



A Guideline for the
Clinical Management of

Opioid Use Disorder



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Health



BRITISH COLUMBIA
CENTRE ON
SUBSTANCE USE

Networking researchers, educators & care providers

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The BC Centre on Substance Use (BCCSU) is a new provincially networked resource with a mandate to develop, implement and evaluate evidence-based approaches to substance use and addiction. The BCCSU's focus is on three strategic areas including research and evaluation, education and training, and clinical care guidance. With the support of the province of British Columbia, the BCCSU aims to help establish world leading educational, research and public health, and clinical practices across the spectrum of substance use. Although physically located in Vancouver, the BCCSU is a provincially networked resource for researchers, educators and care providers as well as people who use substances, family advocates, support groups and the recovery community.

The CIHR Canadian Research Initiative on Substance Misuse (CRISM) is a national research consortium uniquely focused on translational and implementation research targeting substance use and related harms, comprising four regional Research Nodes: British Columbia, the Prairie Provinces, Ontario, and Québec/Maritimes. The BC CRISM Node is an expert network with over 50 members spanning the province, including knowledge users, service providers, community leaders, and research scientists, all firmly committed to translating the best scientific evidence into practice and policy change, promoting evidence-based approaches to addiction, and training the next generation of leaders through our comprehensive education programs.



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Disclaimer for Health Care Providers

The recommendations in this guideline represent the view of the provincial guideline committee, arrived at after careful consideration of the available scientific evidence and external expert peer review. When exercising clinical judgment in the treatment of opioid use disorder, health care professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of patients, their families and other service users, and in light of their duties to adhere to the fundamental principles and values of the Canadian Medical Association Code of Ethics, especially compassion, beneficence, non-maleficence, respect for persons, justice and accountability, as well as the required standards for good clinical practice of the College of Physicians and Surgeons of BC and any other relevant governing bodies. The application of the recommendations in this guideline does not override the responsibility of health care professionals to make decisions appropriate to the circumstances of an individual patient, in consultation with that patient and their guardian(s) or family members, and, when appropriate, external experts (e.g., specialty consultation). Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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

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As of June 5, 2017, the BCCSU will be responsible for the educational and clinical care guidance activities for all health care professionals who are prescribing medications to treat opioid addiction (i.e., methadone, buprenorphine/naloxone, slow release oral morphine). This includes the authorization process for those seeking an exemption under Section 56 of the Controlled Drugs and Substances Act to prescribe methadone. It is important to note that the exemption process for prescribers of methadone for analgesic purposes is the responsibility of the College of Physicians and Surgeons of BC.

As part of this process, as of June 5, 2017, this guideline, “A Guideline for the Clinical Management of Opioid Use Disorder”, will serve as the provincial clinical practice guideline for all clinicians who wish to prescribe oral opioid agonist treatments (i.e., buprenorphine/naloxone, methadone, and slow-release oral morphine) for treatment of patients with opioid use disorder. This guideline will replace the previous provincial guideline released by the College of Physicians and Surgeons of BC, “Methadone and Buprenorphine: Clinical Practice Guideline for Opioid Use Disorder”.

Please refer to the the BCCSU website for more information about this transition: <http://www.bccsu.ca/provincial-opioid-addiction-treatment-support-program/>.

Executive Summary

Opioid use disorder is one of the most challenging forms of addiction facing the health care system in British Columbia and a major driver of the recent surge in illicit drug overdose deaths in the province. In the context of the current public health emergency, there is an urgent need for a provincial evidence-based guideline articulating the full range of therapeutic options for the optimal treatment of adults and youth with varying presentations of opioid use disorder. This lack of a comprehensive guideline has been a challenge for the provincial health system, and has resulted in a lack of awareness and use of the full scope of medical and psychosocial interventions available to treat opioid use disorder among care providers across the addiction care continuum.

To address this, an interdisciplinary committee comprising individuals representing each of the Provincial Health Authorities (Fraser, Interior, Northern, Vancouver Coastal, Vancouver Island), the First Nations Health Authority, the Provincial Health Services Authority, and the Ministry of Health have developed the following expert guideline. Key health systems partners, community and family advocacy groups, and provincial, national and international experts in the field subsequently reviewed the guideline. The guideline was developed using the AGREE II evaluation framework and recommendations are based on a structured literature review and use of a traditional hierarchy of evidence, whereby meta-analyses of randomized clinical trials were assigned the most weight, followed by individual clinical trials, observational reports and expert opinion. The guideline is intended for use for all BC physicians, nursing and allied health professionals, and other care providers involved in the treatment of individuals with opioid use disorder.

While this guideline supports the diversity of possible treatments available for individuals with opioid use disorder, it strongly recommends against a strategy involving withdrawal management alone, since this approach has been associated with elevated risk of HIV and hepatitis C transmission, elevated rates of overdose deaths in comparison to providing no treatment, and nearly universal relapse when implemented without plans for transition to long-term evidence-based addiction treatment (e.g., opioid agonist treatment). However, this guideline also acknowledges the importance of strengthening the residential treatment system with a view to aiding individuals seeking long-term cessation of opioid use who do not wish to pursue pharmacological treatment, but may still wish to use other various pharmacotherapies for symptom management during withdrawal.

This guideline strongly endorses the use of buprenorphine/naloxone as the preferred first-line treatment when opioid agonist therapy is being considered for the treatment of opioid use disorder and when contraindications have been ruled out. This recommendation is in line with the growing body of research suggesting that buprenorphine has a safety profile six times greater than methadone in terms of overdose risk, in addition to other comparative advantages (see [Table 2](#)). Notably, methadone has recently been reported to be involved in approximately 25% of prescription-opioid-related deaths in British Columbia. However, this guideline does endorse the use of methadone as a first-line therapy when appropriate and contraindications to buprenorphine/naloxone exist, and supports the use of methadone as a second-line option when buprenorphine/naloxone treatment proves to have limitations or is initially ineffective. Beyond these three possible first- and second-line approaches using buprenorphine/naloxone or methadone, this guideline also reviews the international evidence regarding slow-release oral morphine, and describes when and how it could be considered for use.

Finally, this guideline supports using a stepped and integrated care approach, where treatment intensity is continually adjusted to match individual patient needs and circumstances over time, and recognizes that many individuals may benefit from the ability to move between treatments. This includes intensification (e.g., initiating pharmacotherapy when a non-pharmacotherapy-based strategy is unsuccessful) as well as routine strategies to de-intensify treatment (e.g., transition from methadone to buprenorphine/naloxone, opioid agonist taper) when patients achieve successful outcomes and wish to transition to treatments that allow for more flexible take-home dosing or medication discontinuation.

With the greater incorporation of evidence-based medicine principles into the treatment of opioid use disorder through adherence to data-driven therapeutic guidelines, there is substantial potential to reduce the burden of disease and health and social service costs associated with untreated opioid use disorder.

Summary of Recommendations

Recommendation	Quality of evidence*	Strength of recommendation*	Refer to Evidence Summary (pp.)
<i>Approaches to avoid</i>			
1. Withdrawal management alone (i.e., detoxification without immediate transition to long-term addiction treatment [†]) is not recommended, since this approach has been associated with elevated rates of relapse, HIV infection and overdose death. This includes rapid (< 1 week) inpatient tapers with methadone or buprenorphine/naloxone.	⊕⊕⊕ Moderate	Strong	17-20
<i>Possible first-line treatment options</i>			
2. Initiate opioid agonist treatment with buprenorphine/naloxone whenever feasible to reduce toxicities and facilitate recovery through safer take-home dosing.	⊕⊕⊕⊕ High	Strong	23-25, Table 2
3. Initiate opioid agonist treatment with methadone when treatment with buprenorphine/naloxone is not preferable (e.g., challenging induction).	⊕⊕⊕⊕ High	Strong	21-25, Table 2
4. If withdrawal management is pursued, for most patients, this can be provided more safely in an outpatient rather than inpatient setting. During withdrawal management, patients should be immediately transitioned to long-term addiction treatment [†] to assist in preventing relapse and associated harms. See also #9.	⊕⊕⊕ Moderate	Strong	17-20
<i>Adjunct or alternative treatment options</i>			
5. For individuals responding poorly to buprenorphine/naloxone, consider transition to methadone.	⊕⊕⊕⊕ High	Strong	23-25, Table 2
6. For individuals responding poorly to methadone, or with successful and sustained response to methadone desiring treatment simplification, consider transition to buprenorphine/naloxone.	⊕⊕⊕ Moderate	Strong	23-25, Table 2
7. For individuals with a successful and sustained response to agonist treatment desiring medication cessation, consider slow taper (e.g., 12 months). Transition to oral naltrexone could be considered upon cessation of opioids.	⊕⊕⊕ Moderate	Strong	29-31
8. Psychosocial treatment interventions and supports should be routinely offered in conjunction with pharmacological treatment.	⊕⊕⊕ Moderate	Strong	20-21

* GRADE criteria were used to ascertain and describe the quality of evidence (possible categories include: high, moderate, low, very low) and strength of recommendation (possible categories include: strong, weak). Please refer to the Guidelines Supplement for more information on how the GRADE approach was applied in formulating guideline recommendations.

† In this context, "addiction treatment" refers to continued care for opioid use disorder delivered by an experienced care provider, which could include pharmacological treatment (opioid agonist or antagonist treatment), evidence-based psychosocial treatment interventions (private or publicly-funded programs), residential treatment, or combinations of these treatments. In isolation, harm reduction services, low barrier housing and unstructured peer-based support would not be considered "addiction treatment." Opioid agonist therapy can be provided as an outpatient or when individuals are admitted to inpatient addiction treatment.

Summary of Recommendations

Recommendation	Quality of evidence*	Strength of recommendation*	Refer to Evidence Summary (pp.)
9. For patients wishing to avoid long-term opioid agonist treatment, provide supervised slow (> 1 month) outpatient or residential opioid agonist taper rather than rapid (< 1 week) inpatient opioid agonist taper. During withdrawal management, patients should be transitioned to long-term addiction treatment to prevent relapse and associated harms. Oral naltrexone can also be considered as an adjunct upon cessation of opioid use.	⊕⊕ Low	Weak	17-20
10. For patients who have been unsuccessful with first- and second-line treatment options, opioid agonist treatment with slow-release oral morphine (prescribed as once-daily witnessed doses) can be considered. Slow-release oral morphine should only be prescribed by experienced addiction practitioners who hold a Section 56 exemption to prescribe methadone or only after specialist consultation (e.g., RACE line). Practitioners who lack experience prescribing slow-release oral morphine for treatment of opioid use disorder, regardless of Section 56 exemption status, should consult with an experienced prescriber prior to initiating treatment.	⊕⊕⊕ Moderate	Strong	27-28
<i>Harm reduction</i>			
11. Information and referral to take-home naloxone programs and other harm reduction services should be routinely offered as part of standard care for opioid use disorder.	⊕⊕⊕ Moderate	Strong	32-33

* GRADE criteria were used to ascertain and describe the quality of evidence (possible categories include: high, moderate, low, very low) and strength of recommendation (possible categories include: strong, weak). Please refer to the Guidelines Supplement for more information on how the GRADE approach was applied in formulating guideline recommendations.

† In this context, "addiction treatment" refers to continued care for opioid use disorder delivered by an experienced care provider, which could include pharmacological treatment (opioid agonist or antagonist treatment), evidence-based psychosocial treatment interventions (private or publicly-funded programs), residential treatment, or combinations of these treatments. In isolation, harm reduction services, low barrier housing and unstructured peer-based support would not be considered "addiction treatment." Opioid agonist therapy can be provided as an outpatient or when individuals are admitted to inpatient addiction treatment.

Introduction

Background

Opioid use disorder is best conceptualized as a chronic relapsing illness which, though associated with elevated rates of morbidity and mortality, has the potential to be in sustained long-term remission with appropriate treatment. Opioid use disorder may involve the use of illicitly manufactured opioids, such as heroin or street fentanyl, or pharmaceutical opioid medications obtained illicitly or used non-medically. While current Canadian estimates are lacking, opioid use disorder is estimated to affect approximately 2.1% of Americans.¹

The state of public health emergency declared in 2016 in response to the sharp increase in overdose deaths in British Columbia underscores the importance of developing a coordinated evidence-based strategy to address untreated opioid use disorder and related harms. The recent emergence of street fentanyl and its analogues, highly potent synthetic opioids increasingly used to replace or dilute (or “cut”) heroin and other illicit opioids, is a pressing public health concern that has contributed significantly to the overdose crisis. Provincial surveillance data indicate that the proportion of drug overdose deaths involving fentanyl has rapidly increased.² From January 1 to December 31 2016, there were 575 overdose deaths where fentanyl was detected, representing 62% of all overdose deaths reported. This is a 281% increase in overdose deaths involving fentanyl compared to 2015 (151 deaths). A key component of an evidence-based provincial response is the delivery of health services that optimize engagement, care and treatment of individuals with opioid use disorder, and recognize the need for a diversity of available treatment options that can be matched to individual patient needs and circumstances.

For many years, methadone has been the most commonly prescribed pharmacotherapy for the clinical management of opioid use disorder in British Columbia.^{3,4} However, recent reports have highlighted the low number of methadone prescribers in British Columbia, particularly in Northern regions, as well as poor retention rates.⁵ In addition, a number of additional treatment options have been under-utilized, and evidence-based reviews have increasingly described the benefits, side-effect profiles and safety of these various approaches to treatment of opioid use disorder. This literature, which is reviewed in detail below, enables the development of treatment strategies for opioid use disorder that employ different approaches based on the comparative safety profile of different treatments, individual patient circumstances and comorbidities, and recognize that treatment can be intensified or simplified depending on patient circumstances as well as short- and long-term response to treatment.

Scope and Purpose

The objective of this guideline is to provide recommendations, supported by current and rigorously reviewed evidence, for the full spectrum of medical and psychosocial interventions available to treat patients with opioid use disorder. In doing so, the guideline aims to provide comprehensive education and clinical care guidance to health care providers spanning the addiction care continuum in the province, which will, in turn, improve access to evidence-based treatment for patients and families, and reduce the significant harms associated with opioid use disorder in British Columbia.

Although the evidence presented here is generally extrapolated from studies conducted in adult populations, the consensus of the committee is that many of these recommendations are equally relevant and applicable to adolescent (aged 12-17 years) and young adult (aged 18-25 years) populations. More specifically, and in line with previous CPSBC recommendations and a recent policy statement from the American Academy of Pediatrics,^{6,7} the committee recommends that any clinician providing care to adolescents and young adults with moderate to severe opioid use disorders should consider offering first-line pharmacotherapy options where indicated and appropriate. If administration of pharmacotherapy to this patient population is beyond scope of practice or expertise, care providers should refer such patients to a health care professional with experience in treatment of adolescents and young adults with substance use disorders.

While this guideline reviews research evidence regarding treatment of opioid use disorder in the general population, future work is required to develop and implement best practices in specific populations, including adolescents and young adults, the elderly, pregnant women, and Indigenous populations (e.g., culturally optimized care pathways), as well as within criminal justice and correctional settings. Additionally, the development of best practices for managing mild concurrent mental health issues in the context of opioid addiction is required. Importantly, clinicians should be aware that treatment options may be limited for individuals subject to provincial or federal workplace-related legislation (e.g., health care professionals), but that these individuals may be eligible for alternative treatment programs (e.g., antagonist medications, and/or non-agonist based residential or psychosocial treatments). In addition, opioid agonist prescribers should be aware that some individuals (e.g., those in safety sensitive positions) may require modification of workplace duties if on opioid agonist therapy and should be aware of the obligation to work with patients and to consult with regulatory bodies and others (e.g., CPSBC, Canadian Medical Protective Association) regarding obligation to notify employers in these circumstances. Best practices for the treatment of opioid use disorder in this context also need to be better defined.

Finally, while primary prevention and the importance of safe prescribing of prescription opioids to prevent misuse and addiction are outside the scope of this guideline, it is acknowledged that for individuals who have developed a physiological dependence to prescription opioids but not opioid addiction, a slow, clinically-supported tapered reduction in prescribed dosage may be most appropriate strategy. If recognized and addressed early, individuals with physiological dependence have the potential to safely undergo a slow tapered dose reduction in an outpatient or primary care setting using non-pharmacotherapeutic approaches. In the long-term, monitoring, early intervention, and primary care management of prescription opioid dependence may reduce or prevent health care expenditures and long-term health care involvement associated with opioid use disorder. Readers are encouraged to consult the College of Physicians and Surgeons of British Columbia Professional Standards and Guidelines for Safe Prescribing of Drugs with Potential for Misuse/Diversion for more information on safer prescription opioid prescribing strategies at www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf.

Intended Audience

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

Methods

Funding and Committee Membership

Guideline development activities were entirely supported by internal funding from the BC Centre on Substance Use (BCCSU), without support from the pharmaceutical industry or associated stakeholders.

Through funding provided by the British Columbia Ministry of Health in 2014 and the work of the BCCSU's Inaugural Governance Board, a strategy to prepare a provincial guideline for the treatment of opioid addiction was initially established in the spring of 2015. Subsequently, in the summer of 2016, in consultation with the provincial government's Joint Task Force on Overdose Response and advisors from the Ministry of Health, three to five candidates were invited from each regional Health Authority and the First Nations Health Authority, as well as representatives from BC Corrections Services and the Ministry of Health, to form a provincial guideline committee. Ultimately, an interdisciplinary committee of 28 individuals was assembled. Consistent with best

practice for guideline development, the BCCSU used the AGREE-II instrument⁸ throughout the development and revision phases to ensure the guideline met international standards for transparency, high quality and methodological rigour.

Conflict of Interest

In keeping with Guidelines International Network's *Principles for Disclosure of Interests and Management of Conflicts*,⁹ committee members were asked to disclose all sources and amounts of direct and indirect remuneration from industry, for-profit enterprises, and other entities (i.e., direct financial conflicts) that could potentially introduce real or perceived risk of bias. In addition, committee members were asked to report indirect conflicts of interest, such as academic advancement, clinical revenue, and professional or public standing that could potentially influence interpretation of evidence and formulation of recommendations. Of importance, no committee members disclosed direct financial conflicts of interest.

Several committee members disclosed indirect conflicts of interest (e.g., involvement with CPSBC Methadone Maintenance Program, addiction medicine expertise, research interests), however, none were deemed to be of sufficient relevance to warrant exclusion from the committee. In order to further mitigate the risk of bias while maximizing the contributions of members in their respective areas of expertise, the chair reminded the committee to disclose any relevant indirect relationships during related guideline development discussions. Members with indirect conflicts of interest contributed to the discussions related to their particular areas of expertise as well as the overarching guideline content in order to ensure that differing viewpoints and experiences were adequately represented.

A summary of individual conflict of interest declarations is included in the Guideline Supplement.

Evidence Selection and Review

Guideline content and recommendations are based on a structured review of the literature, and used a traditional hierarchy to identify relevant research evidence, whereby meta-analyses of randomized clinical trials were given the most weight, followed by individual clinical trials, observational reports, and expert opinion.

The following treatment options and harm reduction services were included in the literature search:

- Medically-assisted withdrawal management (i.e., detoxification) and referral to outpatient and/or residential treatment;
- Residential treatment;
- Long-term opioid agonist therapy such as buprenorphine/naloxone, methadone, and, under special circumstances, slow-release oral morphine (see [Appendix 3](#) and [4](#));
- Opioid antagonist medications such as oral naltrexone;
- Psychosocial treatment interventions and supports provided in conjunction with withdrawal management or opioid agonist treatment programs, including peer-based mutual support groups;
- Harm reduction programs and services, such as take-home naloxone, supervised injection or consumption services, and needle and syringe distribution programs.

Independent BCCSU staff members identified and selected studies included in the literature review and compiled evidence summaries for the committee's review and consideration. Evidence summary tables are available upon request.

Development and Approval of Recommendations

The committee used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool¹⁰ to evaluate the literature reviewed and, subsequently, to derive specific recommendations. The GRADE system takes into account the quality of evidence (based on a range of factors including study design, risk-benefit ratios, potential biases, and scope and consistency of results) to determine the strength of recommendations. Please refer to the Guideline Supplement for a more detailed description of the GRADE system and how it was utilized in guideline development.

The consensus of committee members was sought and secured through group communication, email communication and tracked document review and revision. The draft provincial guideline and supporting materials were circulated for initial review in early August 2016, and feedback was collated and incorporated into a revised draft. The revised draft was circulated prior to a committee meeting held in early September 2016. In this meeting, the committee reviewed the draft and reached consensus on guideline content and recommendations. The committee granted approval for the draft to be sent for external review directly following the implementation of input from the meeting.

External Review

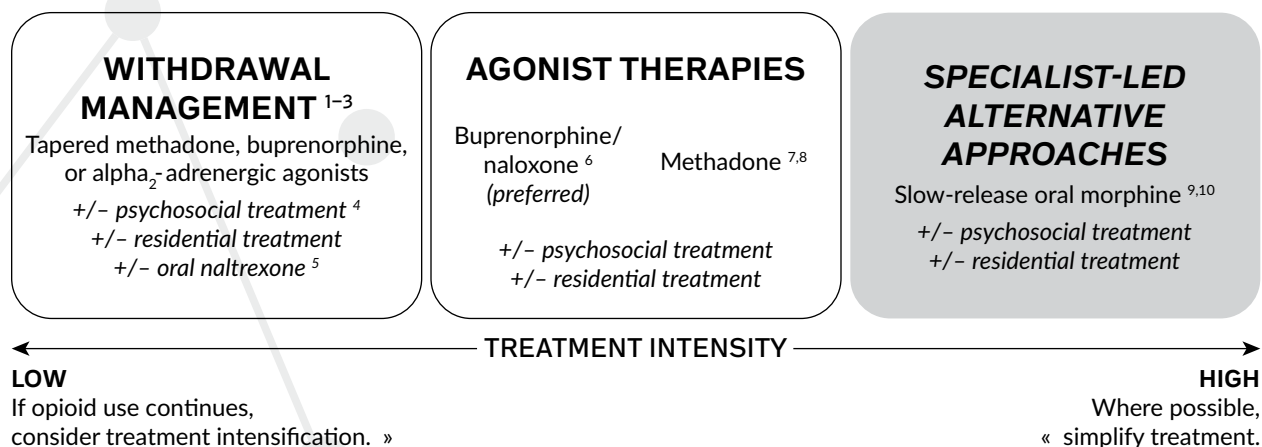
Following revisions, the draft guideline was circulated for review and comment to relevant experts and stakeholders as identified by the committee. As per policy, all external reviewers completed disclosure of interest forms prior to review (please refer to Guideline Supplement for individual disclosures). A second and final committee meeting was held in December 2016, where feedback from the external reviewers was reviewed by the chair and the committee, and incorporated into the guideline as necessary and by majority consensus.

Future Updates

The guideline development committee will conduct annual updates to ensure that advancements in the field reach the intended audience in a timely and effective manner.

Literature review

Table 1. Clinical management of opioid use disorder



HARM REDUCTION¹¹⁻¹³

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

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

Citations

1. Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database Syst Rev* 2013;2:CD003409.
2. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev* 2009:CD002025.
3. Gowing L, Farrell MF, Ali R, White JM. Alpha₂-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev* 2014;2016;5:CD002024.
4. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev* 2011:CD005031.
5. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 2011:CD001333.
6. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014;2:CD002207.
7. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009:CD002209.
8. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *Cochrane Database Syst Rev* 2003:CD002208.
9. Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database Syst Rev* 2013;6:CD009879.
10. Jegu J, Gallini A, Soler P, Montastruc J-L, Lapeyre-Mestre M. Slow-release oral morphine for opioid maintenance treatment: a systematic review. *British Journal of Clinical Pharmacology*. 2011;71(6):832-843.
11. Potier C, Laprevote V, Dubois-Arber F, Cottencin O, Rolland B. Supervised injection services: what has been demonstrated? A systematic literature review. *Drug Alcohol Depend*. 2014;145:48-68.
12. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*. 2016;111(7):1177-1187.
13. MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: A review of reviews to assess evidence of effectiveness. *International Journal of Drug Policy*. 2014;25(1):34-52.

