



a Guideline for the
Clinical Management of

Opioid Addiction

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Vancouver Coastal Health & Providence Health Care Opioid Use Disorder

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CONFLICTS OF INTEREST

None of the committee members had conflicts of interest to declare.

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From Grief to Action Board Members

BC Association of People on Methadone (BCAPOM) Board Members, shared for feedback on August 20, 2015

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Executive summary

Opioid use disorder is one of the most challenging forms of addiction facing the health care system in British Columbia. Despite an excellent guideline by the College of Physicians and Surgeons of British Columbia regarding the safe use of methadone maintenance treatment (MMT), there remains a need for an evidence-based guideline articulating the full range of therapeutic options for the optimal treatment of adults and young adults with varying presentations of opioid use disorder. This lack of a comprehensive guideline has been a challenge for Vancouver Coastal Health (VCH) and the provincial health system, and has resulted in a lack of awareness and use of the full armamentarium of medical and psychosocial treatments available for managing opioid dependence among health care providers in substance use services and the addiction care continuum.

To address this, an interdisciplinary committee comprising individuals from VCH, Providence Health Care and the Ministry of Health developed the following expert guidelines. These guidelines were subsequently peer-reviewed by patient groups, local and international experts in the field. The recommendations in these guidelines are based on a systematic review and use of a traditional hierarchy of evidence whereby meta-analysis of randomized clinical trials was given the most weight, followed by individual clinical trials, observational reports and expert opinion.

While this guideline supports the diversity of possible treatments available for individuals presenting with opioid use disorder, it strongly recommends against a strategy involving only withdrawal management (often referred to as “detox”), since this approach has been associated with elevated rates of infections such as HIV and hepatitis C, 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 treatment. However, this guideline 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 initially pursue pharmacological treatment for opioid dependence, but may still wish to use other various pharmacotherapies for symptom management during withdrawal. In addition, this guideline strongly endorses the use of buprenorphine/naloxone as a preferred first-line treatment when opioid substitution pharmacotherapy is being considered for the treatment of opioid use disorder and contraindications have been ruled out. This recommendation is in line with the growing body of research suggesting that buprenorphine has a six times greater safety profile than methadone in terms of overdose risk, in addition to other comparative advantages. Notably, methadone has recently been reported to be involved in approximately 25% of prescription-opioid-related deaths in British Columbia. However, this guideline also endorses the use of methadone as a first-line therapy when pharmacotherapy is 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-line or second-line treatment approaches, this guideline also reviews the international evidence regarding the use of alternative pharmacotherapies for the treatment of opioid use disorder, including long-acting oral morphine as well as injectable opioid medications that must be provided via witnessed injection in a structured and supervised setting.

Finally, this guideline recognizes that most individuals will benefit from the ability to move between treatments, depending on the individual's initial presentation, comorbidities, treatment preferences and response to treatment. This includes intensification (e.g., initiating a 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) when patients are effectively treated and wish to transition to treatments that allow for more flexible take-home dosing (e.g., buprenorphine/naloxone).

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 improve systems of treatment for opioid use disorder and significantly reduce the burden of disease and health and social service costs associated with untreated opioid addiction. In order to address these costs, while recognizing the finite funding available for health services, prioritization and proportionate funding should be reasonably allocated toward the recommendations laid out in this guideline.

Summary of recommendations

Recommendation	Quality of evidence*	Strength of recommendation*	For more information see page...
<i>Approaches to avoid</i>			
Withdrawal management alone (i.e., detox without transition to longer term treatment) is not recommended, since this approach has been associated with elevated rates of HIV infection and overdose death.	⊕⊕⊕ Moderate	Strong	6
<i>Possible first-line treatment options</i>			
Initiate opioid agonist treatment with buprenorphine/naloxone whenever feasible to reduce toxicities and facilitate safer take home dosing.	⊕⊕⊕⊕ High	Strong	10
Initiate opioid agonist treatment with methadone when treatment with buprenorphine/naloxone is not preferable (e.g., challenging induction, high risk for drop-out).	⊕⊕⊕⊕ High	Strong	9
When opioid withdrawal is being medically supervised, this can generally be safely done on an outpatient rather than inpatient basis but should include ongoing addiction treatment.	⊕⊕⊕ Moderate	Strong	6–7
<i>Adjunct or alternative treatment options</i>			
For individuals responding poorly to buprenorphine/naloxone, transition to methadone.	⊕⊕⊕⊕ High	Strong	14
For individuals with successful and sustained response to methadone desiring treatment simplification, consider transition to buprenorphine/naloxone.	⊕⊕⊕ Moderate	Strong	14
For individuals with successful and sustained response to agonist treatment desiring medication cessation, consider slow taper over 12 months.	⊕⊕⊕ Moderate	Strong	6
Psychosocial supports may be routinely offered in conjunction with pharmacological treatment.	⊕⊕⊕ Moderate	Conditional	16
For patients wishing to avoid initial treatment with an opioid agonist therapy, provide outpatient opioid agonist taper (preferably methadone or buprenorphine/naloxone), with subsequent immediate referral to intensive outpatient or residential addiction treatment. Oral naltrexone can be considered as an adjunct in this context.	⊕⊕ Low	Weak	6, 14

* 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, conditional, weak).¹

Introduction

While Canadian estimates are lacking, opioid use disorder is estimated to affect approximately 1.4% of Americans.² Opioid use disorder may involve the use of illicitly obtained opioids (e.g., heroin) or, increasingly, diverted or misused prescription opioid medications. As a result, opioid use disorder is often a chronic illness associated with elevated rates of morbidity and mortality.

British Columbia has benefited from a well established methadone maintenance program stewarded by the College of Physicians and Surgeons of British Columbia.^{3,4} The Methadone Maintenance Committee, which oversees the methadone maintenance program, has developed an expert guideline for the use of methadone maintenance treatment that is periodically updated and is an excellent resource for physicians wishing to prescribe methadone for opioid use disorder.⁵

However, in recent years, a number of additional opioid agonist treatment options have emerged for the treatment of opioid addiction. Coinciding with this, evidence-based reviews have increasingly described the benefits, side-effect profiles and safety concerns surrounding the various approaches to the treatment of opioid use disorder. This literature, which is reviewed in detail below, enables the development of strategies for the treatment of opioid use disorder that employ different approaches based on individual patient circumstances and comorbidities and recognize that treatment can be intensified or simplified depending on short- and long-term response to treatment.

