Buprenorphine/Naloxone for Opioid Dependence:

Clinical Practice Guideline

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Executive Summary

Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline

Background

- Opioid dependence or "addiction," particularly dependence on prescription opioids, is an increasing clinical and public health problem in Canada.
- Only an estimated 25 per cent of opioid-dependent persons are enrolled in a methadone program.
- Methadone uptake is limited by issues of access, especially in non-urban areas, as well as patient disinterest.
- Buprenorphine/naloxone has the potential to improve access to evidence-based treatment for opioid dependence, due in part to its demonstrated effectiveness and safety in the primary care setting.

Overview

- The objective of this guideline is to provide clinical recommendations for the initiation, maintenance and discontinuation of buprenorphine/naloxone maintenance treatment in the ambulatory treatment of adults and adolescents with opioid dependence in Ontario.
- The guideline intends to contribute to education of practitioners regarding opioid prescribing, improved patient access to treatment for opioid dependence, and safe prescribing and dispensing of buprenorphine/naloxone.
- This evidence-based clinical practice guideline was developed by a multidisciplinary committee, and included specialists in the field of addiction medicine, family medicine and pharmacy.
- A systematic review of the literature formed the evidence base for this guideline, and recommendations were assigned levels of evidence and grades of recommendations based on those developed by the Canadian Task Force on Preventive Health Care.

Summary

Selecting buprenorphine maintenance treatment

- Buprenorphine/naloxone is an effective medication for the maintenance treatment of opioid dependence. It improves outcomes compared to detoxification and, with the exception of retention in treatment, appears to be of equal efficacy compared to methadone.

Clinical assessment

- Contraindications to the initiation of buprenorphine/naloxone are:
  - allergy to buprenorphine/naloxone
  - pregnancy (for buprenorphine/naloxone combination product specifically)
  - severe liver dysfunction
  - acute severe respiratory distress
  - paralytic ileus
  - decreased level of consciousness
  - inability to provide informed consent.
- Exercise caution if baseline liver enzymes are elevated above 3–5x the upper limit of normal.
- The clinical assessment will include the establishment of the diagnosis of opioid dependence ("addiction"), an estimation of degree of the patient's physical dependence on opioids and their level of psychosocial functioning, an appreciation of other concurrent medical and psychiatric diagnoses and an understanding of the patient's treatment goals. Urine drug testing and a small but important selection of other laboratory tests are also essential components of the assessment.

Preparation

- Ensure a clinical assessment has resulted in a diagnosis of opioid dependence, a urine drug test has been interpreted and is positive for opioids, and that there has been a consideration of the contraindications to initiating buprenorphine/naloxone.
- Ensure the patient has provided informed consent to buprenorphine maintenance treatment, is aware of the possible long-term nature of this treatment and has been made aware of other treatment options. A written consent and treatment agreement may be useful.
- Ensure that there are no concurrent substance use disorders, psychiatric illnesses or medical disorders that should be stabilized prior to induction of buprenorphine/naloxone.
- Inform the patient how long to remain abstinent from opioids to maximize the likelihood of beginning their induction in satisfactory withdrawal to minimize the likelihood of precipitated withdrawal during the induction.
- Ensure the patient has no plans to drive a vehicle or operate heavy machinery during the early induction period.

Induction

- Patient presents in moderate opioid withdrawal to the physician's office as early in the day as possible.
- After an assessment to establish the severity of opioid withdrawal, the physician prescribes an initial induction dose of 2–4 mg of buprenorphine/naloxone (though it could be as high as 6 mg), to be administered sublingually.
- The ingestion of the dose is observed by a pharmacist or other health care professional to ensure the tablet has dissolved completely (see Supplement 5).
- Consideration is given to reassessing the patient one hour after the dose to assess for precipitated withdrawal.
- If necessary, the patient is reassessed after approximately three hours to assess effectiveness of the initial dose and consider prescribing an additional observed dose (to a maximum of 8 mg total on the first day). If after this re-assessment the prescriber is unsure about the need for another buprenorphine/naloxone dose, the prescriber may also consider prescribing one or two 2 mg tablets of buprenorphine/naloxone for the patient to take home on that first induction day in case withdrawal symptoms emerge later in the evening (not exceeding 8 mg total on the first day).
- The prescriber either asks to see the patient the next day or writes a prescription for observed once-daily dosing of buprenorphine/naloxone for the next one to two days for the total amount taken by the patient on day 1. At the follow-up appointment the patient is assessed for the effectiveness of the dose and any side effects. The patient is made aware they can present for reassessment earlier than the suggested day if they are feeling the dose is very inadequate or they are having side effects from the dose.
- At each follow-up visit, the buprenorphine/naloxone dose is titrated, generally by 2–4 mg at a time, until an optimal maintenance dose is reached. An optimal dose is one where, among other things, the patient is free of opioid withdrawal symptoms for the full 24-hour dosing interval without experiencing intoxication or sedation from the medication.

Maintenance

- Once at the maintenance dose and more clinically stable, patient visits become gradually less frequent. Even a highly stable patient should be assessed at least every 12 weeks. Visits will again be more frequent during periods of instability.
- At follow-up visits, patient clinical stability is ascertained using the clinical assessment and urine drug testing.
- Areas to cover at follow-up visits include: adequacy of the dose and side effects, substance use, psychiatric symptoms, employment, social relationships and participation in counselling/mutual aid groups.
- Once the patient is at a stable maintenance dose, consideration can be given to alternate day dosing (i.e., double the dose on M/W/F and a single dose on Sunday).
- Patients should not receive a dose of buprenorphine/naloxone if they appear intoxicated or sedated upon presenting for their dose.
- The prescriber should have a structured approach to missed doses.
- The prescriber should have a structured approach to deciding about initiating and increasing the number of take-home doses once the patient achieves clinical stability.

Take-home doses

- Prescribing of take-home doses of buprenorphine/naloxone is a therapeutic intervention with benefits and risks.
- Take-home doses should not be initiated until the patient exhibits features of clinical stability. Exercise caution if patient has recently been suicidal, is injecting, is cognitively impaired or has unstable housing.
- Generally, tighter boundaries should be loosened as the patient displays increased clinical stability rather than tightening initially looser boundaries in response to instability.
- There should be a gradual increase in the number of weekly take-home doses up to a suggested maximum of one to two weeks of consecutive take-home doses dispensed between observed doses.
- Health Canada states that all doses are to be observed, with the exception of weekends and holidays, for at least the first two months on buprenorphine/naloxone. If the prescriber feels that a patient is eligible for additional regular take-home doses earlier than two months, this should be justified in the clinical record and the patient needs to have explicitly consented to this "against label" prescription.
- All patients, when about to receive their first take-home dose(s) should be made aware of the risks to themselves, their family and the public.
- Take-home doses should be reduced or eliminated in response to a loss of clinical stability. If high levels of take-home doses are eliminated all at once and if misuse or diversion of the take-home doses is suspected, the prescriber should strongly consider reducing the buprenorphine/naloxone dose by 25 to 50 per cent. This would reduce the likelihood of opioid toxicity once the patient starts ingesting their buprenorphine/naloxone doses on a daily basis.

Adverse events and safety

- Buprenorphine's partial mu agonist pharmacodynamic properties suggest that there is less risk of overdose and short-term mortality compared to full mu agonists such as methadone. Population level studies appear to consistently and robustly support that hypothesis.
- There is evidence that this medication can be prescribed as safely and effectively from appropriately trained or experienced practitioners in a primary care clinic as it can be in a specialized opioid agonist clinic.
- Risk of harm with buprenorphine does still exist, including the risk of injecting the drug, and so practitioners must be systematic and thorough in their approach to diagnosing opioid dependence, determining eligibility for buprenorphine/naloxone and inducting and maintaining patients on buprenorphine/naloxone maintenance therapy.

Summary of recommendations

Recommendation	Level of evidence and grade of recommendation
Selecting buprenorphine/naloxone maintenance therapy	
1. Once a patient is diagnosed with opioid dependence and is deemed appropriate for opioid agonist treatment, prescribers are encouraged to consider prescribing either buprenorphine/naloxone or methadone in order to increase retention in treatment and decrease opioid misuse.	Level I, Grade A
Clinical assessment	
2. Buprenorphine/naloxone maintenance treatment can be prescribed to patients in either a primary care setting or in a specialized addiction treatment setting.	Level I, Grade A
3. Prior to initiating maintenance opioid agonist treatment the patient should meet the diagnostic criteria for opioid dependence.	Level III, Grade A
4. The decision to initiate opioid agonist therapy with either buprenorphine/naloxone or methadone maintenance should be guided by the individual clinical circumstances and the patient's preferences.	Level III, Grade I
Initiation, maintenance and discontinuation of buprenorphine/naloxone maintenance treatment	
5. A physician should have a structured approach, such as the one suggested in the clinical considerations, to initiating buprenorphine/naloxone maintenance treatment in order to stabilize a patient at their maintenance dose as rapidly as possible while at the same time avoiding oversedation or precipitated withdrawal.	Level III, Grade A
6. Prior to initiation of buprenorphine/naloxone treatment, the patient must provide informed consent and there must be physician documentation that the patient has been informed of the physical dependence on the medication and possible long-term nature of the maintenance treatment.	Level III, Grade A
7. Once a stable maintenance dose is achieved, physicians can consider non-daily dosing of buprenorphine/naloxone as effective as daily dosing of buprenorphine/naloxone with respect to retention in treatment and reduction in illicit drug use.	Level I, Grade A
8. When monitoring a patient on buprenorphine/naloxone maintenance, the physician should adopt a patient–centred urine drug testing strategy that maximizes clinical utility while avoiding testing without indication.	Level III, Grade I

9. In making decisions regarding the provision of take-home doses of buprenorphine/naloxone, providers should use a clinical risk stratification strategy (as described in the clinical considerations) that aims to support patient autonomy while at the same time respecting patient and public safety.	Level III, Grade A
Overdose, mortality and other adverse effects	
10. Policy makers should be aware that in countries where buprenorphine is equally available as methadone, buprenorphine has a lower attributable death rate than methadone.	Level II-3, Grade A
11. Limited public funding is currently the major barrier to accessibility of buprenorphine/naloxone maintenance treatment in Ontario. We recommend that policy makers remedy this barrier.	Level III, Grade B
Clinicians should be aware that there is little in the medical literature to guide them in terms of which opioid maintenance agent to prescribe an individual opioid-dependent patient. In making this decision, the prescriber and patient should consider the following, which is based on clinical experience. 12. Buprenorphine/naloxone may be preferred over methadone to treat opioid dependence in the following patient populations:	
a) When methadone is absolutely or relatively contraindicated, such as:	
i) Presence of, history of or increased risk of prolonged QT interval	Level I, Grade A
ii) History of methadone allergy	Level III, Grade A
b) History of significant side effects on methadone such as:	
i) Sexual side effects on methadone	Level II-2, Grade B
ii) Severe sedation or constipation with methadone	Level III, Grade C
c) Increased risk of toxicity from a full mu agonist:	
i) If suspect a lower tolerance to opioids	Level III, Grade B
ii) If concurrent heavy or unstable use of sedating drugs/medication	Level II-3, Grade B
iii) If elderly	Level III, Grade B
iv) If significant respiratory illness	Level III, Grade B
d) Good prognostic factors:	
i) Briefer history (i.e., less than one year) of opioid misuse	Level III, Grade C
ii) Social supports	Level III, Grade C
iii) Adolescents and young adults	Level III, Grade B
e) Past history of successful stabilization with buprenorphine/naloxone	Level III, Grade I

f) Patient choice and access. In particular patients residing in geographic areas where methadone is not available in a timely manner, or when challenging pharmacy access makes the possibility of alternate day dosing of buprenorphine/naloxone desirable.	Level III, Grade B
13. Methadone may be preferred over buprenorphine/naloxone in the following patient populations:	
a) Pregnancy (specifically avoiding the naloxone component in the buprenorphine/naloxone combination product)	Level III, Grade A
b) Clinical situations where opioid withdrawal during induction is particularly hazardous – i.e., cardiovascular instability	Level III, Grade B
c) Prior inability to stabilize on buprenorphine/naloxone maintenance treatment	Level III, Grade B
d) History of abusing buprenorphine/naloxone via injection	Level III, Grade A
e) Patient side effects with or allergy to buprenorphine/naloxone or to excipients including acesulfame	Level III, Grade A
f) Patients experiencing dry mouth of severity that would interfere with dissolution and absorption of sublingual buprenorphine/naloxone tablets (dry mouth may be due to side effects of concurrent medications, chemotherapy, or conditions causing dry mouth, e.g., Sjogren's syndrome)	Level III, Grade A
g) Past history of successful stabilization with methadone	Level III, Grade I
h) Patient choice and access, in particular patients with limited financial resources that make reliable long-term use of buprenorphine/naloxone uncertain.	Level III, Grade B

Clinical practice guideline

INTRODUCTION

Background

People have suffered from opioid dependence for centuries. Historically, this has largely been in the form of opium and, since the 20th century, heroin dependence [1, 2]. Recently there has been a marked increase in the number of prescription opioid–dependent patients seen in various North American jurisdictions, including Ontario [3, 4]. It has been estimated that there are 30,000 illegal opioid users in Ontario and 80,000 in Canada [5]. However, due to demand characteristics in surveys, the true prevalence of opioid dependence in Canada is unknown. Estimates of prevalence will also overlook many patients who receive legal prescriptions for opioid therapy but whose use of these prescribed opioids has become problematic and suggestive of opioid dependence ("addiction"). Though the actual number of patients who fall into this latter category is unknown, this group may represent a considerable number of patients.

Methadone, a full mu receptor opioid agonist, was first proposed as a treatment for heroin dependence in the 1960s and has been available in Ontario since the 1970s. Meta-analysis has shown methadone to be superior to placebo in terms of retaining people in treatment and decreasing opioid use [6]. Observational studies have also demonstrated a reduction in mortality [7, 8] and reduced HIV seroconversion rates [9] for patients on methadone maintenance treatment (MMT) compared to those off MMT. Observational studies have also demonstrated reduced mortality for a cohort of opioid maintenance patients receiving either methadone or buprenorphine compared to opioid users outside of drug treatment [10]. The prescribing of methadone requires a certain degree of precaution due to a narrow therapeutic index in some patients, especially during the first few weeks of treatment [11]. As a result, methadone is prescribed only by specially licensed physicians who hold an exemption issued by the federal government.