I) Withdrawal management* strategies

IMPORTANT SAFETY NOTICE

Withdrawal management alone is not an effective treatment for opioid use disorder, and offering this as a standalone option to patients is neither sufficient nor appropriate. As will be reviewed in detail below, rates of dropout and relapse to opioid use are high, regardless of treatment modality used.¹¹⁻¹³ Furthermore, the risks of serious harms, including fatal and non-fatal overdose and HIV and hepatitis C transmission, are higher for individuals who have recently completed withdrawal management compared to individuals who receive no treatment.¹⁴⁻¹⁶ To support informed decision-making, patients who request withdrawal management alone should be provided with clear, concise information about the known risks to personal and public safety, and be engaged in supportive, constructive discussion about safer treatment options. Withdrawal management alone is not recommended unless a discharge plan is in place for referral to ongoing addiction treatment (i.e., intensive outpatient treatment, residential treatment, access to long-term opioid agonist treatment, or antagonist treatment).

ALPHA₂-ADRENERGIC AGONISTS

Compared to placebo, alpha₂-adrenergic agonists (e.g., clonidine) have been found to be effective for reducing the severity of opioid withdrawal symptoms and increasing the probability of completing withdrawal management.¹² Signs and symptoms of withdrawal appear to resolve earlier with alpha₂-adrenergic agonists in comparison to tapered methadone doses. The chances of completing withdrawal management are similar between alpha₂-adrenergic agonists and methadone, but alpha₂-adrenergic agonists tend to require shorter treatment durations. However, compared to methadone tapers, alpha₂-adrenergic agonists are somewhat less effective in mitigating withdrawal symptoms, and are more likely to present adverse effects such as hypotension.¹²

AGONIST TAPER – METHADONE

Tapering off opioids with methadone appears to reduce the severity of withdrawal symptoms, but the majority of patients still relapse to opioid use if a strategy involving only withdrawal management is employed.^{17,18} For example, clinical trials report relapse rates ranging from 53.1–66.7% at 1-month, and 61.1–89.2% at 6-months post-methadone taper.¹⁹⁻²¹

Methadone at tapered doses does not appear to differ from other pharmacological treatments (e.g., alpha₂-adrenergic agonists, other opioid agonists) in terms of severity of withdrawal symptoms, adverse effects, withdrawal completion, or sustained abstinence. Compared to placebo, tapered methadone appears to be associated with less severe withdrawal symptoms and lower rates of drop-out.¹⁷

It is important to note that wide variations in the literature were a major limitation when comparing tapered methadone to other treatments (e.g., different studies assessed different outcomes of withdrawal management using methadone versus other treatments, which did not allow for exact comparisons between treatment approaches in certain contexts).¹⁷

AGONIST TAPER – BUPRENORPHINE/NALOXONE

Similar to tapering off opioids with methadone, agonist taper involving buprenorphine/naloxone appears to reduce the severity of withdrawal symptoms, but the majority of patients still relapse to opioid use if a strategy involving only withdrawal management is employed.²² For instance, participants in the Prescription Opioid Addiction Treatment Study demonstrated significantly lower sustained abstinence rates eight weeks after tapering off buprenorphine/naloxone (8.6%) compared to abstinence rates during buprenorphine/naloxone treatment (49.2%).²³

* Sometimes referred to as “detoxification” or “detox”

Buprenorphine may offer some advantages over methadone, in terms of offering faster symptom relief and higher rates of withdrawal completion (61.2% versus 51.8%).²² There does not appear to be a significant difference in terms of withdrawal symptom severity for individuals managed with buprenorphine compared to methadone.²²

Compared to alpha₂-adrenergic agonists, buprenorphine appears to offer more effective relief of withdrawal symptoms, longer retention in treatment and greater likelihood of completing treatment (66.2% versus 42.8%).²² There does not appear to be a significant difference between buprenorphine and alpha₂-adrenergic agonists in adverse effects, except in comparison with clonidine, which is associated with higher rates of drop-out due to side effects.²²

OTHER CONSIDERATIONS FOR WITHDRAWAL MANAGEMENT ONLY

It is the consensus of the committee that most individuals with opioid use disorder should be offered community-based, outpatient withdrawal management as opposed to rapid inpatient withdrawal management. This is consistent with the American Society of Addiction Medicine placement criteria that seek to match patients' clinical needs with the most appropriate care setting and intensity that is simultaneously the least restrictive for patients.²⁴ Outpatient withdrawal management programs permit a slower, more flexible and individualized approach to tapered agonist reduction, and allow for dose readjustment and stabilization in the event that withdrawal symptoms, cravings or lapses to illicit opioid use occur. Outpatient withdrawal management is also less disruptive to the patient and their family, and offers the opportunity to continue with their normal routine of daily living, providing a more realistic environment for the development of coping strategies and support systems on reduction or cessation of opioid use.²⁵

Moreover, traditional assumptions that certain treatment modalities can be delivered only in a particular setting may not be applicable or valuable to patients. Many of the traditional placement criteria that favour inpatient rather than community-based withdrawal management services (e.g., individuals with comorbid mental health issues) should not necessarily apply in the case of opioid use disorder. In these cases, rapid inpatient opioid withdrawal may leave high-risk individuals even more vulnerable to opioid-related harms, including fatal overdose, when discharged from a highly structured treatment setting and returned to their home environment where temptation to use may be high and illicit opioids easily obtained, particularly if no follow-up addiction care is provided.^{26,27} Instead, like all patients without serious comorbidities, these patients can be referred to long-term inpatient or outpatient addiction services, where possible and appropriate, rather than inpatient short-term withdrawal management.²⁸

The lack of effectiveness of withdrawal management alone (i.e., without transition to opioid agonist treatment or continuing addiction care) often rapidly leads to high rates of relapse post-treatment, which, in turn, increases the risk of HIV and hepatitis C transmission, morbidity and mortality.¹⁴⁻¹⁶ As the first point of engagement in clinical care, opioid withdrawal management can serve an important role as a bridge to treatment, but is not recommended unless a strategy is in place for referral to ongoing addiction treatment (e.g., intensive outpatient treatment, residential treatment, access to long-term opioid agonist treatment, or antagonist treatment).

Specifically, a meta-analysis found higher HIV incidence among individuals undergoing withdrawal management only as compared with individuals receiving no treatment.¹⁴ Other past research has shown that individuals who have received inpatient opioid withdrawal management are at increased risk of death from drug overdose compared to those who received no treatment.¹⁵ This phenomenon is believed to be due to loss of tolerance to opioids and is consistent with the increased risk of fatal opioid overdose observed following release from prison.²⁹ Furthermore, relapse to opioid use is common among patients undergoing withdrawal management only, as evidenced by a large US-based observational cohort (n=990) that reported significantly lower rates of sustained abstinence at six-years follow-up for outpatient detoxification (12%) compared to other treatment approaches (18 to 21%).^{18,30}

For individuals who choose withdrawal management over long-term agonist therapy, including those with high opioid tolerance, consider initiating buprenorphine/naloxone treatment to address withdrawal symptoms and slowly tapering under outpatient supervision. Individuals who are unsuccessful with this approach may be offered agonist therapy. In order to reduce the risk of fatal overdose among patients who decline long-term opioid agonist treatment, patients and families should also be advised to undergo take-home naloxone training, a safe and effective intervention to prevent fatal overdose.^{31,32} For more information on take-home naloxone and other harm reduction strategies please refer to [Section VI](#).

PSYCHOSOCIAL TREATMENT INTERVENTIONS PROVIDED WITH WITHDRAWAL MANAGEMENT

Psychosocial treatment interventions appear to be beneficial adjuncts to opioid withdrawal management.³³ When offered in addition to pharmacologically-supported withdrawal management (i.e., opioid agonist taper), psychosocial treatment interventions such as contingency management and psychotherapeutic counselling may be effective in improving treatment retention and completion, sustaining abstinence from illicit opioids, and reducing opioid use during treatment. However, there is currently limited evidence due to small study sample sizes and varying assessment and outcome measurements. There is also insufficient evidence to favour any specific psychosocial treatment modality or patient population who would benefit from this approach.³³ Therefore, further research and patient-specific approaches are needed with regard to psychosocial treatment interventions. Importantly, while psychosocial treatments may improve rates of treatment retention and completion, psychosocial treatment interventions provided during opioid withdrawal management likely do not protect against the elevated risk of HIV infection or fatal overdose if withdrawal management alone is pursued, due to high rates of relapse post-treatment and the negligible benefit of withdrawal management alone.^{14,15,23,34}

RESIDENTIAL TREATMENT

There are no systematic reviews or meta-analyses considering the impacts of residential treatment programs for individuals with opioid use disorder. The overall dearth of evidence does not mean residential treatment is ineffective, but rather that the intervention has been under-studied, thus requiring review of individual studies. There are also no large clinical trials comparing residential treatment to other interventions, and few rigorous evaluations that identify specific characteristics of effective residential treatment programs or patient characteristics that may predict appropriateness of residential treatment referral.

Observational cohort studies in the UK have found that relapse is relatively common among clients discharged from residential treatment for opioid use disorder. For example, Smyth *et al.* (2010) reported outcomes of a six-week residential treatment program in Ireland that included methadone-based withdrawal management, psychosocial therapy (i.e., group, individual and/or family therapy) and an aftercare component. The study found that 80% of participants reported relapse within one month, of whom 59% relapsed within one week of discharge.³⁵ Younger age, not completing the full six weeks of treatment, greater heroin use prior to treatment, history of injecting, and not enrolling in aftercare were associated with a shorter time to relapse. Similarly, in the National Treatment Outcome Research Study (NTORS), approximately 57% of clients reported heroin use within 30 days of discharge, with 31% relapsing to regular levels of heroin use at 1-year follow-up.³⁶ However, for the full cohort of individuals who attended residential treatment for alcohol or substance use disorders, the NTORS study did find that at 4–5 years follow-up, injecting rates dropped from 61% at intake to 29% at follow-up, while abstinence from heroin use increased from 23.2% to 48.6% across the same period.³⁷ Overall, individuals who completed residential treatment also demonstrated improvements in terms of safer injection practices, psychological and physical health, and reductions in criminal behaviour at 4–5 years follow-up.³⁸

Studies of residential treatment in the United States also present varied results. One longitudinal study of abstinence-based treatment programs found similar rates of retention, completion and patient satisfaction among individuals in outpatient and residential treatment programs.³⁹ Another randomized trial found no difference in treatment outcomes for patients enrolled in residential treatment for less than seven weeks compared to those who did not receive any type of treatment.⁴⁰ For patients enrolled in residential treatment for

more than seven weeks, improved outcomes were observed, including increased likelihood of employment or enrolment in school, decreased likelihood of criminal conviction or incarceration, and decreased likelihood of heroin use, compared to patients who did not receive any type of treatment.⁴⁰ An additional study found that a four-week residential treatment program significantly decreased several maladaptive cognitive and behavioural patterns that may contribute to ongoing substance use problems in adults with opioid use disorder.⁴¹ Another randomized clinical trial found that a combination of community reinforcement and family training in addition to residential withdrawal management using buprenorphine, particularly when involving the adult patient's parents, was positively and significantly associated with improved retention in treatment and reductions in opioid and other drug use.⁴² Therefore, patients may benefit from residential treatment that involves fostering family and other social connections.

Although the NTORS study found that residential treatment was associated with reduced rates of non-fatal overdose at one-year follow up (7%) compared to pre-treatment rates (22%),⁴³ providers should be aware of risks associated with loss of tolerance for patients who attend residential treatment programs when not using opioid agonist therapy. For instance, a national cohort study in England found that risk of fatal overdose was twice as high for patients who completed psychosocial treatment only (outpatient or residential treatment) compared to patients who had received opioid agonist treatment.⁴⁴

II) Opioid agonist treatments

IMPORTANT NOTICE REGARDING BC PHARMACARE COVERAGE

As of June 5, 2017, Methadone, buprenorphine/naloxone, and slow-release oral morphine are fully covered under BC PharmaCare's Psychiatric Medications Plan (Plan G). Plan G is available to those with a family adjusted net income below \$42,000 per year (plus \$3,000 per dependent) who meet the clinical criteria. Application forms for Plan G can be accessed here: <http://www2.gov.bc.ca/assets/gov/health/forms/3497fil.pdf>. Full coverage for methadone, buprenorphine/naloxone, and slow-release oral morphine is already available to individuals receiving B.C. Income Assistance (i.e., those covered under Plan C) and to those who do not have a deductible or family maximum under Fair PharmaCare, and for individuals registered in the Non-Insured Health Benefits Plan.

Overall, as described below, opioid agonist treatments have been shown to be superior to withdrawal management alone in terms of retention in treatment, sustained abstinence from opioid use, and reduced risk of morbidity and mortality. The choice of agonist treatment depends on several patient-specific factors such as initial presentation, comorbidities (e.g., liver disease, prolonged QTc interval), drug–drug interactions, treatment preference, and response to treatment, as well as prescriber experience and appropriate authorization (i.e., section 56 exemption to prescribe methadone). Regardless of type of treatment administered, opioid agonist treatment should incorporate provider-led counselling, long-term substance use monitoring (e.g., regular assessment, follow-up and urine drug tests), provision of comprehensive preventive and primary care, and referrals to psychosocial treatment interventions, psychosocial supports, and specialist care as required, to optimize physical and mental wellness as the patient progresses in recovery.

METHADONE

Methadone has been shown to be significantly more effective than non-pharmacological outpatient treatment approaches in terms of treatment retention and suppression of heroin use.⁴⁵ Methadone at higher doses (i.e., between 60–120 mg/day or higher) is more effective than lower doses for treatment retention and reducing heroin and cocaine use during treatment.^{46,47} While methadone dosing should be based on clinical judgment determined individually due to differences in individual metabolism, comorbidities (e.g., liver disease, prolonged QTc interval) and drug interactions,⁴⁸ most studies have suggested that patients who take daily doses

of 80 mg/day or higher have optimal treatment outcomes⁴⁶ and that doses above 120 mg/day may be required to produce full opioid blockade and fully suppress withdrawal.^{49,50}

Despite this, the most recent data from the provincial methadone maintenance program (2013/14) indicates that approximately 50% of all patients enrolled received methadone doses of less than 60 mg per day, the lower limit of what is defined as an optimal daily dose for methadone-based opioid agonist treatment.⁵ In some cases, this may reflect reluctance to increase methadone dose above arbitrary threshold levels believed to be adequate or safe. In terms of adequate dosing (i.e., sufficient dose to control withdrawal symptoms for approximately 24 hours, without signs of overmedication) it should be emphasized that there is a high degree of inter-individual variability in methadone pharmacokinetics and metabolism, and that the optimum methadone dose can vary significantly between patients, necessitating careful, individualized dose titration as opposed to standardized dosing regimens. Further, although patient and public safety is always an important concern with methadone, research suggests that for some patients, when appropriately prescribed, higher methadone doses (> 75 mg/day) can be protective against overdose.^{51,52}

Methadone-based agonist treatment has been shown to reduce injection risk behaviours and the overall risk of hepatitis C and HIV infection among people who inject drugs.^{14,53,54} Furthermore, among HIV-positive individuals, engagement in methadone-based agonist treatment is independently associated with increased adherence to antiretroviral therapy and improved virologic outcomes (e.g., lower HIV viral loads, higher CD4 counts), particularly at higher doses (≥ 100 mg/day).⁵⁵⁻⁵⁷

There is considerable evidence that methadone is effective for the treatment of opioid use disorder and related harms, and safe when dispensed and consumed as directed. However, its unique pharmacological properties compared to other prescription opioids (e.g., narrow therapeutic index, long elimination half-life), and potential for interactions with alcohol and other drugs does increase the relative risk of toxicity and adverse events. For example, in the United States, after controlling for the total number of prescriptions dispensed, methadone-related emergency room visits occur at a rate that is approximately 6 and 23 times higher than the prescription opioids oxycodone and hydrocodone, respectively.⁵⁸ Moreover, although methadone accounts for fewer than 5% of all opioid prescriptions per year in the US, it is identified in more than a third of prescription-opioid-related overdose deaths.⁵⁸ This is consistent with a recent study in British Columbia that reported that methadone was involved in approximately 25% of prescription-opioid-related deaths in British Columbia.⁵⁹

The significantly increased risk of overdose during early stages of prescribed methadone treatment is well described (i.e., during initiation, titration, and dose stabilization), but other factors that have been consistently associated with risk of methadone-involved overdose are non-prescribed, diverted and illicit use (including illicit use when prescribed methadone dose is insufficient to control withdrawal symptoms); unsupervised or non-witnessed doses; combined use with alcohol and benzodiazepines; and when methadone is prescribed for pain management, as opposed to treatment of opioid use disorder where doses are witnessed and titration schedules are strictly enforced.⁶⁰⁻⁶⁴ Witnessed dosing remains one of the more effective methods for preventing methadone-related overdoses; for example, following introduction of supervised dosing in England and Scotland (1995–2005), there was an approximate fourfold reduction in methadone-related overdose deaths per defined daily dose of methadone administered.⁶³

With the recent transition in PharmaCare coverage from the 1 mg/mL to the 10 mg/mL formulation (Methadose™) of methadone in BC, patients have reported challenges with emergent withdrawal symptoms, likely related to change intolerance.^{65,66} In addition, methadone prescribers have reported that dose titration and tapering can be more difficult with the 10 mg/mL dose formulation. Although not presently possible in BC, providing the 1 mg/mL formulation of methadone to those struggling with Methadose™ may have advantages.

For induction and dosing guidelines for methadone, please refer to [Appendix 1](#). Recommendations for take-home methadone doses are included in [Appendix 4](#).

BUPRENORPHINE/NALOXONE

Compared to placebo, buprenorphine at doses greater than 2 mg/day has higher rates of retention in treatment and, at doses greater than 16 mg/day, greater suppression of illicit opioid use.⁶⁷ Compared to methadone, buprenorphine at low doses (≤ 6 mg/day) is less effective for treatment retention compared to low doses of methadone (≤ 40 mg/day), but there is no difference in retention rates for medium (7–16 mg/day) and high buprenorphine doses (≥ 16 mg/day) and approximately equivalent methadone doses (40–85 mg/day and ≥ 85 mg/day). Buprenorphine and methadone appear to be equally effective for reducing illicit opioid use.⁶⁷ A recent meta-analysis comparing buprenorphine and methadone for treatment of prescription opioid dependence reached similar conclusions; buprenorphine and methadone appear to be equally effective in reducing opioid use and retaining individuals in treatment for this specific patient population, although authors note that the evidence base is limited.⁶⁸

For induction and dosing guidelines for buprenorphine/naloxone treatment, refer to [Appendix 2](#). Guidance for take-home buprenorphine/naloxone dosing is included in [Appendix 4](#).

COMPARING BUPRENORPHINE/NALOXONE TO METHADONE

Early trials comparing buprenorphine to methadone have been critiqued for often employing relatively low buprenorphine doses and slower induction approaches than current practice standards.⁶⁹ Newer studies show that sublingual buprenorphine achieves essentially equivalent outcomes to methadone when a sufficient dose, appropriate induction rate and flexible dosing are used.⁶⁹

Regarding side effects and adverse events, the partial agonist properties of buprenorphine may be preferable in terms of reduced overdose potential.⁶⁹ One recent study of more than 19 million prescriptions over a six-year period in the United Kingdom found that buprenorphine was six times safer than methadone in terms of overdose risk.⁷⁰ Other studies have found that methadone has a four-fold higher risk of fatal overdose and a significantly higher risk of non-medical or other problematic use compared to buprenorphine.^{71,72} Recent reports and an expert panel have highlighted the substantial risks of fatal overdose during methadone treatment initiation.^{73,74} Buprenorphine has a lower potential for respiratory depression and standard doses are well below the threshold lethal dose for opioid-naïve adults compared to standard methadone doses, which often exceed the threshold lethal dose.⁷² Furthermore, methadone has higher potential for adverse drug–drug interactions with many common medications (e.g., antibiotics, antidepressants, antiretrovirals), as well as increased risk of cardiac arrhythmias as a result of QT prolongation.⁷⁵ Additionally, because of its partial agonist effect, it is easier to switch from buprenorphine/naloxone to methadone, supporting the use of buprenorphine/naloxone as a preferred first-line option in the absence of contraindications.^{76,77}

Patient-reported concerns with methadone include the potential for tooth decay, which has been largely understudied and possibly under-acknowledged by care providers.^{78,79} There are several side effects common to all opioid medications that can negatively impact oral health, including suppression of salivary secretion, bruxism, and masking pain of oral disease, which could delay seeking treatment.⁷⁹⁻⁸² In addition, the high-sucrose syrup used to administer methadone could contribute to development of dental caries in combination with the above risk factors, although with the transition to the 10 mg/mL Methadose™ formulation, a smaller volume of sugar is consumed compared to previous 1 mg/mL formula.⁸³ Although buprenorphine/naloxone is less frequently associated with oral health issues compared to methadone, a small case series (n=11) reported that sublingual buprenorphine/naloxone can reduce salivary pH and buffering capacity, which in turn, could increase risk of dental caries through repeated exposure of tooth surfaces to an acidic environment.⁸⁴ More research is needed to confirm these findings, however, clinicians should be aware of the general risk of oral health problems in this patient population, and able to provide referrals to low cost or free dental care services in the local area for those who would benefit.

Buprenorphine/naloxone may not be appropriate for all patients due to individual factors, including intolerable symptoms during the partial opioid withdrawal that is required for initiation of buprenorphine/naloxone

treatment (see [Appendix 1](#)), in contrast to methadone treatment.⁸⁵ It is noted that in these cases, admission to an inpatient treatment facility (i.e., inpatient withdrawal management or residential treatment) for supervised, medically-managed buprenorphine/naloxone induction may also be considered, as these facilities can provide more intensive monitoring, support and symptom management to patients during challenging inductions.

Consistent with the relative safety profile of buprenorphine/naloxone in comparison to methadone, as of July 1 2016, physicians in British Columbia no longer have to hold a federal Section 56 exemption from the *Controlled Drugs and Substances Act* in order to prescribe buprenorphine/naloxone. It is recommended, but not required, that all new prescribers, nursing and allied health professionals involved in treatment administration complete an online education program (www.suboxonecme.ca). Furthermore, buprenorphine/naloxone is now listed as an open benefit in the BC PharmaCare and First Nations Health Benefits prescription drug formularies, permitting access without requiring special approval.

Regarding outcomes related to polysubstance use, while opioid agonists are not specifically intended for the treatment of cocaine addiction, a meta-analysis found that opioid agonist treatment, and methadone-based treatment in particular, reduced cocaine use in polysubstance-using individuals using both heroin and cocaine.⁸⁶ A more recent Cochrane review has suggested that methadone and buprenorphine/naloxone are no different in suppressing cocaine use.⁶⁷

In terms of cost effectiveness, the Canadian Agency for Drugs and Technologies in Health has recently noted that, while no Canada-specific studies have been completed, there is evidence that there may be cost-effective benefits of buprenorphine/naloxone in comparison to methadone.⁸⁷ Here, the major potential for cost savings is primarily due to the reduced pharmacy dispensing fees enabled through more flexible take-home dosing schedules that are safe and feasible with buprenorphine/naloxone.⁸⁸⁻⁹¹ There is also potential for additional costs savings during treatment initiation, as buprenorphine/naloxone induction is much faster (days to weeks) than methadone stabilization (weeks to months), requiring fewer clinical visits overall to achieve a stable dose.

In terms of gender-related differences, while opioid use is generally more prevalent among men than women,²² there do not appear to be significant gender-related differences in treatment outcomes for buprenorphine/naloxone compared to methadone.^{92,93} Further research is needed since few studies have examined gender-based outcomes;²² however, forthcoming systematic reviews may provide further insights in this area.⁹⁴ Care providers with gender-specific concerns, including the care of pregnant women with opioid use disorder, should consult with provincial specialist resources at BC Women's Hospital or call the Rapid Access to Consultative Expertise ([RACE](#)) line to speak with an addiction medicine specialist (Vancouver area: 604-696-2131; toll-free: 1-877-696-2131).