To address the health care needs within the vch catchment area, and to best address the needs of patients with opioid use disorder in an evidence-based, cost-effective way, an expert panel was convened by vch to discuss this literature and propose a guideline for vch with respect to the optimal treatment and care of individuals with opioid addiction. What follows is a description of the literature supporting these recommendations and ultimately a description of the treatment pathways being recommended by this panel for use by health care providers across vch. These guidelines relate to the clinical management of established opioid addiction among adults and youth with opioid use disorder,⁶ while treatment options for specialized populations affected by opioid use disorder (e.g., pregnant women) are beyond the scope of this guideline.

Guideline development

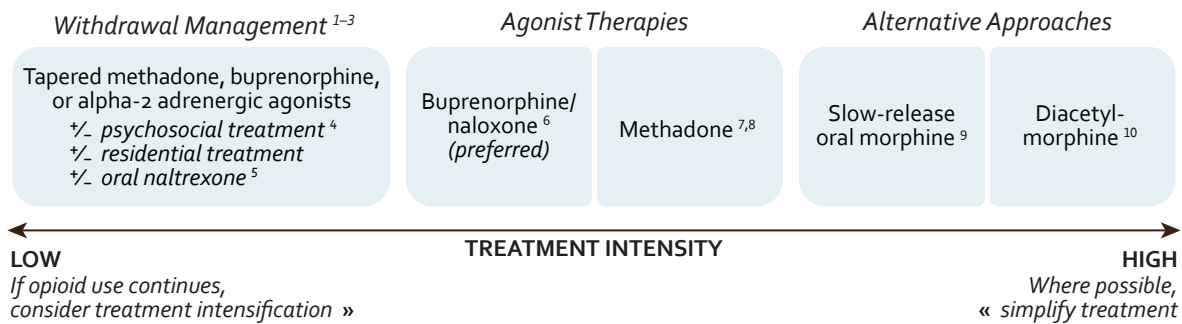
The recommendations in these guidelines are based on a systematic review and use of a traditional hierarchy of evidence whereby meta-analysis of randomized clinical trials was given the most weight, followed by individual clinical trials, observational reports and expert opinion. In addition, the literature reviewed in this guideline was summarized as per the criteria set out by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group,¹ which is a system that has been applied to high-level guideline and systematic review development processes, including all policies and guidelines developed by the World Health Organization.⁷ The GRADE system takes into consideration both the quality of evidence (high, moderate, low or very low, with quality determined by both study design and other important factors such as weighing risks versus benefits, likelihood of bias, or limited or inconsistent results) and the strength of recommendation (strong, conditional, or weak). All members of the vch Opioid Use Disorder Treatment Guideline Committee reviewed and reached a majority agreement on the guidelines and recommendations after several rounds of revision.

Possible treatment approaches

Possible treatment options considered included: withdrawal management from opioid drugs and an outpatient or residential treatment referral; opioid agonist therapy, particularly with methadone, buprenorphine/naloxone or other agonists; and opioid antagonist medications such as naltrexone. The guideline also considered the research regarding the integration of psychosocial treatments and supports for opioid use disorder. Although evidence presented here is generally extrapolated from studies conducted in adult populations, with this caveat, the consensus of the committee is that recommendations are relevant and applicable to adult and young adult populations.

Literature review

TABLE 1. TREATMENT OPTIONS FOR OPIOID USE DISORDER



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I Withdrawal management* strategies

ALPHA-2 ADRENERGIC AGONISTS

Compared to placebo, alpha-2 adrenergic agonists (e.g., clonidine) have been found to be effective for opioid withdrawal management in terms of a lesser likelihood of severe withdrawal symptoms and higher probability of completing treatment.⁸

Signs and symptoms of withdrawal appear to both occur and resolve earlier with alpha-2 adrenergic agonists. The chances of completing treatment of withdrawal are similar between alpha-2 adrenergic agonists and methadone, but alpha-2 adrenergic agonists tend to require shorter treatment durations. However, compared to methadone tapers, alpha-2 adrenergic agonists are somewhat less effective in mitigating withdrawal symptoms, and are more likely to present adverse effects such as hypotension.⁸

The majority of patients still relapse to opioid use if a strategy involving only withdrawal management is employed.

AGONIST TAPER – METHADONE⁹

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.¹⁰

Methadone at tapered doses does not appear to differ from other pharmacological treatments (e.g., adrenergic agonists, other opioid agonists) in terms of treatment completion, sustained abstinence, severity of withdrawal symptoms, or adverse effects. Compared to placebo, tapered methadone appears to be associated with less severe withdrawal symptoms and lower rates of drop-out.⁹

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).⁹

AGONIST TAPER – BUPRENORPHINE/NALOXONE¹¹

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. For instance, patients in the Prescription Opioid Addiction Treatment Study demonstrated significantly lower sustained abstinence rates eight weeks after tapering off buprenorphine/naloxone (8.6%) compared to success rates during buprenorphine/naloxone treatment (49.2%).¹²

At least in inpatient settings, buprenorphine appears to be more advantageous compared to methadone, in terms of offering faster symptom relief and higher rates of treatment completion. There does not appear to be a significant difference in terms of withdrawal symptom severity for individuals managed with buprenorphine compared to methadone.¹¹

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

Buprenorphine is also more effective than alpha-2 adrenergic agonists (e.g., clonidine), as it appears to offer more effective relief of withdrawal symptoms and to promote longer retention in treatment and greater likelihood of completing treatment.¹¹ There does not appear to be a significant difference between buprenorphine and alpha-2 adrenergic agonists in terms of the incidence of adverse effects, except in the case of clonidine, which may be associated with greater drop-out due to adverse effects.¹¹

OTHER CONSIDERATIONS FOR TREATMENT USING WITHDRAWAL MANAGEMENT ONLY

The lack of effectiveness of treatment using withdrawal management alone (e.g., without transition to long-term treatment) often rapidly leads to high rates of relapse post-treatment, which, in turn, increases the risk of HIV transmission, morbidity and mortality.^{13,14} As the first point of engagement in clinical care, opioid withdrawal management can serve an important role as a bridge to further treatment, but is not recommended unless a strategy is in place for referral to ongoing intensive outpatient or residential treatment.