It has been estimated that only 25 per cent of Canadian opioid-dependent patients are in methadone maintenance treatment [5, 12], and that access to treatment is quite limited in certain provinces [5] and in non-urban areas [13]. In addition, the literature describes a fair amount of negative opinion toward methadone maintenance treatment among drug users [14] and some authors have questioned the utility of the same methadone program for both heroin-only users and all prescription opioid users [5]. In a 2002 survey [15], more than 50 per cent of opioid-dependent patients stated they wished there was a different treatment for their condition.

Buprenorphine, a partial mu receptor agonist, has been available as buprenorphine/naloxone for the treatment of opioid dependence in Canada since October 2007. Buprenorphine has been used for the treatment of opioid dependence in countries such as France, U.S.A., United Kingdom and Australia for many years [16, 17, 18, 19. In addition, some of these countries have been prescribing buprenorphine predominantly in a primary care context [16]. This is generally quite different from how those countries prescribe

methadone, which, due to jurisprudence issues, has generally been limited to physicians practicing in formal addiction treatment centres.

Several clinical practice guidelines exist regarding the use of buprenorphine and buprenorphine/naloxone in the treatment of opioid dependence [17, 18, 19, 20]. However, very few of the existing guidelines are based on a systematic review of the literature with recommendations specifically linked to the evidence. This is especially important since it has become increasingly acknowledged that clinical practice guidelines should be produced in a systematic and evidence-based manner [21]. The authors believe these guidelines are novel and unique and will be an important aid to clinicians prescribing buprenorphine/naloxone in their clinical practices.

Scope and purpose

The objective of this guideline is to provide clinical recommendations for the initiation, maintenance and discontinuation of buprenorphine/naloxone maintenance treatment in the ambulatory treatment of adults and adolescents with opioid dependence in Ontario. In doing so, it hopes to contribute to the following:

- Education of practitioners:
  - » helping address overprescribing of opioids
  - » helping physicians recognize and treat opioid dependence
- Improved patient access to treatment for opioid dependence by:
  - » improving physician comfort in prescribing buprenorphine/naloxone
  - » enabling the use of buprenorphine/naloxone in primary care settings, in particular remote regions without specialist care
  - » advocating for increased public funding for buprenorphine/naloxone
- Safe prescribing and dispensing of buprenorphine/naloxone:
  - » providing guidance for safe prescribing and dispensing.
  - » reassuring prescribers and regulators with direction on how to employ the medication more safely.

Intended audience

- Physicians who may initiate, maintain or discontinue buprenorphine/naloxone maintenance therapy.
- Physicians and pharmacists who may identify and/or diagnose opioid dependence even if they do not become buprenorphine/naloxone prescribers or service providers.
- Physicians and pharmacists who may provide care for patients already being prescribed buprenorphine/naloxone.
- Policy makers.

Clarifications and limitations

The only sublingual buprenorphine product that is available in Canada for maintenance treatment is buprenorphine combined with naloxone in a 4:1 ratio (Suboxone). The buprenorphine mono-product (without naloxone) is currently not marketed in Canada and is available only through the Health Canada Special Access Program for specific clinical situations such as use in pregnancy.

This guideline has been written with the primary care physician in mind. However, the authors would like to emphasize that a single clinical practice guideline cannot be relied upon to act as a primer for the entire field of addiction medicine. Physicians should employ other resources, as required, to familiarize themselves with how to diagnose opioid dependence both in patients who are using illicit opioids as well as those who are being prescribed opioids. In addition, physicians should be familiar with different treatment options for opioid dependence and should discuss these options with the patient prior to deciding on opioid agonist treatment. Supplement 1 contains an overview of some important definitions, diagnostic criteria and treatment options that are commonly used in the field of addiction medicine. Health Canada suggests that Suboxone only be prescribed by physicians who have completed an accredited Suboxone education program. Though the authors of this guideline do not necessarily advocate an industry-sponsored educational program, we certainly agree that physicians and pharmacists complete the education and training they feel they require in order to competently use buprenorphine/naloxone in their practices, in particular the indications for the drug, its risks and benefits, its variances in dosages and its methods of administration. In general, if a physician or pharmacist has no clinical experience in assessing or treating opioid-dependent patients, a formal education program would be advisable (see Appendix I for some buprenorphine/naloxone training course options). Ongoing continuing professional development in the area of opioid dependence treatment is also important. In addition, we would also expect that physicians would refer to a colleague with expertise in addiction medicine if there was uncertainty with respect to a patient's diagnosis or the appropriateness of available treatment options. These guidelines are not intended to replace sound clinical judgment.

In writing these guidelines, the authors endeavoured to use evidence from systematic reviews driven by key clinical questions. However, there was an absence of specific guidance from the literature for many of the questions. Much of the guidance in this document, in particular in the Clinical Considerations sections, is largely based on expert opinion. It was felt that in areas where the literature was relatively silent it was important to fill in the gaps with expert opinion to ensure a logical sequence. The resulting guideline is useful for all clinicians, especially those who may be looking to prescribe this medication for the first time.

It is important to make note of the fact that this guideline utilizes the DSM IV diagnosis of "opioid dependence" as opposed to the term "opioid addiction." It is very important that the term "opioid dependence" be distinguished from "physical dependence" on opioids (Supplement 1). Despite the fact that physical dependence on opioids is almost always a feature of opioid dependence (or "addiction"), physical dependence symptoms alone

(i.e., tolerance and withdrawal) do not in and of themselves make the diagnosis of opioid dependence [22].

Sublingual buprenorphine/naloxone is not currently approved in Canada for the treatment of pain and this guideline will not address the use of buprenorphine/naloxone specifically as an analgesic agent. This guideline idoes not intend to counsel prescribers on the use of buprenorphine/naloxone in the context of acute opioid withdrawal management or the use of buprenorphine in pregnancy.

Future research

The systematic review has revealed significant gaps in the literature that if filled would be helpful for clinicians to structure the most effective and safe treatment program for their opioid-dependent patients. Namely:

- studies of patients dependent exculsively on oral opioids and/or with a brief duration of opioid dependence who are randomized to abstinence-based treatment, methadone maintenance or buprenorphine/naloxone maintenance
- long-term clinical studies comparing mortality in patients treated with methadone and buprenorphine/naloxone
- studies examining different protocols for initiation and monitoring of take-home doses of buprenorphine/naloxone
- studies examining treatment outcomes in prescription opioid dependent patients with and without a history of illicit opioid use.

METHODS

Funding and guideline committee membership

The development of this guideline was funded by the Centre for Addiction and Mental Health (CAMH). The funding for this guideline involved financial compensation from internal funds at CAMH to the chair and committee members for time spent in meetings, reviewing articles and abstracting data. The work of the committee was not directly influenced by CAMH. The Guidelines Advisory Committee (GAC) of the Centre for Effective Practice facilitated the guideline development process, and a methodologist was present at committee meetings to ensure methodological rigour.

Committee members were selected with the goal of achieving geographical and stakeholder representation, content expertise and breadth of practice type, and included specialists in the field of addiction medicine, family medicine and pharmacy.

Conflict of interest

As this guideline is somewhat unique in that it addresses the clinical use of a single pharmaceutical product from a single Canadian manufacturer,[1] the committee made it a priority to minimize any real or perceived bias in the guideline development process. The details of this process and a summary of the author conflict of interest declarations are outlined in Appendix C.

Identifying and evaluating the evidence

The Committee first met in late 2008 to discuss the overall scope of the guideline and to generate key clinical questions that they felt to be appropriate to try to answer in the guideline. Shortly thereafter, an analytic framework was developed and four important areas of key clinical questions were identified (Appendix D). The key clinical questions were used to inform the search for evidence, and the literature searches were conducted by Kelly Lang-Robertson, an information specialist with the Guidelines Advisory Committee (GAC). The data were abstracted to evidence tables that described the characteristics of the studies and pertinent clinical outcomes, and the tables were distributed to the committee members for review prior to meetings.

[1] Over the course of the writing of the guideline the manufacturer of Suboxone changed from Schering-Plough to Reckitt-Benckiser to Merck and finally back to Reckitt-Benckiser.

Identification and selection of studies

Search strategies were developed that addressed each key clinical question. Systematic searches were conducted of Medline, Embase, PsycLit, and the Cochrane Library for English language literature published between 1980 and 2009. When we identified existing good quality systematic reviews that addressed one or more of the key clinical questions, our searches were limited to the time frame subsequent to the search used in those reviews. For efficacy studies, only randomized controlled trials and quasi-randomized controlled trials were included for consideration. For other key questions all study designs with a comparison group were considered. For adverse event and mortality outcomes, studies without a comparison group were also considered. Two independent reviewers examined 838 abstracts for possible inclusion. They ultimately reviewed 341 articles in full text (see Appendix E for list). The full search strategy is provided in Appendix B.

Two committee members were assigned to independently review each full text article and abstract data. Information captured in the data tables included study design, description of the intervention, number of study participants (where applicable), primary outcome measures, primary outcome results, secondary outcome measures, secondary outcome results, and any additional comments. Complete evidence tables will be available on request.

Recognizing that the two patient groups can be quite different, the committee attempted to distinguish studies of injection-heroin users versus other types of opioid-dependent patients, in particular those abusing prescribed oral opioids. Effort was also made to distinguish between studies that used buprenorphine mono-product as opposed to the buprenorphine/naloxone agent. Studies using buprenorphine/naloxone have only relatively recently appeared in the literature. As a result, most of the studies used and referred to in this guideline involve the use of burenorphine mono-product. With the exception of the issue of buprenorphine diversion (see section 4. Overdose, mortality and other adverse effects, in Guideline Recommmendations), the authors felt comfortable using studies of the buprenorphine mono-product to inform this guideline. In fact, studies have been done that demonstrated similar outcomes when comparing buprenorphine mono-product to buprenorphine/naloxone [23]. Where possible, the committee also distinguished between studies that employed a sublingual buprenorphine tincture as opposed to the commercially available sublingual tablet, since it has been demonstrated that the absorption can differ between the two delivery forms and that the bioavailability of the tablet is approximately 70 per cent of that of the oral solution [24].

Recommendation development and approval

The committee developed recommendations based on the best available evidence. Certain aspects of the guideline have been informed by a reasonable amount of good quality evidence. Other aspects were crafted exclusively by committee consensus due to a lack of informative evidence. If evidence for buprenorphine was lacking for a particular clinical question and the committee was aware of related evidence regarding methadone,

then the methadone-related evidence was eligible for consideration in formulating a final recommendation. Each recommendation is explicitly linked to the supporting evidence. It has also been noted if the evidence was insufficient for a particular recommendation.

The levels of evidence and grading of recommendations were adapted from the Canadian Task Force on Preventative Health Care and are summarized in Appendix A. The levels of evidence describe the methodological rigour of the study whereas the grades of recommendation comprise the level of evidence and clinical expertise. Areas of disagreement regarding recommendation phrasing or grade of recommendation were resolved through verbal consensus during the meeting or subsequent email correspondence. All recommendations were ultimately voted upon by all committee members.

Legal advice was sought with respect to the appropriateness of making recommendations that would be seen as contradicting Health Canada's restrictions on prescribing buprenorphine/naloxone as outlined within the Suboxone product monograph [25].

Recommendations and other content within the guideline may be less applicable in certain situations or with certain groups of patients. As stated in the introduction, these guidelines are meant to support and not replace the clinical judgment of the clinician when dealing with an individual patient.

It is important for the reader to note that only the key clinical questions in the core guideline were addressed using the methodology of a systematic review. The information contained in Supplements 1 to 10 were not developed following a systematic review and have been included for informational purposes only in order to assist clinicians who may encounter these situations in their clinical work.

External review

The guideline was circulated in May, 2011, for external review and comment by relevant experts and stakeholders as identified by the committee. These included Joel Bordman, Angela M. Carol, Kate Greeneway, Johan Wouterloot, Veronica Mohr, Bernard LeFoll, Heather Badalato, Tina Perlman and Lisa Lefebvre. The guideline was also reviewed by two clinician reviewers, Janet Dollin and Mark Pearce, trained by the Guidelines Advisory Committee in the use of the AGREE Instrument, and by John Axler and Edward Osborne, members of the POCKET Network of family physicians (www.pocketdocs.ca). Reviewers evaluated the guideline using the AGREE II Instrument (www.agreetrust.org) and were also asked to provide feedback on the implementability of the formal recommendations. Lastly the guideline was sent to three senior CAMH Faculty members—Benedikt Fischer, Jurgen Rehm and Tony George—for their review and open-ended feedback on the guideline content. Feedback from the external reviewers was reviewed by the chair and the committee, and was incorporated into the guideline as necessary.

Guideline updates

In order to ensure that the guideline remains up to date and reflects current practice, CAMH plans to establish a working group every three to five years with the task of reviewing new evidence and revisiting the guideline as necessary.

Format of guideline

The guideline is organized according to the key clinical questions. The relevant background information, a summary and critical appraisal of the evidence, and the recommendation statement accompanied by a level of evidence and grade of recommendation follow each question. All the evidence is detailed in tables that are available upon request. A summary of the recommendations is available on pages 5–7.

Guideline recommendations

1. Selecting buprenorphine/naloxone maintenance therapy

Key cinical question 1:

How does buprenorphine compare to alternate treatments for opioid dependence with respect to mortality, treatment retention, decreased opioid use and other related outcomes?

Background

There have been several systematic reviews that have compared buprenorphine maintenance treatment (BMT) to placebo and to methadone maintenance treatment (MMT) in opioid-dependent patients [6, 26]. The Cochrane Library systematic review by Mattick et al. searched the literature for randomized clinical trials up until October 2006 and concluded that buprenorphine was superior to placebo in retaining patients in treatment at all doses. They also concluded that high dose buprenorphine (16 mg) was superior to placebo in self-reported reduction of opioid use.