Table 2. Advantages and disadvantages of methadone vs. buprenorphine/naloxone

METHADONE	BUPRENORPHINE
ADVANTAGES	
<ul style="list-style-type: none"> • Potentially better treatment retention • May be easier to initiate treatment • No maximum dose • Potentially better alternative if buprenorphine was unsuccessful in relieving withdrawal symptoms, or was associated with severe side effects • Approved in Canada for the primary purpose of pain control (as split dose BID or TID dosing; Health Canada exemption to prescribe methadone for analgesia also required) 	<ul style="list-style-type: none"> • Less risk of overdose due to partial agonist effect and ceiling effect for respiratory depression (in the absence of benzodiazepines or alcohol) • Reduced risk of injection, diversion, and overdose due to naloxone component, allowing for safer take-home dosing schedules • Milder side effect profile • Easier to rotate from buprenorphine/naloxone to methadone • More flexible take-home dosing schedules may contribute to increased cost savings and patient autonomy • Shorter time to achieve therapeutic dose (1–3 days) • Potentially more effective analgesic for treatment of concurrent pain (however, see disadvantages) • Fewer drug interactions • Milder withdrawal symptoms and easier to discontinue, thus may be a better option for individuals with lower intensity opioid dependence (e.g., oral opioid dependence, infrequent or non-injectors, short history of opioid dependence, currently abstinent but risk of relapse), and individuals anticipated to be successfully tapered off maintenance treatment in a relatively short period of time • Alternate day dosing schedules (as daily witnessed or take-home doses) are possible • Optimal for rural and remote locations where daily witnessed ingestion at a pharmacy is not possible
DISADVANTAGES	
<ul style="list-style-type: none"> • Higher risk of overdose, particularly during treatment initiation • Generally requires daily witnessed ingestion • More severe side effect profile (e.g., sedation, weight gain, erectile dysfunction, cognitive blunting) • More expensive if daily witnessed ingestion required • Longer time to achieve therapeutic dose (see Appendix 1) • More difficult to transition to buprenorphine once on methadone • Higher potential for adverse drug-drug interactions (e.g., antibiotics, antidepressants, antiretrovirals) • Higher risk of non-medical or other problematic use • Increased risk of cardiac arrhythmias as a result of QTc prolongation • At high doses, may block some of the analgesic effect of concurrent opioid medications administered for pain 	<ul style="list-style-type: none"> • Potentially higher risk of drop-out • If appropriate dose induction schedules are not used (see Appendix 2), may cause precipitated withdrawal • Doses may be suboptimal for individuals with high opioid tolerance • At high doses, may block the analgesic effect of concurrent opioid medications administered for pain • Not approved in Canada for the primary purpose of pain control, though moderate evidence of efficacy • Reversing effects of overdose can be challenging due to pharmacology of buprenorphine

References

1. Maremmani I, Gerra G. Buprenorphine-based regimens and methadone for the medical management of opioid dependence: selecting the appropriate drug for treatment. *Am J Addict* 2010;19:557–68.
2. Bonhomme J, Shim RS, Gooden R, Tyus D, Rust G. Opioid addiction and abuse in primary care practice: a comparison of methadone and buprenorphine as treatment options. *J Natl Med Assoc* 2012;104:342–50.
3. Centre for Addiction and Mental Health (CAMH). Opioid Dependence Treatment Core Course. Module 2: Treatment Options. Choosing between methadone and buprenorphine maintenance treatment. May 2015

III) Alternative agents

SLOW-RELEASE ORAL MORPHINE **

Since November 2014, slow-release oral morphine (24-hour formulation, brand name Kadian®) has been approved by Health Canada's Non-Insured Health Benefits (NIHB) Program for the treatment of opioid use disorder, up to a maximum daily dose of 400mg/day.⁹⁵ The NIHB will consider, on a case-by-case basis, granting coverage for daily slow-release oral morphine doses exceeding 400mg/day if provided with a clinical rationale that a higher dose is required for treatment of opioid use disorder. Limited preliminary evidence suggests that slow-release oral morphine formulations prescribed as agonist treatment may provide similar benefits to methadone-based therapy.⁹⁶ A Cochrane review including three randomized trials found no significant difference in treatment retention, but a higher incidence of adverse events for slow-release oral morphine compared to methadone, although the low number of studies included in the review limited conclusions.⁹⁶ Since this review was published, a number of more recent trials have reported that slow-release oral morphine may be a safe and effective alternative to methadone treatment. For instance, a recent clinical trial found that patients treated with slow-release oral morphine demonstrated shorter QTc intervals, decreased heroin cravings and reduced dysthymic symptoms when compared with patients treated with methadone.⁹⁷ Other studies have found that slow-release oral morphine was superior to methadone in terms of reduced opioid cravings and improvements in mental health, with no significant differences compared to methadone with regard to drug use, retention in treatment and overall physical health.⁹⁸⁻¹⁰⁰ A multi-centre study of patients intolerant to or insufficiently responding to methadone found that transitioning patients from methadone to slow-release oral morphine was relatively easy and well tolerated, with significant advantages observed after switching to slow-release oral morphine (e.g., reduced withdrawal symptoms, reduced cravings, physical and psychological improvements).¹⁰¹ Despite the above findings, like the original randomized trials of methadone and buprenorphine/naloxone, these studies have limitations and there is collectively less evidence regarding slow-release oral morphine in comparison to other opioid agonist therapies. It is important to note that only the once-daily, 24-hour formulation of slow-release oral morphine has been studied in clinical trials for the treatment of opioid use disorder. Other formulations of oral morphine, such as twice-daily, 12-hour sustained- or extended-release formulations (brand name M-Eslon®), have not been empirically studied in this context and are not recommended by this committee for treatment of opioid use disorder.

It is the consensus of the authors of this guideline that opioid agonist treatment with slow-release oral morphine (prescribed as once-daily witnessed doses) can be considered for patients who have been unsuccessful with first- and second-line treatment options, or who have contraindications to first- and second-line treatment options. The committee recommends that health care providers who wish to prescribe slow-release (24-hour) oral morphine for the treatment for opioid use disorder should hold a valid federal Section 56 exemption from the Controlled Drugs and Substances Act to prescribe methadone. Alternatively, for individuals without a methadone exemption, specialist consultation should be sought. In rural and remote locations where addiction specialist support is limited an option would be the provincial Rapid Access to Consultative Expertise ([RACE](#)) line. Regardless of Section 56 exemption status, any practitioner who lacks experience prescribing slow-release oral morphine for treatment of opioid use disorder should consult with an experienced prescriber prior to initiating treatment with slow-release oral morphine.

For induction and dosing guidelines for slow-release oral morphine, refer to [Appendix 3](#). As with methadone, strict policies to prevent misuse, diversion and to ensure patient safety are required with this treatment modality, including regular scheduled and random urine drug testing (see [Appendix 4](#)). However, it is important to note that point-of-care urine drug tests cannot be used to rule out use of illicit heroin or some prescription opioids (e.g., morphine, codeine) in patients treated with slow-release oral morphine, though this distinction can be made through mass spectrometry. Further, clinicians should be aware that active heroin users will often

** Note: Slow-release oral morphine refers to the **24-hour formulation** of extended-release morphine capsules.

test positive for fentanyl in urine drug tests, so long as fentanyl is included in the test being employed. In most cases, slow-release oral morphine should be prescribed as daily witnessed doses. Exceptions to daily witnessed dosing may be considered if the patient has shown exceptional and sustained improvements in clinical and social stability. See [Appendix 4](#) for details.

ANTAGONIST TREATMENTS

Naltrexone is an opioid receptor antagonist that blocks the euphoric effects of opioids at adequate doses.¹⁰² Potential benefits of naltrexone include ease of administration, lack of induced tolerance during long-term treatment, and lack of potential for dependence or misuse.¹⁰³ However, as an opioid antagonist, naltrexone fully blocks the effects of all opioid medications, including opioid analgesics prescribed for pain. Additionally, the reduced tolerance to opioids facilitated by the use of naltrexone may increase the risk of overdose for patients who stop taking the medication and subsequently relapse to opioid use, as demonstrated by a non-randomized study of naltrexone-associated mortality rates that were three to seven times higher than methadone-related mortality rates in Australia.¹⁰⁴

Oral naltrexone, currently the only formulation available in Canada, has been shown to have limited benefits over placebo.¹⁰⁵ For example, a 2011 meta-analysis found no statistically significant differences in retention or abstinence rates for oral naltrexone compared to placebo or no treatment.¹⁰⁵ The only outcome that favoured naltrexone over placebo was reduced re-incarceration rates, but this finding was limited to two of the 13 randomized trials included in the review.¹⁰⁵ Based on limited data, review authors also concluded that oral naltrexone was not superior to psychotherapy alone (two studies), benzodiazepine-based treatment (one study), or buprenorphine monotherapy (one study) in terms of retention in treatment, abstinence from opioid use, and reported side effects.¹⁰⁵ Across studies, treatment retention rates were low with oral naltrexone treatment (28%).¹⁰⁵ Of note, a single randomized trial published subsequent to the meta-analysis reported a significantly higher proportion of opioid-negative urine tests among individuals on oral naltrexone (42.7%) compared to placebo (34.1%).¹⁰⁶

Currently, oral naltrexone is only eligible through BC PharmaCare as a Limited Coverage Drug for the treatment of alcohol use disorder. If prescribed for the treatment of opioid use disorder, oral naltrexone is not eligible for PharmaCare coverage, and patients may need to pay medication costs out-of-pocket. As of November 5, 2016, oral naltrexone is available as an open benefit through the Non-Insured Health Benefits Program for the treatment for opioid use disorder.

In the United States, extended-release naltrexone is available via monthly intramuscular injection,¹⁰⁷ which may promote improved treatment adherence in comparison to oral naltrexone.¹⁰² Several randomized controlled trials have found that injectable naltrexone is superior to placebo in terms of improved retention in treatment, increased abstinence rates and decreased opioid cravings.¹⁰⁸⁻¹¹⁰ In addition, a 1-year open-label extension that offered extended-release naltrexone to all participants in a placebo-controlled efficacy trial retained 62.3% of the original study participants, with 50.9% remaining abstinent for the full 12 months of follow-up, as confirmed by opioid-negative urine drug tests.¹¹¹ At present, extended-release naltrexone is only available in Canada for research purposes or through Health Canada's Special Access Programme. However, it should be noted that 52% of participants in two Vancouver-based cohort studies of people who use illicit drugs reported a high level of willingness to take extended-release naltrexone.¹¹²

In the future, novel pharmacotherapies and delivery systems (e.g., extended-release opioid antagonists, long-acting agonist implants) are likely to become available in Canada as they are now in the United States. These medications are substantially more expensive than traditional daily-dosed medications used to treat opioid use disorder, warranting expert therapeutic guideline committees to identify circumstances where these novel agents may have the largest benefit over traditional approaches.

INJECTABLE MEDICATIONS

Several clinical trials have reported that for individuals who are treatment refractory to methadone, prescription diacetylmorphine (original trade name Heroin) or injectable hydromorphone administered in a highly structured clinic setting may be beneficial in terms of reducing illicit substance use, criminal activity, incarceration, mortality and treatment drop-out.¹¹³⁻¹¹⁵ While these are evidence-based treatments, it is outside the scope of this guideline, which focuses on oral medications, to review this evidence or make recommendations for the use of injectable opioid agonist treatments.

IV) Combination approaches and movement between approaches

Traditionally in BC, residential treatment facilities and opioid agonist treatment programs have often operated independently of one another, despite sharing a common goal to reduce or prevent opioid use and related harms. In recent years, in recognition of the proven benefits of opioid agonist treatment (e.g., reductions in illicit opioid use and opioid-related harms, improvements in mental health, social functioning and quality of life) there have been some efforts made to integrate approaches, with some residential treatment programs re-evaluating admission policies and service provision to be more inclusive of evidence-based treatment and patient preference.¹¹⁶⁻¹¹⁸ This integration also reflects a growing recognition that excluding participants on stable opioid agonist treatment from residential treatment may create barriers to access amongst those in need of a higher intensity of care. In the context of the provincial opioid crisis and known challenges in accessing addiction treatment, it is important to explore strategies that promote inclusiveness and strengthen both the provincial opioid agonist treatment and residential treatment systems through integration of evidence-based treatment and care.

Due to high rates of polysubstance use (e.g., cocaine and heroin) among opioid-dependent individuals in British Columbia, it is important to stress the value of combining opioid agonist or antagonist treatments with residential treatment, which may allow for psychosocial strategies to reduce cocaine use (e.g., counselling, contingency management) to be coupled with treatments that have been proven to promote abstinence from heroin and other opioid use. This may be particularly valuable given the evidence in support of changing the environment of individuals who are seeking treatment for concurrent opioid and cocaine dependence, and who are severely addicted and actively using.^{119,120} Of note, methadone doses may need adjustment as patients transition into and out of cocaine abstinence, as cocaine is a CYP inducer that can increase metabolism of methadone.¹²¹

Regarding transitions between agonist medications, several trials show feasibility when converting to buprenorphine from low to moderate methadone doses (up to 60–70 mg/day).¹²² In general, this practice must be individually tailored, but ideally involves a reduction of the methadone dose or transitioning to a short-acting opioid prior to buprenorphine/naloxone induction. This may be most easily accomplished with specialist support (e.g., [RACE](#)) or in a specialized environment such as an inpatient withdrawal management program. If transitioning directly from methadone, in accordance with induction guidelines, buprenorphine/naloxone should be introduced no sooner than 24 hours, and preferably 48–72 hours, after the last dose of methadone (see [Appendix 2](#)).¹²³ When transitioning from methadone doses that are greater than 70 mg/day, there is an increased risk of significant opioid-withdrawal-related discomfort and consequent risk of relapse. As above, to mitigate this, adjunct medications and/or inpatient treatment (e.g., medical detoxification programs) may be required for rotation to buprenorphine/naloxone from higher doses of methadone.¹²² Clinicians with limited experience in managing challenging transitions from methadone to buprenorphine are advised to consult an addiction medicine specialist before initiating dose reductions.

Conversely, rotation from buprenorphine to methadone is relatively uncomplicated, as methadone is a full agonist and buprenorphine is a partial agonist. Generally, the first dose of methadone can be administered within 24 hours of the last dose of buprenorphine/naloxone, using established protocols for starting methadone treatment in opioid tolerant patients.

Given the relatively superior safety profile of buprenorphine/naloxone (in the absence of concurrent alcohol or benzodiazepine use), ease of transitioning from buprenorphine/naloxone to methadone, and similar overall costs of these treatments,^{88-91,124} a clinical trial was conducted to compare a stepped care strategy (i.e., treatment initiation on buprenorphine/naloxone and escalation to methadone if necessary) to standard methadone treatment.¹²⁵ This study found that the stepped care approach was equally efficacious compared to optimally delivered methadone treatment, and concluded that collective data on the comparatively advantageous safety profile of buprenorphine were sufficient to warrant broader implementation of buprenorphine as a first-line treatment for opioid use disorder.

There is currently limited evidence to guide strategies for transitioning off agonist therapies among patients who have achieved long-term abstinence from opioid use. The majority of tapers from methadone treatment appear to be unsuccessful (approximately 87%), but there are increased odds of success when doses are reduced gradually with longer periods of stabilization.¹²⁶ More specifically, an evaluation of the British Columbia methadone program found a successful taper completion rate of only 13% across 4,917 treatment episodes, with 35% of patients re-entering treatment within 18 months and 24% subsequently hospitalized for opioid-related reasons.¹²⁶ Longer, more gradual stepped-tapering schedules (e.g., > 52 weeks) where dose reductions were scheduled to occur bimonthly or monthly were associated with significantly higher odds of success.¹²⁶ Gradual tapering in a therapeutic manner at an appropriate time for the patient may be advantageous as demonstrated by a review that found that the pooled abstinence rates for voluntary “therapeutic detoxification” patients was 48% compared to 22% among non-voluntary, “non-therapeutic detoxification” patients.¹²⁷ Another concern with abrupt discontinuation of opioid agonist treatment is the possibility of temporarily induced pain at healed injury sites, a phenomenon that has been reported to be a barrier to opioid cessation and be a risk factor for opioid re-initiation.¹²⁸

Finally, while there is limited evidence to guide strategies involving multiple attempts using a specific type of opioid agonist treatment, practitioners should be aware that patients might require several attempts with a certain therapy before they successfully achieve opioid abstinence, or before an alternative treatment strategy is implemented.

V) Psychosocial Treatment Interventions and Supports

As the standard of care for management of any complex or chronic medical condition, all clinicians should provide medical management, including general support and unstructured counselling, to patients with opioid use disorder. In this context, medical management is defined as medically-focused, informal counselling that includes, but is not limited to, health and mental wellness checks, offering non-judgmental support and advice, assessing motivation and exploring barriers to change, developing a holistic treatment plan, promoting alternative strategies for managing stress, and providing referrals to health and social services when requested or appropriate. Establishing a trusting, respectful and collaborative therapeutic relationship with patients remains a cornerstone of treating substance use disorders in clinical practice.

Due to the higher prevalence of a history of trauma and comorbid post-traumatic stress disorder among individuals with substance use disorders compared to the general population,¹²⁹ clinicians should be familiar with the principles of trauma-informed practice (e.g., trauma awareness; safety and trustworthiness; choice, collaboration and connection; strengths-based approaches and skill building). The provincial trauma-informed practice (TIP) guide may be a useful resource when counselling this patient population.¹³⁰

In addition, clinicians and staff should consider undertaking cultural safety training to improve ability to establish positive partnerships with Indigenous clients seeking care for substance use and related harms. The San'yas Indigenous Cultural Safety Training Program, developed by the Provincial Health Services Authority (PHSA) Aboriginal Health Program, is an online training program designed to increase knowledge, enhance self-awareness, and strengthen the skills of those who work both directly and indirectly with Aboriginal people,

and is an excellent resource for clinicians seeking to build their cultural competency. Please refer to the San'yas program website for more information: www.sanyas.ca.

Recent meta-analyses and randomized controlled trials suggest that the addition of structured psychosocial treatment interventions (e.g., cognitive behavioural therapy, contingency management) to opioid agonist treatment programs does not confer additional benefits in terms of retention in treatment, abstinence from opioid use during or after treatment, treatment adherence, psychiatric symptoms, depression, or treatment completion rates when compared to treatment programs employing standard medical management alone.¹³¹⁻¹³³ Further research is required to assess the effect of psychosocial treatment interventions versus psychosocial supports (e.g., housing, employment, and legal support services) on outcomes that may indirectly reduce drug use in the long term (e.g., social assistance, increased social support, vocational training).¹³¹

Attention to assessing, treating and monitoring emotional and mental health is an essential component of care for patients with opioid use disorder, especially given the high prevalence of concurrent medical and mental health diagnoses among this population (e.g., post-traumatic stress disorder, depression, anxiety).¹³⁴⁻¹³⁶ While there is no strong empirical evidence that addition of structured psychosocial treatment interventions to opioid agonist treatment result in improved health outcomes compared to standard medical management approaches, structured psychosocial interventions may be beneficial for some individuals. There have been a limited number of controlled studies of psychosocial treatment interventions for substance use disorders in more complex patient populations, but there is some evidence that inclusion of psychosocial treatment interventions can improve outcomes for individuals with concurrent substance use and/or mental health disorders, including post-traumatic stress disorder and severe mental illness (e.g., schizophrenia, schizoaffective disorder), although the evidence tends to be of lower quality with effect sizes that are generally small to moderate in scale.¹³⁷⁻¹⁴¹

The addition of psychosocial supports to opioid agonist treatment and standard medical management may be helpful in supporting overall recovery in terms of improving individuals' psychosocial circumstances and other survival needs. Although no systematic reviews have examined the impact of providing supports for various social needs (e.g., housing support, vocational and skills training, social supports, financial assistance), previous studies have demonstrated how housing and other survival needs may have a significant impact on opioid agonist treatment outcomes.¹⁴²⁻¹⁴⁴ There is likely a benefit to opioid use disorder care being offered in the context of interdisciplinary care teams that are equipped to address these needs when possible. Where patients have struggled to engage in care, intensive case management, peer navigation and outreach may also be effective at improving retention in addictions treatment.

Peer-based support groups are widely available, no-cost community resources that are often recommended as an adjunct to clinical management of substance use disorders, or as a source of additional guidance and support for sustained abstinence following treatment (e.g., aftercare). A widely recognized example is Narcotics Anonymous (NA), an international fellowship of support groups comprised of individuals in recovery, which offers emotional support and a structured "12-step" approach to achieving abstinence. Research and evaluation of peer-based support groups has primarily focused on twelve step facilitation (TSF) approaches, which refers specifically to 12-step programs that are led by a trained professional, such as a substance use counsellor. There have been no well-designed, controlled studies of the effectiveness of these groups in supporting treatment goals of individuals with opioid use disorder, although a small number of observational studies have reported associations between active participation in twelve-step programs and improved treatment outcomes among individuals with substance use disorders.¹⁴⁵⁻¹⁴⁷

It should be noted that the abstinence-based TSF recovery model is not always supportive of the use of opioid agonist medications for the treatment of opioid use disorder. Qualitative studies of participant experiences with TSF indicate that underlying philosophical conflicts with opioid agonist treatment, if present, can negatively affect engagement and disclosure, and are a deterrent to regular attendance.¹⁴⁸ If patients identify incompatibilities between personal belief systems and TSF philosophies as barriers to affiliation, alternative options can be provided where possible. For example, some individuals may prefer peer support groups with a secular mandate

(e.g., SMART Recovery[®], LifeRing), or groups designed for specific populations (e.g., youth, Indigenous peoples, individuals with concurrent mental health issues, women). The effectiveness of these peer support groups has not been empirically studied. Nevertheless, all patients should be advised of these peer support opportunities and practitioners should maintain lists of nearby groups.

Referrals to psychosocial treatment interventions and community-based supports, including peer-support groups, may be routinely offered to patients in conjunction with pharmacological treatment, however, it must be emphasized that a patient's decision not to participate in psychosocial treatment should not preclude or delay provision of evidence-based pharmacological treatment.¹⁴⁹ Care providers should be aware of local resources, including wait-lists, costs to patients, and practitioner expertise and approach, in order to provide informed referrals appropriate to individual patient needs.

VI) Harm reduction strategies

Broadly defined, harm reduction refers to policies, programs and practices that aim to reduce the adverse health, social and economic consequences of licit and illicit substance use.¹⁵⁰ In British Columbia, established harm reduction initiatives include needle/syringe distribution programs, overdose prevention with take-home naloxone, and supervised injection or consumption services. Including these harm reduction approaches within the continuum of addiction care provides additional mechanisms for promoting health and safety in diverse patient populations, including individuals who have difficulties achieving abstinence, or relapse to opioid use.

A commonly cited barrier to routinely offering harm reduction in clinical practice is concern that patients or the wider public could perceive this as an endorsement of continued drug use.¹⁵¹⁻¹⁵⁴ It is important to emphasize that there is no evidence that participation in any of the above mentioned harm reduction services leads to increased opioid use or initiation of injection use among clients.¹⁵⁵⁻¹⁵⁸ There is, however, substantial evidence that uptake of harm reduction services is associated with significant decreases in substance-related harms, including risky behaviours, HIV and hepatitis C infection, and overdose deaths.^{16,159-165} In addition, research has shown that participation in harm reduction services can promote entry into addiction treatment.¹⁶⁶⁻¹⁶⁹ For these reasons, if a patient is at risk of opioid-related harms, providing information and referrals to harm reduction services is a reasonable and appropriate clinical decision, particularly in the current environment of heightened overdose risk.

There are a number of actions clinicians can take to increase awareness of harm reduction services among patients, starting with routinely including information and education about harm reduction and safer injection practices when appropriate in discussions with patients and families. In order to provide informed referrals, clinicians should also be aware of harm reduction programs available in the local area and services provided. A current listing of harm reduction services that provide needles, syringes and other injection supplies, overdose prevention training, and take-home naloxone kits can be found on the Toward the Heart website (towardtheheart.com/site-locator). In addition, as part of the provincial response to the overdose crisis, emergency-use naloxone was recently unscheduled and deregulated in BC, and patients can be advised that naloxone may be purchased without a prescription at community pharmacies, healthcare sites, treatment centres and community agencies. For individuals enrolled in the First Nations Health Benefits program, naloxone and injection supplies are fully covered benefits and available at no-cost from any pharmacy that carries naloxone; no prescription or paperwork is required. With these recent regulatory changes, community-based clinics can also consider providing naloxone kits and overdose prevention education directly to patients and families who would benefit.

Expert guideline

Patients with opioid use disorder can be offered pharmacological and/or psychosocial treatments and supports based on their clinical presentation with respect to addiction severity, comorbidities, and present psychosocial circumstances (e.g., homelessness), personal preferences, as well as the accessibility of possible treatment options. While this guideline supports the diversity of possible treatments available for individuals presenting with opioid use disorder, it strongly recommends against strategies involving withdrawal management alone, since this approach has been associated with elevated risks of HIV and hepatitis C infection and overdose deaths in comparison to providing no treatment.¹⁴⁻¹⁶ Brief inpatient withdrawal may be particularly dangerous.