Specifically, a meta-analysis found higher HIV incidence among individuals undergoing withdrawal management only compared with individuals receiving no treatment.¹³ 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.¹⁴ 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.¹⁵ Furthermore, relapse is common among patients undergoing withdrawal management only, with a significantly lower rate of abstinence at discharge (12%) compared to abstinence rates associated with other opioid treatment approaches (18 to 21%).^{10,16} In order to reduce the risk of fatal overdose among high-risk patients, take-home naloxone prescriptions ought to be considered as a safe and effective fatal overdose prevention strategy.^{17,18}

PSYCHOSOCIAL SUPPORTS PROVIDED WITH WITHDRAWAL MANAGEMENT

Psychosocial supports appear to be beneficial adjuncts to opioid withdrawal management.¹⁹ When offered in addition to pharmacologically-supported withdrawal management (i.e., taper with opioid medication), psychosocial therapies such as contingency management and psychotherapeutic counselling are effective in terms of 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 approach.¹⁹ Therefore, further research and patient-specific approaches are needed with regard to psychosocial treatments. Importantly, while psychosocial treatments may improve rates of treatment retention and completion, psychosocial treatments 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.^{12-14,20}

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 there are few rigorous evaluations that would help identify specific characteristics of effective residential treatment programs or patient characteristics that may predict appropriateness of residential treatment referral.

Among the evaluations that have specifically examined the impacts of residential treatment for opioid dependence, relapse has been shown to be relatively common among clients referred to residential treatment for opioid use disorder. Smyth *et al.* (2010) evaluated patients with opioid use disorder admitted to a six-week residential treatment program with methadone withdrawal management, psychosocial therapies (e.g., group, individual and/or family therapy) and an aftercare component. The study found that 80% reported relapse within one month, of whom 59% relapsed within one week of discharge.²¹ Additionally, younger age, failure to complete six weeks of treatment, greater heroin use prior to treatment, history of injecting and a failure to enter aftercare were associated with a shorter time to relapse.

In a study conducted among clients recruited from over 20 residential treatment programs (using methadone, lofexidine or codeine for withdrawal management, with the goal of achieving abstinence from opioids) in the United Kingdom,²² clients demonstrated improvements in terms of reduced injecting, sharing of injection equipment, heavy drinking and criminal behaviour after residential treatment.²³ A follow-up study of this cohort found that approximately 57% of clients used heroin within 30 days of discharge from residential treatment.²⁴ Longer stays in treatment were predictive of better one-year outcomes.

Studies of residential treatment in the United States also present varied results. When data up to 42 months after trial enrolment were considered in the Prescription Opioid Addiction Treatment Study, it is noteworthy that the greatest predictor of abstinence was being on agonist therapy, but also that more than 30% of patients diagnosed with opioid addiction were abstinent from opioids and not on agonist therapy.²⁵ One longitudinal study found similar rates of treatment retention, completion and patient satisfaction among individuals in outpatient and residential treatment programs.²⁶ Similarly, one randomized trial found that patients enrolled in residential treatment for less than seven weeks showed no significantly different outcomes compared to patients who did not receive any type of treatment.²⁷ 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.²⁷ 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 opioid-dependent adults.²⁸

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.²⁹ Therefore, patients may benefit from residential treatment that involves fostering family and other social connections.

Importantly, concerns regarding fatal overdose as a result of loss of tolerance during residential treatment without agonist therapy should be considered. In this regard, there is evidence from a national UK-based study that residential treatment is associated with reduced rates of overdose.³⁰ Nevertheless, health care providers must be vigilant in assessing for risk of relapse and consider implementing strategies to reduce the risk of fatal overdose (e.g., take-home naloxone, sterile syringe provision, starting opioid agonist therapy), given the known protective effects of these strategies against opioid use and related harms, particularly when individuals leave or are discharged from residential treatment and are at high risk of relapse.³¹

II Agonist maintenance treatments

Overall, as described below, opioid agonist maintenance treatments have been shown to be superior to withdrawal management in terms of retention in treatment, sustained abstinence from opioid use, and reduced risk of morbidity (e.g., HIV transmission) and mortality. The choice of agonist treatment depends on several patient-specific factors such as initial presentation, comorbidities (e.g., liver disease, prolonged OT), treatment preference, and response to treatment, as discussed below. Regardless of type of treatment administered, agonist maintenance treatment should incorporate long-term addiction monitoring, including regular follow-up, urine drug screens and mental health care.

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.³² Methadone at higher doses (e.g., between 60–120 mg/day or higher) is more effective than lower doses in terms of treatment retention and reducing heroin and cocaine use during treatment.^{33,34} Methadone maintenance treatment has also been shown to reduce injection risk behaviours and the overall risk of hepatitis C and HIV infection among people who inject drugs.^{13,35,36} Furthermore, among HIV-positive individuals, engagement in methadone maintenance therapy 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).^{37–39} While methadone dosing should be based on clinical judgment determined individually due to differences in individual metabolism, comorbidities (e.g., liver disease, prolonged OT) and drug interactions,⁴⁰ most studies have suggested that patients who take daily doses of 80 mg/day or higher have optimal treatment outcomes³³ and that doses well above 120 mg/day may be required to produce full opioid blockade and fully suppress withdrawal.^{41,42} Challenges with withdrawal have been reported with the recent transition in PharmaCare



coverage from methadone to Methadose™ in BC, likely related to change intolerance.⁴³ Where possible, providing methadone to those struggling with Methadose™ may have advantages.

For induction and dosing guidelines for methadone maintenance treatment, practitioners are advised to refer to the College of Physicians and Surgeons of BC's *Methadone Maintenance Program: Clinical Practice Guideline*.⁵

BUPRENORPHINE/NALOXONE

Buprenorphine is superior to placebo in terms of greater treatment retention at doses greater than 2 mg/day, and greater suppression of illicit opioid use at doses greater than 16 mg/day.⁴⁴ Compared to methadone, buprenorphine at low doses (\leq 6 mg/day) is less effective in terms of treatment retention compared to low doses of methadone (\leq 40 mg/day). At medium and high doses, buprenorphine does not markedly differ from methadone in terms of treatment retention. Buprenorphine and methadone are equally effective in terms of reducing of illicit opioid use.⁴⁴

For induction and dosing guidelines for buprenorphine/naloxone maintenance treatment, refer to Appendix 1.

