
- I will not sell or share my medication with another person. I understand that doing so is dangerous and may lead to loss of access to take-home doses or removal from the program.
- I will assume responsibility for my take-home doses, and I understand that take-home doses cannot be replaced if they are lost, stolen, spilled, or vomited.
- I will provide a urine sample when asked to do so by program staff. If I do not provide a sample as requested, or non-prescribed drugs are found in my sample, I may lose access to one or more take-home doses.
- I will bring my medication to my clinic or pharmacy if asked to do so. If I do not, I may lose access to one or more take-home doses including return to daily witnessed ingestion.

Patient Name: _____ Date: _____

Signature: _____

Witness Name: _____ Date: _____

Signature: _____

MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

4.1 Alternative Treatment Approaches to Opioid Use Disorder Including Slow-Release Oral Morphine (Kadian®)

GENERAL CONSIDERATIONS

While Opioid Agonist Therapy (OAT) with buprenorphine/naloxone is the preferred and evidenced based first-line treatment for the management of Opioid Use Disorder (OUD), a subset of patients with this condition may benefit from treatment with methadone^{1,2}. These first- and second-line options are discussed in detail throughout this manual. Occasionally, prescribers may assess a patient with OUD for whom OAT with buprenorphine/naloxone and methadone is either unavailable or unacceptable. For such patients, alternate treatment approaches exist.

It is important to note that the alternatives to first- and second-line OAT medications discussed in this chapter:

- Are not considered routine interventions.
- Lack the robust body of evidence reported for buprenorphine/naloxone and methadone.
- Should only be considered in carefully selected clinical environments and patient populations.

These alternate approaches to OUD management must be reviewed in consultation with addiction medicine specialists* in Manitoba, who have experience with these treatment modalities in our local context.

*For the purpose of this manual, an **addiction medicine specialist** is a Manitoban physician with robust training, knowledge, and clinical experience in the management of substance use disorders, including OUD, *and* who passed an addiction medicine exam proctored by the International Society of Addiction Medicine (ISAM), the American Board of Addiction Medicine (ABAM), or the American Board of Preventive Medicine (ABPM), *or* with Canadian Society of Addiction Medicine (CCSAM) certification, *or* a Certificate of Added Competence in Addiction Medicine (CCFP(AM)).

SPECIFIC CONSIDERATIONS

The alternate treatment approaches discussed in this chapter include:

- 1) Home-Based Withdrawal Management or “Detox”
- 2) Slow-Release Oral Morphine (SROM)
- 3) Injectable Opioid Agonist Therapy (iOAT)

HOME-BASED WITHDRAWAL MANAGEMENT OR “DETOX”

A subset of patients will seek out “detox” as treatment, or to prepare themselves for further treatment programming, for a multitude of reasons. These reasons may be circumstantial, particularly in areas where OAT is not available, and/or personal. These patients may be unwilling to commit to a longer-term structured treatment plan involving OAT with buprenorphine or methadone.

“Detox” Admission Not Recommended

Admitting such individuals to a hospital or community-based detoxification unit for abstinence-based “detox” (i.e., the abrupt discontinuation or rapid tapering of opioids over 10 -14 days) is **not recommended due to the substantial risk of serious harms**. These potential harms include death by overdose given the lost tolerance created by an abstinence-based detoxification admission. However, home “detox” may be an alternative option for some individuals. Home “detox” is defined as a self-guided process of tapering a low to moderate dose of opioids, or abstinence from opioids over a predetermined period, outside of an established clinical or institutional setting. **It is important to consider that this approach has limited evidence and carries significant risk³.**

During a period of abstinence, symptoms of opioid withdrawal can be both physically and psychologically challenging for individuals. While opioid withdrawal is not fatal, these symptoms can be very distressing. Patients that have limited clinical and social support during their “detox” are especially vulnerable and at high risk of relapse. In as little as 3-7 days, opioid tolerance can reduce rapidly⁵. Individuals with OUD are already at a higher risk of relapse and this rapid loss of tolerance puts them at an even greater risk of fatal overdose^{3,6}.