Opioid agonist tapers should only be considered appropriate for individuals viewed, in the best clinical judgment of the treating healthcare provider, to have a high chance of successful recovery without the additional support of long-term agonist treatment. In these cases, the responsible provider should ensure that individuals are still linked with continued addiction treatment, made aware of harm reduction programs, and, if appropriate, psychosocial supports (e.g., housing) in the community. While residential treatment programs have not been rigorously evaluated, there is some evidence to support that changing the environment of individuals with severe forms of opioid use disorder may be beneficial.^{119,120} For this reason, referral to a residential treatment facility should be considered as a preferred option for individuals who wish to avoid long-term opioid agonist treatment. With respect to this recommendation, consistent with past reports, separate initiatives will need to be undertaken to improve the accessibility and quality of residential treatment.¹⁷⁰

Although the committee strongly recommends against withdrawal management alone, it is recognized that some patients may express a preference for an opioid agonist taper over long-term agonist treatment when initially seeking treatment. In these scenarios, the higher relative risk of relapse and overdose associated with withdrawal management only approach should be carefully explained, and benefits of opioid agonist treatment should be discussed. Whenever possible, engaging patients in outpatient opioid agonist treatment is preferred over withdrawal management alone to optimize safety and stability and to prevent relapse. Once stabilized, patients who continue to express a preference toward tapering off opioid agonist treatment can be slowly tapered as an outpatient under close supervision while receiving ongoing addiction care, which permits rapid intervention, treatment intensification, and re-initiation of agonist treatment if relapse risk emerges. The evidence suggests that achieving sustained abstinence from illicit opioids is most likely if taper duration is 12 months or longer.

As a first-line treatment approach for individuals with opioid use disorder, the committee recommends buprenorphine/naloxone when induction is feasible and there are no contraindications to its use. Induction and dosing guidelines for buprenorphine/naloxone are provided in [Appendix 2](#), and guidance for take-home dosing is provided in [Appendix 4](#). As is the case throughout this guideline, the choice of treatment should be determined on a case-by-case basis, taking into account the patient's history and commitment to a particular management strategy, and weighing the risks and benefits of treatment options, and including discussion of PharmaCare or First Nations Health Benefits drug plan coverage and any out-of-pocket costs that may be incurred by patients. In cases where both methadone and buprenorphine/naloxone are suitable options, buprenorphine/naloxone may be considered as a first-line treatment. Buprenorphine/naloxone may have particular advantages in circumstances where long-term daily witnessed ingestion at a pharmacy is a substantial barrier or deterrent to retention in treatment, and/or in remote locations where daily-witnessed pharmacy dispensation is impractical.

Methadone is an acceptable alternative first-line option in cases where it will be challenging to induce onto buprenorphine/naloxone or where loss to follow-up could be highly problematic from the perspective of individual or public health (e.g., risk of HIV transmission). For instance, methadone may be preferred for severely unstable individuals with high-intensity use, for whom buprenorphine/naloxone doses may be sub-optimal leading to poorer retention rates.¹⁷¹ Limitations of methadone are the side effect profile ([Table 2](#)) and

the need for a longer duration of daily witnessed ingestion. For induction and dosing guidelines, please refer to [Appendix 1](#) and for take-home dosing guidelines [Appendix 4](#).

For individuals responding poorly to either methadone or buprenorphine/naloxone despite efforts to address barriers to successful treatment, transitioning to the alternative first-line agent may be considered. As described above, buprenorphine/naloxone has a number of advantages over methadone ([Table 2](#)), and initiating treatment with buprenorphine/naloxone or transitioning from methadone to buprenorphine/naloxone is recommended for these reasons. Certainly, for a patient who struggles with ongoing illicit opioid use while on adequately dosed buprenorphine/naloxone, methadone is an appropriate second-line option. For patients wishing to taper off methadone treatment due to dissatisfaction with daily witnessed ingestion requirements, difficulty obtaining take-home doses, and other common concerns, transitioning from methadone to buprenorphine/naloxone may be advantageous.^{69,76}

Clinical trial evidence suggests that oral naltrexone is less effective than other pharmacological treatments for opioid use disorder, and in some cases no different than placebo, in reducing opioid use and retaining individuals in treatment. However, there are some circumstances where oral naltrexone may be an appropriate option. For example, individuals who wish to avoid opioid agonist treatment who are highly motivated to stay abstinent, including individuals in safety sensitive positions that in some cases may prohibit opioid agonist treatment. The lack of evidence and safety risks associated with oral naltrexone should be carefully reviewed with patients prior to initiating treatment, particularly the high rates of relapse and risk of serious harms, including fatal overdose, due to loss of opioid tolerance. Oral naltrexone should only be prescribed to patients who are engaged in ongoing addiction care and can be assessed regularly on follow-up for risk or signs of relapse to opioid use.

Alternatively, slow-release oral morphine (24-hour formulation, brand name Kadian®) is increasingly being studied and used for individuals unsuccessfully treated with first- or second-line options. While a largely out-dated systematic review of slow-release oral morphine provided mixed evidence, more recent studies have demonstrated that safety and effectiveness outcomes are comparable to methadone, with potentially greater reductions in heroin craving.^{97,98,101,172} For safety reasons, it is the consensus of this committee that health care providers who wish to prescribe slow-release oral morphine as an opioid agonist treatment should hold a valid federal Section 56 exemption from the *Controlled Drugs and Substances Act* to prescribe methadone, or have formally consulted with a skilled addiction medicine practitioner prior to initiating treatment. Regardless of Section 56 exemption status, any practitioner who lacks experience prescribing slow-release oral morphine for treatment of opioid use disorder should consult with an experienced prescriber prior to initiating treatment. To limit potential for diversion, it is recommended that slow-release oral morphine be provided via daily witnessed ingestion, preferably administered by opening the extended-release capsules and releasing the enclosed pellets for immediate consumption in order to reduce the risk of diversion. Dosing guidelines for slow-release oral morphine are provided in [Appendix 3](#).

While out of scope of the current guideline, several clinical trials have reported that for individuals who are treatment refractory to methadone, prescription diacetylmorphine (original trade name Heroin) or injectable hydromorphone administered in a highly structured clinic setting may be beneficial in terms of reducing illicit substance use, criminal activity, incarceration, mortality and treatment drop-out.¹¹³⁻¹¹⁵

Regarding inclusion of structured psychosocial treatment interventions (e.g., cognitive behavioural therapy) alongside pharmacotherapy, for uncomplicated patient populations, the evidence does not suggest clear benefits over standard medical management traditionally provided as per standard of care for treatment of opioid use disorder (i.e., general support and unstructured clinician-led counselling). However, this does not suggest that pharmacotherapy should be offered in isolation, but rather that ongoing assessment, monitoring and support for physical, emotional, mental and spiritual health remain equally important components of treating opioid use disorder, and addressing these needs should be considered standard of care. There is some evidence that structured psychosocial treatment interventions are beneficial in improving treatment outcomes for opioid

use disorder among patients with concurrent substance use disorders (i.e., polysubstance use) and/or psychiatric disorders. Evidence-based psychosocial supports focused on individual circumstances (e.g., housing, employment) and other survival needs (e.g., social assistance) may also be helpful in supporting recovery from opioid use disorder. Psychosocial interventions directly aimed at maintaining abstinence may also play a role in post-detoxification relapse prevention, but further research is needed in this area.

To facilitate shared decision making and improve ability to make informed referrals to psychosocial treatment interventions, care providers should be familiar with available options in the community as well as any barriers patients may experience in accessing these services. For example, care providers should be aware of which peer-support groups are active locally, and should be familiar with publicly- and privately-funded counselling services and residential treatment facilities in the community. If a patient is regularly attending counselling or peer support groups, providers should inquire during routine or follow-up visits about the patient's experiences and provide positive feedback and encouragement to support continued attendance. If a patient attends residential treatment, care providers should follow-up to assess the patient's experiences including participation in any aftercare services, and actively support ongoing treatment goals. If a patient becomes lost to care, care providers should be familiar with any available local outreach teams and intensive case management services that can potentially provide support for clients to re-engage in treatment.

Finally, patients with opioid use disorder may benefit from harm reduction interventions, including education about sterile syringe use and safer injection practices to reduce the risk of blood-borne (HIV, hepatitis C) and soft tissue infections, as well as promoting access to take-home naloxone, syringe distribution programs, and supervised consumption services to reduce risk of blood-borne infection and fatal overdose among high-risk patients or patients with ongoing opioid use.^{31,32} In particular, due to increased risk of overdose following cessation of opioid use (e.g., withdrawal management, residential treatment) responsible health care providers should routinely make clients aware of how to re-engage in addiction care as well as available harm reduction services as a standard item in discharge plans (e.g., take-home naloxone, opioid agonist therapy programs, supervised consumption services).¹⁷³

Opioid use disorder is a chronic disease that is associated with significantly elevated rates of morbidity and mortality. It is important that all patients are offered evidence-based treatment for their illness. Patients and clinicians may work toward finding appropriate treatment plans that can be adjusted along a continuum in order to promote optimal health and wellbeing.



Appendices

Preface

The following appendices have been provided to support clinical practice and were developed using a different methodology than the main body of the guideline. Here, recommendations have been derived through discussion and consensus of the guideline committee, and informed by opinion of expert reviewers, personal communication with study authors, and review of existing national and international evidence-based clinical practice guidelines, and position papers and practice bulletins issued by recognized addiction medicine professional organizations and authorities. In addition, where appropriate, Health Canada-approved drug product monographs, and previous and current guidance from the College of Physicians and Surgeons of BC (CPSBC) and Health Canada were consulted so as to comply with provincial and national safety regulations and standards for practice. Recommendations adhere to the CPSBC Professional Standards and Guidelines for Safe Prescribing of Drugs with the Potential for Misuse/Diversion (www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf). Please refer to the Guideline Supplement for more detailed information on guideline development and methodology.

Appendix 1: Induction and dosing guidelines for methadone

1 ASSESSMENT

Common contraindications

- Hypersensitivity to methadone hydrochloride
- Currently taking monoamine oxidase inhibitors (MAOIs) or use within past 14 days
- Severe respiratory compromise or obstructive disease
- Severe respiratory distress
- Delirium tremens
- Acute alcohol intoxication
- If pre-existing risk of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, concomitant QT-prolonging medications, hypokalemia, hypomagnesaemia), more intensive monitoring is required

Baseline assessment

- Physical and mental health assessment
- DSM-5 confirmed diagnosis of opioid use disorder (see [Appendix 5](#))
- Urine drug test (positive for opiates, fentanyl, oxycodone or hydromorphone)
- Note: An opioid positive urine drug test is not a necessary prerequisite for opioid agonist treatment. For example, an individual with a documented history of opioid use disorder who is currently abstinent from opioids but at high risk of relapse may be a candidate for treatment.
- Laboratory tests: CBC; kidney and liver function panels; HIV and hepatitis A,B,C serology; syphilis, gonorrhea, and chlamydia serology; TB; pregnancy test (women of childbearing age); and ECG if indicated (i.e., cardiac disease, history of arrhythmia, syncope, or other risk factors for QTc prolongation)
- If clinically indicated, methadone can be started before investigations are reported
- Addiction history including assessment for tobacco and other substance use disorders, in particular, concurrent use of alcohol, benzodiazepines, and/or sedatives (i.e., CNS depressants)
- Review of PharmaNet and other requirements outlined in CPSBC Professional Standards and Guidelines for Safe Prescribing of Drugs with the Potential for Misuse/Diversion. (Please refer to www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf for more information)
- Document clinical plan and rationale for why a less intensive treatment like buprenorphine/naloxone was not initiated
- Clinicians are encouraged to call the Rapid Access to Consultative Expertise ([RACE](#)) line to speak with an addiction medicine specialist if any questions or concerns:



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NOTE: All patients starting methadone-based agonist treatment should receive information about where to access naloxone for home use in event of overdose. Take-home naloxone kits are available at no cost through the BCCDC and most provincial harm reduction programs. Some patients may opt to purchase naloxone from a pharmacy, health care site, treatment centre or community agency without a prescription. All patients enrolled in the First Nations Health Benefits program (i.e., Non-Insured Health Benefits, or NIHB) are eligible to access naloxone and injection supplies at no cost from pharmacists without a prescription.

2 INITIATION

During initiation, patients should be seen at least weekly to carefully monitor treatment response. For safety reasons, an in-person clinical assessment is always necessary before adjusting methadone doses, due to the unique pharmacokinetic properties of methadone (long half-life, slow bioaccumulation) compared to other opioids, and the high degree of individual variability in absorption rates, metabolism, potency and cross-tolerance with other opioids. Due to risk of overdose from drug-drug interactions, current substance use, including alcohol and prescription medications, should be reviewed with patients at every visit and confirmed with PharmaNet records. Periodic check-in with the dispensing pharmacy is strongly recommended for collateral information on patient wellbeing (e.g. intoxication) and adherence to daily witnessed ingestion requirements.

Induction

- Review risks and benefits of treatment, obtain informed consent, and complete Methadone Treatment Agreement and Consent Form (see [Appendix 8](#)).
- The initial dose should not exceed 30 mg/day.
- Individuals with increased opioid tolerance can be started on a higher dose than individuals with low or unknown tolerance, as shown in the table below:

Level of tolerance	Recommended starting dose
No tolerance opioid-naive High risk of toxicity. Includes patients who have completed withdrawal management and/or those not currently using opioids but at risk of relapse.	5–10 mg/day
Unknown tolerance Moderate risk of toxicity. Includes patients who use alcohol, benzodiazepines and other substances (prescribed and non-prescribed).	10–20 mg/day
Known tolerance Lower risk of toxicity. Patients actively using opioids.	20–30 mg/day

Dose Escalation

- Doses should be slowly titrated upward by 5–10 mg at a time.
- The dose can be increased at a rate of 5–10 mg every five or more days. More rapid dose titrations should only be attempted under close supervision of an experienced provider and and/or in specialized care settings that permit enhanced monitoring (e.g., inpatient withdrawal management or residential treatment settings).
- After a dose increase, it can take several days for methadone to reach a steady concentration and maximum therapeutic effect, which can also cause delayed emergence of serious adverse effects like respiratory depression.
- Patients should be assessed at least weekly during dose escalation.
- If there are concerns of methadone toxicity, see the patient at 3-hours post dose.

A slower dose escalation is recommended for individuals who may be at higher risk of opioid toxicity, including individuals with recent loss of tolerance (e.g., recent discharge from withdrawal management, residential treatment, or correctional facilities), severe respiratory illness, or decompensated liver disease; individuals using alcohol, benzodiazepines, sedatives, or prescribed medications that affect methadone metabolism (i.e., CYP inhibitors and inducers); and older adults (e.g., over 55 years of age).

3 STABILIZATION

An effective stabilization dose is reached when withdrawal symptoms are controlled for more than 24 hours and craving for opioids is reduced or eliminated, without causing excessive sedation or other intolerable side effects. Most patients achieve stability with daily doses of 60 to 120 mg, although higher doses may be required, if tolerated, to achieve therapeutic goals.

4 MISSED DOSES

Tolerance is rapidly lost when methadone treatment is interrupted or discontinued. Loss of tolerance may occur in as little as three days, so restarting at the previous stabilization dose may be excessive or dangerous. Pharmacists are required to notify prescribers of missed doses and clinicians must document review of PharmaNet profiles. Prescribers and patients should be aware that if three consecutive doses are missed, the dispensing pharmacy will cancel the prescription and notify the prescribing clinician.

- **One or two days missed:** No change in dose is required as long as there is no other reason to withhold methadone. The reasons for the missed doses should be discussed and documented at the next visit.
- **Three or four days missed:** Prescribers and patients should be aware that if three consecutive doses are missed, the dispensing pharmacy should cancel the prescription and notify the prescriber. Reasons for missed doses should be discussed during subsequent clinical visit and documented. Following in-person reassessment, patients should be restarted on a reduced dose (see table below), and, once tolerance is demonstrated, the dose can be rapidly titrated at a maximum rate of 10 mg/per day, with frequent (daily or alternating day) clinical reassessment until a stabilization dose has been re-established. A slower dose escalation is recommended for patients who are not clinically or socially stable, and those using alcohol, benzodiazepines or other sedative/hypnotics.
- **Five or more consecutive days missed:** Methadone should be held pending in-person reassessment and the remainder of the prescription should be cancelled. Reasons for missed doses should be discussed during subsequent clinical visit and documented. Restart at a maximum dose of 30 mg, then titrate with frequent re-evaluation until stable.

Suggested Protocol for Managing Missed Doses

Missed Days (consecutive)	Dose	Suggested Dose Adjustment
1–2	Any dose	Same dose (no change)
	30 mg	Same dose (no change)
3–4	31–60 mg	Restart at 30 mg (lower dose if safety concerns)
	> 60 mg	Restart at 50% of previous dose
5 or more	Any dose	Restart at 5–30 mg (depending on tolerance)

5 URINE DRUG TESTING

Regular urine drug testing (UDT) is the standard of care in opioid agonist programs and can be used to assess adherence to treatment, validate self-reported use of opioids or other substances, detect use of other substances which may affect safety (e.g., benzodiazepines), and evaluate treatment response and outcomes (i.e., abstinence from heroin or other opioids).

Point-of-care urine drug testing is useful for providing immediate feedback to patients and for making prompt treatment decisions (e.g., prescribing take-home doses). Physicians are compensated through MSP (fee code P15039) for performing and interpreting point-of-care UDT as part of opioid agonist treatment up to a maximum of 26 UDT per patient per year. Typically, point-of-care UDT can be used to detect amphetamines,

benzodiazepines, cocaine, opioids (morphine, codeine, heroin metabolite, opium and sometimes hydromorphone), oxycodone, buprenorphine and methadone; specific substances tested for will vary by product and manufacturer. Given the epidemiology of substance use in British Columbia, point-of-care tests should include fentanyl when possible.

Laboratory UDT may also be used periodically to verify point-of-care UDT results, particularly if there is a discrepancy with self-reported substance use. In addition, laboratory UDT offer improved sensitivity and specificity, as well as targeted detection of specific substances, such as amphetamines (amphetamine, dextro- and methamphetamine, MDMA (Ecstasy)), benzodiazepines (diazepam, oxazepam, temazepam, triazolam), cocaine (benzoylecgonine metabolite), methadone (EDDP metabolite), and opioids (heroin metabolite, morphine, codeine). Urine drug testing for fentanyl must be specifically requisitioned. Availability, cost and general process for requesting UDT for specific substances should be confirmed with local or hospital laboratory services.

During initiation and dose escalation, urine drug testing should be performed monthly, or more frequently as required to confirm self-reported abstinence from illicit opioid use and/or when patients wish to pursue take-home dosing. More frequent urine drug tests are not necessarily required if ongoing substance use is fully disclosed by the patient. During stabilization, both scheduled and random UDT should be employed as appropriate. It is recommended that patients receiving take-home doses (see [Appendix 4](#)) should have at least eight random UDTs per year, or more frequent as required if there are safety concerns (e.g., relapse, diversion). Patients who fail to comply with random or scheduled UDT should be reassessed as this may indicate risk of relapse, misuse or diversion.

References:

1. Mallinckrodt Canada ULC. Methadose™ (Methadone Hydrochloride Oral Concentrate USP, 10 mg/mL). [amended 2016 Feb 15; cited 2016 Sept 23]. In: Mylan Pharmaceuticals ULC, [Internet]. Saint-Laurent, QC: Mallinckrodt Canada ULC. 2016. Available from: <http://www2.mallinckrodt.com/Templates/Pages/productdetail.aspx?id=1639>.
2. College of Physicians and Surgeons of British Columbia. Methadone and Buprenorphine: Clinical Practice Guideline for Opioid Use Disorder. July 2016. Accessed online on 21 Jul 2016 at: <https://www.cpsbc.ca/files/pdf/MBMT-Clinical-Practice-Guideline.pdf>.
3. Baxter LE, Sr., Campbell A, Deshields M, et al. Safe methadone induction and stabilization: report of an expert panel. *J Addict Med.* 2013;7(6):377–386.

Appendix 2: Induction and dosing guidelines for buprenorphine/naloxone

1 GENERAL CONSIDERATIONS

- For new buprenorphine/naloxone prescribers, nursing and allied health professionals, completion of an online education program (e.g., www.suboxonecme.ca) is recommended, but not required. In addition, consultation with an addiction medicine specialist experienced in buprenorphine/naloxone prescribing is recommended, which could include accessing the provincial Rapid Access to Consultative Expertise ([RACE](#)) line service.
- Emergency department clinicians and first responders are reminded that patients with a buprenorphine/naloxone overdose may present with typical signs and symptoms of opioid toxicity that could be less responsive to naloxone (e.g., *Narcan*®) due to the pharmacodynamics of buprenorphine (i.e., high affinity for opioid receptors, long duration of action). Naloxone is still recommended in event of an overdose, but repeated doses (initial dose may range up to 2 mg, repeated every 2–3 minutes) or continuous intravenous administration may be required to reverse an overdose. In addition, as naloxone will be cleared more rapidly than buprenorphine, patients must continue to be monitored closely for re-emergence of overdose symptoms.

2 ASSESSMENT

Common contraindications to buprenorphine/naloxone initiation:

- Allergy to buprenorphine, naloxone, or any other components of the drug product
- Pregnancy: The Health Canada-approved buprenorphine/naloxone product monograph no longer lists pregnancy as a contraindication to its use. Clinicians treating pregnant women or women who become pregnant with established clinical stability on buprenorphine/naloxone are advised to consult an addiction medicine specialist, the [RACE](#) line, or provincial resources for expert guidance on management.
- Severe liver dysfunction: Careful assessment of risks and benefits of initiating treatment is advised for patients with liver enzymes > 3–5 times normal upper limit.
- Severe respiratory distress
- Delirium tremens
- Acute alcohol intoxication

Baseline assessment

- Physical and mental health assessment
- DSM-5 confirmed diagnosis of opioid use disorder (see [Appendix 5](#))
- Urine drug test (positive for opioids, fentanyl, oxycodone or hydromorphone)
 - Note: An opioid positive urine drug test is not a necessary prerequisite for buprenorphine/naloxone agonist treatment. For example, an individual with a documented history of opioid use disorder who is currently abstinent from opioids but at high risk of relapse may be a good candidate for treatment.
- Laboratory tests: CBC; kidney and liver function panels; HIV and hepatitis A,B,C serology, syphilis, gonorrhea, and chlamydia serology; TB; pregnancy test (women of childbearing age)
- Liver function tests should be repeated 4 weeks after treatment initiation to check for elevated liver enzymes, particularly if patients have pre-existing hepatitis or hepatic dysfunction.
- Addiction history including assessment for other substance use disorders, including alcohol, tobacco, cocaine, and benzodiazepine use disorders
- Concurrent use of alcohol, benzodiazepines, and sedatives (i.e., CNS depressants)
- Review of PharmaNet and other requirements outlined in CPSBC Professional Standards and Guidelines for Safe Prescribing of Drugs with the Potential for Misuse/Diversion. Please refer to www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf for more information.

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3 INDUCTION

Note: buprenorphine/naloxone is available as 2 mg/0.5 mg or 8 mg/2 mg sublingual tablets. Tablets can be halved and/or combined to achieve target doses described below.

Preparation

- a. Review risks and benefits of buprenorphine/naloxone treatment. Obtain informed consent and complete Buprenorphine/Naloxone Treatment Agreement and Consent Form (see [Appendix 8](#)).
- b. Instruct patient to discontinue opioid use 12–24 hours prior to the morning of the first day of scheduled buprenorphine/naloxone induction.
- c. Emphasize to patient that starting buprenorphine/naloxone too early (e.g., within 12–24 hours of opioid use) may worsen rather than alleviate withdrawal symptoms.
- d. Ensure patient is aware not to drive or operate heavy machinery during induction.
- e. Emphasize that induction cannot take place during acute alcohol intoxication, and that dosing and titration may be adjusted or reduced for patients who are actively using alcohol, benzodiazepines or other sedative medications due to increased overdose risk.
- f. If patient is on methadone, aim to taper to a methadone dose of < 60 mg per day, with an ideal dose of \leq 30 mg per day for a minimum of 6–7 days prior to buprenorphine/naloxone induction. Seek specialist support as needed.
- g. Wait at least 24 hours, but preferably 48–72 hours after last methadone dose if patient can tolerate withdrawal symptoms, before beginning buprenorphine/naloxone induction, as per Day 1 guidelines below.
- h. Utilize the Clinical Opiate Withdrawal Scale (see [Appendix 6](#)) to assess withdrawal symptom severity.