Studies that employ a flexible dosing protocol are more relevant to this guideline because they more closely resemble how physicians prescribe opioid agonist treatment in actual clinical practice. When Mattick et al. isolated the eight studies from their review that employed flexible dose buprenorphine (ranges 2-32 mg) and methadone (ranges 20–150 mg), buprenorphine was slightly poorer compared to methadone in terms of retention in treatment (RR 0.85, 0.73–0.98), but there was no difference between the methadone and buprenorphine groups in terms of opioid or benzodiazepine use or criminal activity. Older randomized controlled trials (RCTs) not included in the Mattick review [27, 28] have also concluded superiority of methadone over buprenorphine in terms of retention in treatment. However, some RCTs and observational studies published after October 2006 have suggested no difference in retention rates between the two opioid agonist medications [29, 30, 31, 32, 33, 34]. Though the number of studies is limited, buprenorphine appears superior to clonidine [28] and naltrexone [27] in terms of retention in treatment. In addiction medicine, treatment retention is considered an important predictor of other patient outcomes such as survival, reduced illicit drug use and reduced HIV risk-taking behaviour [35, 36, 37].

One study in the Mattick review [38] is an RCT that demonstrates a reduction in mortality in the buprenorphine group compared to the placebo group over a 12-month period (no deaths vs. four deaths). The other three RCTs in the Mattick review that comment on

a mortality outcome conclude either no reported deaths in buprenorphine vs. placebo studies [39, 40] or no difference in death rates when buprenorphine was compared to methadone [41]. None of the efficacy studies published after October 2006 examine mortality as an outcome.

The systematic review of clinical and cost-effectiveness by Connock et al. in 2007 [26] draws many of the same conclusions regarding efficacy of buprenorphine as the Mattick 2008 review. They conclude buprenorphine is superior to placebo and that there is slightly increased treatment retention for flexible dose methadone compared to flexible dose buprenorphine (RR 1.40, 1.15–1.69).

Studies published subsequent to October 2006 have concluded no difference between buprenorphine and methadone treatments in terms of reduced opioid use [30, 31]. One observational study [34] suggested reduced illicit opioid use in the buprenorphine group compared to methadone. Buprenorphine also appears superior to naltrexone [42, 43] in terms of reducing substance use.

One study in the Mattick review concludes no difference in criminal activity between the buprenorphine and methadone groups. An additional study finds that methadone is superior to buprenorphine in terms of decreasing sexual risk taking [44] whereas another study showed that there is no difference in this particular outcome between buprenorphine and naltrexone [42]. Outcomes examining quality of life with buprenorphine and methadone are mixed [33, 45, 46].

Most buprenorphine studies have been conducted on heroin-dependent patients. It is not clear how heroin-dependent patients might differ from prescription opioid dependent patients. One recent study of 200 patients [47] found on univariate analysis that prescription opioid dependent patients were younger, earned more income, were more likely to be white, had less prevalence of Hepatitis C infection, had fewer years of opioid use and less drug treatment history when compared to patients receiving treatment for heroin dependence. Their addiction severity scores were also greater. Whether these differences between the two subsets of opioid-dependent patients in this one study can be reproduced in larger studies or whether there is an impact in terms of treatment options and prognosis has yet to be established. For the purposes of this guideline, we have generalized the studies of heroin-dependent patients to be applicable to prescription opioid dependent patients.

In summary, placebo controlled trials have found that buprenorphine maintenance is superior to clonidine detoxification and naltrexone in retaining patients in treatment and decreasing opioid use. The effect of buprenorphine on reducing mortality is not certain. Methadone and buprenorphine are equally effective in reducing opioid use, but there is inconsistent evidence that methadone is marginally superior with respect to treatment retention. Studies examine primarily heroin users so no firm conclusions can be drawn about prescription opioid abusers.

RECOMMENDATION

1. Once a patient is diagnosed with opioid dependence and is deemed appropriate for opioid agonist treatment, prescribers are encouraged to consider prescribing either buprenorphine/naloxone or methadone in order to increase retention in treatment and decrease opioid misuse.

Level of Evidence: I
Grade of Recommendation: A

Clinical considerations

Like all areas of clinical medicine, pharmacotherapy is only initiated following a careful consideration of contraindications, evidence-based benefits, potential risks, other available treatment options and cost. With the exception of allergy, pregnancy (for buprenorphine/naloxone combination product specifically) severe liver dysfunction, acute severe respiratory distress, decreased level of consciousness, paralytic ileus and inability to provide informed consent there are no other absolute contraindications to initiating buprenorphine/naloxone (bup/nlx) therapy. The evidence-based benefits of buprenorphine/naloxone maintenance therapy have been outlined in the previous section. Potential risks will be covered thoroughly in section 4. Overdose, mortality and other adverse effects, in Guideline Recommendations. Bup/nlx is costlier than methadone, though has been shown in one review to be less costly than no treatment [26].

Despite a shortage of evidence, most clinicians feel that pharmacotherapy for substance use disorders should be accompanied by voluntary psychosocial counselling [48], participation in formal treatment programs and/or attendance at mutual aid groups such as Narcotics Anonymous [49].

Some authorities suggest that given the potential risks, cost and demands of opioid agonist treatment, it is good practice for an opioid-dependent patient new to opioid treatment to consider a trial of non-agonist treatment such as withdrawal management and outpatient or residential psychosocial counselling prior to embarking on an opioid agonist maintenance treatment option, especially if their opioid use disorder is less than one year long [50]. We were unable to locate any evidence supporting this suggested one year threshold and given the documented superiority of opioid agonist maintenance treatment over other treatments, such a decision should only be taken after a discussion of the risks and benefits of all different treatment options with the patient [49].

The College of Physicians and Surgeons of Ontario's (CPSO) Methadone Maintenance Treatment Standards and Guidelines specifically suggest that alternate treatments be attempted prior to methadone maintenance treatment in adolescents [51]. It may be that buprenorphine/naloxone has a particular role to play in such scenarios as both buprenorphine [53] and bup/nlx [52] have been studied in the adolescent and young adult population. Some authors have explicity stated a preference to use buprenorphine over

methadone in the treatment of opioid-dependent adolescents or young adults [54, 55] (see Supplement 7).

CONTRAINDICATIONS TO BUPRENORPHINE/NALOXONE

Pregnancy (buprenorphine/naloxone specifically)
Allergy
Severe liver dysfunction
Acute severe respiratory illness
Decreased level of consciousness
Paralytic ileus
Inability to provide informed consent
Possibly elevated transaminases beyond 3–5x ULN

2. Clinical assessment

Key clinical question 2:

Where and how does the physician approach the clinical assessment of the opioid-dependent patient?

Introduction

Allowing opioid-dependent patients to access opioid agonist treatment from their primary care provider is one potential way to increase access to opioid dependence treatment [56]. The use of opioid agonist treatment in primary care settings has been described in a variety of studies both for buprenorphine [57, 58, 59, 23] and for methadone [60, 61]. One small randomized trial [62] found that patients receiving buprenorphine in a primary care clinic had a statistically significant decrease in opioid use compared to patients getting care in an opioid maintenance clinic. Retention in treatment was the same in the two groups. One other randomized trial [63] demonstrated no difference in retention at 90 days, self-reported heroin use or adverse events in patients who received post-withdrawal buprenorphine treatment in a general practice setting compared to a specialty clinic. One cohort study [64] demonstrated improved retention and abstinence rates in smaller primary care clinics compared to larger specialized treatment centres. However in this study there was also a non-statistically significant increase in mortality in the primary care group. One cross-sectional study conducted in France [65] demonstrates increased misuse of buprenorphine and illicit drug use when buprenorphine is prescribed by a "GP" instead of an addiction centre. However, the generalisability of this descriptive study is limited due to differences in the baseline characteristics of the study participants.

It is important to note that in the studies comparing primary care prescribing with specialist clinic prescribing [62, 63], the primary care practitioners/GPs were somewhat experienced in working with opioid-dependent patients though they weren't necessarily experienced with the use of buprenorphine specifically. Notably, when buprenorphine became available in France in the 1990s, general practititioners were encouraged to prescribe the drug without any formal training requirement. This appears to have led to an increase in the number of opioid dependent patients receiving maintenance treatment and a reduction in the number of overdose deaths in the country (149).

Some studies have compared subgroups of patients to see how these particular groups respond to treatment with buprenorphine. One cohort study [66] found no difference in retention in treatment between housed and homeless patients receiving buprenorphine maintenance treatment. Another observational study [47] found that prescription opioid dependent patients receiving buprenorphine/naloxone had increased treatment retention

and opioid-negative urine samples compared to heroin-dependent patients receiving buprenorphine/naloxone.

There were no studies that specifically identified which patients would be more likely to benefit from bup/nlx maintenance treatment compared to methadone or other interventions such as withdrawal management. The recommendations in section 4. Overdose, mortality and other adverse effects, outlne the clinical situations where a prescriber might recommend bup/nlx over methadone and vice versa.

In summary, the evidence suggests that primary care practitioners, most often either having some training in the use of buprenorphine or posessing some prior experience with opioid-dependent patients, are as effective in prescribing buprenorphine as practitioners in specialized addiction clinics. Buprenorphine appears to be effective in a variety of subpopulations with opioid dependence. There is no evidence supporting a particular clinical approach over another. Further guidance as to the clinical approach appears below in the clinical considerations.

RECOMMENDATIONS

2. Buprenorphine/naloxone maintenance treatment can be prescribed to patients in either a primary care setting or in a specialized addiction treatment setting.

   Level of Evidence: I
   Grade of Recommendation: A

3. Prior to initiating maintenance opioid agonist treatment the patient should meet the diagnostic criteria for opioid dependence (Supplements 1 and 3).

   Level of Evidence: III
   Grade of Recommendation: A

4. The decision to initiate opioid agonist therapy with either buprenorphine/naloxone or methadone maintenance should be guided by the individual clinical circumstances and the patient's preferences.

   Level of Evidence: III
   Grade of Recommendation: I

Clinical considerations

Existing buprenorphine clinical guidelines outline a specific history, physical examination and laboratory testing panel that should be followed for every patient being considered for opioid agonist treatment [17, 20]. No evidence was identified in our systematic review that could guide physicians working in this area in terms of how they should be clinically assessing their patients. Nevertheless, there are important parts of an addiction medicine assessment that should be included in any initial patient assessment. The approach outlined in Supplement 3 is one suggestion as to how to structure the clinical assessment of a patient for whom a diagnosis of opioid dependence is suspected and opioid agonist treatment with buprenorphine/naloxone is being considered.

The clinical assessment is important in order to:

1. Confirm the diagnosis of opioid dependence (see Supplement 1)

DSM-IV CRITERIA FOR SUBSTANCE DEPENDENCE

(American Psychiatric Association, 1994)

At least three of the following in a 12-month period*:

- tolerance
- withdrawal
- taking larger amounts than intended
- unsuccessful efforts to reduce drug use
- preoccupation with the drug—great deal of time spent acquiring and using it
- reduction of important activities because of the drug
- continued use despite knowledge of drug-related physical or psychological problems.

** This means that at least three of the criteria need to have been present in the same 12-month period. The criteria do not have to have been present for a duration of 12 months in order to make the diagnosis.*

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2. Estimate the current degree of physical dependence on opioids:
   - » establish patient's history of opioid tolerance and withdrawal
   - » determine the degree of prescriber confidence that the patient will tolerate induction doses of buprenorphine/naloxone.
3. Establish the patient's treatment goals.
4. Identify and explore any concurrent diagnoses that may complicate the induction process:
   i. the use of other substances of abuse, in particular alcohol and/or benzodiazepines
   ii. the presence of concurrent psychiatric disorders (see Supplement 6)
   iii. the presence of a chronic pain problem (See Supplement 10)
   iv. current pregnancy (see Supplement 8)
   v. pre-existing liver disease (see Supplement 9).

5. Assess the patient's psychosocial functioning:
   - » may influence the choice of opioid agonist treatment
   - » provides a baseline to demonstrate improved function with treatment.

   Due to the risk of spontaneous abortion with opioid withdrawal, a baseline pregnancy test is an important part of the assessment of opioid-dependent women of childbearing age who may be pregnant. This is particularly important when considering buprenorphine/naloxone as naloxone has not been approved for use in pregnancy. Also, the induction process will involve opioid withdrawal symptoms that could put the patient at risk of spontaneous abortion.

   Due to case reports of toxic hepatitis following mostly injection misuse of buprenorphine [67], some expert groups are presently recommending baseline and periodic monitoring of liver enzymes [68]. Patients who are at risk for blood borne virus (BBV) infections should be offered appropriate testing.

IMPORTANT COMPONENTS OF THE CLINICAL ASSESSMENT

Comprehensive clinical assessment (see Supplement 3 for more detail)
Establishing that the client meets the DSM-IV criteria for opioid dependence
Urine drug test, specifically for opioids including methadone and buprenorphine (see Supplement 4 for more detail)
Pregnancy test
Liver enzymes
Hepatitis B, Hepatitis C and HIV testing

OPIOID DEPENDENCE VS. "PSEUDOADDICTION" VS. PHYSICAL DEPENDENCE

"Opioid dependence" is characterized by:

- Control—loss of control over use
- Consequences—continued use despite knowledge of harmful consequences
- Compulsion to use
- Cravings

"*Pseudoaddiction*" is the phenomenon of a patient displaying behaviours that to the health care provider appear suggestive of addiction, but that are actually being driven by inadequately treated physical pain.

"*Physical dependence*" refers to tolerance and withdrawal. This is expected with chronic opioid therapy and does not in and of itself diagnose opioid dependence.

It is expected that in many cases the diagnosis of opioid dependence will be quite evident to the clinician (for example a patient with no chronic pain history, one who is acquiring opioids illicitly or who is using opioids intranasally or by injection). In other cases, the diagnosis of opioid dependence will be more challenging, in particular when the patient has a chronic non-cancer pain problem and is using legally prescribed opioids. It is quite likely that prescribers of opioids will encounter some patients receiving chronic opioid therapy whose use of opioids has become problematic and who may have in fact developed opioid dependence (i.e., "addiction"). Readers should be aware of the *Canadian Guideline for the Safe and Effective Use of Opioids for Chronic Non Cancer Pain* [69] for guidance on the clinical clues that should lead an opioid prescriber to consider a diagnosis of opioid dependence in their opioid-prescribed patient. It is important to reinforce that the development of opioid dependence (i.e., "addiction") is not synonymous with the development of physical dependence on opioids. Our opinion is that making the diagnosis of opioid dependence (i.e., "addiction") is important, and it is particularly important to differentiate opioid dependence from "pseudoaddiction." Pseudoaddiction is the phenomenon of a patient displaying behaviours that to the health care provider appear suggestive of addiction, but that are actually being driven by inadequately treated physical pain.