Considerations for Home “Detox”

Providers and patients should decide together, where resources and patient supports permit, the treatment plan that is most appropriate. Patients wishing to pursue abstinence should consider attending a **long-term residential treatment program** (e.g., therapeutic community) following successful “detox”⁴. The therapeutic community environment provides patients with more support, time, and skill-building opportunities for additional relapse-prevention.

For patients pursuing home “detox” careful attention must be paid to:

- Initial assessment to establish appropriateness for home “detox”.
- Close follow up and appropriate escalation of treatment intensity/intervention (e.g., OAT induction should ideally be readily available should the patient consent to it).
- Pharmacological management of opioid withdrawal symptoms, while remaining mindful of safe medication management (controlled dispensing) and avoiding polypharmacy (see [PRESCRIBING ESSENTIALS](#) below).
- Social and clinical supports should be optimized, based on community capacity (e.g., counselling, peer support, preferably **long-term** residential treatment after “detox”).
- Relapse and overdose education, prevention, and management (e.g., take-home naloxone and other harm reduction supplies and training).

PRESCRIBING ESSENTIALS: AVOIDING POLYPHARMACY

For the purpose of this manual, **polypharmacy is defined as the concurrent prescribing of five or more medications with sedating and/or psychoactive properties.**

Notwithstanding this definition, it is important to note that the inherent risks of polypharmacy also apply in situations where licit substances (e.g., alcohol and cannabis) and/or illicit drugs/prescription medications, and/or over-the-counter medications with sedating/psychoactive properties, are combined with prescribed medications with similar properties. It is important for the prescriber to educate patients regarding these risks on a regular basis. See [Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in OAT](#) for further guidance.

Assessment & Consultation

The high risk of fatal overdose during, and immediately after, pursuing opioid abstinence means the *significant risks* associated with home “detox” must be carefully weighed against the benefits.

Providers and patients need to be aware that maintaining long-term abstinence is difficult and relapse rates are high¹. Careful documentation, patient selection, and consultation with addiction medicine specialists, are all critical to optimize patient safety and outcomes.

If home-based “detox” towards abstinence is the chosen treatment plan for OUD, whenever possible, ensure patients and their families are informed about all treatment options available. They should have information about and access to ongoing addiction care, namely, conversion to OAT if abstinence is not sustainable and/or if opioid use recurs.

Pharmacological Management of Opioid Withdrawal

The withdrawal symptoms experienced during home-based “detox”, in the context of OUD and pursuing abstinence, can be pharmacologically managed with:

- Tapering doses of long-acting opioids, including buprenorphine/naloxone or methadone.

Please note that when buprenorphine/naloxone or methadone is used in the context of home-based “detox”, **the same regulatory requirements apply as for patients taking these medications long-term as OAT** (i.e., prescribing approvals are required to prescribe these medications and the witnessed dosing/dispensing requirements are the same as for OAT patients).

- Alpha-agonists (e.g., clonidine) for diaphoresis and insomnia (note that these are all off-label uses of clonidine).
- Antiemetics (e.g., ondansetron) for nausea.
- Non-opioid analgesia (e.g., acetaminophen and/or ibuprofen) for myalgia.
- Antidiarrheals (e.g., loperamide) for diarrhoea.

The management of opioid-withdrawal symptoms in the early induction phase of OAT is discussed further in other chapters of this manual. Specifically, see the chapters on [Conventional Buprenorphine Induction](#) and [Methadone Induction](#) further details.

SLOW-RELEASE ORAL MORPHINE (24-Hour Formulation, Kadian®)

Slow-release oral morphine (SROM) lacks robust evidence for the treatment of OUD when compared to first- and second-line OAT medications like buprenorphine/naloxone and methadone^{2,7}. Offering SROM to patients with OUD as a first- or second-line treatment option is **not recommended**.