Day 1

- a. Plan induction of buprenorphine/naloxone for weekday morning dosing, allowing for reassessment in the afternoon.
- b. At the time of the first dose of buprenorphine/naloxone, the risk of precipitated withdrawal is lower if the patient has signs of at least moderate opioid withdrawal. A Clinical Opiate Withdrawal Scale (cows) score greater than 12 at the time of induction is associated with lower risk of precipitated withdrawal. For cows score less than 12, consider postponing first dose of buprenorphine/naloxone until later in the day or the following day, when the patient is demonstrating more severe withdrawal. For more information on clinical management of precipitated withdrawal, please refer to [Box 2](#).

- In general, the duration of time between last opioid dose and onset of moderate withdrawal (COWS score > 12) is as follows:

Short-acting opioids	12–16 hours since last dose	Examples: heroin, morphine, hydrocodone, immediate-release oxycodone
Intermediate-acting opioids	17–24 hours since last dose	Examples: slow-release oral morphine, controlled-release hydromorphone, sustained-release oxycodone
Long-acting opioids	30–48 hours, or more since last dose	Example: methadone

- c. The most common starting dose is two 2 mg/0.5 mg sublingual tablets of buprenorphine/naloxone (equivalent to total dose of 4 mg/1 mg buprenorphine/naloxone) when COWS > 12 and no long-acting opioid has been used for at least 30 hours.
- Witnessed ingestion of the first dose is recommended, to ensure that the tablet is appropriately taken and fully dissolved sublingually.
 - Instruct patient to keep the tablet under their tongue until it dissolves, which may take up to 10 minutes, and to avoid swallowing, talking, eating, drinking, and smoking during this time.
 - If there is a high risk of precipitated withdrawal (e.g., transition from long-acting opioids), or if patient is currently abstinent from opioid use, starting dose may be lowered to one 2 mg/0.5 mg buprenorphine/naloxone tablet.
 - If the patient is experiencing severe withdrawal symptoms at the time of induction (e.g., COWS > 24), starting dose may be increased to three 2 mg/0.5 mg buprenorphine/naloxone tablets (equivalent to total dose of 6 mg/1.5 mg buprenorphine/naloxone) under supervised conditions.
 - Alternatively, to reduce potential for precipitated withdrawal, a buprenorphine patch (e.g., BuTrans®) can be applied the day prior to buprenorphine/naloxone induction (at least 12 hours after last methadone dose, or at least 4 hours after last short acting opioid dose). Here, specialist support or consultation is warranted, as there is limited evidence to guide this decision. In addition, PharmaCare and First Nations Health Benefits drug benefit plans may not provide coverage for this indication, and patients may incur out-of-pocket costs.
 - For challenging inductions, referral to an inpatient withdrawal management program, community withdrawal management team or residential treatment facility for induction can be considered.
 - Under certain circumstances, and at the discretion of the treating provider, unobserved or “home” induction may be an option to consider for patients deemed appropriate, and who have a reliable caregiver in the home to monitor treatment response and contact the treating clinician in the event of a problem. It is recommended that home induction should only be offered and supervised by experienced clinicians familiar with buprenorphine/naloxone induction and treatment. General considerations for home induction are outlined below in Box 1.

Box 1. General Considerations for Home or Unobserved Buprenorphine/Naloxone Inductions

- Patients that have previous experience with buprenorphine/naloxone treatment, demonstrated reliability, a sufficiently stable home environment and ability to store medication safely may be good candidates for home induction. Patients with significant barriers to office attendance (e.g., work, school, child-care) and/or retention in care who meet the preceding criteria, or who have a caregiver that does, may also be considered.
 - Patients who express significant apprehension or fear of experiencing withdrawal, or those with concurrent alcohol and sedative use or misuse, are not likely to be good candidates for home induction, unless adequate monitoring can be provided from a responsible caregiver.
 - Prior to home induction, discussion of risks and benefits of home induction must be documented and informed consent secured from the patient.
 - During home induction, clinicians should be willing and able to provide regular follow-up and support via telephone. All such contact should be documented in the patient's chart. It is recommended that patients be seen in-person within 2 days of home induction. Patients with previous experience taking buprenorphine/naloxone may require less intensive support.
 - Patients should be provided with clinic/office contact information, in-person education and written instructions for dosing and timing, including use of the Subjective Opioid Withdrawal Scale (sows, see [Appendix 7](#)) to assess withdrawal symptoms and determine when to start induction (sows score ≥ 17), if appropriate.
 - Patients and/or caregivers should be instructed to contact the office immediately in the event of any problems and be willing to come in for clinical assessment as required.
- d. Since precipitated withdrawal (see [Box 2](#)) can become evident within 30 minutes of the first dose of buprenorphine/naloxone, reassess 30–60 minutes from the time of first dose.
- **If withdrawal symptoms are adequately relieved after 1–3 hours**, the induction for Day 1 is complete. Prescribe the same total dose (as administered on Day 1) for the following day.
 - **If withdrawal symptoms are not adequately relieved**, administer additional dose(s). A maximum total of 12 mg/3 mg buprenorphine/naloxone may be administered on Day 1 depending on the individual patient's requirement. If uncertain about the need for an additional dose, consider prescribing one or two 2 mg/0.5 mg buprenorphine/naloxone tablets as take-home doses for withdrawal that may occur later in the evening.
 - **If withdrawal symptoms are adequately relieved with additional dose(s)**, then the induction for Day 1 is complete. Prescribe the same total dose (as administered on Day 1) for the following day.
 - **If withdrawal symptoms are not adequately treated with additional dose(s)**, manage withdrawal symptoms symptomatically (see step e) and continue induction the following day.
- e. In rare cases, short-term symptomatic relief may be offered by prescribing a non-opioid, non-sedative agent. For example:
- Clonidine tablets (instruct patients to take 0.1–0.2 mg every 4 hours PRN for < 12 hours)
 - PRN oral anti-emetic, anti-diarrheals, NSAIDs, acetaminophen can also be considered

Box 2. Management of Precipitated Withdrawal

- Precipitated withdrawal can occur when the first dose of the partial opioid agonist buprenorphine/naloxone is administered to a patient using full agonist opioids (e.g., heroin, fentanyl, oxycodone) before they have achieved a moderate stage of opioid withdrawal. Because buprenorphine has a high affinity but low activity at the mu receptor, it rapidly displaces any full agonist opioids that are present at the receptor, which can result in a net decrease in overall opioid effects. Among patients who have used full agonist opioids recently, the sudden replacement of the full agonist opioid with buprenorphine and rapid decrease in net opioid agonist effects can precipitate significant opioid withdrawal symptoms.
- In the event that a patient develops precipitated withdrawal, clinicians may either continue or stop the induction, as outlined below.
- Both options require supportive treatment, reassurance that symptoms will resolve, and careful explanation of what has occurred to patients.
- Deciding between these two options can be guided by clinician experience, patient preference and severity of precipitated withdrawal. For less experienced practitioners, specialty consultation (e.g., [RACE](#)) is recommended. Additional doses of buprenorphine/naloxone can result in worsening of withdrawal symptoms before improvement.

Option 1: Continue Induction (preferred)

- Explain to the patient what has occurred.
- Discuss options for management and obtain informed consent to continue with induction.
- Administer additional doses of 2 mg/0.5 mg buprenorphine/naloxone every 1–2 hours (up to the Day 1 maximum of 12 mg/3 mg buprenorphine/naloxone) until withdrawal symptoms are resolved.
- If the Day 1 maximum (12 mg/3 mg buprenorphine/naloxone) does not fully suppress withdrawal symptoms, offer non-opioid symptomatic treatment for withdrawal (see item Day 1.e above).

Option 2: Stop Induction

- Explain to the patient what has occurred.
- Discuss options for management and obtain informed consent to stop induction.
- Provide reassurance that symptoms will resolve as opioid withdrawal runs its course.
- Offer non-opioid symptomatic treatment for withdrawal (see item e above).
- Schedule an appointment for another trial of induction on a future date, preferably the next day if possible.

Day 2 onward

- a. If no withdrawal symptoms present since last dose, continue a once-daily dose equal to the total amount of buprenorphine/naloxone administered on the previous day titrating up as needed in subsequent days aiming for a target dose of 16 mg/4mg or greater.
- b. If withdrawal symptoms present since last dose, administer dose equal to the total amount administered on previous day, plus an additional 4 mg/1 mg buprenorphine/naloxone. The maximum total dose on Day 2 should not exceed 16 mg/4 mg buprenorphine/naloxone.
 - If symptoms are relieved after 2–3 hours, prescribe this total dose for the next day.
 - If symptoms are not relieved after 2–3 hours, a second 4 mg/1 mg dose of buprenorphine/naloxone can be administered, unless this would exceed the maximum total of 16 mg/4 mg buprenorphine/naloxone on Day 2. If symptoms resolve 2–3 hours after the second additional dose, prescribe this total daily dose for the following day.

- **If patient has already reached the maximum daily dose of 16 mg/4 mg buprenorphine/naloxone**, or if symptoms persist 2–3 hours after a second additional dose of 4 mg/1 mg buprenorphine/naloxone, manage withdrawal symptomatically for the remainder of Day 2 (refer to Day 1.e).
 - **If withdrawal symptoms are not relieved with initial or repeated buprenorphine/naloxone doses**, it is important to confirm that tablets are being taken and/or administered correctly (i.e., placing under tongue, waiting for tablet(s) to dissolve completely, no swallowing, eating, drinking, or smoking until tablet has fully dissolved).
- c. On the following induction days, if withdrawal symptoms, craving, or illicit opioid use persists, continue dose increases as per the above schedule. Target dose is generally 12 mg/3 mg to 16 mg/4 mg buprenorphine/naloxone per day by the end of the first week.
- d. Titrate as needed (by 2 mg/0.5 mg to 4 mg/1 mg buprenorphine/naloxone at a time) to achieve an optimal stable dose that can sustain an entire 24-hour dosing interval with no withdrawal symptoms and no medication-related intoxication or sedation (hold buprenorphine/naloxone dose if intoxicated or sedated), up to a maximum dose of 24 mg/6 mg buprenorphine/naloxone per day. According to the Suboxone® product monograph, doses greater than 24 mg/6 mg daily have not been demonstrated to provide clinical advantage. Clear documentation and justification should be included in the patient record for doses that exceed 24 mg/6 mg buprenorphine/naloxone. Of note, us guidelines state that some patients may require doses up to 32 mg/8 mg buprenorphine/naloxone per day.
- e. Once optimal dose is achieved, continue to follow up once per week (or more frequently, as needed) to assess for dose effectiveness and side effects.

4 STABILIZATION

- a. Continue to assess at least every 1–2 weeks with the option to decrease follow-up visits as increasing clinical stability is achieved.
- b. Follow-up assessments should include adequacy of dosage, side effects, substance use (via urine testing, when indicated), and psychosocial functioning.
- c. For clinically stable patients at stable doses, one can consider:
 - Alternate day dosing for patients who are on a stable daily dose of up to 12mg/3mg. (If transitioned to an alternate day dosing schedule, daily doses above 12mg/3mg would exceed Health Canada recommendations that the dose given on any one day should not exceed 24mg/6mg).
 - For example, a patient who receives a stable daily dose of 8mg/2mg could transition to taking 16mg/4mg on alternate days.
 - Gradually increasing take-home doses if stable. Always educate patients on risks to self and others when giving take-home doses. If diversion or misuse is suspected, strongly consider eliminating take-home dosing and possibly altering the dose to minimize risk of opioid toxicity once daily witnessed ingestion is resumed. Patients who continue to use illicit opioids, stimulants or alcohol are not eligible for take-home doses of medication.

5 MISSED DOSES

Due to buprenorphine's partial agonist properties, adjusting and re-titrating a patient's buprenorphine/naloxone dose following missed doses does not require the same degree of vigilance as methadone. However, missed doses can contribute to a loss of tolerance to buprenorphine, and dose adjustment and re-stabilization may be required if 6 or more consecutive daily doses are missed. It is recommended to schedule an appointment to assess clinical and social stability, and to check for any signs of relapse, misuse or diversion of buprenorphine/naloxone. Reasons for missed doses should be clearly documented

- a. For missed doses ≤ 5 days, resume previous dose.
- b. For missed doses ≥ 6 days, a conservative dosing guideline is:

Dose	Number of Missed Days	Suggested Dose Adjustment
2 mg/0.5 mg–4 mg/1 mg	≥ 6 days	No change
6 mg/1.5 mg–8 mg/2 mg	≥ 6 days	Restart at 4 mg/1 mg
> 8 mg/2 mg	6–7 days	Restart at 8 mg/2 mg
> 8 mg/2 mg	> 7 days	Restart at 4 mg/1 mg

- c. For missed doses with relapse or return to full agonist opioid use, advise patient to suspend use of buprenorphine/naloxone until they are ready to resume opioid agonist treatment. Schedule a new induction date and proceed as described in steps 1 and 2 above.
- d. For missed doses with an alternating day schedule, it is recommended that if a patient misses two consecutive alternating day doses, buprenorphine/naloxone should be suspended pending reassessment by a clinician. Patients should be returned to a daily dose schedule, possibly at a lowered dose, to re-stabilize prior to resuming an alternating day schedule.

6 URINE DRUG TESTING

Regular urine drug testing is the standard of care in opioid agonist programs and can be used to assess adherence to buprenorphine/naloxone treatment, validate self-reported use of opioids or other substances, detect use of other substances which may affect safety (e.g., benzodiazepines), and evaluate treatment response and outcomes (i.e., abstinence from heroin or other opioids).

Point-of-care urine drug testing is useful for providing immediate feedback to patients and for making prompt treatment decisions (e.g., prescribing take-home doses). Physicians are compensated through MSP (fee code P15039) for performing and interpreting point-of-care UDT as part of opioid agonist treatment, up to a maximum of 26 per patient each year. Typically, point-of-care UDT can be used to detect amphetamines, benzodiazepines, THC, cocaine, opioids, oxycodone, buprenorphine, methadone and fentanyl; specific performance characteristics may vary by manufacturer.

Laboratory UDT may be used periodically to verify point-of-care UDT results, particularly if there is a discrepancy with self-reported substance use. In addition, laboratory UDT offer improved sensitivity and specificity, as well as targeted detection of specific substances, such as amphetamines (amphetamine, dextro- and methamphetamine, MDMA (Ecstasy)), benzodiazepines (diazepam, oxazepam, temazepam, triazolam), cocaine (benzoylecgonine metabolite), methadone (EDDP metabolite), and opioids (heroin metabolite, morphine, codeine, opium, and sometimes hydromorphone).

Urine drug testing for fentanyl and other synthetic opioids must be specifically requisitioned. Availability, cost and general process for requesting UDT for specific substances should be confirmed with local or hospital laboratory services.



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Urine drug testing should be conducted at least monthly during induction and dose titration, until patient has reached a stable dose of buprenorphine/naloxone, or more frequently as required to confirm self-reported abstinence from illicit opioid use and/or to confirm presence of buprenorphine when patients wish to pursue take-home dosing. More frequent urine drug tests are not necessarily required if ongoing substance use is fully disclosed by the patient. It is recommended that patients receiving take-home doses should have at least four random UDTs per year to confirm presence of buprenorphine, or more frequent as required if there are safety concerns (e.g., relapse, diversion). Please refer to [Appendix 4](#) for more detailed information.

7 RAPID INDUCTION

The induction schedules provided above are based on the most up-to-date Suboxone® product monograph approved by Health Canada. However, it is important to note that with increasing clinical and research experience, there is increasing evidence that buprenorphine/naloxone induction protocols that utilize a higher dose trajectory with shorter latency to achieving a stable maintenance dose (i.e., a dose that adequately controls withdrawal symptoms for 24 hours duration) are associated with improved treatment outcomes, as evidenced by a recent analysis of the NIDA-funded START trial (n=740). The START protocol allowed a flexible approach to dosing, with minimal instructions to study clinicians (e.g., maximum upper limit of 16 mg/4 mg buprenorphine/naloxone on Day 1, and 32 mg/8 mg buprenorphine/naloxone on Days 2–168). Other than recommending dose adjustment to address participant symptoms, dose escalation rates were not explicitly outlined in the START protocol, and study clinicians employed a range of induction trajectories. The analysis explored higher versus lower dose trajectories during the first three days of induction and latency to achieve a stable dose.

The authors found that participants who were started at a moderate dose (16 mg/4 mg buprenorphine/naloxone) and shifted quickly over 3 days to a high dose (16 mg/4 mg–32 mg/8 mg buprenorphine/naloxone) were three times less likely to drop out in the first 7 days than participants who were started and maintained at a low dose (8 mg/2 mg–16 mg/4 mg buprenorphine/naloxone). Participants who were stabilized at an optimal dose quickly had less opioid use in the last 28 days of treatment than those who were slowly titrated to their optimal dose, without an increase in adverse events in the first or last 28 days of treatment. Currently, Health Canada recommends a maximum starting dose of 12mg/3mg and a maximum total dose of 24mg/6mg of buprenorphine/naloxone, however, as safety and efficacy evidence continues to accumulate, dosing recommendations may be adjusted in future to optimize the balance between patient safety and treatment effectiveness.

References:

1. Centre for Addiction and Mental Health. Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline. November 2012. Accessed online on March 15, 2015 at http://knowledgex.camh.net/primary_care/guidelines_materials/Documents/buprenorphine_naloxone_gdlns2012.pdf.
2. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.
3. Farmer CM, Lindsay D, Williams J, Ayers A, Schuster J, Cilia A, Flaherty MT, Mandell T, Gordon AJ, and Stein BD. Practice Guidance for Buprenorphine for the Treatment of Opioid Use Disorders: Results of an Expert Panel Process. Substance Abuse 2015;36:209–216.
4. Suboxone (buprenorphine and naloxone) product monograph. Indivior UK Limited: Berkshire, UK. Control No. 195433. 2016.
5. Casadonte PP, Sullivan MA. 2013. Buprenorphine induction. Providers clinical support system for medication assisted treatment, PCSS guidance. August 9, 2006 (Updated November 27, 2013). Available at: pcssmat.org/wp-content/uploads/2014/02/PCSS-MATGuidanceBuprenorphineInduction.Casadonte.pdf.
6. Gunderson EW, Levin FR, Rombone MM, Vosburg SK, Kleber HD. Improving Temporal Efficiency of Outpatient Buprenorphine Induction. Am J Addictions 2011; 20(5):397–404.
7. Jacobs P, Ang A, Hillhouse MP, et al. Treatment Outcomes in Opioid Dependent Patients With Different Buprenorphine/Naloxone Induction Dosing Patterns and Trajectories. American Journal on Addictions 2015;24:667–75.
8. Kraus ML, Alford DP, Kotz MM, et al. Statement of the American Society of Addiction Medicine Consensus Panel on the Use of Buprenorphine in Office-Based Treatment of Opioid Addiction. Journal of Addiction Medicine. 2011;5(4):254–263

Appendix 3: Dosing recommendations for slow-release oral morphine

Slow-release oral morphine—which refers to the **24-hour formulation** of the extended-release capsules (brand name Kadian®)—is a potential option for individuals who respond poorly to buprenorphine/naloxone and methadone and may require an alternative treatment approach (see Table 1). These guidelines are based on the protocols used in randomized controlled trials that demonstrated efficacy of slow-release oral morphine for opioid dependence. It is important to note that there is currently no “best” clinical treatment protocol established for agonist treatment with slow-release oral morphine. Thus, treatment with slow-release oral morphine requires diligent measures to avoid overdose (i.e., close monitoring of initiation and stabilization, appropriate titration and, where appropriate, specialist referral) and diversion (see [Appendix 4](#)). As such, patients require close monitoring until stability is achieved. It is important to note that only the once-daily, 24-hour formulation of slow-release oral morphine has been studied in clinical trials for the treatment of opioid use disorder. Other formulations of oral morphine, such as twice-daily, 12-hour sustained- or extended-release formulations (brand name M-Eslon®), have not been empirically studied in this context and are not recommended by this committee for treatment of opioid use disorder.

As part of the CPSBC prescription monitoring process, starting June 5, 2017, there will be a new Product Identification Number (PIN) to be used by pharmacists to enter claims for each of the various dosing strengths of Kadian® slow-release oral morphine when used as opioid agonist treatment. Similar to methadone, the current Drug Identification Numbers (DINs) will be used by pharmacists for claims for analgesia, and the new PINs will be used for claims for Kadian® for OAT. For this reason, prescribers **must designate the indication of opioid agonist treatment or “OAT” on every prescription.**

The CPSBC has set safe prescribing standards for the use of opioids for treatment of chronic non-cancer pain. Since the use of slow-release oral morphine for opioid agonist therapy is currently off-label and the dose needed to stabilize a highly tolerant patient with an OUD can exceed 90 mg morphine milligram equivalents (MME), clear and careful assessment, patient consent, and documentation is needed.

It is strongly recommended that physicians who wish to prescribe slow-release oral morphine as an opioid agonist treatment should hold a valid federal Section 56 exemption from the *Controlled Drugs and Substances Act* to prescribe methadone, or only after formal consultation with an addiction medicine specialist (e.g., [RACE](#)).

Clinicians are also encouraged to call the Rapid Access to Consultative Expertise ([RACE](#)) line to speak with an addiction medicine specialist if any questions or concerns:

1 ELIGIBILITY

These recommendations are most applicable to patients who are:

- Adults (≥ 19 years in BC) with opioid use disorder
- Switching to slow-release oral morphine from methadone or while actively using another opioid
- Not pregnant or breastfeeding

Common contraindications to initiation:

- Hypersensitivity to morphine sulfate or any component of the formulation
- Significant respiratory depression
- Acute or severe bronchial asthma
- Known or suspected paralytic ileus
- Currently taking monoamine oxidase inhibitors (MAOIs) or use within past 14 days
- Severe respiratory compromise or obstructive disease
- Severe respiratory distress
- Delirium tremens
- Acute alcohol intoxication

2 PHARMACOLOGY

- Slow-release oral morphine is administered via once-daily oral doses.
- Slow-release oral morphine is released over 24 hours.
- Peak plasma levels are achieved within 8½ to 10 hours.
- Elimination half-life: The terminal elimination half-life of morphine following a single dose of slow-release oral morphine administration is approximately 11 to 13 hours. However, this is primarily due to the delayed absorption of the pellets. Once absorption is complete, the plasma elimination half-life is the same as immediate-release morphine (2 to 4 hours).

3 ADMINISTRATION

- Slow-release oral morphine must be swallowed whole. Crushing, chewing, or dissolving slow-release oral morphine capsules or pellets can cause rapid release and absorption of a potentially fatal dose of morphine sulphate.
- To reduce risk of diversion, daily witnessed ingestion via opening capsules and sprinkling the enclosed pellets for immediate ingestion is strongly recommended. Pellets must not be chewed or crushed.
- Pellets may be sprinkled onto a small amount of applesauce and ingested immediately. Alternatively, in settings where applesauce may not be available or patient allergies are a concern, pellets may be sprinkled into a 30 mL medicine cup and ingested followed by a cup of water to ensure all pellets have been swallowed.
- Those prescribing slow-release oral morphine are encouraged to call and discuss these requirements and review instructions for witnessed ingestion with the dispensing pharmacy.

4 ASSESSMENT AND MONITORING

Baseline assessment

- Addiction history including assessment for tobacco and other substance use disorders, in particular, concurrent use of alcohol, benzodiazepines, and sedatives (i.e., CNS depressants)
- Review of PharmaNet and other requirements outlined in CPSBC Professional Standards and Guidelines for Safe Prescribing of Drugs with the Potential for Misuse/Diversion. Please refer to www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf for more information.

Monitoring treatment efficacy:

- Urinalysis, other opioids and other drug use, cravings, withdrawal
 - ◆ Note: Non-quantitative point-of-care (POC) urine drug tests cannot be used to rule out use of illicit heroin or some prescription opioids (i.e., morphine) among patients treated with slow-release oral morphine.
 - ◆ Lifelabs® and other local or hospital laboratories are able to perform mass spectrometry urine drug testing that can distinguish between illicit heroin and prescribed slow-release oral morphine. With the support of a laboratory, distinguishing between heroin, acetaminophen with codeine, and slow-release oral morphine can be made using laboratory urine drug tests that employ mass spectrometry, as follows:
 - Heroin: variably high morphine, 5–10% codeine, heroin metabolite 6-acetylmorphine (6-AM) may be present
 - Acetaminophen with codeine (Tylenol® #3): high codeine, relatively low morphine
 - Slow-release oral morphine: very high morphine, trace levels of codeine (i.e., < 50 mg/mL)
 - These data may not be reported unless specifically requisitioned for individuals on slow-release oral morphine, point-of care urine drug tests will be positive for the morphine metabolite and

it may be difficult to distinguish on UDT between illicit heroin and prescribed slow-release oral morphine.