It is for the above reasons that Recommendation 3 is given an A Grade despite the fact that it is only expert opinion that supports that recommendation. The experience of the committee members is such that success with buprenorphine/naloxone maintenance treatment hinges on a proper diagnosis, making this a certain prerequisite before embarking on maintenance treatment.

If a physician is having difficulty with the diagnosis, it is our suggestion that they consult with a colleague or a provider experienced in addiction medicine. Some less experienced physicians may also be more comfortable having an eligible patient assessed and inducted on buprenorphine/naloxone by a more experienced colleague and then assume the prescribing of buprenorphine once the dose is stabilized. We feel that this is a reasonable approach, but caution against having buprenorphine/naloxone subjected to the same challenges as methadone treatment whereby patients requiring treatment have to wait several weeks or months to be inducted on treatment due to a lack of physicians prepared to assist them with that service.

3. Initiation, maintenance and discontinuation of buprenorphine maintenance treatment

Key clinical question 3:

What is the suggested approach to initiating, maintaining and discontinuing buprenorphine maintenance treatment in order to maximize effectiveness of the treatment? This includes suggestions around monitoring the patient with urine drug tests and the provision of take-home doses.

Introduction

Opioid agonist treatment is generally considered a long-term and possibly lifelong treatment. One RCT [52] compares 154 opioid-dependent young adults randomized to either a 14-day buprenorphine/naloxone detoxification or 12 weeks of buprenorphine/naloxone maintenance treatment. The authors found that there were significantly more opioid positive urines in the detoxification group at weeks 4 and 8, but that this finding disappeared by week 12 once the maintenance arm was tapered off their agonist medication. There was also improved treatment retention, less injection and less drug use overall in the maintenance arm. An observational study [70] demonstrates much improved retention in treatment in a buprenorphine maintenance group compared to a detoxification group. One uncontrolled study of 75 young adults receiving buprenorphine [71] demonstrated that the only three deaths in the study occurred while the patients were tapering off buprenorphine after six months of maintenance treatment.

One advantage of the inherent increased safety of a partial mu agonist opioid such as buprenorphine is that the medication should be able to be titrated more rapidly than a full mu receptor agonist such as methadone. Though of uncertain statistical significance, one study [72] concluded that lower buprenorphine induction doses resulted in more relapses during the induction process compared to higher doses which were "well tolerated" (51.2 per cent relapse at 2 mg vs 20.6 per cent at 10 mg) and another study [73] demonstrated a benefit in retention in treatment when doses were adjusted weekly instead of every two weeks. Treatment retention at four weeks is improved when patients are inducted more rapidly [74].

Several studies also conclude that a higher maintenance dose of buprenorphine is superior to a lower dose of the drug both in terms of retaining patients in treatment and reducing illicit opioid use. However, the vast majority of studies analyzing this question were performed using fixed buprenorphine dosing schedules, which does not accurately depict actual clinical practice [28, 75, 76, 77]. The maximum doses of buprenorphine used in these fixed dose studies ranged from 4–32 mg per day.

One study [78] randomized 119 mostly heroin-dependent patients in Australia to receive buprenorphine/naloxone daily observed dosing or to pick up all their doses weekly. It was discovered that there was no difference between the two groups in terms of retention in treatment or self-reported heroin use at three months, but there were five serious adverse events in the weekly pick-up group vs. one in the daily-observed dosing group. Also, there were 18 reported cases of buprenorphine/naloxone diversion, including five reported cases of injection of the drug. It is also worth noting that it was less expensive after 13 study weeks in the weekly pick-up group compared to the daily-observed group. A cross-sectional survey [65] found that there was more illicit drug use and more injecting and snorting of buprenorphine when it was prescribed without any supervision.

One area where there exists a wealth of literature is that of daily versus alternate day dosing of buprenorphine. Several studies (59, 130–141) were identified in our systematic review that, when examined collectively, essentially demonstrate no significant difference between alternate day vs. daily dosed buprenorphine in terms of retention in treatment and illicit opioid use.

In summary, evidence suggests that buprenorphine maintenance treatment improves several outcomes compared to detoxification. Increasing the buprenorphine dose rapidly does have some benefit in terms of retention in treatment and higher maintenance doses of buprenorphine improves retention in treatment and illicit opioid use. Daily and alternate day dosing seem to have equal efficacy and safety profiles. Providing a high number of take-home doses early in treatment appears to be associated with injection of buprenorphine/naloxone.

RECOMMENDATIONS

5. A physician should have a structured approach, such as the one suggested in the clinical considerations, to initiating buprenorphine/naloxone maintenance treatment in order to stabilize a patient at their maintenance dose as rapidly as possible while at the same time avoiding oversedation or precipitated withdrawal.

   Level of Evidence: III
   Grade of Recommendation: A

6. Prior to initiation of buprenorphine/naloxone treatment, the patient must provide informed consent and there must be physician documentation that the patient has been informed of the physical dependence on the medication and possible long-term nature of the maintenance treatment.

   Level of Evidence: III
   Grade of Recommendation: A

7. Once a stable maintenance dose is achieved, physicians can consider non-daily dosing of buprenorphine/naloxone as effective as daily dosing of buprenorphine/naloxone with respect to retention in treatment and reduction in illicit drug use.

   Level of Evidence: I
   Grade of Recommendation: A

8. When monitoring a patient on buprenorphine/naloxone maintenance, the physician should adopt a patient-centred urine drug testing strategy that maximizes clinical utility while avoiding testing without indication.

   Level of Evidence: III
   Grade of Recommendation: I

9. In making decisions regarding the provision of take-home doses of buprenorphine/naloxone, providers should use a clinical risk stratification strategy (as described in the clinical considerations) that aims to support patient autonomy while at the same time respecting patient and public safety.

   Level of Evidence: III
   Grade of Evidence: A

Clinical considerations

Buprenorphine/naloxone maintenance treatment: Informed consent

It is important that patients be informed of all available treatment options to manage their opioid dependence including the option of withdrawal management ("detoxification") and non-pharmacological treatment programs (See Supplement 1). At the same time, patients should be made aware that the evidence demonstrates that opioid maintenance treatment is superior to all forms of detoxification with respect to the outcomes of reducing illicit drug use, improving retention in treatment and reducing injecting behaviour [6, 52, 70]. Patients will have to weigh these benefits against the potential side effects of the medication (as discussed in section 4. Overdose, mortality and other adverse effects) as well as the probable long-term nature of maintenance treatment. Supplement 1 outlines some patient characteristics that might make a trial of withdrawal management a reasonable option. There may also be certain circumstances where clinicians and patients are aware that the patient plans to taper off agonist treatment after a brief period of stabilization (for example three to six months as opposed to the years that are typically encountered with opioid agonist maintenance treatment). Patients with better prognostic factors who are not interested in detoxification or who have relapsed following detoxification may fall into this category. If short-term stabilization on buprenorphine/naloxone and taper is an expressed goal of the patient, then consideration should be given to using buprenorphine/naloxone over methadone as there is some evidence that the withdrawal symptoms tapering off buprenorphine may be less prolonged than when tapering off methadone [79].

Patients who decide to enter into detoxification or who desire to taper off buprenorphine/naloxone treatment after a brief maintenance period require continued close monitoring and appropriate counselling and treatment. Physicians and other practitioners also need to educate patients that both detoxification from opioids and discontinuation of agonist treatment increase overdose risk in the face of a relapse due to loss of tolerance.

It is important to note that buprenorphine/naloxone has not been approved by Health Canada specifically as a detoxification agent in Canada.

SUMMARY

Opioid maintenance treatment vs withdrawal management ("detoxification")

Opioid agonist maintenance treatment results in improved treatment retention and decreased substance use compared to all forms of opioid detoxification.

There may, however be certain types of patients for whom a trial of medical withdrawal management may be reasonable (see Supplement 1). There should be a follow up plan in place and the patient must be made aware of the potential risks following withdrawal management.

These same types of patients may instead express interest in tapering opioid agonist treatment after only a brief maintenance period. In such situations consideration should be given to using buprenorphine/naloxone over methadone.

Buprenorphine/naloxone maintenance treatment: Preparation

Once the diagnosis of opioid dependence is made and the patient has provided informed consent, it is important to review the following pre-induction steps prior to the initiation of buprenorphine/naloxone (bup/nlx) maintenance treatment:

- Ensure no contraindications to bup/nlx (see sidebar page 23).
- If a patient has an active severe dependence on a sedating substance such as alcohol or benzodiazepines, those dependencies should be stabilized prior to initiating bup/nlx therapy. Referral to a specialist in Addiction Medicine should be considered in such patients.
- A urine drug test has been interpreted and is positive for opioids. This initial urine drug test should also be examined for the presence of methadone and buprenorphine.
- The patient has acknowledged they have secured safe travel to and from the office and are not driving or operating machinery on the days of induction.
- A written treatment agreement between the patient and the physician may be helpful. If a patient's pre-treatment urine drug test is positive for methadone or buprenorphine the prescriber will need to satisfy themselves that the patient is not actively receiving opioid agonist treatment from another provider. It would be appropriate for the provider to gather consent from the patient and contact their province's methadone program to see if the patient is an active patient in a methadone program. If the patient indicates that the urine result is a result of trafficked methadone or buprenorphine, the provider may choose to delay the induction process until subsequent urine tests are negative for methadone or buprenorphine.

An induction is best planned when physician availability is assured for the subsequent three days. This will allow the patient, family member, pharmacist or other health care professional to access the prescriber to address any questions or unforeseen issues.

It is important that the patient be told that in order to avoid precipitated withdrawal (see definition on page 35) they need to present to the physician's office on the induction day in opioid withdrawal of at least moderate intensity. Suggested hours of abstinence prior to induction in order to establish withdrawal are: 6–12+ (preferably 12) hours for immediate release opioids or 12–24+ (preferably 24) hours for delayed release. If a patient is chewing or otherwise manipulating the sustained-release coating of an opioid tablet then it is likely acting as an immediate-release opioid. For those initiating bup/nlx from methadone, waiting for at least three to five days after the last dose of methadone before starting bup/nlx is recommended. The methadone dose should also be tapered to 30 mg or less before initiating bup/nlx.

SUMMARY

Preparation

Ensure a clinical assessment has been performed, a urine drug test has been interpreted and is positive for opioids and that there has been a consideration of the contraindications to initiating buprenorphine/naloxone.

Ensure the patient has provided informed consent to buprenorphine/naloxone maintenance treatment and has been made aware of other treatment options. A written consent and treatment agreement may be useful.

Ensure that there are no concurrent substance use disorders, psychiatric or medical disorders that should be stabilized prior to induction of buprenorphine/naloxone.

Inform the patient how long to remain abstinent from opioids to maximize the likelihood of arriving for their induction in satisfactory opioid withdrawal to minimize the likelihood of precipitated withdrawal during the induction.

Ensure the patient has no plans to drive a vehicle or operate heavy machinery during the induction period.

Buprenorphine/naloxone maintenance treatment: Induction (see Appendix G for an induction algorithm)

On the day of induction, the patient should arrive in opioid withdrawal of at least moderate intensity. Prescribers may find it useful to employ an objective scale of opioid withdrawal such as the COWS or CINA scales (see Appendix K) [80, 81, 82] to assist in determining the degree of withdrawal severity. For example, a COWS score of greater than 12 would be considered a sufficient degree of opioid withdrawal to provide an initial 2–4 mg dose of buprenorphine/naloxone. A specific quantitative withdrawal scale may not be necessary if there are obvious symptoms and signs of opioid withdrawal. It is preferable for the patient to present for induction as early in the day as possible so that their induction can be readily monitored throughout the day.

The initial bup/nlx dose should be observed by the physician or pharmacist. This can be accomplished in one of three ways:

- prescribed by physician, dispensed and dosing observed by pharmacist
- prescribed by physician, dispensed by pharmacist, dosing observed in physician's office
- prescribed, dispensed and observed in the physician's office.

Many factors, including geographical location, will affect the decision as to which of the above protocols will be employed on the patient's induction day. Buprenorphine/naloxone is administered sublingually. It will take several minutes under the tongue for the medication to dissolve completely (see Supplement 5) and as a result may be challenging for an inexperienced provider to ensure proper dissolution of the tablet. If a physician will be dispensing buprenorphine from the office, they should follow appropriate practices of storing and dispensing medications from the office [83, 84]. Good communication between prescriber and pharmacist is essential. It is prudent under most circumstances for the prescriber to call the patient's pharmacist prior to writing the first prescription in order to ensure the pharmacy has the medication in stock and is aware of how bup/nlx is dispensed and monitored, especially early in treatment. Strong consideration should be given to faxing a copy of Supplement 5 to the pharmacy along with the initial prescription.

Following the initial induction dose, the physician might consider reassessing the patient at one hour (to assess for precipitated withdrawal) and at approximately three hours (to assess for effectiveness of the initial dose in improving withdrawal symptoms). Precipitated withdrawal can occur when the patient ingests their initial dose of buprenorphine/naloxone when they are not in satisfactory opioid withdrawal. In such a circumstance, the high affinity partial mu agonist will displace the full mu agonist opioid of abuse from the mu receptor causing a rapid decrease in receptor activity and the precipitation of opioid withdrawal symptoms [85]. Typically the patient will present with much worse withdrawal one hour after their induction dose. When this occurs, the physician should explain what has occurred, reassure the patient that the symptoms should resolve in less than 12 hours and consider providing non-opioid symptomatic treatment for withdrawal (see Supplement 1). An additional dose of bup/nlx should not be provided during acute precipitated withdrawal as it may further worsen the precipitated withdrawal syndrome. The patient should present for another trial of induction at a future date.

DEFINITION

Precipitated withdrawal

Precipitated withdrawal can occur when the patient is provided with their initial dose of buprenorphine/naloxone when they are not in satisfactory opioid withdrawal. In such a circumstance, the high affinity partial mu agonist buprenorphine will displace the full mu agonist opioid of abuse from the mu receptor causing a rapid decrease in receptor activity and the precipitation of opioid withdrawal symptoms.