However, SROM can serve as a third-line treatment option for carefully selected patients with OUD. Occasionally, a patient’s rural/remote living situation, unique circumstances, medical comorbidities, or severity of disease may warrant consideration of SROM treatment.

Populations in whom SROM could be considered include:

- 1) Patients with continued opioid use, in the context of adequate therapeutic trials of first- and second-line treatment options (buprenorphine/naloxone and methadone), with significant ongoing instability (i.e., first- and second-line treatment options have been unsuccessful).

- 2) For patients with suspected or confirmed OUD awaiting further assessment or treatment, to provide controlled once-daily dosing of opioids as an *interim and time-limited bridging option* to a **confirmed** OAT induction appointment or addiction specialist consultation visit.
- 3) In the context of a tapering regime for select patients as part of a home-based “detox” program (see section above), especially when buprenorphine/naloxone and methadone are not available or acceptable to the patient. In this context, SROM must be **daily witnessed** at a pharmacy, community health facility, or nursing station.
- 4) As a discharge option from hospital for patients with OUD who were not interested in engaging with OAT care, but who were prescribed harm reduction opioids during their hospital admission to facilitate medical treatment. Under these circumstances, SROM is prescribed as:
 - A **daily witnessed** bridge to OAT intake/assessment, or
 - A structured daily-witnessed opioid taper to zero.
- 5) Patients who are experiencing ongoing opioid withdrawal symptoms while on OAT with methadone and who may benefit from the addition of oral extended-release morphine in the context of:
 - A prolonged QTc preventing further titration of methadone, or
 - As a *temporary bridge* while methadone continues to be titrated up to a more effective dose.
- 6) Patients with concurrent OUD and **confirmed** chronic pain, who may benefit from a trial of additional opioids (with better 24-hour analgesic benefit) for chronic pain management, as an alternative or in-addition to once-daily methadone.

Additional Recommendations for SROM Use

There are several **important recommendations** that prescribers must acknowledge if pursuing SROM as a third-line option for select patients.

- SROM refers to the **24-hour formulation** of the extended-release morphine capsules (i.e., brand name Kadian®). Other forms of oral morphine (e.g., 12-hour sustained- or extended-release formulations) have not been studied empirically for treating OUD, and thus are not to be used in this context.
- **SROM is typically dispensed/witnessed once daily, for all indications discussed in this document.** If due to any reason, including patient or provider preference, SROM is to be dispensed/witnessed at a time of day when the pharmacy is closed (e.g., evenings), that does **NOT** justify the authorization of carry doses beyond the recommendations in this guidance document.

Otherwise stated, the same witnessed dosing and carry recommendations apply, as per the *Stability & Take-Home Dosing* section below. This means that the patient **MUST** have pharmacy/nursing station/community health facility access at the time of day they plan to attend for witnessed ingestion of SROM. Additionally, the absolute minimum of three witnessed doses per week would still apply to patients who qualify for carries and who may otherwise take SROM in the evenings on a regular basis.

- **SROM must be dispensed via witnessed ingestion, for all indications discussed in this document** (unless being dispensed as a carry for patients who qualify for take-home doses as outline in the stability section below).

Additionally, a note must also be included on the prescription instructing pharmacists/nurses to “open and sprinkle” all witnessed doses of Kadian® capsules (e.g., into a medicine cup or onto soft food, like applesauce) before administering the contents to the patient in the pharmacy/nursing station/community health facility. If SROM pellets are dispensed in a medicine cup, this must be followed by at least 30 mL of water to ensure all the pellets have been swallowed. This approach is aimed at optimizing compliance with therapy and minimizing diversion risk.

Prescribers are strongly encouraged to contact the pharmacy to review the treatment plan and the instructions for witnessed ingestion because crushing, chewing, or dissolving SROM pellets can cause the rapid absorption of a potentially fatal dose of morphine sulphate.