- ◆ Clinical interpretation, availability, cost, and general process for requesting UDT can be discussed with local laboratory services when needed. Clinicians should also be aware that fentanyl may be present in urine drug tests for many active heroin users in BC.
- ◆ Urine drug testing should be performed monthly, or more frequently as required to confirm self-reported abstinence from illicit opioid use and/or when patients wish to pursue take-home dosing. During stabilization, both supervised and random UDT should be employed as appropriate. It is recommended that patients receiving take-home doses (see Appendix 4) should have at least eight random UDTs per year, or more frequent as required if there are safety concerns (e.g., relapse, diversion). Patients who fail to comply with random or scheduled UDT should be reassessed as this may indicate risk of relapse, misuse or diversion.
- **Adverse effects:** most common are stomach cramps, abdominal pain, headache, dizziness, hyperhidrosis, toothache, dry mouth, constipation, frequent urination, nausea, vomiting, and insomnia.
- **As with other types of chronic opioid therapy, there is potential for opioid-induced hyperalgesia**, which may require weaning the slow-release oral morphine dosage downward, introducing an opioid-sparing adjuvant for analgesia, or rotating to an alternative treatment. For this reason, only one or two dose escalations should be permitted in the years after initial stabilization. If the patient continues to build tolerance or develops hyperalgesia, then transition to buprenorphine/naloxone or methadone is strongly recommended.

5 INDUCTION AND DOSING

- Prior to treatment start, review risks and benefits of slow-release oral morphine. Obtain informed consent and complete Slow-release Oral Morphine Treatment Agreement and Consent Form (see [Appendix 8](#)).
- Begin with a 1-week adjustment/titration phase aiming to achieve a stable daily dosage.
- Because of the sustained-release properties of slow-release oral morphine (see Pharmacology section above), dosage increases should generally be separated by 48 hours.
- For individuals using street opioids other than methadone, refer to induction example below.

Switching from methadone oral solution to slow-release oral morphine:

- No wash-out of previous treatment is required (to minimize potential for withdrawal symptoms). Withdrawal symptoms may recur temporarily during the switch-over period.
- Generally a switch will require an ultimate dose of 1:6 to 1:8, but the committee suggests beginning with a 1:4 induction with titration upwards based on withdrawal scores and craving. Titrate upward in incremental doses according to withdrawal scores.

Sample dosing schedules:

There are a variety of dosing schedules described in the literature. Examples include:

Example 1: MMT to slow-release oral morphine	Example 2: Daily or lower frequency heroin use
<ul style="list-style-type: none"> • Begin with estimated methadone-to-slow-release oral morphine dose equivalence of 1:4 on Day 1 (e.g., 60 mg methadone = 240 mg slow release oral morphine), and then increase incrementally according to withdrawal scores. • Several studies have found an average methadone-to-slow-release oral morphine stabilization dose of approximately 1:7.75 to be appropriate. 	<ul style="list-style-type: none"> • Day 1: 30 to 60 mg slow-release oral morphine • Titrate dose upward according to individual patient's withdrawal. • Because of the sustained-release properties of slow-release oral morphine (see Pharmacology section above), dosage increases should generally be separated by 48 hours.

According to existing literature, the average (mean) slow-release oral morphine dose ranges from 235–791 mg/day. The full range of slow-release oral morphine doses described in the literature is 60–1200 mg/day.

6 MISSED DOSES

- Despite delayed absorption, the underlying short morphine half-life results in the potential for rapid loss of tolerance following missed doses, and the possibility of harmful over-sedation or overdose.
- To mitigate this, prescribers should work very closely with pharmacists regarding missed doses and daily patient assessments.
- In determining dose adjustments after missed doses, clinical judgment must take into account: (i) total daily dose, (ii) number of missed doses, (iii) possibility of diversion, and (iv) other opioid use during periods of missed dosing.

Sample missed dosing schedules:

There are a number of possible approaches to dealing with missed doses of slow-release oral morphine—all based upon expert opinion and limited clinical experience or research data:

Number of missed days	Missed dosing schedule	
	<i>Example prescribed dose = 200 mg</i>	<i>Example prescribed dose = 800 mg</i>
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)

Due to lack of clinical experience or clinical trials for slow-release oral morphine re-induction protocols, patients should be seen daily to assess for intoxication or withdrawal, with dose increases or decreases titrated accordingly.

7 STABILIZATION

The goal is to stabilize the once-daily dose at the lowest dose that relieves withdrawal symptoms and suppresses illicit opioid use. Currently, there is no published literature to guide treatment decisions beyond the 36-week duration of clinical trials. The committee recommends following similar stabilization and tapering practices as methadone and buprenorphine/naloxone.

References:

1. Beck T, Haasen C, Verthein U, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction* 2014;109:617-26.
2. Eder H, Jagsch R, Kraigher D, et al. Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. *Addiction* 2005;100:1101-9.
3. Ferri M, Minozzi S, Bo A, et al. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database Syst Rev* 2013;6:CD009879.
4. Hammig R, Kohler W, Bonorden-Kleij K, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat* 2014;47:275-81.
5. Jegu J, Gallini A, Soler P, et al. Slow-release oral morphine for opioid maintenance treatment: a systematic review. *Br J Clin Pharmacol* 2011;71:832-43.
6. Giacomuzzi S, Kemmler G, Ertl M, et al. Opioid addicts at admission vs. slow-release oral morphine, methadone, and sublingual buprenorphine maintenance treatment participants. *Subst Use Misuse* 2006;41:223-44.
7. BGP Pharma ULC. Kadian® Capsules (Morphine Sulphate Sustained Release Capsules, Mfr. Std.). [amended 2015 Aug 11; cited 2016 Aug 24]. In: Mylan Pharmaceuticals ULC, [Internet]. Etobicoke, ON: BGP Pharma ULC. 2015. Available from: <http://www.mylan.ca/-/media/mylanca/documents/english/kadian-pm-2015.08.11.pdf>.
8. Actavis Pharma, Inc. Kadian® (morphine sulfate) Extended-Release Capsules, for oral use. [amended 2014 Apr; cited 2016 Aug 24]. In: Kadian® Morphine Sulfate Extended-Release Capsules, [Internet]. Parsippany, NJ: Actavis Pharma, Inc. 2014. Available from: <http://www.kadian.com/>.
9. Verthein U, Beck T, Haasen C, et al. Mental symptoms and drug use in maintenance treatment with slow-release oral morphine compared to methadone: results of a randomized crossover study. *Eur Addict Res* 2015;21:97-104.
10. Verthein U, personal communication, August 19, 2016.
11. Yi P, Pryzbylkowski P. Opioid Induced Hyperalgesia. *Pain Med* 2015;16 Suppl 1:S32-6.
12. Palaty J, personal communication, November 9, 2016

Appendix 4: Take-home Dosing Recommendations and Strategies to Reduce Diversion for Oral Agonist Therapy

Take-home dosing of oral agonist therapy may be beneficial in terms of improved motivation to participate in agonist treatment, improved treatment retention, increased patient autonomy and flexibility, positive reinforcement of abstinence, decreased treatment burden, and decreased costs related to daily witnessed ingestion. However, these benefits must be balanced against patient and public health risks associated with take-home dosing.

1 GENERAL CONSIDERATIONS

Due to the increased risk of overdose when opioid agonists are combined with other CNS depressants, benzodiazepines and other sedative medications should not be prescribed concurrently, and as per CSPBC guidance, PharmaNet should be reviewed at each clinical visit to confirm that another care provider has not prescribed these medications.

Major individual and public safety differences exist between different opioid agonist therapies. For instance, an estimated 25% of prescription opioid overdose fatalities in British Columbia in recent years have involved methadone, whereas deaths resulting from buprenorphine/naloxone are very uncommon, even in settings where rates of take-home dosing of buprenorphine/naloxone prescription are high. Hence, for buprenorphine/naloxone, take-home dosing can be considered a common part of treatment, whereas for methadone and slow-release oral morphine, treatment should involve daily witnessed ingestion, with graduated take-home dosing provided only when patient stability is clearly demonstrated and routinely assessed as described below.

Prior to prescribing take-home doses of opioid agonist treatments, it is recommended that prescribers and patients complete a Patient Agreement Form for Receiving Take-Home Dosing (see [Appendix 8](#)). The signed form should be filed with the patient's medical records, and a copy should be provided to the patient.

2 BUPRENORPHINE/NALOXONE

Take-home dosing of buprenorphine-naloxone may be provided at any time at the discretion of the treating clinician, once a patient is deemed clinically stable and able to safely store medication at home (e.g., secure, locked containers or cabinets). Previous research has not demonstrated improved patient outcomes when buprenorphine/naloxone is provided via daily witnessed ingestion,³⁻⁵ and there is some evidence that quick transition to take-home dosing can improve treatment adherence and retention.^{6,7} In addition, where circumstances permit (e.g., stable housing) and no contraindications are present (e.g., sedative use) several studies have reported that unobserved home buprenorphine/naloxone inductions are comparable to office-based inductions in terms of safety, patient retention and reductions in opioid use.⁸⁻¹⁰ Generally, when offered, take-home dosing is provided for one to two weeks' worth of medication at a time. Ideally, prescribers should include instruction to the pharmacy for take-home doses to be blister-packed (e.g., compliance packs) to lessen the chance of diversion. Prescribers may request patients present medication packs regularly at scheduled clinic appointments or via random call-backs for pill counts.

Considerations for restricting patients to daily witnessed ingestion of buprenorphine/naloxone can include:^{1,11,12}

- Potential for promotion of patient safety and treatment adherence via increased engagement with health care provider (i.e., physician, pharmacist) in early weeks of treatment
- Homelessness or other reasons for inability to safely store medication
- Evidence of patient diversion of medication
- Ongoing substance use, especially benzodiazepines, alcohol or other sedatives
- Length and track record of clinic attendance
- Severe behavioural issues, cognitive impairment or unstable mental health

It is the responsibility of the treating clinician to decide when take-home dosing is advisable and whether ongoing daily witnessed ingestion of buprenorphine/naloxone is optimal from a patient and public safety perspective. While Canadian guidelines and those from some other jurisdictions recommend initial daily witnessed ingestion of buprenorphine/naloxone,^{1,13,14} us guidelines are much more flexible, with recent federal amendments removing maximum take-home dose restrictions (previously restricted to a one-month take-home supply) for buprenorphine/naloxone, due to its relatively low risk for misuse and adverse events. While there are no established protocols for take-home dosing of buprenorphine/naloxone, clinicians may consider that Health Canada recommends that buprenorphine/naloxone doses should be dispensed daily under the supervision of a healthcare professional until the patient has demonstrated sufficient clinical stability and is able to safely store take-home doses. In some cases, sufficient clinical stability could be evident after buprenorphine/naloxone induction (as early as 1–3 days), in the best judgment of the treating clinician.

Consideration can also be given to providing take-home buprenorphine/naloxone doses during induction when multiple same-day visits may not be possible or practical.^{15,16} Specifically, take-home doses may be prescribed in combination with witnessed doses, while ensuring that patients are provided with detailed instructions and telephone numbers for patient support. For example, following an initial 4 mg/1 mg starting dose of buprenorphine/naloxone in the clinic, a patient who is not able to return for reassessment that same day may be given a second take-home dose of 4 mg/1 mg buprenorphine/naloxone to be taken in the event of recurrence of withdrawal symptoms, in order to help decrease the likelihood of illicit opiate use.

It is also important for care providers to understand that daily witnessed ingestion requirements are a common reason for patient dropout. Here, the limited risks of take-home dosing of buprenorphine/naloxone must be balanced against the risks of fatal overdose or other harms if individuals are lost from care due to daily witnessed ingestion requirements that some patients may find unacceptable and impractical. Also, as noted above, data of improved outcomes associated with daily witnessed ingestion of buprenorphine/naloxone are lacking and some data suggest that more flexible take-home dosing improves adherence and retention.¹⁷

3 METHADONE

Due to its inferior safety profile in circumstances of diversion, co-ingestion or overdose, methadone should generally be prescribed as daily-witnessed doses ingested under the supervision of a pharmacist until patients demonstrate a persistent high degree of stability including a stable dose, which typically takes months. In addition, in comparison to other treatment options, more restrictive criteria must be met prior to provision of take-home methadone doses due to these increased public safety risks. The decision to initiate take-home doses can only be made by the prescribing clinician, and rationale, including confirmation that criteria listed below have been met, must be clearly documented. Clinicians must ensure that take-home doses are safe for both patients and the public, as unsafe storage, misuse and diversion of methadone may result in lethal consequences.

Prior to provision of take-home methadone doses, the following patient criteria should be met:

- Appropriate (e.g., no evidence of cocaine, amphetamine or illicit opioid use) UDTs for a minimum of 12 weeks and established on a stable methadone dose for a minimum of 4 weeks
- Social, cognitive and emotional stability as confirmed by attending all scheduled appointments, no record of missed doses, improved social relationships or returning to work or school
- Ability to safely store methadone at home (i.e., secure, locked containers or cabinets)
- No signs of injection drug use during the 12 week monitoring phase and in follow-up

Take-home methadone dosing schedules should start with one take-home dose per week, progressing to additional take-home doses per week slowly and at the clinician's discretion. The first dose should always be witnessed in the pharmacy on the day the prescription is picked up. Take-home doses should be dispensed in individual, appropriately sized, child-resistant containers. Containers with tamper-proof seals may also be available at some pharmacies, and should be requested if available. Most stable patients are established on a twice-weekly witnessed ingestion schedule with random medication checks as described in section 5.

4 SLOW-RELEASE ORAL MORPHINE (24-hour formulation)

As there are no established protocols for slow-release oral morphine take-home dosing, it is recommended that tighter restrictions for daily witnessed ingestion be implemented, as outlined above for methadone. The standard should be indefinite daily witnessed ingestion due to the challenges in monitoring for heroin use, the diversion potential of the drug, and the potential lethality of the drug to non-tolerant individuals. In exceptional cases where patients have demonstrated high clinical stability, or when daily-witnessed dosing schedules are a significant barrier to treatment (e.g., employment, school, childcare), graduated take-home dosing can be considered on a case-by-case basis as per the best judgement of the treating clinician, and with appropriate monitoring and follow-up to prevent misuse or diversion.

The following should be clearly documented prior to the consideration of provision of take-home doses:

- Appropriate UDTs for a minimum of 16 consecutive weeks confirming no other drug use and established on a stable slow-release oral morphine dose for a minimum of 4 weeks
- Social, cognitive and emotional stability as confirmed by attending all scheduled appointments, no missed doses, improved social relationships
- Return to work, school or childcare that necessitates take-home doses or a significant physical disability that precludes daily visits to the pharmacy
- Ability to safely store slow-release oral morphine at home (i.e., secure, locked containers or cabinets)
- No signs of injection drug use or nasal insufflation during the 16 week monitoring phase and in follow-up. Ideal candidates for take-home doses of slow-release oral morphine have no history of injection drug use.
- No history of diversion or drug dealing (patients with this history are poor candidates for take-home doses of this medication — only with proof of extensive lifestyle change and rehabilitation should take-home doses be considered).

Take-home slow-release oral morphine schedules should start with one take-home dose per week, progressing to additional take-home doses per week every month or two months. The first slow-release oral morphine dose should always be witnessed in the pharmacy on the day the prescription is picked up. Most stable patients are established on twice-weekly witnessed ingestion. This represents a reasonable balance between safety and patient inconvenience. Ideally, prescribers should include instruction to the pharmacy for take-home doses to be blister-packed to discourage diversion and allow for better monitoring during random medication call-backs.

5 MONITORING OF TAKE-HOME DOSING

Patients with take-home buprenorphine/naloxone, methadone, or slow-release oral morphine dosing privileges should be seen at least monthly to assess progress and stability. Prescribing clinicians should be vigilant in monitoring for signs of relapse to opioid use, alcohol and other (non-opioid) substance use, social instability, and diversion. For buprenorphine/naloxone, at least four unannounced urine drug tests should be performed and four unannounced pill counts should be requested during the first year, in addition to dispensed medication counts at each scheduled visit. For methadone and slow-release oral morphine, at least eight unannounced urine drug tests should be performed and four unannounced dose/pill counts should be requested during the first year, in addition to dispensed medication counts at each scheduled visit. When possible, a 24-hour phone call protocol is suggested wherein patients are given 24-hours notice of mandatory attendance at the clinic or laboratory for urine drug tests and the clinic for random pill/dose counts.

Factors that would indicate need for follow-up and reassessment of take-home dosing privileges include:

- Self-reported or other indication of substance use, such as UDT results or evidence of injection drug use on physical exam
- Missed appointments
- Missed doses
- Requests to increase a previously stable dose
- Reports of lost, spilled, stolen or vomited doses
- Non-attendance for random urine drug testing
- Non-compliance with request for random pill counts or evidence of tampering with blister-pack

For patients prescribed take-home buprenorphine/naloxone showing signs of major instability, individual patient circumstances should be considered when reducing the number of take-home doses of buprenorphine/naloxone, as limiting take-home dosing may result in loss to care. Following discussion with the patient about any underlying issues contributing to treatment instability, clinicians can consider reducing the number of take-home doses with return to more frequent witnessed ingestion (e.g., daily, alternating days); limiting the number of take-home doses to a single dose at a time; increasing the frequency of clinical appointments in order to provide more intensive support, monitoring and assessment; and/or providing referrals to adjunct psychosocial and community-based supports, as appropriate. If treatment intensification does not adequately address clinical or social instability, clinicians and patients can consider transitioning from buprenorphine/naloxone- to methadone-based agonist treatment. Evidence of diversion (e.g., UDT negative for buprenorphine) warrants immediate discontinuation of take-home dosing and consideration of dose reduction upon re-introduction of daily witnessed ingestion.

For patients prescribed take-home methadone showing signs of instability, prescribing clinicians should immediately reduce take-home dosing days per week and consider return to daily-witnessed ingestion if appropriate, following discussion with the patient. Clinicians should also increase the frequency of clinical appointments and provide referrals to adjunct psychosocial treatment and community-based supports. If treatment intensification and adjunct support does not address issues underlying instability, clinicians and patients can consider transitioning to an alternative agonist treatment including buprenorphine/naloxone if take-home dosing is required, or daily-witnessed slow-release oral morphine if an alternative agent is desired. Evidence of diversion (e.g., UDT negative for methadone) warrants immediate discontinuation of take-home dosing, consideration of dose reduction upon re-introduction of DWI or of stopping methadone.

For patients prescribed take-home slow-release oral morphine showing signs of instability, prescribing clinicians should immediately reduce take-home dosing days per week and consider return to daily-witnessed ingestion, following discussion with the patient. Clinicians should also increase the frequency of clinical appointments and provide referrals to adjunct psychosocial treatment and community-based supports. Evidence of diversion (e.g., UDT negative for morphine metabolite) warrants immediate discontinuation of take-home dosing and consideration of dose reduction upon re-introduction of DWI, or, depending on circumstances, discontinuation of slow-release oral morphine treatment.

References:

1. Centre for Addiction and Mental Health. Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline. November 2012. Available at http://knowledge.camh.net/primary_care/guidelines_materials/Documents/buprenorphine_naloxone_gdlns2012.pdf.
2. College of Physicians and Surgeons of British Columbia. Methadone and Buprenorphine: Clinical Practice Guideline for Opioid Use Disorder. July 2016. Accessed online on 21 Jul 2016 at: <https://www.cpsbc.ca/files/pdf/MBMT-Clinical-Practice-Guideline.pdf>
3. Bell J, Shanahan M, Mutch C, et al. A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine-naloxone for heroin dependence. *Addiction*. 2007;102(12):1899–1907.
4. Montesano F, Mellace V, Grp A-DP. The effects of a novel take-home treatment strategy in patients with opioid-dependence receiving long-term opioid replacement therapy with buprenorphine/naloxone in Italy: a cost analysis. *Heroin Addiction and Related Clinical Problems*. 2013;15(1):45–51.
5. Holland R, Maskrey V, Swift L, et al. Treatment retention, drug use and social functioning outcomes in those receiving 3 months versus 1 month of supervised opioid maintenance treatment. Results from the Super C randomized controlled trial. *Addiction*. 2014;109(4):596–607.
6. Amass L, Kamien JB, Mikulich SK. Thrice-weekly supervised dosing with the combination buprenorphine-naloxone tablet is preferred to daily supervised dosing by opioid-dependent humans. *Drug and Alcohol Dependence*. 2001;61(2):173–181.
7. Marsch LA, Moore SK, Borodovsky JT, et al. A randomized controlled trial of buprenorphine taper duration among opioid-dependent adolescents and young adults. *Addiction*. 2016;111(8):1406–1415.
8. Gunderson EW, Wang XQ, Fiellin DA, Bryan B, Levin FR. Unobserved versus observed office buprenorphine/naloxone induction: a pilot randomized clinical trial. *Addict Behav* 2010;35:537–40.
9. Cunningham CO, Giovanniello A, Li X, Kunins HV, Roose RJ, Sohler NL. A comparison of buprenorphine induction strategies: Patient-centered home-based inductions versus standard-of-care office-based inductions. *Journal of Substance Abuse Treatment*. 2011;40(4):349–356
10. Lee JD, Vocci F, Fiellin DA. Unobserved “Home” Induction Onto Buprenorphine. *Journal of Addiction Medicine*. 2014;8(5):299–308.
11. Substance Abuse and Mental Health Services Administration (SAMHSA), US Department of Health and Human Services. Opioid drugs in maintenance and detoxification treatment of opiate addiction; proposed modification of dispensing restrictions for buprenorphine and buprenorphine combination as used in approved opioid treatment medications. Final rule. *Federal Register* 2012;77(235):72752–61.
12. Substance Abuse and Mental Health Services Administration (SAMHSA), US Department of Health and Human Services. Opioid drugs in maintenance and detoxification treatment of opiate addiction. Final rule. *Federal Register* 2001;66(11):4076–102.
13. Australasian Chapter of Addiction Medicine (ACAM). Clinical Guidelines: Assessing suitability for unsupervised medication doses in the treatment of opioid dependency. October 2006. Available at http://www.gacguidelines.ca/site/GAC_Guidelines/assets/pdf/295_Winstock_2006.pdf.
14. Kahan M, Srivastava A, Ordean A, Cirone S. Buprenorphine: new treatment of opioid addiction in primary care. *Can Fam Physician* 2011;57:281–9.
15. Casadonte PP, Sullivan MA. 2013. Buprenorphine induction. Providers’ clinical support system for medication assisted treatment, PCSS guidance. August 9, 2006 (Updated November 27, 2013). Available at <http://pcssmat.org/wp-content/uploads/2014/02/PCSS-MATGuidanceBuprenorphineInduction.Casadonte.pdf>.
16. Gunderson E. Models of Buprenorphine Induction. Providers’ Clinical Support System (PCSS) For Medication Assisted Treatment (MAT Training). Available at <http://pcssmat.org/wp-content/uploads/2015/02/Buprenorphine-Induction-Online-Module.pdf>.
17. Lofwall MR, Walsh SL. A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. *J Addict Med*. 2014;8(5):315–326.

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

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

DSM-5 Criteria for Opioid Use Disorder¹

1	Opioids are often taken in larger amounts or over a longer period than was intended	<p>The presence of at least 2 of these symptoms indicates an Opioid Use Disorder (OUD)</p> <p>The severity of the OUD is defined as:</p> <p>MILD: The presence of 2 to 3 symptoms</p> <p>MODERATE: The presence of 4 to 5 symptoms</p> <p>SEVERE: The presence of 6 or more symptoms</p>
2	There is a persistent desire or unsuccessful efforts to cut down or control opioid use	
3	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects	
4	Craving or a strong desire to use opioids	
5	Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home	
6	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids	
7	Important social, occupational, or recreational activities are given up or reduced because of opioid use	
8	Recurrent opioid use in situations in which it is physically hazardous	
9	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.	
10	Tolerance,* as defined by either of the following: <ol style="list-style-type: none"> a) Need for markedly increased amounts of opioids to achieve intoxication or desired effect b) Markedly diminished effect with continued use of the same amount of opioid 	
11	Withdrawal,* as manifested by either of the following: <ol style="list-style-type: none"> a) Characteristic opioid withdrawal syndrome b) Same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms 	

* Patients who are prescribed opioid medications for analgesia may exhibit these two criteria (withdrawal and tolerance), but would not necessarily be considered to have a substance use disorder.

Reference:

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

Appendix 6. 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 this 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 style="text-align: center;">Total Score _____</p> <p style="text-align: center;"><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.