COMPARING METHADONE TO BUPRENORPHINE/NALOXONE

Early trials comparing buprenorphine to methadone have been critiqued for often employing relatively low buprenorphine doses and buprenorphine induction approaches that are slower than the current practice standards.⁴⁵ Newer studies show that sublingual buprenorphine achieves essentially equivalent outcomes to methadone when a sufficient dose, appropriate induction rate and flexible dosing are used.⁴⁵

Regarding side effects and adverse events, buprenorphine as a partial opioid agonist may be preferable in terms of reduced overdose potential.⁴⁵ One recent study of more than 19 million prescriptions over a six-year period in the United Kingdom found that buprenorphine is six times safer than methadone in terms of overdose risk.⁴⁶ Additionally, recent provincial mortality data indicate that methadone is implicated in approximately 25% of prescription-opioid-related deaths in British Columbia.⁴⁷ 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.^{48,49} It is also worth noting that recent reports and a recent expert panel have highlighted the substantial risks of fatal overdose during methadone treatment initiation.^{50,51} Buprenorphine has lower potential for respiratory depression and is well below the threshold lethal dose for opioid-naïve adults compared to standard methadone doses for opioid use disorder that often exceed the threshold lethal dose.⁴⁹ 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.⁵² Patient-reported concerns with methadone include the potential for tooth decay, which has been largely under-acknowledged by care providers.^{53,54} Additionally, because of its partial agonist effect, it is easier to switch from buprenorphine/naloxone to methadone, supporting buprenorphine/naloxone as a preferred first-line option in the absence of contraindications.^{55,56} However, buprenorphine/naloxone may not be feasible for all patients due to individual patient factors, including intolerable symptoms during the prerequisite partial opioid withdrawal that is required for initiation of buprenorphine/naloxone treatment, in contrast to methadone treatment.⁵⁷

Consistent with the relative safety profile of buprenorphine/naloxone in comparison to methadone, it is noteworthy that Alberta, Ontario, Nova Scotia and Quebec do not require physicians to have a federal Section 56 exemption from the *Controlled Drugs and Substances Act* in order to prescribe buprenorphine/naloxone. In BC, PharmaCare coverage is undergoing changes to allow access to buprenorphine/naloxone without requiring that patients first try methadone. Historically, coverage has been restricted to patients for whom methadone treatment was inadequate or contraindicated (e.g., high risk of QTc prolongation, intolerance or hypersensitivity to methadone).⁵⁸

Regarding outcomes related to polysubstance use, while opioid agonists are not specifically intended for the treatment of cocaine addiction, past meta-analyses have shown that effective treatment of opioid addiction reduces cocaine use in polysubstance-using individuals using both heroin and cocaine.⁵⁹ To this end, a recent Cochrane review has suggested that methadone and buprenorphine/naloxone are no different in suppressing cocaine use.⁴⁴

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.⁶⁰ Here, the major potential for cost savings is primarily due to the reduced pharmacy dispensation fees enabled through more flexible take-home dosing schedules that are safe and feasible with buprenorphine/naloxone.⁶¹⁻⁶⁴

In terms of gender-related differences, while opioid use is generally more prevalent among males,¹¹ there do not appear to be significant gender-related differences in outcomes associated with buprenorphine/naloxone compared to methadone treatment.^{65,66} Further research is needed since few studies have examined gender-based outcomes;¹¹ however, forthcoming systematic reviews may provide insight on potential gender-related differences in outcomes related to opioid agonist therapy.⁶⁷

6x
Buprenorphine has a six times greater safety profile than methadone in terms of overdose risk

25%
Methadone is implicated in 1 in 4 prescription-opioid-related deaths in BC

TABLE 2. ADVANTAGES AND DISADVANTAGES OF METHADONE VS. BUPRENORPHINE/NALOXONE

A D V A N T A G E S	
METHADONE	BUPRENORPHINE/NALOXONE
<ul style="list-style-type: none"> • Potent opioid agonist • Potentially better treatment retention, particularly for severely unstable opioid-dependent individuals (e.g., injectors) who may be more prone to drop-out • No precipitated withdrawal/easier to initiate treatment • 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 opioid users, infrequent or non-injectors, short history of opioid dependence) and individuals anticipated to be successfully tapered off maintenance treatment in a relatively short period of time
D I S A D V A N T A G E S	
METHADONE	BUPRENORPHINE/NALOXONE
<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) • More expensive if daily witnessed ingestion required • Longer time to achieve therapeutic dose (> 35 days) • 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 	<ul style="list-style-type: none"> • Potentially higher risk of drop-out • May cause precipitated withdrawal if induced inappropriately • Doses may be suboptimal for individuals with high opioid tolerance • May block opioid analgesics used for concurrent pain treatment • Not approved in Canada for the primary purpose of pain control

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III Alternative agents

SLOW-RELEASE ORAL MORPHINE *

Since November 2014, slow-release oral morphine (**24-hour formulation**) has been approved by Health Canada's Non-Insured Health Benefits (NIHB) Program for the treatment of opioid use disorder.⁶⁸ Limited preliminary evidence suggests that slow-release oral morphine prescribed for maintenance treatment may reduce illicit opioid use and depressive symptoms.⁶⁹ However, slow-release oral morphine did not appear to make a significant difference in treatment retention compared to methadone treatment, and the risk of adverse events may be greater with slow-release oral morphine.⁶⁹ Since this preliminary evidence was published, a number of more recent trials have suggested that slow-release oral morphine may be a beneficial 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.⁷⁰ Another study found that slow-release oral morphine was superior to methadone in terms of reduced cravings, patient preference and reduced side effects, with similar outcomes to methadone in terms of drug use and physical and psychological health.⁷¹ 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, and significant advantages were observed after switching to slow-release oral morphine (e.g., reduced withdrawal symptoms, reduced cravings, physical and psychological improvements).⁷²

For induction and dosing guidelines for slow-release oral morphine, refer to Appendix 2.

DIACETYLMORPHINE

Among patients who are treatment refractory to methadone, prescription diacetylmorphine (original trade name Heroin) administered in a clinic setting may be beneficial in terms of reducing illicit substance use, criminal activity, incarceration, mortality and drop-out.⁷³ While still considered an experimental treatment in Canada, this treatment is an established standard of care in other settings and generally involves flexible doses of supplementary oral methadone at the patient's and clinician's discretion. However, because of concerns about possible diversion and higher rates of adverse events (e.g., concurrent use of other illicit drugs leading to risk of overdose or seizures, continued use of needles with attendant risks of venous disease),⁷³ prescription of diacetylmorphine is generally only provided within highly supervised clinic settings for patients who have repeatedly failed other treatment approaches.