- In remote/rural living environments with no access/limited access to OAT (and other OUD treatment resources) via a pharmacy, nursing station, or community health facility, **preferential consideration may be given to liberal dispensing of buprenorphine/naloxone to engage and support patients with OUD**. Unwitnessed SROM is not an appropriate alternative in this setting due to the potential patient and community safety risks.

Such patient presentations should be discussed with a specialist to determine how to best connect the patient to an OAT prescriber who can develop and manage an appropriate treatment plan, with assistance from local care providers. Collaboration between an experienced OAT prescriber and a local clinician will typically be required to facilitate such a treatment plan, especially if the OAT prescriber does not practice in the community where the patient is seeking treatment.

OAT Prescribing Approvals & SROM Use

Brief time-limited prescribing of SROM does not require a CPSM prescribing approval, but it *does* require expert consultation. Prescribing SROM as third-line treatment option for OUD and associated contexts, requires *both* consultation and OAT prescribing approvals for methadone and buprenorphine/naloxone.

Detailed recommendations are as follows:

- In populations 2 and 3 above – prescribing SROM as a time-limited bridging option to a confirmed OAT induction appointment or addiction specialist consultation, or prescribing SROM as part of a home-based “detox” tapering regime – does not require a CPSM prescribing approval. **However, prescribing SROM for these indications MUST be done in consultation with an addiction medicine specialist. Such consultative discussions must be clearly documented in the patient’s medical record. This also applies to dose titrations over time.** The prescriber must also include the indication on the M3P prescription, as well as the phrase “... as discussed with Dr _____ (name of addiction medicine specialist)”.
- Prescribing SROM for chronic non-cancer pain management in the absence of OUD, as an alternative to other long-acting opioids (to lessen the pill/dosing burden), *does not* require a specific CPSM prescribing approval. The indication must be noted on the M3P prescription to provide relevant context to the pharmacy.
- In populations 1, 5, and 6 above – when SROM is prescribed as a third-line treatment option for OUD, or in addition to methadone, or in the treatment of patients with concurrent OUD and chronic pain – **the treatment plan must be reviewed in consultation with an addiction medicine specialist.** Such consultative discussions must be clearly documented in the patient’s medical record. This also applies to dose titrations over time. Additionally, when using SROM as a third-line treatment option for these populations with OUD, **the prescriber must have CPSM prescribing approvals for the use of methadone and buprenorphine/naloxone in the context of OAT.** This requirement is consistent with national guideline recommendations around the use of SROM as a third-line treatment for OUD^{1,4}.

Assessment & Documentation

A thorough risk-benefit assessment, documented in a detailed manner, is critical to ensure the treatment plan involving SROM is the safest and most appropriate option for the patient. Providers should clearly document the relevant benefits and risks discussed with the patient. Providers must also ensure they have documented all relevant components of specialist consultation as part of the decision-making process.

Induction & Titration of SROM

SROM starting doses are between 30-200 mg PO per day, with dose increases every 24-48 hours.

SROM can be titrated up by 100 mg every 24-48 hours, based on documented clinical response/Clinical Opiate Withdrawal Scale (COWS), ongoing opioid use, and documented evidence of retention/engagement in treatment^{2,7}.

The average total daily SROM dose range can be as broad as 200-1,200 mg per day^{2,7,8}. The most recent guidance from the British Columbia Centre on Substance Use (BCCSU) [OUD Practice Update](#) indicates the titration approach should be determined by clinical discretion, individual circumstances, and frequent assessment; patients should be assessed in-person or virtually (with video) prior to any dose increases. Additionally, BCCSU recommends, “Prescribers should use caution, with respect to side effects, when prescribing above 1,200 mg and clearly document the rationale for doses above 1,200 mg”⁸.