Appendix 7. Subjective Opiate Withdrawal Scale (sows)¹

The sows is a self-administered scale for grading opioid withdrawal symptoms. It contains 16 symptoms whose intensity the patient rates on a scale of 0 (not at all) to 4 (extremely), and takes less than 10 minutes to complete.

Patient Instructions: please score each of the 16 items below according to how you feel right now. Circle one number only.

Item	Symptom	Not at all	A little	Moderately	Quite a bit	Extremely
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Total Score: _____

Reference:

1. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two New Rating Scales for Opiate Withdrawal. 1987. American Journal of Alcohol Abuse 13, 293-308.

Appendix 8. Opioid Agonist Treatment Agreement and Consent Forms

METHADONE TREATMENT AGREEMENT AND CONSENT FORM

Patient Information	
Surname: _____	Given name(s): _____
Date of birth: _____	PHN: _____

Patient Agreement
<p>I UNDERSTAND AND AGREE THAT:</p> <ul style="list-style-type: none"><input type="checkbox"/> I am being started/continued on:<ul style="list-style-type: none"><input type="checkbox"/> Methadone for the treatment of opioid addiction. While I may choose to taper off this treatment at any time, I understand that most patients benefit from at least one year of treatment or longer.<input type="checkbox"/> While I am receiving methadone treatment, I will only get opioid prescriptions from my methadone prescriber and will not get any from other doctors or clinics.<input type="checkbox"/> For my safety, I give consent to my methadone prescriber to communicate with my pharmacist and any other physicians involved in my care, and to check my PharmaNet profile.<input type="checkbox"/> I will work with my methadone prescriber to develop a treatment plan and set goals. We will review them regularly and change as needed.<input type="checkbox"/> In addition to methadone, I can participate in counseling or peer-support groups and other programs as part of my treatment plan. My methadone prescriber will give me information about the options and programs available in my community.<input type="checkbox"/> I can expect confidentiality about my treatment from my doctor and other healthcare providers. My personal information will not be shared except with other healthcare providers as I agreed to above.<input type="checkbox"/> I can choose my clinic and pharmacy and can decide to change either if necessary.<input type="checkbox"/> I can decide if I want to continue, stop or change my treatment plan at any time. I agree to make this decision with my prescriber.<input type="checkbox"/> Beginning methadone treatment will require daily trips to the pharmacy and regular visits to my prescriber, which may impact my work, school or other responsibilities.<input type="checkbox"/> My prescriber may need to make changes to my treatment plan to provide the safest and best possible care. These changes might include dosage, how often I pick up my medication, how often I visit the clinic, and how often my urine is tested. Until I am stable, I will receive methadone through daily witnessed ingestion at a pharmacy or another healthcare provider.<input type="checkbox"/> Once I am stable, my prescriber will work with me to determine if take-home doses are appropriate.

Patient Agreement (continued)

- If I am interested in take home dosing, my prescriber will require that I have:
 - At least 12 weeks of urine drug tests with no sign of cocaine, amphetamine, or other drugs
 - No alcohol or benzodiazepine use that is considered by my prescriber as unsafe with methadone
 - At least 4 weeks of receiving a stable methadone dose
 - Stability in my life including no missed appointments or doses, improved relationships with family and/or friends, or returning to work or school
 - Ability to safely store methadone at home (i.e., secure, locked containers or cabinets)
 - No signs of illicit drug use during the last 12 weeks
- I will not give my prescriptions or medications to anyone else.
- I will not take my medication more often or at higher doses than my prescription states.
- I am the only person who may pick up my methadone prescription from the pharmacy.
- Missing more than two doses of methadone may cause a loss of tolerance and may require that I take a lower dose until I stabilize, for my safety.
- If I do not pick up my methadone from the pharmacy for three or more days in a row, my prescription will be cancelled until my prescriber has been told the reason for my missed doses. I will be restarted on a lower dose of methadone after multiple missed doses to prevent overdose.
- Like any prescribed medication, the pharmacy cannot replace my medication if it is lost or stolen. I cannot pick my medication up early from the pharmacy.
- I will not be cut off from treatment. If methadone is not providing the results expected, my prescriber will work with me to try other medications. If my prescriber can no longer provide care for me, they will refer me to another person who can.

I UNDERSTAND THAT I AM EXPECTED TO:

- Provide urine for drug testing on a regular basis.
- Provide urine samples at the clinic and that these samples are not to be altered. Urine samples that are cold or appear to have been altered will be treated as a serious issue and may affect my treatment plan and ability to receive take-home doses.
- Avoid using alcohol or other drugs, such as prescription or over the counter opioid medications, sleeping pills, or tranquilizers. I understand that combining these medications with methadone can lead to overdose and other serious harms and may affect my treatment plan and ability to receive take-home doses.
- Notify any health care provider that I receive care from that I am taking methadone.
- Do my best to keep appointments as scheduled. I understand that missing or skipping scheduled appointments may affect my treatment plan and ability to receive take-home doses.
- Treat others and be treated with respect. I understand that treating staff with disrespect for any reason is unacceptable and may lead to discharge from the program.
- Keep a Narcan (naloxone) kit on hand in case of overdose and receive training in how to use it.
- Notify my primary care provider if I become pregnant (if applicable)**
I understand that I must inform my prescriber if I am pregnant, suspect I may be pregnant, or if I am planning a pregnancy.

Patient Identified Goals

- _____
- _____
- _____
- _____

Prescriber Agreement

I confirm that:

- This form has been reviewed in detail with the patient and they understand its content fully. This should be reviewed again when the patient is not in withdrawal.
- The patient was given time to ask questions and seek clarification before signing this document.
- The evidence for other treatment options was reviewed, and the patient agrees to methadone.
- Information and resources to support psychosocial treatment interventions and supports will be provided to the patient.
- PharmaNet was reviewed to identify other prescribed medications, and will be checked at each subsequent appointment.
- It is my responsibility to decrease the possibility of diversion. If and when the patient is assessed as ready to receive take-home doses, guideline standards for random urine drug screens and medication checks will be pursued and clinical judgement used in an effort to limit risks of diversion.
- A treatment plan with clear goals was developed with the patient, and will be reviewed and documented regularly during treatment.

Consent

Patient's signature: _____ Date: _____

Prescriber's signature: _____ Date: _____

BUPRENORPHINE/NALOXONE TREATMENT AGREEMENT AND CONSENT FORM

Patient Information	
Surname: _____	Given name(s): _____
Date of birth: _____	PHN: _____

Patient Agreement
<p>I UNDERSTAND AND AGREE THAT:</p> <ul style="list-style-type: none"><input type="checkbox"/> I am being started/continued on:<ul style="list-style-type: none"><input type="checkbox"/> Buprenorphine/naloxone (often called Suboxone®) for the treatment of opioid addiction. While I may choose to taper off this treatment at any time, I understand that most patients benefit from at least one year of treatment or longer.<input type="checkbox"/> While I am receiving buprenorphine/naloxone treatment, I will only get opioid prescriptions from my buprenorphine/naloxone prescriber and will not get any from other doctors or clinics.<input type="checkbox"/> For my safety, I give consent to my buprenorphine/naloxone prescriber to communicate with my pharmacist and any other physicians involved in my care, and to check my PharmaNet profile.<input type="checkbox"/> I will work with my buprenorphine/naloxone prescriber to develop a treatment plan and set goals. We will review them regularly and change as needed.<input type="checkbox"/> In addition to buprenorphine/naloxone, I can participate in counselling or peer-support groups and other programs, as part of my treatment plan. My buprenorphine/naloxone prescriber will give me information about the options and programs available in my community.<input type="checkbox"/> I can expect confidentiality about my treatment from my doctor and other healthcare providers. My personal information will not be shared except with other healthcare providers as I agreed to above.<input type="checkbox"/> I can choose my clinic and pharmacy and can decide to change either if necessary.<input type="checkbox"/> I can decide if I want to continue, stop or change my treatment plan at any time. I agree to make this decision with my prescriber.<input type="checkbox"/> Beginning buprenorphine/naloxone treatment may require daily trips to the pharmacy and regular visits to my prescriber, which may impact my work, school or other responsibilities.<input type="checkbox"/> My prescriber may need to make changes to my treatment plan to provide the safest and best possible care. These changes might include dosage, how often I pick up my medication, how often I visit the clinic, and how often my urine is tested. Until I am stable, I will receive buprenorphine/naloxone through daily witnessed ingestion at a pharmacy or another healthcare provider.<input type="checkbox"/> Once I am stable, my prescriber will work with me to determine if take-home doses are appropriate.<input type="checkbox"/> I will not give my prescriptions or medications to anyone else.<input type="checkbox"/> I will not take my medication more often or at higher doses than my prescription states.<input type="checkbox"/> I am the only person who may pick up my buprenorphine/naloxone prescription from the pharmacy.<input type="checkbox"/> Missing more than one dose of buprenorphine/naloxone may lead to withdrawal, and missing more than 6 consecutive daily doses may cause a loss of tolerance to buprenorphine/naloxone, requiring that I take a lower dose until I stabilize.

Patient Agreement (continued)

- If I do not pick up my buprenorphine/naloxone from the pharmacy for 3 or more consecutive days, my prescription may be cancelled until my prescriber has been told the reason for my missed doses. I may receive a lower dose of buprenorphine/naloxone after multiple missed doses to prevent overdose.
- Like any prescribed medication, the pharmacy cannot replace my medication if it is lost or stolen. I cannot pick my medication up early from the pharmacy.
- I will not be cut off from treatment. If buprenorphine/naloxone is not providing the results expected, my prescriber will work with me to try other medications. If my prescriber can no longer provide care for me, they will refer me to another person who can.

I UNDERSTAND THAT I AM EXPECTED TO:

- Abstain from opioid use for 12-24 hours before I begin outpatient treatment with buprenorphine/naloxone, and that I will need to work with my doctor closely when first starting buprenorphine/naloxone. Those currently taking methadone may need to abstain longer than 72 hours.
- Provide urine for drug testing on a regular basis.
- Provide urine samples at the clinic and that these samples are not to be altered. Urine samples that are cold or appear to have been altered will be treated as a serious issue and may affect my treatment plan and ability to receive take-home doses.
- Avoid using alcohol or other drugs, such as prescription or over the counter opioid medications, sleeping pills, or tranquilizers. I understand that combining these medications with buprenorphine/naloxone can lead to overdose and other serious harms and may affect my treatment plan and ability to receive take-home doses.
- Notify any health care provider that I receive care from that I am taking buprenorphine/naloxone.
- Do my best to keep appointments as scheduled. I understand that missing or skipping scheduled appointments may affect my treatment plan and ability to receive take-home doses.
- Take my medication as prescribed. I understand that buprenorphine/naloxone contains naloxone which will cause immediate withdrawal if injected or snorted.
- Treat others and be treated with respect. I understand that treating staff with disrespect for any reason is unacceptable and may lead to discharge from the program.
- Keep a Narcan (naloxone) kit on hand in case of overdose and receive training in how to use it.
- Notify my primary care provider if I become pregnant (if applicable)**
I understand that for safety I must inform my prescriber if I am pregnant, suspect I may be pregnant, or if I am planning a pregnancy.

Patient Identified Goals

- _____
- _____
- _____
- _____

Prescriber Agreement

I confirm that:

- This form has been reviewed in detail with the patient and they understand its content fully. This should be reviewed again when the patient is not in withdrawal.
- The patient was given time to ask questions and seek clarification before signing this document.
- The evidence for other treatment options was reviewed, and the patient agrees to buprenorphine/naloxone.
- Information and resources to support psychosocial treatment interventions and supports will be provided to the patient.
- PharmaNet was reviewed to identify other prescribed medications, and will be checked at each subsequent appointment.
- It is my responsibility to decrease the possibility of diversion. If and when the patient is assessed as ready to receive take-home doses, guideline standards for random urine drug screens and medication checks will be pursued and clinical judgement used in an effort to limit risks of diversion.
- A treatment plan with clear goals was developed with the patient, and will be reviewed and documented regularly during treatment.

Consent

Patient's signature: _____ Date: _____

Prescriber's signature: _____ Date: _____

SLOW-RELEASE ORAL MORPHINE TREATMENT AGREEMENT AND CONSENT FORM

Patient Information	
Surname: _____	Given name(s): _____
Date of birth: _____	PHN: _____

Patient Agreement
<p>I UNDERSTAND AND AGREE THAT:</p> <ul style="list-style-type: none"><input type="checkbox"/> I am being started/continued on:<ul style="list-style-type: none"><input type="checkbox"/> Slow-release oral morphine for the treatment of opioid addiction. While I may choose to taper off this treatment at any time, I understand that most patients benefit from at least one year of treatment or longer.<input type="checkbox"/> Slow-release oral morphine was originally developed to treat pain, but, based on new research findings, is now also used outside of its currently approved indications (“off label”) to treat opioid addiction. I will be receiving medication “off label”.<input type="checkbox"/> While I am receiving slow-release oral morphine treatment, I will only get opioid prescriptions from my slow-release oral morphine prescriber and will not get any from other doctors or clinics.<input type="checkbox"/> For my safety, I give consent to my slow-release oral morphine prescriber to communicate with my pharmacist and any other physicians involved in my care, and to check my PharmaNet profile.<input type="checkbox"/> I will work with my slow-release oral morphine prescriber to develop a treatment plan and set goals. We will review them regularly and change as needed.<input type="checkbox"/> In addition to slow-release oral morphine, I can participate in counselling or peer-support groups and other programs as part of my treatment plan. My slow-release oral morphine prescriber will give me information about the different options and programs available in my community.<input type="checkbox"/> I can expect confidentiality about my treatment from my doctor and other healthcare providers. My personal information will not be shared except with other healthcare providers as I agreed to above.<input type="checkbox"/> I can choose my clinic and pharmacy and can decide to change either if necessary.<input type="checkbox"/> I can decide if I want to continue or stop treatment at any time. I agree to make this decision with my prescriber.<input type="checkbox"/> Beginning slow-release oral morphine treatment will require daily trips to the pharmacy and regular visits to my prescriber, which may impact my work, school or other responsibilities.<input type="checkbox"/> My prescriber may make changes to my treatment to provide the safest and best possible care. These changes might include dosage, how often I pick up my medication, how often I visit the clinic, and how often my urine is tested. Until I am stable, I will receive slow-release oral morphine through daily witnessed ingestion at a pharmacy or another healthcare provider.<input type="checkbox"/> Once I am stable, my prescriber will work with me to determine if take-home doses are appropriate. Generally, for individuals who want take-home dosing, alternative medications are more appropriate.<input type="checkbox"/> I will not give my prescriptions or medications to anyone else.<input type="checkbox"/> I will not take my medication more often or at higher doses than my prescription states.

Patient Agreement (continued)

- I am the only person who may pick up my slow-release oral morphine prescription from the pharmacy.
- Missing more than one dose of slow-release oral morphine may cause a loss of tolerance to slow-release oral morphine, requiring that I take a lower dose until I stabilize.
- If I do not attend the pharmacy and take my slow-release oral morphine for two or more consecutive days, my prescription will be cancelled until my prescriber has been told the reason for my missed doses. I may receive a lower dose of slow-release oral morphine after multiple missed doses to prevent overdose.
- Like any prescribed medication, the pharmacy cannot replace my medication if it is lost or stolen. I cannot pick my medication up early from the pharmacy.
- I will not be cut off from treatment. If slow-release oral morphine is not providing the results expected, my prescriber will work with me to try other medications. If my prescriber can no longer provide care for me, they will refer me to another person who can.

I UNDERSTAND THAT I AM EXPECTED TO:

- Provide urine for drug testing on a regular basis.
- Provide urine samples at the clinic and that these samples are not to be altered. Urine samples that are cold or appear to have been altered will be treated as a serious issue and may affect my treatment plan and ability to receive take-home doses.
- Take my medication as directed by the pharmacist. Attempting to “cheek” or hold medication in my mouth for use at a later time may require that I be switched to an alternative medication. This medication will be opened and sprinkled and the pharmacist will witness an open mouth to ensure the medication is taken.
- Avoid using alcohol or other drugs, such as prescription or over the counter opioid medications, sleeping pills, or tranquilizers. I understand that combining these medications with slow-release oral morphine can lead to overdose and other serious harms and may affect my treatment plan.
- Notify any health care provider that I receive care from that I am taking slow-release oral morphine to treat opioid addiction and they can talk to my prescriber if needed.
- Do my best to keep appointments as scheduled. I understand that missing or skipping scheduled appointments may affect my treatment plan and ability to receive take-home doses.
- Treat others and be treated with respect. I understand that treating staff with disrespect for any reason is unacceptable and may lead to discharge from the program.
- Keep a Narcan (naloxone) kit on hand in case of overdose and receive training in how to use it.
- Notify my primary care provider if I become pregnant (if applicable)**
I understand that I must inform my prescriber if I am pregnant, suspect I may be pregnant, or if I am planning a pregnancy.

Patient Identified Goals

- _____
- _____
- _____
- _____

Prescriber Agreement

I confirm that:

- This form has been reviewed in detail with the patient and they understand its content fully. This should be reviewed again when the patient is not in withdrawal.
- The patient was given ample time to ask questions and seek clarification before signing this document.
- The evidence for other treatment options was reviewed, and the patient agrees to slow-release oral morphine.
- Information and resources to support psychosocial treatment interventions and supports will be provided to the patient.
- PharmaNet was reviewed to identify other prescribed medications, and will be checked at each subsequent appointment.
- It is my responsibility to decrease the possibility of diversion. This includes phoning the pharmacy to confirm they can safely dispense slow release oral morphine by opening the gel cap and witnessing the swallowing of the granules with a sip of water. While this medication is generally limited to daily witnessed ingestion, if and when the patient is assessed as ready to receive take-home doses, guideline standards for random urine drug screens and medication checks will be pursued and clinical judgement used in an effort to limit risks of diversion.
- The need for close monitoring of this medication for adherence has been explained to the patient as standard of care, not on a per patient basis.
- A treatment plan with clear goals was developed with the patient, and will be reviewed and documented regularly during treatment.

Consent

Patient's signature: _____ Date: _____

Prescriber's signature: _____ Date: _____

PATIENT AGREEMENT FOR RECEIVING TAKE-HOME DOSING

In order to receive take-home doses of my medication, I, _____, agree to the following conditions to receive take-home (or “carry”) doses.

- I am aware that the accidental ingestion of even a small amount of my medication in a child or other person who is not a regular user could result in overdose or death.
- I will store my medication in a safe, locked location 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 provide a urine sample within 24 hours of being asked. If I do not provide a sample as requested, or illicit drugs are found in my sample, I may lose access to take-home doses.
- I will bring my medication to my clinic or pharmacy within 24 hours if asked to do so. If I do not, I may lose access to take-home doses and have to return to daily witnessed ingestion.
- I am aware that I need to always bring my medication to my medical appointments for assessment by clinic staff. If I do not do this as requested, my carry privileges will be re-evaluated and possibly revoked.
- I understand that I must be able to meet the above requirements to receive carry doses. If my situation changes and I can no longer meet them I may lose access to take-home doses.

Patient Signature: _____ Date: _____

Witness: _____

If applicable, I, _____, agree to share responsibility

(Name and relationship)

For ensuring the above person’s medication is taken as prescribed.

Witness: _____

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REFERENCES

- Grant BF, Saha TD, Ruan WJ, et al. Epidemiology of DSM-5 Drug Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry*. 2016;73(1):39-47.
- Office of the Chief Coroner, British Columbia Coroners Service. Fentanyl-Detected Illicit Drug Overdose Deaths, January 1, 2012 to February 28, 2017 [internet]. Available at: <http://www2.gov.bc.ca/assets/gov/public-safety-and-emergency-services/death-investigation/statistical/fentanyl-detected-overdose.pdf> [released April 19 2017, accessed May 5 2017].
- Nosyk B, Marsh DC, Sun H, Schechter MT, Anis AH. Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996–2006. *J Subst Abuse Treat*. 2010;39(1):22–31.
- Nosyk B, Joe RS, Krajden M, Tupper KW, Montaner JSG, Wood E. On the successes of the BC opioid substitution treatment system, and how we can build upon them. *BC Med J*. 2014;56(10):498–500.
- Office of the Provincial Health Officer, British Columbia Ministry of Health. BC Opioid Substitution Treatment System, Performance Measures 2013/2014. Released July 2015. Available at: <http://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/reports-publications/special-reports/bc-ost-system-measures-2013-2014.pdf>. Accessed 3 Jan 2017.
- AAP Committee on Substance Use and Prevention. Medication-Assisted Treatment of Adolescents With Opioid Use Disorders. *Pediatrics*. 2016;138(3):e20161893.
- College of Physicians and Surgeons of British Columbia. Methadone and Buprenorphine: Clinical Practice Guideline for Opioid Use Disorder. Released July 2016. Available at: <https://www.cpsbc.ca/files/pdf/MBMT-Clinical-Practice-Guideline.pdf>. Accessed 21 Jul 2016.
- Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182(18):E839–E842.
- Schünemann HJ, Al-Ansary LA, Forland F, et al. Guidelines international network: principles for disclosure of interests and management of conflicts in guidelines. *Ann Intern Med*. 2015;163(7):548–553.
- Guyatt Gordon H, Oxman Andrew D, Vist Gunn E, Kunz Regina, Falck-Ytter Yngve, Alonso-Coello Pablo et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924.
- Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2009(3).
- Gowing L, Farrell M, Ali R, White JM. Alpha₂-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2016(5).
- Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2013(2).
- MacArthur GJ, Minozzi S, Martin N, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. *BMJ*. 2012;345:e5945.
- 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.
- MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and hepatitis C in people who inject drugs: A review of reviews to assess evidence of effectiveness. *Int J Drug Policy*. 2014;25(1):34–52.
- Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2013;2:CD003409.
- Luty J. What works in drug addiction? *Adv Psychiatr Treat*. 2003;9:280–288.
- Wright NMJ, Sheard L, Adams CE, et al. Comparison of methadone and buprenorphine for opiate detoxification (LEEDS trial): a randomised controlled trial. *Brit J Gen Pract*. 2011;61(593):e772–780.
- Tennant FS, Russell BA, Casas SK, Bleich RN. Heroin detoxification — comparison of propoxyphene and methadone. *JAMA*. 1975;232(10):1019–1022.
- Kleber HD, Riordan CE, Rounsaville B, et al. Clonidine in outpatient detoxification from methadone-maintenance. *Arch Gen Psychiatry*. 1985;42(4):391–394.
- Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2009(3):CD002025.
- Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238–1246.
- Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 45. DHHS Publication No. (SMA) 06-4131. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2006.
- Day E, Ison J, Strang J. Inpatient versus other settings for detoxification for opioid dependence. *Cochrane Database Syst Rev*. 2005(2):CD004580.