Evaluations of cost effectiveness have suggested that, for patients who responded poorly to methadone maintenance treatment, diacetylmorphine significantly reduced use of illicit heroin compared to methadone treatment, and realized significant cost savings primarily related to reduced criminal activity.^{74,75} Diacetylmorphine also appears to be associated with slightly superior outcomes related to social functioning, in comparison with reinitiating methadone treatment in individuals previously unsuccessfully treated with methadone.⁷³

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

Comparisons between diacetylmorphine and hydromorphone are currently limited.^{76,77} Notably, a small number (n=50) of former patients from the Study to Assess Longer-term Opioid Medication Effectiveness (SALOME) are maintained on injectable and oral hydromorphone. Other injectable medications, such as intravenous methadone, have also not been extensively studied.⁷⁴ Further, no studies have yet compared injectable diacetylmorphine to treatment with buprenorphine/naloxone.

Although diacetylmorphine has been available for treatment of opioid dependence for several years in other countries (e.g., United Kingdom, Switzerland and other European countries),⁷⁸ currently the treatment is only accessible in Canada through Health Canada's Special Access Programme.

ANTAGONIST TREATMENTS

Naltrexone is an opioid receptor antagonist that blocks the euphoric effects of opioids at adequate doses.⁷⁹ Potential benefits of naltrexone include its ease of administration, its lack of induced tolerance during long-term treatment, and its pharmacological makeup that is not addictive or prone to abuse.⁸⁰ However, as an opioid antagonist, naltrexone fully blocks the effects of all opiate 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 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.⁸¹

Presently, oral naltrexone is not scientifically proven to be superior to other forms of treatment for opioid use disorder.⁸² Limited evidence suggests that there are no significant differences in maintenance treatment using oral naltrexone compared to placebo (except reduced incarceration in two studies), psychotherapy (based on a single study), benzodiazepines (based on a single study), or buprenorphine (based on a single study).⁸² Treatment retention rates appear to be low with oral naltrexone maintenance treatment (28%).⁸² However, a recent randomized trial observed fewer positive urine tests among individuals on oral naltrexone compared to placebo.⁸³

In the United States, extended-release naltrexone is available via monthly intramuscular injection,⁸⁴ which may promote improved treatment adherence in comparison to oral naltrexone.⁷⁹ Injectable naltrexone has demonstrated efficacy compared to placebo in terms of improved retention in treatment, increased abstinence and decreased opioid cravings.⁸⁵⁻⁸⁷

Presently, extended-release naltrexone is only available in Canada for research purposes or through Health Canada's Special Access Programme. However, it is noteworthy to mention that there appears to be a high level of willingness to take extended-release naltrexone among 52% of opioid users in two cohort studies of people who use illicit drugs in Vancouver.⁸⁸

IV Combination approaches and movement between approaches

Due to high rates of polysubstance use (e.g., cocaine and heroin) among opioid-dependent individuals in Lower Mainland 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 proven to promote abstinence from heroin 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, but are severely addicted and actively using.^{89,90} 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.⁹¹

Regarding transitions between agonist medications, several trials show feasibility when converting to buprenorphine from low to moderate methadone doses of up to 60–70 mg/day.⁹² In general, this practice must be individually tailored, but ideally involves a reduction of the methadone dose to 30 mg per day or less, if possible, for a minimum of one week prior to inducing buprenorphine. Then, buprenorphine/naloxone should be introduced according to induction guidelines (see Appendix 1) no sooner than 24 hours after the last dose of methadone.⁹³ 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. To mitigate this, adjunct medications and/or inpatient treatment may be required for rotation to buprenorphine/naloxone from higher doses of methadone.⁹² Conversely, rotation from buprenorphine to methadone is relatively uncomplicated, as methadone is a full agonist and buprenorphine is a partial agonist. Established protocols for rotating between agonist therapies are available, and some guidance is provided in the College of Physicians and Surgeons of British Columbia's *Methadone Maintenance Program: Clinical Practice Guideline*.⁵

Given the relatively superior safety profile of buprenorphine/naloxone (in the absence of concurrent alcohol or benzodiazepine ingestion),^{61–64} and similar overall costs of methadone versus buprenorphine/naloxone treatment,⁹⁴ research has investigated the feasibility of a stepped care strategy involving initiating agonist treatment with buprenorphine/naloxone followed by methadone among buprenorphine/naloxone treatment non-responders in comparison to initiating agonist treatment with methadone.⁹⁵ This study found that the stepped treatment approach was equally efficacious compared to optimally delivered methadone maintenance 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 maintenance treatment appear to be unsuccessful (approximately 87%), but there are increased odds of success when doses are reduced gradually with longer periods of stabilization.⁹⁶ 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.⁹⁶ Longer, more gradual stepped-tapering schedules (e.g., > 52 weeks) in which dosages decrease in no more than half of the weeks during the total taper period were significantly more likely to result in success.⁹⁶ Gradual tapering in a therapeutic manner at an appropriate time for the patient may be advantageous, as demonstrated by a review of voluntary “therapeutic detoxification” patients who demonstrated a 48% pooled abstinence rate compared to a pooled abstinence rate of 22% among non-voluntary, “non-therapeutic detoxification” patients.⁹⁷

Finally, while there is limited evidence to guide strategies involving multiple attempts using a specific type of opioid substitution treatment, practitioners should be aware that patients may often require

Research Summary

Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study.

NOSYK B, SUN HY, EVANS E, ET AL.
ADDICTION 2012;107:1621–9.

Ten years: 1996–2006

Outcome:

Sustained successful taper

(no treatment re-entry, opioid-related hospitalization or death for 18 months following last dose)

Out of **4917** taper attempts,
646 sustained success (**13%**)

FACTORS

For every 1% increase in adherence

+2%
increased odds of success

Taper over a *long period* (3 months–1 year)

Taper over 12–52 weeks vs < 12 weeks

+258%
increased odds of success

Plan dose reductions to occur *bi-weekly or monthly*

As opposed to more or less frequently

+61%
increased odds of success

several attempts with a certain therapy before they successfully achieve opioid abstinence, or before an alternative treatment strategy is implemented.