If precipitated withdrawal has not occurred and if after approximately three hours the patient's withdrawal is slightly improved but they still experiencing significant opioid withdrawal symptoms, or if the withdrawal symptoms initially abated, but returned, the physician may prescribe an additional 2–4 mg dose (to a maximum of 8 mg on day 1). Health Canada recommends buprenorphine/naloxone be dispensed daily under the

supervision of a health professional for a minimum of two months, except for weekends and holidays [25]. By contrast, other jurisdictions will provide doses of buprenorphine/naloxone for patients to take home during the induction [17]. One could argue that it makes little sense to deny a patient 2–4 mg of buprenorphine/naloxone to take home during their first induction day to use if opioid withdrawal symptoms emerge in the evening or overnight. Failure to provide the patient with these doses could lead to underdosing during the induction process with subsequent risk of the patient abusing illicit full mu agonist opioids at home or dropping out of treatment. There is also the risk that failure to provide these take-home doses could in fact lead to oversedation on day 1 because in order to minimize the risk of inadequately treated withdrawal, the prescriber feels compelled to give the full 8 mg dose on day 1, which may actually have been a higher dose than was actually required. After this first induction day, all decisions about take-home doses of buprenorphine/naloxone should be made as outlined on pages 39 to 44.

It is important to note that the deaths that have been reported involving buprenorphine almost always involve an additional sedating substance, most often benzodiazepines.

In order to minimize the risk of overdose and death, patients should be instructed to avoid using alcohol or starting any new sedating substances or medications until they have achieved their maintenance dose. Once at their maintenance dose of buprenorphine/naloxone patients should be instructed to continue to be cautious when using any sedating medication or substance of abuse, including alcohol. Patients should not receive their dose of buprenorphine/naloxone if they appear intoxicated or sedated upon presenting for their dose. In such a situation, good communication between the pharmacist, prescriber and patient is important. Ideally these patients will be reassessed by the prescriber before they are provided with another dose of buprenorphine/naloxone, since the dose of bup/nlx or of other potentially sedating medications may need to be adjusted.

SUMMARY

Induction

1. Patient presents in moderate opioid withdrawal to the physician's office as early in the day as possible.

2. After an assessment to establish that the patient is in satisfactory withdrawal, the physician prescribes initial induction dose of 2–4 mg of buprenorphine/naloxone (though could be as high as 6 mg), to be administered sublingually.

3. The ingestion of the dose is observed by a pharmacist or other health care professional to ensure the tablet has dissolved completely (see Supplement 5).

4. Consideration is given to reassessing the patient one hour after the dose to assess for precipitated withdrawal.

5. If necessary, the patient is reassessed after approximately three hours to assess effectiveness of the initial dose and consider prescribing an additional observed dose (to a maximum of 8 mg on the first day). Alternatively, the prescriber may consider prescribing one or two 2 mg tablets of buprenorphine/naloxone for the patient to take home on that first induction day in case withdrawal symptoms emerge later in the evening (again, not exceeding 8 mg total on the first day).

6. The prescriber either asks to see the patient the next day or writes a prescription for observed dosing of buprenorphine/naloxone for the next one to two days for the total amount taken by the patient on day 1. Prescriber communication with t he pharmacist is very important. At the follow-up appointment the patient is assessed for effectiveness of the dose and side effects. The patient is made aware they can present for reassessment earlier than the suggested day if they are feeling the dose is very inadequate or they are having side effects from the dose.

7. The patient is initially seen once or twice per week or more in order to have the adequacy of their buprenorphine/naloxone dose reassessed.

Buprenorphine/naloxone maintenance treatment: Maintenance

As described above, the patient should be reassessed by a physician within one to three days of the induction day. If the patient continues to have significant opioid withdrawal symptoms, the bup/nlx dose can be increased to a maximum of an additional 8 mg as early as the second induction day, though more often a smaller increase in dosage, generally 2–4 mg, will actually be required. The prescriber needs to balance the fact that outcomes in bup/nlx treatment are more favourable with more rapid inductions with the fact that because of buprenorphine's long half–life, the true effect of a particular dose of bup/nlx may not be fully evident until a patient has had that dose for three to five days.

An optimal maintenance dose is one where the patient is free of opioid withdrawal symptoms for the full 24 hour dosing interval without experiencing intoxication or sedation from the medication. At the maintenance dose there will also likely be an improvement in drug cravings. Cravings will likely not resolve completely with bup/nlx alone and strategizing around these cravings is an area to focus on during concomitant psychosocial therapy. Generally, average maintenance doses have been found to be 8–12mg per day [49, 74], though 24 mg per day is the maximum approved single daily dose in Canada [25]. It is difficult for the clinician to predict what a particular patient's bup/nlx maintenance dose will be therefore the general principle is to carefully titrate the bup/nlx dose to effect.

DETERMINING THE OPTIMUM MAINTENANCE DOSE

Adequacy of the buprenorphine/naloxone dose is determined by:

- The patient is not experiencing opioid withdrawal for the entire 24 hour dosing interval
- Reduction of cravings
- Cessation of opioid abuse
- A slip or relapse to opioids does not result in a euphoric effect due to opioid receptor blockade with buprenorphine
- Absence of sedation and minimal other opioid side effects

The frequency of physician visits during the maintenance phase will be determined by the length of time the patient has been in treatment, whether the patient is at their stable maintenance dose and whether their clinical stability is improving. During the induction process, the physician will likely see the patient one to two times per week. Once the patient is at their maintenance dose the visits will likely be every one to two weeks. Once the patient has achieved clinical stability and has started to be eligible for take-home doses, the visits may be every one to three months. Visit frequency will be increased if a previously stable patient begins to demonstrate signs of clinical instability (eg: decreased adherence to the treatment program, change in mental status exam, positive urine drug tests, etc).

At follow-up physician visits the patient's level of clinical stability should be ascertained by focusing on any missed doses, cravings and the use of substances including alcohol. The patient's use and perceived effectiveness/side effects of bup/nlx should be reviewed. The physician should also inquire about the patient's mood, sleep and other psychiatric symptoms. Assessment of the patient's level of functioning with respect to engagement in psychosocial treatment, self-help and mutual aid groups, occupation and personal relationships is also important. The clinician should be formulating a mental status examination by observing the level of consciousness, degree of agitation and evidence of opioid or other drug toxicity (slurred speech, nodding off in interview, pinpoint pupils, evidence of track marks). Urine drug testing complements this assessment and the results should be reviewed to verify adherence to treatment and patient-reported use of other substances.

DEFINITION

Clinical Stability

Clinical stability is determined by certain patient characteristics, namely:

- no evidence of ongoing problematic substance use, including alcohol
- no evidence of acute or unstable psychiatric symptoms
- stable behaviour and social situation
- secure enough housing to safely store the medication.

Once a patient is on their maintenance dose for a period of time, it is possible to modify their bup/nlx to an alternate day schedule (for example, double the dose on M/W/F and a single dose on Sunday). This allows the patient to decrease the number of visits they make to the pharmacy without needing to provide take-home doses. Patients should be cautioned that in the first few days they may notice some increased sedation in the peak time after taking the double bup/nlx dose. Also, they may also find that the dose starts to wear off, with opioid withdrawal symptoms emerging, before the end of the 48-hour dosing interval. The bup/nlx dose can be adjusted accordingly. It is also worth noting that the maximum single daily dose remains 24 mg. This alternate day schedule may be problematic for patients who regularly miss their medication doses for no obvious reason.

SUMMARY – MAINTENANCE

1. Once at maintenance dose and more clinically stable, patient visits become gradually less frequent. Visits will again be more frequent during periods of instability.

2. At follow-up visits, patient clinical stability is ascertained using the clinical assessment and urine drug testing.

3. Areas to cover at follow-up visits include: adequacy of the dose and side effects, substance use, psychiatric symptoms, employment, social relationships, participation in counselling/mutual aid groups.

4. Once the patient is at a stable maintenance dose consideration can be given to alternate day dosing.

5. Patients should not receive a dose of buprenorphine/naloxone if they appear intoxicated or sedated upon presenting for their dose.

6. The prescriber should have a structured approach to missed doses.

7. The prescriber should have a structured approach to deciding about initiating and increasing the number of take-home doses once the patient achieves clinical stability.

Take-home dosing of buprenorphine

Take-home bup/nlx dosing is one way to increase patient autonomy and to assist patients in achieving increased flexibility in their lives. It has been shown in the methadone literature that providing take-home methadone doses in response to abstinence confirmed by negative urine drug tests can be an effective means of encouraging abstinence [86]. Though it may be reasonable to assume that patients on bup/nlx maintenance would respond similarly, we were unable to locate equivalent evidence that buprenorphine take-home doses were effective in encouraging abstinence from problematic substances.

There were studies [87], which concluded that patients on buprenorphine maintenance treatment were more likely to abstain and leave negative urine drug tests as long as they were receiving escalating monetary incentives to do so. Obviously the clinical utility of such a protocol in primary care settings is questionable.

When making decisions about take-home doses of bup/nlx, the prescriber must balance the benefits of treatment retention, positive reinforcement of clinical stability, less treatment burden on the patient and decreased cost with the risk of misuse, injection or diversion of buprenorphine and the possible resultant adverse events. There will need to be clinical decisions made for each individual patient regarding the initiation and maintenance of take-home dosing of bup/nlx. "In order to provide unsupervised dosing while minimizing diversion there needs to be good clinical assessment of appropriateness for take-home doses and ongoing careful clinical monitoring. This can take the form of: client self-report, physical examination, urine drug testing, adherence with dosing schedules and behaviour at the point of dosing." [88]

The universal take-home dose restrictions that are present in Ontario's methadone-prescribing paradigm are likely unnecessary and undesirable for all patients being prescribed buprenorphine/naloxone. However, in approving buprenorphine/naloxone for use in Canada Health Canada has recommended that patients have their buprenorphine/naloxone doses supervised by a health professional for the first two months of treatment, with the exception of weekends and holidays. We were unable to locate any evidence in our review of the literature justifying this particular restriction on buprenorphine/naloxone. As mentioned earlier, there are some jurisdictions outside Canada that provide take-home doses of buprenorphine to the patient immediately following their initial induction dose [17]. Yet other jurisdictions suggest three months of observed dosing prior to take-home doses being prescribed [18]. We feel that the most sensible approach to take-home dosing is one of individual risk assessment as is currently employed in Australia [88].

The committee determined that patients newly inducted on buprenorphine/naloxone maintenance treatment will likely fall into one of three clinical categories:

1. Patients who are clinically unstable to the point that they should initially not receive any take-home doses, including on weekends and holidays. For example, patients who are exhibiting:
   - » recent injection
   - » recent suicidality
   - » cognitive impairment
   - » unstable housing
   - » ongoing opioid use
   - » other active alcohol or drug dependencies.

2. Patients whose degree of clinical stability makes initial weekend and holiday take-home doses appropriate within the first two months on the program. For example, patients who exhibit none of the features listed in the category above.

3. Patients whose degree of clinical stability make it appropriate for additional take-home doses beyond weekends and holidays within the first two months on the program. For

example, patients who:

» have clinical stability beyond that of category 2
» dependent primarily on prescribed opioids from one prescriber
» exhibits stable behaviour in the office and the pharmacy
» no severe psychiatric symptoms
» particularly stable social situation.
» work and/or family responsibilities make a high number of observed doses overly restrictive and may lead to treatment drop out.

In the Canadian setting, the provision of take-home doses earlier than two months other than on weekends and holidays would technically be "against label." The committee was very mindful of the fact that buprenorphine is listed as Schedule 1 in the Controlled Drugs and Substances Act or is classified as a narcotic as defined in the Narcotic Control Regulations in Canada and as such we sought independent expert legal advice regarding the possibility of a prescriber providing additional take-home doses of buprenorphine/naloxone within the first two months of treatment and in doing so making this an "against label" prescription. The ultimate conclusion was that if after a thorough clinical assessment the physician decides that a patient would benefit from and has a degree of clinical stability that makes he or she eligible for additional take-home doses earlier than two months, then these take-home doses could be provided so long as the patient has been made aware that this is against the Health Canada label and that a discussion has occurred with the patient outlining all the possible additional risks of receiving take-home dosing early in treatment such as overdose, careless storage and unintended ingestion by others, injection and diversion. The patient should also be very carefully monitored over time to ensure that he or she is actually benefiting from the take-home doses. The physician should document these discussions as well as the clinical rationale for the against-label provision of take-home doses. In general, even patients who are deemed appropriate for higher numbers of take-home doses within the first two months should have the actual number of take-home doses increased gradually.

ADDITIONAL TAKE-HOME DOSES WITHIN FIRST TWO MONTHS OF BUPRENORPHINE/NALOXONE TREATMENT

- The patient must have a satisfactory level of clinical stability.
- It must be evident how the earlier take-home doses will benefit the patient (e.g., fulfilling work commitments) and that they have a lower risk of misuse or diversion of the take-home doses.
- The patient should be made aware of the "against-label" nature of these take home doses and informed of the potential risks.
- Take-home doses should be increased gradually and Tthe patient should be carefully monitored to ensure he or she continues to benefit from these take home doses.
- All the above should be documented in the clinical record.

There are also some general considerations with respect to take-home buprenorphine/naloxone doses:

It is preferable to have tighter boundaries which subsequently loosened in response to patient stability than to have initially looser boundaries subsequently tightened in response to patient non-stability [78, 89]: This evidence supports the approach that patients have observed dosing initially until their dose is stabilized and they begin to demonstrate improved control of their opioid dependence. This approach is supported by authorities in the field [49].

Graduated take-home dosing schedule is preferred to receiving all take-homes at once: Once there is subjective and objective evidence of patient stability and the prescriber feels that the benefits of take-home dosing outweigh the risks, the physician can consider the initiation of a small number of take-home doses. This will allow the prescriber to assess how well a patient is able to control their use of a limited number of take-home doses before prescribing large amounts of take-homes all at once. Once the decision is made to initiate take-home doses, the patient should be informed of the risks of take-home doses to him or herself, their families and/or the larger community. Patients should be asked how they plan to store their take-home doses and safe storage should be emphasized with the patient. This informed consent around the storage and use of take-home doses may take the form of a written take-home agreement between the patient and the physician.

Special circumstances: There may occasionally be circumstances where a patient will request take-home doses of buprenorphine/naloxone before they would ordinarily be eligible. This could be for reasons of travel, compassionate reasons, etc. In these situations, the physician will need to weigh the risks of providing take-home doses to the patient prior to stabilization with the risks of not providing the patient with take-homes when they are truly required and having them possibly drop out of treatment. Often there are alternatives to providing take-homes (for example, switching to alternate day dosing or locating a more convenient pharmacy that can dispense an observed dose) that can be mobilized without having to provide a take-home dose when it goes against the clinician's better judgment.