26. Day E, Strang J. Outpatient versus inpatient opioid detoxification: A randomized controlled trial. *J Subst Abuse Treat.* 2011;40(1):56–66.
27. Sievewright, N. *Community Treatment of Drug Misuse: More Than Methadone.* Cambridge, UK: Press Syndicate of the University of Cambridge; 2000.
28. National Collaborating Centre for Mental Health (UK). *Drug Misuse: Opioid Detoxification.* Leicester (UK): British Psychological Society. Released 2008. (NICE Clinical Guidelines, No. 52.) 8, Settings for Opioid Detoxification. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK50626/>. Accessed 20 Nov 2016.
29. Merrall EL, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction.* 2010;105(9):1545–1554.
30. Simpson DD, Friend HJ. Legal status and long-term outcomes for addicts in the DARP followup project. *NIDA Res Monogr.* 1988;86:81–98.
31. Dettmer K, Saunders B, Strang J. Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. *BMJ.* 2001;322(7291):895–896.
32. Oluwajenyo Banjo M, Tzemis D, Al-Qutub D, Amlani A, Kesselring S, Buxton JA. A quantitative and qualitative evaluation of the British Columbia Take Home Naloxone program. *CMAJ Open.* 2014;2(3):E153–161.
33. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev.* 2011(9):CD005031.
34. Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med.* 2006;355(4):365–374.
35. Smyth BP, Barry J, Keenan E, Ducray K. Lapse and relapse following inpatient treatment of opiate dependence. *Ir Med J.* 2010;103(6):176–179.
36. Gossop M, Stewart D, Browne N, Marsden J. Factors associated with abstinence, lapse or relapse to heroin use after residential treatment: protective effect of coping responses. *Addiction.* 2002;97(10):1259–1267.
37. Stewart D, Gossop M, Marsden J, Strang J. Variation between and within drug treatment modalities: data from the National Treatment Outcome Research Study (UK). *Eur Addict Res.* 2000;6(3):106–114.
38. Gossop M, Marsden J, Stewart D, Rolfe A. Treatment retention and 1 year outcomes for residential programmes in England. *Drug Alcohol Depend.* 1999;57(2):89–98.
39. Hser YI, Evans E, Huang D, Anglin DM. Relationship between drug treatment services, retention, and outcomes. *Psychiatr Serv.* 2004;55(7):767–774.
40. Bale RN, Van Stone WW, Kuldau JM, Engelsing TM, Elashoff RM, Zarcone VP, Jr. Therapeutic communities vs methadone maintenance. A prospective controlled study of narcotic addiction treatment: design and one-year follow-up. *Arch Gen Psychiatry.* 1980;37(2):179–193.
41. Shorey RC, Stuart GL, Anderson S, Strong DR. Changes in early maladaptive schemas after residential treatment for substance use. *J Clin Psychol.* 2013;69(9):912–922.
42. Brigham GS, Slesnick N, Winhusen TM, Lewis DF, Guo X, Somoza E. A randomized pilot clinical trial to evaluate the efficacy of Community Reinforcement and Family Training for Treatment Retention (CRAFT-T) for improving outcomes for patients completing opioid detoxification. *Drug Alcohol Depend.* 2014;138:240–243.
43. Stewart D, Gossop M, Marsden J. Reductions in non-fatal overdose after drug misuse treatment: results from the National Treatment Outcome Research Study (NTORS). *J Subst Abuse Treat.* 2002;22(1):1–9.
44. Pierce M, Bird SM, Hickman M, et al. Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England. *Addiction.* 2016;111(2):298–308.
45. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev.* 2009(3):CD002209.
46. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *Cochrane Database Syst Rev.* 2003(3):CD002208.
47. Nosyk B, MacNab YC, Sun H, et al. Proportional hazards frailty models for recurrent methadone maintenance treatment. *Am J Epidemiol.* 2009;170(6):783–792.
48. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet.* 2002;41(14):1153–1193.
49. Donny EC, Walsh SL, Bigelow GE, Eissenberg T, Stitzer ML. High-dose methadone produces superior opioid blockade and comparable withdrawal suppression to lower doses in opioid-dependent humans. *Psychopharmacology (Berl).* 2002;161(2):202–212.
50. Leavitt SB, Shinderman M, Maxwell S, Eap CB, Paris P. When “enough” is not enough: new perspectives on optimal methadone maintenance dose. *Mt Sinai J Med.* 2000;67(5–6):404–411.
51. van Ameijden EJC, Langendam MW, Coutinho RA. Dose-effect relationship between overdose mortality and prescribed methadone dosage in low-threshold maintenance programs. *Addict Behav.* 1999;24(4):559–563.
52. Liao DL, Chen PC, Chen CH, et al. Higher methadone doses are associated with lower mortality in patients of opioid dependence in Taiwan. *J Psychiatr Res.* 2013;47(10):1530–1534.

53. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database Syst Rev*. 2011(8):CD004145.
54. Nolan S, Dias Lima V, Fairbairn N, et al. The impact of methadone maintenance therapy on hepatitis C incidence among illicit drug users. *Addiction*. 2014;109(12):2053–2059.
55. Palepu A, Tyndall MW, Joy R, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. *Drug Alcohol Depend*. 2006;84(2):188–194.
56. Lappalainen L, Nolan S, Dobrer S, et al. Dose-response relationship between methadone dose and adherence to antiretroviral therapy among HIV-positive people who use illicit opioids. *Addiction*. 2015;110(8):1330–1339.
57. Joseph B, Kerr T, Puskas CM, Montaner J, Wood E, Milloy MJ. Factors linked to transitions in adherence to antiretroviral therapy among HIV-infected illicit drug users in a Canadian setting. *AIDS Care*. 2015;1–9.
58. Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Med*. 2011;12 Suppl 2:s26–35.
59. Gladstone EJ, Smolina K, Morgan SG. Trends and sex differences in prescription opioid deaths in British Columbia, Canada. *Inj Prev*. 2016;22(4):288–90.
60. Jones CM, Baldwin GT, Manocchio T, White JO, Mack KA. Trends in Methadone Distribution for Pain Treatment, Methadone Diversion, and Overdose Deaths — United States, 2002–2014. *MMWR Morb Mortal Wkly Rep*. 2016;65(26):667–671.
61. Tjagvad C, Skurtveit S, Linnet K, Andersen LV, Christoffersen DJ, Clausen T. Methadone-Related Overdose Deaths in a Liberal Opioid Maintenance Treatment Programme. *Eur Addict Res*. 2016;22(5):249–258.
62. Duffy P, Mackridge AJ. Use and diversion of illicit methadone — under what circumstances does it occur, and potential risks associated with continued use of other substances. *J Subst Abuse*. 2014;19(1–2):48–55.
63. Strang J, Hall W, Hickman M, Bird SM. Impact of supervision of methadone consumption on deaths related to methadone overdose (1993–2008): analyses using OD4 index in England and Scotland. *BMJ*. 2010; 341:c4851.
64. Peles E, Schreiber S, Adelson M. 15-Year survival and retention of patients in a general hospital-affiliated methadone maintenance treatment (MMT) center in Israel. *Drug Alcohol Depend*. 2010;107(2–3):141–148.
65. McNeil R, Kerr T, Anderson S, et al. Negotiating structural vulnerability following regulatory changes to a provincial methadone program in Vancouver, Canada: a qualitative study. *Soc Sci Med*. 2015;133:168–176.
66. Greer AM, Hu S, Amlani A, Moreheart S, Sampson O, Buxton JA. Patient perspectives of methadone formulation change in British Columbia, Canada: outcomes of a provincial survey. *Subst Abuse Treat Prev Policy*. 2016;11:3.
67. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;2:CD002207.
68. Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. *Cochrane Database Syst Rev*. 2016;5:CD011117.
69. Maremmani I, Gerra G. Buprenorphine-based regimens and methadone for the medical management of opioid dependence: selecting the appropriate drug for treatment. *Am J Addict*. 2010;19(6):557–568.
70. Marteau D, McDonald R, Patel K. The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. *BMJ Open*. 2015;5(5):e007629.
71. Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug Alcohol Depend*. 2009;104(1–2):73–77.
72. Luty J, O’Gara C, Sessay M. Is methadone too dangerous for opiate addiction? *BMJ*. 2005;331(7529):1352–1353.
73. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *BMJ*. 2010;341:c5475.
74. Baxter LE, Sr., Campbell A, Deshields M, et al. Safe methadone induction and stabilization: report of an expert panel. *J Addict Med*. 2013;7(6):377–386.
75. Chou R, Weimer MB, Dana T. Methadone overdose and cardiac arrhythmia potential: findings from a review of the evidence for an American Pain Society and College on Problems of Drug Dependence clinical practice guideline. *J Pain*. 2014;15(4):338–365.
76. Breen CL, Harris SJ, Lintzeris N, et al. Cessation of methadone maintenance treatment using buprenorphine: transfer from methadone to buprenorphine and subsequent buprenorphine reductions. *Drug Alcohol Depend*. 2003;71(1):49–55.
77. Walsh SL, June HL, Schuh KJ, Preston KL, Bigelow GE, Stitzer ML. Effects of buprenorphine and methadone in methadone-maintained subjects. *Psychopharmacology (Berl)*. 1995;119(3):268–276.
78. Brondani M, Park PE. Methadone and oral health — a brief review. *J Dent Hyg*. 2011;85(2):92–98.
79. Robinson PG, Acquah S, Gibson B. Drug users: oral health-related attitudes and behaviours. *Brit Dent J*. 2005;198(4):219–224.

80. D'Amore MM, Cheng DM, Kressin NR, et al. Oral health of substance-dependent individuals: Impact of specific substances. *J Subst Abuse Treat.* 2011;41(2):179–185.
81. Titsas A, Ferguson MM. Impact of opioid use on dentistry. *Aust Dent J.* 2002;47(2):94–98.
82. Winocur E, Gavish A, Volfin G, Halachmi M, Gazit E. Oral motor parafunctions among heavy drug addicts and their effects on signs and symptoms of temporomandibular disorders. *J Orofac Pain.* 2001;15(1):56–63.
83. Nathwani NS, Gallagher JE. Methadone: dental risks and preventive action. *Dent Update.* 2008;35(8):542–544, 547–548.
84. Suzuki J, Mittal L, Woo SB. Sublingual buprenorphine and dental problems: a case series. *Prim Care Companion CNS Disord.* 2013;15(5):PCC.13101533.
85. Rosado J, Walsh SL, Bigelow GE, Strain EC. Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100mg of daily methadone. *Drug Alcohol Depend.* 2007;90(2–3):261–269.
86. Castells X, Kosten TR, Capella D, Vidal X, Colom J, Casas M. Efficacy of opiate maintenance therapy and adjunctive interventions for opioid dependence with comorbid cocaine use disorders: A systematic review and meta-analysis of controlled clinical trials. *Am J Drug Alcohol Abuse.* 2009;35(5):339–349.
87. CADTH Rapid Response Reports. Suboxone versus Methadone for the Treatment of Opioid Dependence: A Review of the Clinical and Cost-effectiveness. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 2013.
88. Iwersen-Bergmann S, Jungen H, Andresen-Streichert H, et al. Intravenous methadone application as a serious risk factor for an overdose death: methadone-related fatalities in Hamburg from 2007 to 2012. *Int J Legal Med.* 2014;128(5):751–764.
89. Heinemann A, Iwersen-Bergmann S, Stein S, Schmoltdt A, Puschel K. Methadone-related fatalities in Hamburg 1990–1999: implications for quality standards in maintenance treatment? *Forensic Sci Int.* 2000;113(1–3):449–455.
90. Soyka M, Penning R, Wittchen U. Fatal poisoning in methadone and buprenorphine treated patients — are there differences? *Pharmacopsychiatry.* 2006;39(3):85–87.
91. Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in France. *JAMA.* 2001;285(1):45.
92. Gerra G, Borella F, Zaimovic A, et al. Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. *Drug Alcohol Depend.* 2004;75(1):37–45.
93. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med.* 2000;343(18):1290–1297.
94. Bawor M, Dennis BB, Anglin R, Steiner M, Thabane L, Samaan Z. Sex differences in outcomes of methadone maintenance treatment for opioid addiction: a systematic review protocol. *Syst Rev.* 2014;3:45.
95. Health Canada and Express Scripts Canada. NIHB Newsletter (Fall 2014): 1–4. Non-Insured Health Benefits (NIHB) Program. Released Fall 2014. Available at: [http://health.chiefs-of-ontario.org/sites/default/files/files/Health Canada NIHB Pharmacy Newsletter Fall 2014.pdf](http://health.chiefs-of-ontario.org/sites/default/files/files/Health%20Canada%20NIHB%20Pharmacy%20Newsletter%20Fall%202014.pdf). Accessed 13 Jan 2015.
96. Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database Syst Rev.* 2013(6):CD009879.
97. Hammig R, Kohler W, Bonorden-Kleij K, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat.* 2014;47(4):275–281.
98. Mitchell TB, White JM, Somogyi AA, Bochner F. Slow-release oral morphine versus methadone: a crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapies for opioid dependence. *Addiction.* 2004;99(8):940–945.
99. Verthein U, Beck T, Haasen C, Reimer J. Mental Symptoms and Drug Use in Maintenance Treatment with Slow-Release Oral Morphine Compared to Methadone: Results of a Randomized Crossover Study. *Eur Addict Res.* 2015;21(2):97–104.
100. Falcato L, Beck T, Reimer J, Verthein U. Self-Reported Cravings for Heroin and Cocaine During Maintenance Treatment With Slow-Release Oral Morphine Compared With Methadone A Randomized, Crossover Clinical Trial. *J Clin Psychopharmacol.* 2015;35(2):150–157.
101. Kastelic A, Dubajic G, Strbad E. Slow-release oral morphine for maintenance treatment of opioid addicts intolerant to methadone or with inadequate withdrawal suppression. *Addiction.* 2008;103(11):1837–1846.
102. Sullivan MA, Bisaga A, Mariani JJ, et al. Naltrexone treatment for opioid dependence: does its effectiveness depend on testing the blockade? *Drug Alcohol Depend.* 2013;133(1):80–85.
103. Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. *Curr Psychiatry Rep.* 2010;12(5):448–453.
104. Gibson AE, Degenhardt LJ. Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. *Drug Alcohol Rev.* 2007;26(4):405–410.
105. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev.* 2011(2):CD001333.

106. Krupitsky E, Zvartau E, Blokhina E, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. *Arch Gen Psychiatry*. 2012;69(9):973–981.
107. Substance Abuse and Mental Health Services Administration. Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder: A Brief Guide. HHS Publication No. (SMA) 14–4892R. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015.
108. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2006;63(2):210–218.
109. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet*. 2011;377(9776):1506–1513.
110. Krupitsky EM, Blokhina EA. Long-acting depot formulations of naltrexone for heroin dependence: a review. *Curr Opin Psychiatry*. 2010;23(3):210–214.
111. Krupitsky E, Nunes EV, Ling W, Gastfriend DR, Memisoglu A, Silverman BL. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. *Addiction*. 2013;108(9):1628–1637.
112. Ahamad K, Milloy MJ, Nguyen P, et al. Factors associated with willingness to take extended release naltrexone among injection drug users. *Addict Sci Clin Pract*. 2015;10:12.
113. Strang J, Groshkova T, Uchtenhagen A, et al. Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction. *Br J Psychiatry*. 2015;207(1):5–14.
114. Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database Syst Rev*. 2011(12):CD003410.
115. Oviedo-Joekes E, Guh D, Brissette S, et al. Hydromorphone Compared With Diacetylmorphine for Long-term Opioid Dependence A Randomized Clinical Trial. *JAMA Psychiatry*. 2016;73(5):447–455.
116. Sorensen JL, Andrews S, Delucchi KL, et al. Methadone patients in the therapeutic community: A test of equivalency. *Drug Alcohol Depend*. 2009;100(1–2):100–106.
117. Chen T, Masson CL, Sorensen JL, Greenberg B. Residential Treatment Modifications: Adjunctive Services to Accommodate Clients on Methadone. *Am J Drug Alcohol Abuse*. 2009;35(2):91–94.
118. Greenberg B, Hall DH, Sorensen JL. Methadone maintenance therapy in residential therapeutic community settings: Challenges and promise. *J Psychoactive Drugs*. 2007;39(3):203–210.
119. Roozen HG, Boulogne JJ, van Tulder MW, van den Brink W, De Jong CA, Kerkhof AJ. A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. *Drug Alcohol Depend*. 2004;74(1):1–13.
120. Volkow ND, Li TK. Drug addiction: the neurobiology of behaviour gone awry. *Nat Rev Neurosci*. 2004;5(12):963–970.
121. McCance-Katz EF, Jatlow P, Rainey PM. Effect of cocaine use on methadone pharmacokinetics in humans. *Am J Addict*. 2010;19(1):47–52.
122. Mannelli P, Peindl KS, Lee T, Bhatia KS, Wu LT. Buprenorphine-mediated transition from opioid agonist to antagonist treatment: state of the art and new perspectives. *Curr Drug Abuse Rev*. 2012;5(1):52–63.
123. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.
124. Harris AH, Gospodarevskaya E, Ritter AJ. A randomised trial of the cost effectiveness of buprenorphine as an alternative to methadone maintenance treatment for heroin dependence in a primary care setting. *Pharmacoeconomics*. 2005;23(1):77–91.
125. Kakko J, Gronbladh L, Svanborg KD, et al. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial. *Am J Psychiatry*. 2007;164(5):797–803.
126. Nosyk B, Sun H, Evans E, et al. Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study. *Addiction*. 2012;107(9):1621–1629.
127. Kornor H, Waal H. From opioid maintenance to abstinence: a literature review. *Drug Alcohol Rev*. 2005;24(3):267–274.
128. Rieb LM, Norman WV, Martin RE, et al. Withdrawal-associated injury site pain (WISP): A descriptive case series of an opioid cessation phenomenon. *Pain*. 2016.
129. Grant BF, Saha TD, Ruan WJ, et al. Epidemiology of DSM-5 Drug Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry*. 2016;73(1):39–47.
130. Arthur E, Seymour A, Dartnall M, et al. Trauma-Informed Practice Guide. Released May 2013. Vancouver, BC: BC Centre of Excellence in Women's Health. Available at: http://bcccewh.bc.ca/wp-content/uploads/2012/05/2013_TIP-Guide.pdf. Accessed 4 Sept 2016.
131. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus

- agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev*. 2011(10):CD004147.
132. Ling W, Hillhouse M, Ang A, Jenkins J, Fahey J. Comparison of behavioral treatment conditions in buprenorphine maintenance. *Addiction*. 2013;108(10):1788–1798.
 133. Schwartz RP, Kelly SM, O'Grady KE, Gandhi D, Jaffe JH. Interim methadone treatment compared to standard methadone treatment: 4-month findings. *J Subst Abuse Treat*. 2011;41(1):21–29.
 134. Goldner EM, Lusted A, Roerecke M, Rehm J, Fischer B. Prevalence of Axis-1 psychiatric (with focus on depression and anxiety) disorder and symptomatology among non-medical prescription opioid users in substance use treatment: systematic review and meta-analyses. *Addict Behav*. 2014;39(3):520–531.
 135. Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA*. 2012;307(9):940–947.
 136. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006;166(19):2087–2093.
 137. Martin GW, Rehm J. The effectiveness of psychosocial modalities in the treatment of alcohol problems in adults: a review of the evidence. *Can J Psychiat*. 2012;57(6):350–358.
 138. Tiet QQ, Mausbach B. Treatments for patients with dual diagnosis: a review. *Alcohol Clin Exp Res*. 2007;31(4):513–536.
 139. Hunt GE, Siegfried N, Morley K, Sitharhan T, Cleary M. Psychosocial interventions for people with both severe mental illness and substance misuse. *Cochrane Database Syst Rev*. 2013;10:CD001088.
 140. Magill M, Ray LA. Cognitive-behavioral treatment with adult alcohol and illicit drug users: A meta-analysis of randomized controlled trials. *Stud Alcohol Drugs*. 2009;70(4):516–527.
 141. Roberts NP, Roberts PA, Jones N, Bisson JJ. Psychological therapies for post-traumatic stress disorder and comorbid substance use disorder. *Cochrane Database Syst Rev*. 2016;4:CD010204.
 142. Appel PW, Tsemberis S, Joseph H, Stefancic A, Lambert-Wacey D. Housing First for severely mentally ill homeless methadone patients. *J Addict Dis*. 2012;31(3):270–277.
 143. Strathdee SA, Patrick DM, Currie SL, et al. Needle exchange is not enough: lessons from the Vancouver injecting drug use study. *AIDS*. 1997;11(8):F59–F65.
 144. Jackson LA, Buxton JA, Dingwell J, et al. Improving psychosocial health and employment outcomes for individuals receiving methadone treatment: a realist synthesis of what makes interventions work. *Bmc Psychol*. 2014;2(1):26.
 145. Weiss RD, Griffin ML, Gallop RJ, et al. The effect of 12-step self-help group attendance and participation on drug use outcomes among cocaine-dependent patients. *Drug Alcohol Depend*. 2005;77(2):177–184.
 146. Toumbourou JW, Hamilton M, U'Ren A, Stevens-Jones P, Storey G. Narcotics Anonymous participation and changes in substance use and social support. *J Subst Abuse Treat*. 2002;23(1):61–66.
 147. Fiorentine R, Hillhouse MP. Drug treatment and 12-step program participation: the additive effects of integrated recovery activities. *J Subst Abuse Treat*. 2000;18(1):65–74.
 148. Suzuki J, Dodds T. Clinician recommendation of 12-step meeting attendance and discussion regarding disclosure of buprenorphine use among patients in office-based opioid treatment. *Subst Abuse*. 2016;37(1):31–34.
 149. Davoli M, Amato L, Clark N, et al. The role of Cochrane reviews in informing international guidelines: a case study of using the Grading of Recommendations, Assessment, Development and Evaluation system to develop World Health Organization guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. *Addiction*. 2015;110(6):891–898.
 150. Harm Reduction International. What is harm reduction? A position statement from Harm Reduction International. Available at: <https://www.hri.global/what-is-harm-reduction>. Accessed 28 Sept 2016.
 151. Gatewood AK, Van Wert MJ, Andrada AP, Surkan PJ. Academic physicians' and medical students' perceived barriers toward bystander administered naloxone as an overdose prevention strategy. *Addict Behav*. 2016;61:40–46.
 152. Binswanger IA, Koester S, Mueller SR, Gardner EM, Goddard K, Glanz JM. Overdose Education and Naloxone for Patients Prescribed Opioids in Primary Care: A Qualitative Study of Primary Care Staff. *J Gen Intern Med*. 2015;30(12):1837–1844.
 153. Tobin KE, Gaasch WR, Clarke C, MacKenzie E, Latkin CA. Attitudes of emergency medical service providers toward naloxone distribution programs. *J Urban Health*. 2005;82(2):296–302.
 154. Bazazi AR, Zaller ND, Fu JJ, Rich JD. Preventing Opiate Overdose Deaths: Examining Objections to Take-Home Naloxone. *J Health Care Poor Underserved*. 2010;21(4):1108–1113.
 155. Hyshka E, Strathdee S, Wood E, Kerr T. Needle exchange and the HIV epidemic in Vancouver: lessons learned from 15 years of research. *Int J Drug Policy*. 2012;23(4):261–270.
 156. Wood E, Tyndall MW, Montaner JS, Kerr T. Summary of findings from the evaluation of a pilot medically supervised safer injecting facility. *CMAJ*. 2006;175(11):1399–1404.

157. Doe-Simkins M, Quinn E, Xuan ZM, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. *BMC*. 2014;14.
158. Werb D, Kerr T, Buxton J, et al. Patterns of injection drug use cessation during an expansion of syringe exchange services in a Canadian setting. *Drug Alcohol Depend*. 2013;132(3):535–540.
159. Marshall BDL, Milloy MJ, Wood E, Montaner JSG, Kerr T. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. *Lancet*. 2011;377(9775):1429–1437.
160. Walley AY, Xuan ZM, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013;346.
161. Milloy MJ, Kerr T, Tyndall M, Montaner J, Wood E. Estimated drug overdose deaths averted by North America's first medically-supervised safer injection facility. *PLoS One*. 2008;3(10):e3351.
162. Salmon AM, van Beek I, Amin J, Kaldor J, Maher L. The impact of a supervised injecting facility on ambulance call-outs in Sydney, Australia. *Addiction*. 2010;105(4):676–683.
163. Turner KME, Hutchinson S, Vickerman P, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction*. 2011;106(11):1978–1988.
164. Potier C, Laprevote V, Dubois-Arber F, Cottencin O, Rolland B. Supervised injection services: what has been demonstrated? A systematic literature review. *Drug Alcohol Depend*. 2014;145:48–68.
165. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*. 2016;111(7):1177–1187.
166. DeBeck K, Kerr T, Bird L, et al. Injection drug use cessation and use of North America's first medically supervised safer injecting facility. *Drug Alcohol Depend*. 2011;113(2–3):172–176.
167. Small W, Van Borek N, Fairbairn N, Wood E, Kerr T. Access to health and social services for IDU: The impact of a medically supervised injection facility. *Drug Alcohol Rev*. 2009;28(4):341–346.
168. Strathdee SA, Celentano DD, Shah N, et al. Needle-exchange attendance and health care utilization promote entry into detoxification. *J Urban Health*. 1999;76(4):448–460.
169. Wood E, Tyndall MW, Zhang R, Montaner JSG, Kerr T. Rate of detoxification service use and its impact among a cohort of supervised injecting facility users. *Addiction*. 2007;102(6):916–919.
170. British Columbia Medical Association. Stepping Forward: Improving Addiction Care in British Columbia. Released Mar 2009. Available at: https://www.doctorsofbc.ca/sites/default/files/addiction_stepping_forward.pdf. Accessed 3 Jan 2017.
171. Proctor SL, Copeland AL, Kopak AM, Herschman PL, Polukhina N. A naturalistic comparison of the effectiveness of methadone and two sublingual formulations of buprenorphine on maintenance treatment outcomes: findings from a retrospective multisite study. *Exp Clin Psychopharmacol*. 2014;22(5):424–433.
172. Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database Syst Rev*. 2013;6:CD009879.
173. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend*. 2009;105(1–2):9–15.