V Psychosocial supports

Recent meta-analyses and randomized controlled trials have suggested that there does not appear to be an additional benefit to more structured psychosocial treatment interventions (e.g., cognitive behavioural therapy, contingency management) in conjunction with standard agonist maintenance treatments in terms of retention in treatment, abstinence from opioid use during and by completion of treatment, treatment compliance, psychiatric symptoms, depression or treatment completion rates, when compared to maintenance treatment with standard medical management involving routine counselling.^{98–100} Further research is required to assess the effect of psychosocial treatments versus psychosocial supports (e.g., to facilitate housing) on outcomes that may indirectly reduce drug use in the long term (e.g., social assistance, increased social support, vocational training).⁹⁸

While the evidence for structured psychosocial treatments is poor, the addition of evidence-based psychosocial supports in combination with pharmacological opioid agonist treatment and standard medical management may be helpful in supporting overall recovery from opioid addiction in terms of improving individuals' psychosocial circumstances and other survival needs (e.g., housing). 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. Regardless, 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.^{101–103} Therefore, psychosocial supports may be routinely offered to patients in conjunction with pharmacological treatment.¹⁰⁴

Expert guideline

Summary of recommendations

Recommendation	Quality of evidence*	Strength of recommendation*	For more information see page...
Approaches to avoid			
1. Withdrawal management alone (i.e., detox without transition to longer term treatment) is not recommended, since this approach has been associated with elevated rates of HIV infection and overdose death.	⊕⊕⊕ Moderate	Strong	6
Possible first-line treatment options			
2. Initiate opioid agonist treatment with buprenorphine/naloxone whenever feasible to reduce toxicities and facilitate safer take-home dosing.	⊕⊕⊕⊕ High	Strong	10
3. Initiate opioid agonist treatment with methadone when treatment with buprenorphine/naloxone is not preferable (e.g., challenging induction, high risk for drop-out).	⊕⊕⊕⊕ High	Strong	9
4. When opioid withdrawal is being medically supervised, this can generally be safely done on an outpatient rather than inpatient basis but should include ongoing addiction treatment.	⊕⊕⊕ Moderate	Strong	6–7
Adjunct or alternative treatment options			
5. For individuals responding poorly to buprenorphine/naloxone, transition to methadone.	⊕⊕⊕⊕ High	Strong	14
6. For individuals with successful and sustained response to methadone desiring treatment simplification, consider transition to buprenorphine/naloxone.	⊕⊕⊕ Moderate	Strong	14
7. For individuals with successful and sustained response to agonist treatment desiring medication cessation, consider slow taper over 12 months.	⊕⊕⊕ Moderate	Strong	6
8. Psychosocial supports may be routinely offered in conjunction with pharmacological treatment.	⊕⊕⊕ Moderate	Conditional	16
9. For patients wishing to avoid initial treatment with an opioid agonist therapy, provide outpatient opioid agonist taper (preferably methadone or buprenorphine/naloxone), with subsequent immediate referral to intensive outpatient or residential addiction treatment. Oral naltrexone can be considered as an adjunct in this context.	⊕⊕ Low	Weak	6, 14

* 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, conditional, weak)¹

Patients presenting with opioid use disorder can be offered a range of treatment options based on their clinical presentation with respect to their addiction severity, comorbidities, present psychosocial circumstances (e.g., homelessness), 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 rates of HIV infection and overdose deaths in comparison to providing no treatment.^{13,14}

Therefore, a possible option is to engage patients in outpatient opioid maintenance (preferably methadone or buprenorphine/naloxone) to achieve stability and retention, followed by a very slow opioid agonist taper under close supervision aimed at continuing opioid maintenance if relapse risk emerges, with ongoing intensive outpatient or inpatient addiction treatment. In this context, while residential treatment programs have not been rigorously evaluated, given the evidence in support of changing the environment of individuals who are severely addicted and actively using opioids,^{89,90} referral to a residential treatment facility is a preferred option for individuals willing to pursue a tapered agonist treatment option. With respect to this recommendation, separate initiatives will need to be undertaken to improve the accessibility of the quality of residential treatment, consistent with past reports.¹⁰⁵ Given the evidence that opioid tapers result in a high rate of relapse, this option should only be recommended to individuals viewed to have a high chance of successful recovery without long-term agonist treatment.

A second first-line option would be the initiation of opioid agonist treatment with either methadone or buprenorphine/naloxone. Patients do not have to go through a trial of medically managed withdrawal and subsequent relapse in order to be candidates for opioid agonist maintenance. The committee recommends, for the reasons articulated above, that buprenorphine/naloxone be given consideration as a first-line agent in instances where induction onto buprenorphine/naloxone is feasible and does not promote barriers to retention. Guidance for take-home dosing is provided in Appendix 3. Induction and dosing guidelines for buprenorphine/naloxone are provided in Appendix 1. 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. In cases where both methadone and buprenorphine/naloxone are suitable options, buprenorphine/naloxone may be considered as a first-line treatment.

Alternatively, methadone is an acceptable 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 the individual (e.g., an individual for whom precipitated withdrawal or treatment retention is a major concern) or of public health (e.g., risk of HIV transmission). For instance, methadone may be preferable for severely chaotic patients or individuals with higher opioid tolerance due to high-intensity use, for whom buprenorphine/naloxone doses may be suboptimal and may lead to poorer retention outcomes.¹⁰⁶ For induction and dosing guidelines, practitioners should refer to the College of Physicians and Surgeons of BC guideline.⁵

For individuals responding poorly to either methadone or buprenorphine/naloxone despite multiple attempts and despite efforts to address barriers to successful treatment, consideration may be paid

to attempting treatment with an alternative first-line agent. As described above, for reasons of safety with respect to diversion as well as its side effect profile, buprenorphine/naloxone has a number of advantages over methadone, and transitioning from methadone to buprenorphine/naloxone or initiating with buprenorphine/naloxone is recommended for these reasons. Certainly, for a client who struggles with ongoing illicit opioid use while on adequately dosed buprenorphine/naloxone, methadone would be an appropriate second-line option. For clients wishing to taper off agonist treatment due to dissatisfaction with methadone maintenance treatment related to the inconvenience of daily witnessed ingestion requirements, difficulty obtaining take-home or “carried” doses, and other common concerns, transitioning from methadone to buprenorphine/naloxone may be advantageous.^{45,55}

Alternatively, slow-release oral morphine (24-hour formulation) is increasingly being used for individuals unsuccessfully treated with first-line options. While completed systematic reviews of slow-release oral morphine have provided mixed evidence, more recent studies have demonstrated a good safety profile and high degree of patient satisfaction.^{69–72} 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 sprinkling the enclosed pellets (e.g., on top of apple sauce) in order to reduce the risk of diversion. Dosing guidelines for slow-release oral morphine are provided in Appendix 2.