Progression of take-homes doses: The actual rate of increasing the number of take-home doses will depend on the degree of clinical stability of the patient. There is currently no evidence to guide clinicians on the optimal rate of progression or the maximum number of routine take-home doses in a buprenorphine/naloxone maintenance program. The authors felt that one to two weeks was a reasonable maximum number of routine consecutive take-home doses. Consideration could be given to providing a greater number of consecutive take-home doses if this would facilitate the patient's retention in treatment and overall level of functioning without compromising safety. It is important that the prescriber and pharmacist are aware that take-home doses are dispensed between the observed doses. See sample prescriptions in Supplement 5.

Risks of take-home doses: Whenever take-home doses are initiated, it is important that the patient be aware that misuse of their take-home doses could lead to overdose or death, especially if used with other sedating substances. Particular caution should be exercised

in initiating or maintaining take-home doses for patients who have recently acknowledged suicidal ideation, injection drug use, have unstable housing or cognitive impairment.

They should also be aware that ingestion of the buprenorphine/naloxone by someone other than themselves could lead to serious CNS depression, especially when children are involved. A recent case series of 86 paediatric ingestions of buprenorphine [90] demonstrated no deaths in those children. Seven per cent had serious CNS or respiratory symptoms. Any accidental ingestion of buprenorphine/naloxone should be referred to the emergency department for monitoring and possible naloxone administration. It is important that everyone involved be aware of the clinical implications of the long half-life of buprenorphine (see page 52).

Monitoring of take-home doses: If the clinical stability of the patient deteriorates, then closer monitoring (such as: more frequent visits and urine drug tests, more observed doses) or referral to more intensive treatment is required. For example, relapse to problematic substance use, significant unstable mental illness, unwillingness to provide urine drug tests when requested, loss of stable housing and evidence of diversion of buprenorphine/naloxone (i.e., requests for early refills, frequent lost prescriptions) would be some reasons the prescriber would strongly consider increasing the number of observed ingestions of bup/nlx and possibly discontinuing all take-home doses altogether.

If a prescriber finds themselves in a position where, due to the patient's sudden instability, they are changing their patient from a high level of take-home bup/nlx doses per week to daily observed dosing, they should be aware that if the patient has been diverting many of their take-home bup/nlx doses they will have lost some or all of their tolerance to opioids and by suddenly receiving daily observed doses in the pharmacy, they could develop sedation, overdose or precipitated withdrawal. In situations where diversion is likely to have occurred, prescribers should reduce or discontinue the patient's dose of bup/nlx by 25 to 50 per cent, and should consider discussing the case with a physician with expertise in addiction medicine.

SUMMARY

"Take-Home" Buprenorphine/Naloxone Doses

1. Prescribing of take-home doses of buprenorphine/naloxone is a therapeutic intervention with benefits and risks

2. Take-home doses should not be initiated until the patient has been deemed to exhibit features of clinical stability. Exercise caution if patient has recently been suicidal, injecting, has cognitive impairment or unstable housing.

3. Generally, tighter boundaries should be loosened as the patient displays increased clinical stability rather than initially looser boundaries be tightened in response to instability.

4. There should be a gradual increase in the number of weekly take-home doses up to a suggested maximum of one to two weeks of consecutive take-home doses dispensed between observed doses.

5. Health Canada encourages all doses to be observed, with the exception of weekends and holidays, for at least the first two months on buprenorphine/naloxone. If the prescriber feels that a patient is eligible for additional regular take-home doses earlier than two months, this should be justified in the clinical record and the patient needs to have explicitly consented to this "against label" prescription.

6. All patients, when about to receive their first take-home dose(s) should be made aware of the risks to family and the public.

7. Take-home doses should be reduced or eliminated in response to a loss of clinical stability. If a high level of take-home doses are eliminated all at once, and diversion is suspected, the prescriber should consider reducing the buprenorphine/naloxone dose by 25 to 50 per cent.

Missed doses

We were unable to identify any evidence in the systematic review related to the handling of missed bup/nlx doses. Missed doses are notable as they will contribute to a loss of tolerance to buprenorphine. Due to buprenorphine's partial mu agonist properties and lower risk of overdose, the policy of adjusting and re-titrating a patient's bup/nlx dose likely does not require the same degree of vigilance as with the full mu agonist methadone.

If a patient has missed five days or less of bup/nlx, they may resume their previous dose of bup/nlx. If the patient misses more than five days, the pharmacist should ask the patient to revisit the physician for a dose adjustment. The physician should consider following *Table 1* below.

Table 1: Suggestions for Managing Missed Doses [19]

Buprenorphine Dose	Number of Consecutive Days Missed	New Starting Dose
> 8 mg	> 7 days	4 mg
> 8 mg	6–7 days	8 mg
6–8 mg	6 or more days	4 mg
2–4 mg	6 or more days	2–4 mg

If the patient has relapsed to full agonist opioids, the patient should be advised to suspend resumption of their bup/nlx until they are in moderate opioid withdrawal due to the risk of precipitated withdrawal.

Missing doses when receiving bup/nlx on an every other day schedule can be challenging. If a patient misses two consecutive every other day doses they should not be dosed until they see the physician to be switched back to daily dosing, likely with a lowered dose, in order to re-stabilize their dose.

Urine drug testing

Much like the decision around the provision and maintenance of take-home doses, it is very important that clinicians use their clinical judgment with respect to the frequency of urine drug testing. The clinician should always record the result of the urine drug tests in the clinical record and should be able to demonstrate that the result has informed their clinical actions (for example, reflecting the urine result back to the patient to recognize their ongoing abstinence or reflecting the result as a consideration in the decision to adjust or maintain the number of observed and take-home doses). There is an argument to be made for physicians ordering urine drug tests "for cause" as opposed to the every one-to-four-week urine drug *screening* of that is typically employed in a methadone maintenance program. How frequently a patient is asked to provide a urine drug test will be determined by the pre-test likelihood that there will be important information to be gleaned from that urine test. In general, it would be appropriate to perform a urine drug test during or immediately following each patient appointment. More or less frequent testing should be performed for a clinically justifiable reason.

It is important to be aware that most laboratories will likely not routinely test for the presence of buprenorphine in the urine. This request for buprenorphine and buprenorphine metabolites needs to be specifically indicated on the laboratory requisition.

See Supplement 4 for more information about the specifics of urine drug testing.

Unsuccessful stabilization on buprenorphine/naloxone

If a patient fails to stabilize on bup/nlx maintenance therapy despite appropriate dose titration, regular physician visits and psychosocial treatment and reasonable management of concurrent disorders, the physician may want to have a discussion with the patient about a possible switch in treatment modalities. This could include remaining on bup/nlx and referring the patient for more intensive counselling or to a residential treatment program. It could involve referring the patient to a physician experienced in addiction medicine for consideration of a switch from bup/nlx to methadone maintenance treatment. If the patient is displaying persistent problematic use of non-opioid substances, consideration should be given to referring for intensive psychosocial treatment or consulting with a physician experienced in addiction medicine for management of these disorders.

Tapering stable patients

As discussed previously, bup/nlx maintenance treatment is generally considered a long-term treatment with no predetermined end point to treatment. That said, there will be patients for whom a taper off of bup/nlx maintenance has been agreed upon by the patient and prescriber.

Ideally, patients taper off of bup/nlx maintenance while drug free, functioning well and with ongoing psychosocial support. In some circumstances patients may choose to taper off of bup/nlx treatment under less then ideal circumstances (e.g., ongoing drug use or ongoing social instability).

Regardless of the clinical circumstance, the bup/nlx should be tapered gradually, perhaps 2mg per week initially and the taper rate adjusted based on the patient's experience of the taper. Throughout the taper patients should be monitored carefully for withdrawal, cravings and lapses to drug use. If clinical stability is lost during the taper, retitration of the bup/nlx dose should be recommended to the patient.

4. Overdose, mortality and other adverse effects

Key clinical question 4:

What are the possible adverse effects of buprenorphine/naloxone of which the clinician needs to be aware? How do these adverse effects compare to other treatments for opioid dependence and how might they influence the treatment selection?

Introduction

The relative similarity in efficacy between buprenorphine and methadone is but one consideration regarding the choice of treatment. As outlined in Supplement 2, buprenorphine has been classified as partial mu receptor agonist. It has been demonstrated that buprenorphine will display a "ceiling effect" in non-dependent opioid users with respect to its mu agonist effects, such as respiratory depression and opioid agonist psychological effects [91, 92]. In other words, beyond a certain serum concentration of buprenorphine, there will be no additional mu agonist effect. This phenomenon differs significantly from methadone and other full mu agonists in the sense that higher concentrations of full mu agonists will always result in an increased mu effect (euphoria, analgesia, sedation, respiratory depression). These pharmacodynamic differences between buprenorphine and methadone are what have led many authorities to argue that buprenorphine is a safer drug with respect to the risk of overdose [17]. We did identify some clinical evidence supporting this claim [93, 94], and one non-statistically significant study inconsistent with it [95]. The issue of increased safety with buprenorphine is an important one as past experience has been that the risk of methadone overdose can be quite high, especially within the first two weeks of treatment [96].

Despite the above studies demonstrating buprenorphine's partial mu agonist properties and decreased risk of overdose compared to methadone, there are other studies that describe important clinical measurements consistent with increased respiratory depression with parenteral buprenorphine compared with placebo in non-dependent opioid using individuals [91]. In three other studies comparing respiratory effects of parenteral buprenorphine with other opioids, including methadone, in opioid-dependent subjects, there was no difference in physiologic measurements in the buprenorphine group compared to the full mu opioids [97, 98, 99]. This means that even though there is a ceiling to the degree of mu effect buprenorphine will impose on an individual, buprenorphine clearly does still exhibit mu agonist effects.

Four RCT studies in the Mattick 2008 Cochrane systematic review described a mortality outcome. Three of these studies were buprenorphine vs. placebo [38, 39, 40]. One of these studies [38] reported four deaths in the placebo group and no deaths in the buprenorphine group which was a statistically significant reduction in mortality in the treatment group (P=0.015). There were no reported deaths in the other two studies. A fourth study [41] compared fixed dose buprenorphine and fixed dose methadone and though there were two deaths in the study, the authors concluded that there was no difference between the study groups.

Irrespective of the fact that many of the available studies are underpowered to detect important mortality outcomes, on balance it would appear that individual level data favours buprenorphine over methadone with respect to less mortality among patients receiving buprenorphine. In addition, three post-mortem file reviews [100, 101, 102] conclude that buprenorphine is implicated in fewer deaths than methadone. However, two observational studies [103, 104] do not appear to demonstrate mortality differences between buprenorphine and methadone and three retrospective cohort studies [93, 94, 95] appear to describe contradictory findings with respect to overdose risk when comparing buprenorphine and methadone.

Despite the possibility of confounding and other bias in population-level studies, it is the population-level mortality data from France [105] that should be most compelling data for policy makers. This French data indicates that from 1994 to 1998 the death rate from methadone was three times greater than the death rate from buprenorphine.

There are several case reports of diversion of buprenorphine to the injection route, both amongst patients receiving a prescription [106, 107, 108, 109] as well as people acquiring trafficked buprenorphine [110]. One cross-sectional study [65] demonstrates an increased prevalence of IV or intranasal abuse of buprenorphine compared to methadone (P<0.001). In this study, there was virtually no IV/intranasal abuse in the methadone group. The majority of these studies/reports involve buprenorphine mono-product. It has been hypothesized that the addition of naloxone in the buprenorphine/naloxone product will act as a deterrent and minimize the risk of parenteral abuse of buprenorphine/naloxone [68]. The available data (discussed under clinical considerations) suggests that there is still considerable risk of injection with the combination product.

There are studies that describe no QT interval prolongation with buprenorphine, whereas methadone does prolong the QT interval [111]. There are also several studies that suggest that there are fewer sexual side effects (142–145) and cognitive side effects (146–148) with buprenorphine compared to methadone.

There are case reports of drug-induced toxic hepatitis with buprenorphine [112, 68]. This phenomenon has generally been described in people with pre-existing liver disease or who are abusing buprenorphine parenterally. Some studies have shown both an increase in liver enzymes [113] and a normalization of liver enzymes [114] in Hepatitis C positive patients receiving buprenorphine.

In summary, the evidence does suggest that despite buprenorphine's mu effect on respiratory rate and oxygen saturation, it appears to display less overdose and mortality

risk compared to full mu opioids such as methadone. This is likely due to the partial agonist pharmacodynamic profile of the drug. This increased safety profile has not been demonstrated in large randomized controlled trials of opioid-dependent patients receiving opioid agonist treatment. The long term morbidity and mortality from the possible injection of buprenorphine-naloxone is currently unclear.

RECOMMENDATIONS

10. Policy makers should be aware that in countries where buprenorphine is equally available as methadone, buprenorphine has a lower attributable death rate than methadone.

    Level of Evidence: II-3
    Grade of Recommendation: A

11. Limited public funding is currently the major barrier to accessibility of buprenorphine/naloxone maintenance treatment in Ontario. We recommend that policy makers remedy this barrier.