For patients who are switching from methadone to SROM, use a methadone-to-morphine ratio of 1:4 on day 1 (i.e., 60 mg methadone = 240 mg morphine) and titrate upward based on symptoms and cravings. Stabilization dose ranges are reported to be between 1:6 and 1:8 ².

Stability & Take-Home Dosing

A patient is considered clinically stable once they reach the lowest dose of SROM required to achieve reasonable control of opioid withdrawal symptoms for 24 hours and adequate suppression of illicit opioid use. The criteria for clinical stability can be summarized as follows:

- Absence of opioid withdrawal symptoms and significantly reduced cravings.
- Absence or significant reduction in illicit substance use (self-reported and supported by urine drug testing).
- Financial and/or employment stability.
- Housing stability.
- Improvements in self-care and wellness practices.
- Strengthening of supportive relationships.
- Improvements in mental and physical health.

SROM is typically dispensed via daily witnessed dosing. Daily witnessed doses are self-administered under the direct supervision of a pharmacist, approved prescriber, or a nurse, until the patient demonstrates clinical stability to be *considered* for take-home doses. Once clinical stability has been achieved, take-home doses may be considered on a *case-by-case basis* in patients for whom daily witnessed dosing creates a barrier to ongoing participation in treatment. Take-home doses should be awarded in a gradual fashion, similar to current guidance for authorizing [Methadone Take-Home \(Carry\) Doses](#). However, contrary to the guidance for methadone carries, **the maximum number of weekly take-home doses that may be awarded to patients on SROM is four. In other words, a minimum of three daily-witnessed doses per week must be maintained at all times to promote safety and stability.**

To receive SROM carries, patients must also have a lock box or the ability to store their medication supply safely in a locked cabinet at home.

Misses Doses

As with other opioids, including OAT, loss of tolerance can result from missed doses of SROM. Close collaboration with pharmacists, regular assessment, and clinical judgment are essential to lessen the risk of over-sedation/overdose if patients miss doses^{2,7}. There is a lack of clinical evidence to guide the management of SROM missed doses and re-induction protocols. Clinical judgment should consider the total daily dose, number of missed doses, and the possibility of diversion or other opioid use surrounding missed doses⁷.

After two or more consecutively missed days of SROM the pharmacist will cancel the prescription. Restarting SROM requires clinical assessment and frequent follow-up by the prescriber. **A new prescription with clear instructions to guide the restart is required.** A collaborative discussion between the prescriber and pharmacist regarding the plan and further monitoring can build in additional safety. The examples outlined in the **PRESCRIBING ESSENTIALS** box below require daily assessment for signs of intoxication or withdrawal.

PRESCRIBING ESSENTIALS: MISSED SROM DOSING SCHEDULE^{2,7}

Number of Missed Days*	Example Prescribed Dose SROM 200 mg PO OD	Prescribed Dose Example SROM 800 mg PO OD
1	200 mg	800 mg
2	120 mg (40% reduction)	480 mg (40% reduction)
3	80 mg (60% reduction)	320 mg (60% reduction)
4	40 mg or starting dose (e.g., 60 mg), whichever is higher (80% reduction)	160 mg (80% reduction)
5	Resume at initiation dose (e.g., 60 mg)	Resume at initiation dose (e.g., 60 mg)

*After ≥ 2 days, the pharmacist will cancel the prescription. A new prescription is needed to restart OAT. The pharmacist must report all missed doses to the prescriber/clinic team daily.

INJECTABLE OPIOID AGONIST THERAPY (iOAT, i.e., diacetylmorphine/heroin or hydromorphone)

A subset of patients with severe OUD and injection drug use (IDU) may experience ongoing cravings, withdrawal symptoms, and/or inadequate improvement in health and functional status, *despite* adequate trials of first-, second-, and third-line options for OAT. Some patients with severe injection-based OUD may not tolerate oral OAT medication due to drug reactions, severe side effects, or negative treatment experiences.