As described above, a number of settings have initiated diacetylmorphine programs, provided via witnessed injection at specialized clinics for patients who respond poorly to methadone maintenance treatment. Unfortunately, at present, within VCH there is only one clinic offering this treatment, and for regulatory, legal and cost-constraint reasons, this treatment is not widely available. Providing guidelines for the safe prescribing of diacetylmorphine is outside the scope of this guideline.

Regarding standardized psychosocial treatments (e.g., cognitive behavioural therapy) coupled with pharmacotherapies, the evidence does not suggest clear benefits over standard medical management traditionally provided with opioid agonist therapies. However, this does not suggest that pharmacotherapy should be offered in isolation, but rather that, provided along with opioid agonist treatments, evidence-based psychosocial supports focused on psychosocial circumstances (e.g., housing, vocation) and other survival needs (e.g., social assistance) may be helpful in supporting recovery from opioid addiction. 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. Ongoing assessment, treatment and monitoring of emotional, medical and mental health is an important component of treating opioid use disorder.

Finally, these interventions may benefit from additional harm reduction interventions, including education about sterile syringe use and take-home naloxone for reducing the risk blood borne infections or the risk of fatal overdose among high-risk patients or patients with ongoing opioid use.^{17,18}

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.

Appendix 1: Induction and dosing guidelines for buprenorphine/naloxone

1. ASSESSMENT

Common contraindications

- Buprenorphine/naloxone (*bup/nlx*) allergy
- Pregnancy (refer to specialist care)
- Severe liver dysfunction (caution if liver enzymes > 3–5 times normal upper limit)

Baseline assessment

- Diagnosis of opioid use disorder
- Urine drug test (positive for opioids) and other laboratory tests

2. INDUCTION

Preparation

- a. If patient is on methadone, aim to taper to a methadone dose of ≤ 30 mg per day (or at least < 60 mg per day) for a minimum of 6–7 days prior to bup/nlx induction. Wait at least 24 hours after the last dose of methadone before beginning bup/nlx induction, as per Day 1 guidelines below.
- b. For the patient not on methadone, instruct patient to discontinue opioid use 12–24 hours prior to the morning of the first day of scheduled bup/nlx induction.
- c. Emphasize to patient that opioid use within 12–24 hours of induction may exacerbate rather than alleviate withdrawal symptoms.
- d. Ensure patient is aware not to drive or operate heavy machinery during induction.

Day 1

- a. Plan induction of bup/nlx for weekday morning dosing, allowing for reassessment in the afternoon.
- b. At the time of the first dose of bup/nlx, 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 less risk of precipitated withdrawal. For *cows* < 12, consider postponing first dose of bup/nlx until later in the day or the following day, when the patient is demonstrating more severe withdrawal.
- c. The most common starting dose is 4/1 mg sublingual bup/nlx when *cows* > 12 and no long-acting opioid has been used recently. This dose may be lowered to 2/0.5 mg if there is a high risk of precipitated withdrawal, or it may be increased up to 6/1.5 mg if the patient is experiencing severe withdrawal symptoms at the time of the induction. Witnessed ingestion is recommended, to ensure that the tablet is appropriately administered and dissolved sublingually, though take-home induction is an option (instruct patient to keep the tablet in their mouth until it dissolves, which may take up to 5 minutes).

- d. Since precipitated withdrawal can become evident within the first few hours after the first dose of bup/nlx, reassess after 2–3 hours from the time of first dose.
- *If withdrawal symptoms are adequately relieved after 2–3 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, consider additional dose(s)*. A maximum **total** of 12/3 mg bup/nlx may be administered on Day 1 depending on the individual patient's requirement, though newer U.S. recommendations allow for 16/4 mg on Day 1. If uncertain about the need for an additional dose, consider prescribing 1–2 2/0.5 mg take-home tablets 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 some cases, short-term symptomatic relief may be offered by prescribing a non-opioid, non-sedative agent. For example:
- Clonidine (0.1–0.2 mg q4h prn for < 12 hours)
 - PRN anti-emetic, antidiarrheal, NSAID, acetaminophen

Days 2 onward

- a. If no withdrawal symptoms since last dose, continue a once-daily dose equal to the total amount of bup/nlx administered on the previous day titrating up as needed in subsequent days aiming for a target dose of 16/4 mg or greater.
- b. If withdrawal symptoms present since last dose, administer dose equal to the total amount administered on previous day, plus an additional 4/1 mg bup/nlx.
- If symptoms relieved after 2–3 hours, prescribe this total dose for the next day.
 - If symptoms not relieved after 2–3 hours, administer a second additional 4/1 mg dose of bup/nlx (to a maximum total of 16/4 mg bup/nlx on Day 2). If symptoms relieved after 2–3 hours after the second additional dose, prescribe this total daily dose for the following day. If symptoms not relieved 2–3 hours after the second additional dose, manage withdrawal symptomatically for the remainder of Day 2.
- c. On the following induction days, if withdrawal symptoms persist, continue dose increases as per the above schedule. Titrate as needed (by 2/0.5 to 4/1 mg bup/nlx at a time), up to a maximum total of 24/6 mg bup/nlx per day (as stipulated by Health Canada; however, U.S. guidelines state that some patients may require doses up to 32/8 mg bup/nlx per day). An optimal maintenance dose is achieved when the patient is able to sustain an entire 24-hour dosing interval with no withdrawal symptoms and no medication-related intoxication or sedation (hold bup/nlx dose if intoxicated or sedated). Target dose is generally 12/3 mg to 16/4 mg bup/nlx per day by the end of first week.

- d. Once optimal dose achieved, continue to follow up once or twice per week (or more frequently, as needed) to assess for dose effectiveness and side effects.

3. MAINTENANCE

- a. Once clinical stability is achieved at a maintenance dose, frequency of follow-up may be gradually reduced. Once stable, continue to assess at least every 1–2 weeks with the option to decrease follow-up visits as increasing stability is achieved.
- b. Follow-up assessments: adequacy of dosage, side effects, substance use (via urine testing, when indicated), psychosocial functioning
- c. For clinically stable patients at stable doses, consider:
 - Alternate day dosing (e.g., single dose on Sundays and double doses on Mondays, Wednesdays and Fridays)
 - Gradually increasing take-home doses. Generally, consideration can be given to witnessed dosing for at least 2 months after a stable dose is achieved, although this can be individualized with carry doses offered immediately, as is the standard of care in the U.S. Always educate patients on risks to self and others when giving take-home doses. If diversion or misuse is suspected, consider reducing or eliminating take-home dosing and altering the dose to minimize risk of opioid toxicity once daily witnessed ingestion is resumed.
- d. For missed doses (when other opioids have not been used) ≤ 5 days, resume previous dose. For missed doses ≥ 6 days, a conservative dosing guideline is:

Buprenorphine dose	Number of missed days	Start new dose at...
2–4 mg	6+ days	2–4 mg
6–8 mg	6+ days	4 mg
> 8 mg	6–7 days	8 mg
> 8 mg	> 7 days	4 mg

If ≥ 6 days have been missed and patient has returned to illicit opioid use, reinduction may be necessary.