    Level of Evidence: III
    Grade of Recommendation: B

12. Clinicians should be aware that there is little in the medical literature to guide them in terms of which maintenance agent to prescribe an individual opioid-dependent patient. In making this decision, the prescriber and patient should consider the following, which is based on clinical experience:

    Buprenorphine/naloxone may be preferred over methadone to treat opioid dependence in the following patient populations:

    a) When methadone is absolutely or relatively contraindicated, such as:
       i) Presence of, history of or increased risk of prolonged QT interval
          Level of Evidence: I
          Grade of Recommendation: A

       ii) History of methadone allergy
          Level of Evidence: III
          Grade of Recommendation: A

    b) History of significant side effects on methadone such as:
       i) Sexual side effects on methadone
          Level of Evidence: II-2
          Grade of Recommendation: B

       ii) Severe sedation or constipation with methadone
          Level of Evidence: III

Grade of Recommendation: C

c) Increased risk of toxicity from a full mu agonist:
   i) If suspect a lower tolerance to opioids
   Level of Evidence: III
   Grade of Recommendation: B

   ii) If concurrent heavy or unstable use of sedating drugs/medication
   Level of Evidence: II-3
   Grade of Recommendation: B

   iii) If elderly
   Level of Evidence: III
   Grade of Recommendation: B

   iv) If significant respiratory illness
   Level of Evidence: III
   Grade of Recommendation: B

d) Good prognostic factors:
   i) Briefer history (i.e., Less than 1 year) of opioid misuse
   Level of Evidence: III
   Grade of Recommendation: C

   ii) Social supports
   Level of Evidence: III
   Grade of Recommendation: C

   iii) Adolescents and young adults
   Level of Evidence: III
   Grade of Recommendation: B

e) Past history of successful stabilization with buprenorphine/naloxone
   Level of Evidence: III
   Grade of Recommendation: I

f) Patient choice and access. In particular patients residing in geographic areas where methadone is not available in a timely manner, or when challenging pharmacy access makes the possibility of alternate day dosing of buprenorphine/naloxone desirable.
   Level of Evidence: III
   Grade of Recommendation: B

13. Methadone may be preferred over buprenorphine/naloxone in the following patient populations:

    a) Pregnancy (specifically avoiding the naloxone component in the buprenorphine/naloxone combination product)
       Level of Evidence: III
       Grade of Recommendation: A

    b) Clinical situations where opioid withdrawal during induction is particularly hazardous – i.e., cardiovascular instability
       Level of Evidence: III
       Grade of Recommendation: B

    c) Prior inability to stabilize on bupenorphine/naloxone maintenance treatment
       Level of Evidence: III
       Grade of Recommendation: B

    d) History of abusing buprenorphine via injection
       Level of Evidence: III
       Grade of Recommendation: A

    e) Patient side effects with or allergy to buprenorphine or to excipients including acesulfame
       Level of Evidence: III
       Grade of Recommendation: A

    f) Patients experiencing dry mouth of severity that would interfere with dissolution and absorption of sublingual buprenorphine/naloxone tablets (dry mouth may be due to side effects of concurrent medications, chemotherapy, or conditions causing dry mouth e.g. Sjogren's Syndrome)
       Level of Evidence: III
       Grade of Recommendation: A

    g) Past history of successful stabilization with methadone
       Level of Evidence: III
       Grade of Recommendation: I

    h) Patient choice and access, in particular patients with limited financial resources that make reliable long-term use of buprenorphine/naloxone uncertain
       Level of Evidence: III
       Grade of Recommendation: B

Clinical considerations

It is important to reinforce that the vast majority of the above considerations are based on expert consensus alone. With the exception of QT interval prolongation, sexual dysfunction and cognitive functioning, empirical evidence is lacking for many of the suggestions in the above recommendation. Clinicians should consider the above suggestions in conjunction with other factors such as treatment availability, cost and patient preference in deciding on an agonist treatment agent.

The prescriber should be aware of the risk of injection of buprenorphine/naloxone. Despite the fact that the addition of naloxone to buprenorphine appears to offer some protection against the drug being injected by full mu agonist opioid-dependent individuals due to the risk of precipitation of opioid withdrawal [115, 116, 117] there is evidence that the combination product, when injected, provides a pleasurable effect to non-dependent opioid abusers [118, 119] and to some buprenorphine/naloxone maintained individuals [78]. Some authors conclude that the injection and diversion risk with buprenorphine/naloxone is in fact as great as with buprenorphine mono-product [120]. There is also data demonstrating that buprenorphine/naloxone is frequently diverted and is most often acquired illicitly from an individual who has a legitimate prescription for the drug [121]. The fact that the ingestion of the buprenorphine sublingual tablet is more difficult for a practitioner to observe than the oral methadone liquid might also contribute to injection or diversion of buprenorphine.

Due to its pharmacologic properties and the presence of naloxone, injection of buprenorphine may not contribute to short-term mortality amongst patients who are being prescribed the drug or who are acquiring the drug illegally but could contribute to increased morbidity or longer term mortality from the act of injecting itself such as bacterial endocarditis, toxic hepatitis or bloodborne virus transmission.

If a clinician suspects that a patient is injecting their doses of buprenorphine-naloxone, they should be placed on daily observed dosing and strong consideration should be given to switching them onto a methadone maintenance program. Such a patient should be referred to a physician knowledgeable in addiction medicine.

The recommendation to consider buprenorphine/naloxone over methadone in opioid-dependent patients who have existing unstable use of other sedating substances should be interpreted carefully. As discussed above, there are respiratory depressant effects of buprenorphine even when administered to opioid-dependent individuals. Studies identified in the systematic review conclude that the vast majority of deaths involving buprenorphine also involved other sedating drugs, especially benzodiazepines [122, 123]. Therefore the prescriber cannot assume that their patient will not come to harm as a result of polysubstance abuse simply because buprenorphine is employed instead of methadone. As discussed in the previous section, it would generally be a more prudent course of action for the clinician to stabilize any misuse of other sedating substances before initiating buprenorphine/naloxone maintenance treatment.

Until further studies are available, it is worth considering baseline and periodic monitoring of liver enzymes while a patient is receiving buprenorphine. If the baseline liver enzymes are significantly elevated (i.e., >5x upper limit of normal), one may hold off on the induction of buprenorphine until the liver enzymes fall.

If a woman becomes pregnant while being prescribed buprenorphine/naloxone, she should be maintained on her buprenorphine-naloxone maintenance treatment and referred without delay to a physician knowledgeable in addiction medicine to arrange for either buprenorphine mono-product or a switch to methadone maintenance.

In the event of suspected overdose in which buprenorphine is likely to be involved one must assess the patient's airway, breathing and circulation. If the patinent is demonstrating cardiorespiratory compromise or if the patient is severely obtunded, emergency services should be deployed and parenteral naloxone should be administered at the first opportunity. The emergency responders should be informed of the patient's use of buprenorphine and the high affinity of the drug for the mu opioid receptor and the long half-life of the drug that may necessitate a longer period of naloxone treatment and patient observation. If possible, the emergency room physician should be telephoned in order to provide the same information. All other substances that patient is known to have recently consumed must also be communicated.

In Ontario buprenorphine/naloxone (Suboxone) is available for public funding only through the Exceptional Access Program (EAP) for patients for whom methadone is either contraindicated or who are at high risk of methadone toxicity. Patients are also eligible for coverage through EAP if methadone is not available or there is a wait list of three months or longer. There is an EAP renewal requirement at one year. Further information on EAP requirements can be found at www.health.gov.on.ca/english/providers/program/drugs/eap_criteria.html

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Appendices

Appendix A

Levels of evidence and grades of recommendation

Levels of evidence

I	Evidence from randomized, controlled trial(s)
II-1	Evidence from controlled trial(s) without randomization
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group
II-3	Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Grades of recommendation

A	There is good evidence to recommend the action.
B	There is fair evidence to recommend the action.
C	The existing evidence is conflicting and does not allow making a recommendation for or against the use of the action; however, other factors may influence decision-making.
D	There is fair evidence to recommend against the action.
E	There is good evidence to recommend against the action.
I	There is insufficient evidence (in quantity and/or quality) to make a recommendation; however, other factors may influence decision-making.

Adapted from Definitions of Levels of Evidence and Grades of Recommendations of the Canadian Task Force on Preventive Health Care. Available from: http://www.cmaj.ca/cgi/content/full/170/6/976/DC1

Appendix B

Literature search strategy

Three Cochrane systematic reviews that addressed important aspects of the key clinical questions were initially identified. Systematic searches were conducted to update the information from these reviews and to more fully address the key questions where there were identified gaps. Searches were conducted in January and February 2009 using Ovid MEDLINE, Ovid EMBASE and EBSCO PsycINFO.

There was a significant amount of overlap among the results found for the different key clinical questions, so the overall search strategies, rather than separate strategies for each question, are outlined below.

Ovid MEDLINE

(exp *Buprenorphine/ and exp *Opioid-Related Disorders/ and (exp clinical trial/ or clinical trial.pt. or random.mp. or tu.xs)) limited to English language, 2006–2009

(exp *Buprenorphine/ and exp *Opioid-Related Disorders/ and (exp clinical trial/ or clinical trial.pt. or random.mp. or tu.xs) and (exp placebo.mp or exp *Naltrexone/ or exp Clondine/)) limited to English language, 1980–2005

(exp *Buprenorphine/ and (exp Mortality/ or mortality.ti or Quality of Life/ or exp Patient Compliance/ or Treatment Refusal/ or Patient Dropouts/) or Buprenorphine/to, po, ae) limited to English language, 1980–2009

Ovid EMBASE

(exp *Buprenorphine/ and exp *Opioid-Related Disorders/) and (exp clinical trial/ or random.mp or tu.xs) limited to English language, 2006–2009

(exp *Buprenorphine/ and (exp Clondine/ or exp Naltrexone Derivative/ or exp Naltrexone/) and (exp clinical trial/ or random.mp or tu.xs) limited to English language, 1980–2009

(exp *Buprenorphine/ and (exp Side Effect/ or "adverse effect".mp or *Buprenorphine/ ae, to or exp mortality/ or mortality.m_titl. or exp "quality of life"/)) limited to English language, 1980–2009

EBSCO PsycINFO

((buprenorphine(KW) and (trial or random or placebo)KW and human(TW))

Limited to English language, 1980–2009

((buprenorphine)(KW) and (adverse or "quality of life" or mortality)TW)

Limited to English language, 1980–2009

Appendix C

Conflict of interest

The committee chair was selected because of his expertise in both primary care and addiction medicine and lack of any potential conflicts of interest with the manufacturer of buprenorphine/naloxone.

All committee members were required to fill out a conflict-of-interest disclosure statement both at the beginning and at the end of the guideline development process. These statements were reviewed by the committee chair. Several committee members disclosed potential conflicts of interest with the former and/or current manufacturer of buprenorphine/naloxone. In order to determine a strategy of managing potential conflict of interest in developing the guideline, the chair, with support from the guideline committee members, consulted very early in the process with the chief of staff at CAMH as well as CAMH bioethicist Barbara Russell. Ms. Russell offered several suggestions to the chair for managing any potential conflicts of interest and thus minimizing bias in the development of the guideline.

The chair ultimately decided that all committee members would continue to participate fully on the committee, as their clinical expertise was extremely valuable to the process, but that the chair would be the sole principal author of the guideline and that fewer than 50 per cent of co-authors would have a declared potential conflict with the manufacturer of buprenorphine/naloxone. During the initial meeting of the committee, the chair was also given the authority to make the final decision about a particular recommendation if the committee was not able to achieve unanimity. Therefore, in the event that a dispute arose about a particular recommendation and consensus was not achievable, the chair was able to consider each committee member's potential conflict of interest in deciding on a final recommendation.

Ms. Russell was also able to assist the committee chair in determining that CAMH did not have an institutional conflict of interest with Schering-Plough, the manufacturer of Suboxone at the time the guideline work began.

Specific author potential conflict-of-interest disclosure statements

As discussed in the Methods section, all authors were invited to invoice CAMH for payment of honoraria related to the time they worked on the guidelines.

Dr. Handford received honoraria from Pfizer Inc. in 2006 for educational presentations; **Dr. Kahan** received honorarium from Schering-Plough for reviewing an online course, received paid expert testimony from Schering-Plough for a presentation to Health Canada regarding the buprenorphine/naloxone notice of compliance, received reimbursement for travel expenses to NIHB from Reckitt Benckiser and was paid by Reckitt Benckiser for attendance at a physician advisory board meeting; **Dr. Srivastava** received an honorarium from Schering-Plough for sitting on its Suboxone National Advisory Board and for developing educational program content, received an educational grant from Schering-Plough and received a paid consultancy from Reckitt Benckiser; **Dr. Cirone** declared no conflict; **Ms. Sanghera** declared no conflict; **Dr. Palda** declared no conflict; **Dr. Lester** declared no conflict; **Ms. Janacek** received an honorarium to develop and review educational material; **Dr. Franklyn** received honoraria from Reckitt Benckiser for attending an advisory board meeting and speaking at a conference; **Dr. Cord** received paid consultancies from the Nova Scotia Chronic Pain Collaborative Care Network, the College of Physicians and Surgeons of Ontario and CAMH, he received payment for the development of educational presentations from the Ontario College of Family Physicians, the General Practitioner Psychotherapy Association and the Toronto Psychoanalytic Society, and he received Advisory Board payments from Purdue Pharma Canada; **Dr. Selby** received grants and research support from Health Canada, Smoke-Free Ontario, MHP, CTCRI, CIHR, Alberta Health Services (formerly Alberta Cancer Board), Vancouver Coastal Authority, Pfizer, OLA, ECHO, NIDA and CCS, he received Speakers Bureau honoraria from Schering Canada, Johnson & Johnson Consumer Health Care Canada, Pfizer Inc. Canada, Pfizer Global, Sanofi-Synthelabo Canada, GSK Canada, Genpharm and Prempharm Canada and NABI Pharmaceuticals, and he received consulting fees from Schering Canada, Johnson & Johnson Consumer Health Care Canada, Pfizer Inc. Canada, Pfizer Global, Sanofi-Synthelabo Canada, GSK Canada, Genpharm and Prempharm Canada, NABI Pharmaceuticals, V-CC Systems Inc. and EHealth Behaviour Change Software Co. AstraZeneca Canada Inc.

Appendix D

Key clinical questions

The following are the key clinical questions originally developed by the committee to guide the guideline development process.

1. Does the initiation of buprenorphine maintenance treatment compared to methadone maintenance treatment, clonidine detoxification, naltrexone or placebo in adults and adolescents with opioid dependence decrease morbidity/mortality or improve quality of life? [As well as intermediate outcomes: treatment retention and adherence, decreased opioid use, decreased substance use, global harm reduction (e.g., criminal activity)].

2a. Among adolescents or adults with opioid dependence, can a group who is most likely/least likely to benefit from buprenorphine maintenance treatment be reliably identified by history and physical examination?

b. Which tests should be ordered prior to starting therapy to identify patients at increased risk of adverse effects?

c. Which tests should be ordered prior to starting therapy to identify patients who have specialized needs that require follow-up?

3a. What is the ideal treatment regimen to optimize effectiveness?

b. What is the optimal starting dose? How frequently should doses be increased and by what increment? What is the optimal maintenance dose?

c. Is there evidence that urinary drug screening and/or contingency management changes treatment outcomes? What is the ideal regimen of urine drug testing (frequency/type)? How should the tests be ordered? What are the key elements of contingency management with which precribers should be familiar? When can take-home doses be safely started?

d. When should a primary care practitioner refer the opioid-dependent patient to a practitioner with addiction medicine expertise?

e. When should buprenorphine treatment be discontinued? How should the drug be tapered and stopped? Does the taper regimen differ when discontinuation is involuntary?