For patients who have not achieved adequate benefit from OAT trials as above, and/or who are considered treatment refractory with ongoing risk related to opioid IDU (e.g., blood borne infectious disease, overdose), injectable opioids (i.e., diacetylmorphine or hydromorphone) used under supervision in a structured and supported clinical environment have shown some benefit as a harm reduction treatment strategy⁹.

Despite evidence of benefit, iOAT as a treatment option is not currently available in Manitoba and therefore will not be discussed in detail in this manual.

IN SUMMARY

While buprenorphine/naloxone and methadone remain the treatment approaches of choice for patients with OUD, there will be a subset of individuals that require alternatives to engage in care and mitigate the harms of substance use. The risks and benefits of alternative approaches must be weighed and discussed with patients, while taking into account their psychosocial contexts. Consultation with addiction medicine specialists is essential to navigate these approaches with carefully selected patients.

References

1. Bruneau J, Ahamad K, Goyer M-È, et al. Management of opioid use disorders: a national clinical practice guideline. *CMAJ*. 2018; 190(9):E247-E257. doi: 10.1503/cmaj.170958
2. Centre for Addiction and Mental Health (CAMH). *Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder*. CAMH; 2021. Available at: <https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf>
3. Dunlap B, Cifu AS. Clinical management of opioid use disorder. *JAMA*. 2016; 316(3):338-339. doi: 10.1001/jama.2016.9795.
4. Canadian Research Initiative in Substance Misuse (CRISM) National Guideline Review Committee. *CRISM National Guideline for the Clinical Management of Opioid Use Disorder*. CRISM; 2018. Available at: https://crism.ca/wp-content/uploads/2018/03/CRISM_NationalGuideline_OUD-ENG.pdf
5. Torres-Lockhart KE, Lu TY, Weimer MB, Stein MR, Cunningham CO. Clinical management of opioid withdrawal. *Addiction*. 2022;117(9): 2540-2550. doi: 10.1111/add.15818
6. Strang J, McCambridge J, Best D, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. *BMJ*. 2003;326(7396): 959-960. doi: 10.1136/bmj.326.7396.959
7. Provincial Opioid Use Disorder Treatment Guideline Committee. *A Guideline for the Clinical Management of Opioid Use Disorder*. British Columbia Centre on Substance Use (BCCSU) and BC Ministry of Health; 2017. Available at: <https://www.bccsu.ca/care-guidance-publications/>
8. British Columbia Centre on Substance Use (BCCSU). *Opioid Use Disorder Practice Update*. BCCSU and BC Ministry of Health; 2022. Available at: <https://www.bccsu.ca/wp-content/uploads/2022/02/Opioid-Use-Disorder-Practice-Update-February-2022.pdf>
9. Oviedo-Joekes E, Marchand K, Lock K, MacDonald S, Guh D, Schechter MT (2015). The SALOME study: recruitment experiences in a clinical trial offering injectable diacetylmorphine and hydromorphone for opioid dependency. *Substance Abuse Treatment, Prevention, and Policy*. 2015; 10(3): 1-9. doi:10.1186/1747-597X-10-3

© 2023 College of Physicians & Surgeons of Manitoba (CPSM)

Recommended Citation

The College of Physicians & Surgeons of Manitoba Opioid Agonist Therapy Recommended Practice Working Group. *Manitoba Opioid Agonist Therapy Recommended Practice Manual*. CPSM; 2023. Available at: bit.ly/OATmanual

CPSM acknowledges this manual is the result of extensive collaboration among regulators, practitioners, and colleagues, including the College of Pharmacists of Manitoba (CPhM) and the College of Registered Nurses of Manitoba (CRNM).

Questions regarding this manual and content herein can be directed to CPSM or providers' respective regulatory bodies.

Phone: (204) 774-4344

Toll Free: (877) 774-4344

Email: cpsm@cpsm.mb.ca