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Appendix 2: Dosing recommendations for slow-release oral morphine (SROM)

Slow-release oral morphine (SROM)—which refers to the **24-hour formulation** of the extended-release capsules—is a potential option for individuals who respond poorly to other maintenance treatments. While these guidelines are based on the protocols used in several randomized controlled trials that demonstrated efficacy of SROM for opioid dependence, it is important to note that there is currently no established “best” clinical treatment protocol for SROM maintenance, requiring diligent measures to avoid overdose (e.g., close monitoring of initiation and stabilization in a specialized treatment setting, appropriate titration, specialist referral).

1. ELIGIBILITY

These recommendations are most applicable to patients who are:

- Adults (≥ 18 years) with opioid use disorder
- Switching to SROM from methadone or another opioid
- Not pregnant or breastfeeding

2. SUMMARY

- SROM maintenance is administered via once-daily oral doses.
- SROM is released over 24 hours. Peak plasma levels are achieved within 2–6 hours.
- Daily witnessed ingestion via opening capsules and sprinkling the enclosed pellets (e.g., on top of apple sauce) is strongly recommended to avoid diversion.

3. ASSESSMENT AND MONITORING

- **Treatment efficacy:** urinalysis, heroin and other drug use, cravings, withdrawal
- **Psychosocial:** assess for depression, anxiety at baseline and every 1–2 months thereafter
- **Adverse effects:** most common are stomach cramps, abdominal pain, headache, dizziness, hyperhidrosis, toothache, dry mouth, constipation, frequent urination, nausea, vomiting, insomnia

4. INDUCTION

- No wash-out of previous treatment is required (to minimize potential for withdrawal symptoms). Withdrawal symptoms may recur temporarily during the switch-over period.
- Begin with a 1-week adjustment/titration phase aiming to achieve a stable daily dosage.
- Switch from methadone oral solution to SROM. Generally a switch will require an ultimate dose of 1:6–1:8, but we suggest beginning with a 1:4 induction with titration upwards based on withdrawal scores and craving. Titrate upward in incremental doses according to withdrawal scores.

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

Example 1 MMT to sROM	Example 2 Daily lower frequency heroin use
<ul style="list-style-type: none">• Begin with estimated methadone-to-sROM dose equivalence of 1:4, then increase incrementally according to withdrawal scores	<ul style="list-style-type: none">• Day 1: 30–60 mg sROM• Titrate dose upward according to individual patient’s withdrawal scores

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

5. MAINTENANCE

- The goal is to stabilize the once-daily dose to a maximum of 1200 mg/day. Currently, there is no published literature to guide treatment decisions beyond 36 weeks (8 months).

Note, for individuals on sROM, urine drug screens will be positive for morphine metabolite meaning it may be difficult to distinguish on UDS between illicit heroin or supervised sROM use.

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Appendix 3: Take-home dosing recommendations for oral agonist therapy

Take-home dosing of oral agonist therapy may be beneficial in terms of improved treatment retention, increased patient autonomy and flexibility, positive reinforcement of abstinence, decreased treatment burden, and decreased costs related to daily witnessed ingestion.¹ This must be balanced against patient and public health risks.

1. METHADONE MAINTENANCE TREATMENT

Specific instructions regarding the provision of take-home dosing may be found in the College of Physicians and Surgeons of British Columbia's *Methadone Maintenance Program: Clinical Practice Guideline*.²

2. BUPRENORPHINE/NALOXONE

Take-home dosing of buprenorphine/naloxone may be provided at any time at the discretion of the treating physician. Previous research has demonstrated some improved patient outcomes when buprenorphine/naloxone is initially provided via daily witnessed ingestion before individuals are able to graduate to receiving take-home doses.³⁻⁶ Generally, take-home dosing can be provided for one to two weeks' worth of medication at a time.

Considerations for restricting patients to daily witnessed ingestion of buprenorphine/naloxone can include:^{1,7,8}

- Improved patient-clinician therapeutic relationship, promotion of patient safety and treatment compliance via increased engagement with health care provider (i.e., physician, pharmacist) in early weeks of recovery
- 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 physician to decide when take-home dosing is advisable and whether ongoing daily witnessed ingestion is optimal from a patient and public safety perspective. Generally, Canadian guidelines and those from some other settings (e.g., Australia) recommend that initial daily witnessed ingestion of buprenorphine/naloxone be followed by a gradual increase in take-home doses, up to one to two weeks' worth of medication at a time between observed doses, according to individual risk assessments.^{1,9,10} Notably, U.S. 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 lower risk for abuse and adverse events compared to methadone.⁷ While there are no established protocols for take-home dosing of buprenorphine/naloxone, clinicians may consider the following:

- Health Canada recommends that all doses of buprenorphine/naloxone should be observed for at least the first two months of treatment, with the exception of weekends and holidays. Take-home doses may be prescribed earlier than two months, provided that:
 1. the patient has explicitly consented to receiving this “against label” prescription, and has been made aware of the potential risks to self and others; and
 2. the physician has clearly documented these discussions and the clinical rationale for take-home dosing.¹
- As with methadone maintenance treatment, the provision of take-home doses of buprenorphine/naloxone in response to negative random urine drug screen results may be an effective method of reinforcing abstinence.^{1,4}

Consideration can also be given to providing take-home medication during buprenorphine/naloxone induction, when multiple same-day visits may not be possible or practical.^{11,12} 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 starting dose in the clinic, a patient who may not be able to return for reassessment that same day may be given a second take-home dose of 4 mg to be taken in the event of recurrence of withdrawal symptoms, in order to help decrease the likelihood of illicit opiate use.

3. SLOW-RELEASE ORAL MORPHINE (24-HOUR FORMULATION)

It is recommended that similar restrictions for daily witnessed ingestion be implemented as per the College of Physicians and Surgeons of British Columbia’s current recommendations for methadone maintenance treatment.²

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