4a. What are the adverse effects of buprenorphine treatment and how do they differ from methadone and clonidine?

b. Which elements of the treatment protocol decrease adverse effects?

c. Does differing availability of opioid agonists affect their adverse effect profile?

d. How does the shorter course of treatment used in buprenorphine as compared to methadone affect the lifelong adverse effect risk?

Appendix E

Resources used to support guideline development

The following resources were all reviewed in full text, and were used as the basis for developing the recommendations.

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Appendix F

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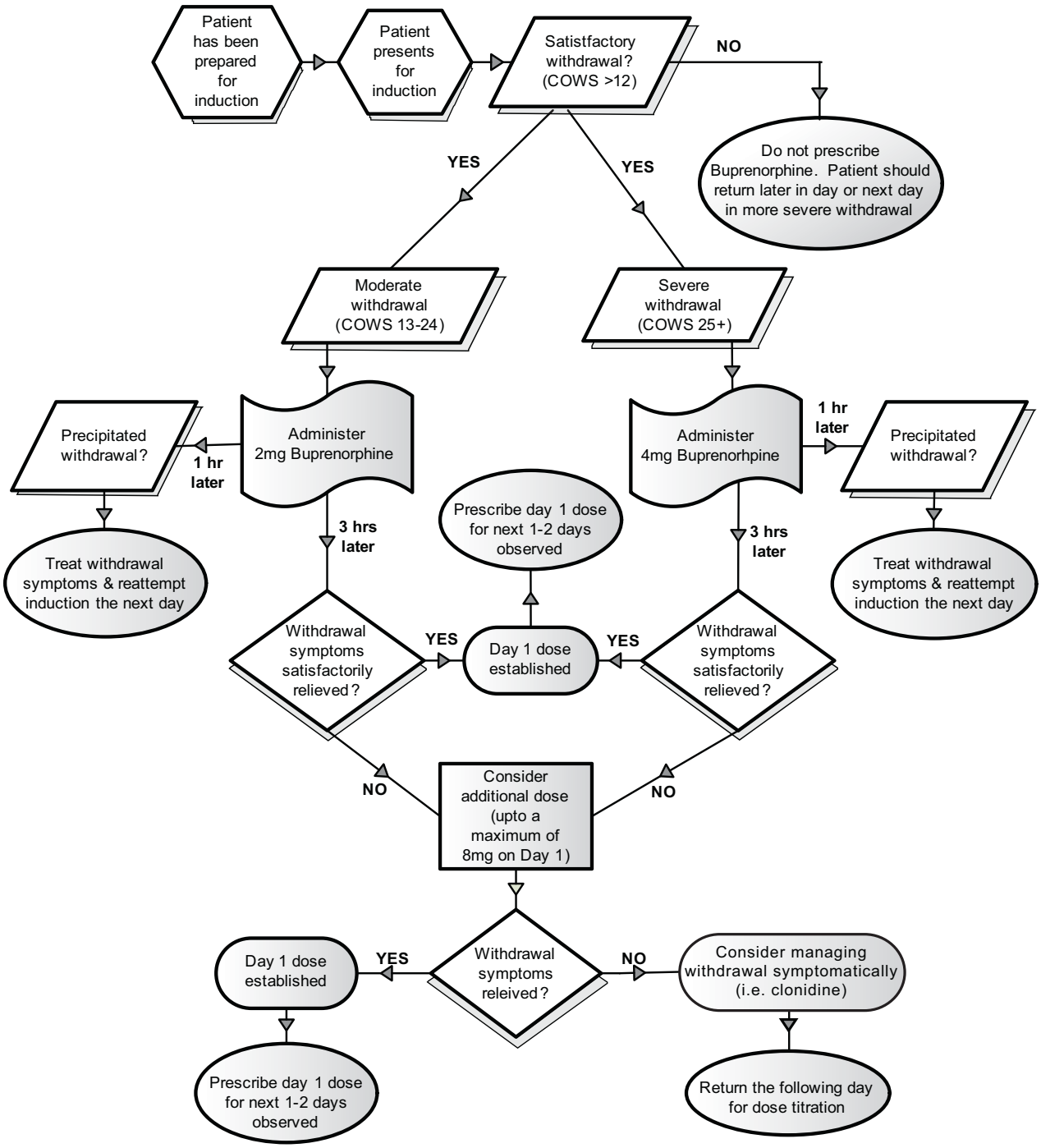
Appendix G

Sample buprenorphine/naloxone induction algorithm



Appendix H

Buprenorphine/naloxone availability in Canada

Province	Drug Available?	Restrictions on who can prescribe	Training requirement	Funding/coverage
Ontario (CPSO)	Yes	None (all physicians can prescribe)	None, but recommended: - Completion of prescribing course in buprenorphine that provides appropriate training for treating opioid dependency - Completion of a one-day clinical observership of an opioid-dependency practice - Ongoing continuing medical education in opioid-dependency treatment and/or addiction medicine - Obtaining a methadone exemption permitting the prescribing of methadone for opioid dependence	Coverage provided (8 mg tablets only) if: - methadone has failed, is not tolerated or is contraindicated - methadone treatment is not accessible (waiting list > 3 mo) - patient is at high risk of methadone toxicity (elderly, benzodiazepine user, heavy drinker, low opioid tolerance, respiratory illness, taking medications that interfere with methadone metabolism)
Alberta (CPSA)	Yes – Suboxone & Butrans	- Suboxone: Prescribers must have a methadone exemption for dependence - Butrans: Prescribers do not require a methadone exemption and no additional training is required by Health Canada	Completion of a prescribing course in buprenorphine required by Health Canada	Coverage restricted for methadone prescribers

Province	Drug Available?	Restrictions on who can prescribe	Training requirement	Funding/coverage
British Columbia (CPSBC)	Yes	Prescribers must have a methadone maintenance exemption	Completion of the online buprenorphine education module from Schering-Plough or Reckitt-Benckiser.	No coverage
Manitoba (CPSM)	Yes – Suboxone & Butrans	- Suboxone: Prescribers must have a methadone exemption for dependence - Butrans: All physicians can prescribe	Completion of an accredited Suboxone education program	No coverage
New Brunswick (CPSNB)	Yes	Prescribers must be authorized to prescribe methadone or have experience in the treatment of opioid dependence	None	- Coverage restricted to methadone prescribers - Coverage provided only if methadone is contraindicated
Newfoundland & Labrador (CPSNL)	Yes	None (all physicians can prescribe)	None, but recommended: - Exemption to prescribe methadone - Completion of a training program for the prescribing of buprenorphine(and provision of evidence of successful completion to the college) - Completion of a minimum one-day clinical observership at the Opioid Treatment Centre in the province	No coverage
Quebec (CMQ)	Yes	None (all physicians can prescribe)	For physicians with no history in treating opioid dependence, completion of a training program for the prescribing of buprenorphine and provision of evidence of successful completion to the college	Coverage provided if: - methadone has failed, is not tolerated or is contraindicated - methadone treatment is not available or accessible
Nova Scotia (CPSNS)	Yes	Prescribers must have a methadone exemption for dependence	None	- Coverage restricted to methadone prescribers - Coverage provided only if methadone is contraindicated

Province	Drug Available?	Restrictions on who can prescribe	Training requirement	Funding/coverage
Saskatchewan (CPSS)	Yes	Prescribers must have received an exemption from Health Canada to prescribe methadone or have spent a minimum of one day with another physician who has received an exemption from Health Canada to prescribe methadone	- Completion of an educational program on prescribing of buprenorphine approved by the Council - Participation in a program of continuing medical education that includes a minimum of six hours every two years in addiction medicine	- Coverage provided under exception - Given drug status (for treatment of opioid dependency in patients for whom methadone is contraindicated)
P.E.I. (CPSPEI)	Yes – but used rarely	None (all physicians can prescribe)	None	No coverage
Northwest Territories	No (data unavailable)	N/A	N/A	No coverage
Nunavut	No (data unavailable)	N/A	N/A	No coverage
Yukon	No (data unavailable)	N/A	N/A	No coverage

Appendix I – Buprenorphine training courses

Provider:	Training Course Available:
Centre for Addiction and Mental health (CAMH)	**Opioid Dependence Treatment (ODT) Core course** Online and in-person course Comprised of 5 online modules as well as a 1-day workshop Website: http://www.camh.net/education/Online_courses_webinars/methmaint_online_overview.html ODT Core course Fee: $450 (physicians); $350 (pharmacists or counsellors)
American Society for Addiction Medicine (ASAM)	**Buprenorphine Training Program** Online course 9-hour ASAM DATA 2000-qualifying buprenorphine training comprised of 12 modules; start and stop at own pace Website: Buppractice.com Course Fee: $175
American Psychiatric Association (APA)	**Buprenorphine and Office-Based Treatment of Opioid Dependence** Online course 8-hour DATA 2000-qualifying buprenorphine training based on the experience of live training with added online features Comprised of 3 video and audio/slide lectures with multiple-choice tests, 3 interactive case study discussions, 4 filmed vignettes portraying situations the physician may encounter in providing this treatment and an update information section Website: www.apaeducation.org Course Fee: $100 (APA members); $200 (non-members); free (APA member residents)
American Academy of Addiction Psychiatry	**AAAP Buprenorphine Training** Online course 8-hour DATA 2000-Qualifying Buprenorphine Training course comprised of 13 modules Covers review of legislation regarding office-based opioid-addiction treatment, pharmacology, safety and effectiveness, patient assessment and selection, clinical management, special treatment populations, dosing, urine testing and patient confidentiality Website: http://www2.aaap.org/buprenorphine/web-training Course fee: $171 (non-members) or $99 (AAAP members)

Appendix J

Sample buprenorphine/naloxone treatment agreement

Client name _____

Heath record # _____

The prescribing and dispensing of buprenorphine is regulated by provincial and federal guidelines, as well as by policies unique to this facility. The purpose of this agreement is both to both inform you about buprenorphine/naloxone maintenance therapy and to document that you agree to the rules and obligations contained in this agreement.

Acknowledgments

I acknowledge that:

1. Buprenorphine is a partial opioid agonist (opioids are drugs like heroin, codeine, morphine, Percocetâ, etc.), and will result in the development of physical dependence to this medication. Sudden decreases in dose or discontinuation of this medication will likely lead to symptoms of opioid withdrawal.

2. I am already physically dependent on at least one type of opioid and that I have been unable to discontinue my use of opioids.

3. I have tried to the best of my ability other possible treatments for opioid dependence, and that these attempts have been unsuccessful.

4. Taking any mood-altering substance with buprenorphine can be potentially dangerous. There have been reported deaths caused by the combination of buprenorphine with alcohol, opioids, cocaine, barbiturates and/or tranquillizers (e.g., Valiumâ, Ativanâ, etc.).

5. I may voluntarily withdraw from the buprenorphine treatment program at any time.

6. It is important for me to inform any physician or dentist who prescribes me an opioid that I am also taking buprenorphine. I understand that failure to do so could be dangerous and is considered double doctoring, which is a criminal offense.

7. Regarding pregnancy, I understand that there can be effects on a developing fetus caused by buprenorphine, and that specialized care will be required to reduce any harm to my fetus if I am or become pregnant while on buprenorphine. I acknowledge that I will need to be switched from Suboxone to the buprenorphine mono-product, Subutex.

8. It may be unsafe for me to drive a motor vehicle or operate machinery during the stabilization period after starting buprenorphine and during future dose adjustments.

9. Poppy seeds and certain over-the-counter medications may result in positive drug urine screen(s).

10. The common side effects of buprenorphine are sweating, constipation, decreased sexual function, drowsiness, weight gain, constipation and water retention. These symptoms are usually mild and can be lessened with assistance from my doctor. There are no known serious long-term effects from taking buprenorphine/naloxone. Many of these side effects will go away in time.

11. The clinic's doctor is not my family doctor. I will need a family doctor while I am on the program to deal with medical problems not related to buprenorphine maintenance. The clinic's physician will not be able to help me with ODSP forms, non-buprenorphine prescriptions or notes for work unless they are directly related to being on buprenorphine. My therapist may be able to assist me with some of these needs.

12. It is my responsibility to make and keep appointments at the clinic and to make sure that my buprenorphine prescription does not run out.

13. Buprenorphine treatment will be stopped if my physician determines that it has become medically unsuitable (for example, because treatment is not effective or because I develop a medical condition that could be made worse by taking buprenorphine).

Behaviour while in our clinic

Behaviour that is not acceptable in our clinic includes:

1. Any violence or threatened violence directed toward the staff or other clients.

2. Disruptive behaviour in the clinic or the area around the facility.

3. Any illegal activity, including selling or distributing any kind of illicit drug in the clinic or the area around the facility.

4. Any behaviour that disturbs the peace of the clinic or the area around the facility.

5. I agree to maintain positive, respectful behaviour toward other program clients and staff at

all times when in the clinic. Threats, racist or sexist remarks, physical violence, theft, property vandalism or mischief, the possession of weapons, and selling or buying illicit substances while on the clinic property are extremely serious program violations and may result in the termination of my treatment at this clinic.

Obligations of being on this program

1. I agree to pick up my medication during pharmacy dispensing hours and to take the medication according to the pharmacist's directions.

2. It is important to inform any prescribing physician or dentist who may treat me for any medical or psychiatric condition that I am receiving buprenorphine, so my treatment can be tailored to prevent potentially dangerous interactions with buprenorphine. I will bring my prescriptions and/or medication bottles to my doctor's appointments and to the pharmacy for verification.

3. I agree to provide a supervised urine sample when requested by program staff. Failure to provide this sample may result in my not receiving take-home doses, and/or in a delay in obtaining my prescription.

4. Failure to provide a urine sample may also mean that my record will be marked as a sample assumed to contain drugs and that this could further affect my level of carries (take-home doses) or requests for special carries.

5. I understand that tampering with my urine sample in any way is a serious violation of the program that might affect my future status in the program.

6. I agree to have a non-harmful clinical marker placed in my buprenorphine from time to time, to ensure that I am taking my buprenorphine and providing valid urine samples.

7. I understand that I will be offered counselling while I am in the program. I understand that counselling is not mandatory but is highly recommended.

8. I agree to keep all my appointments with the physician who is prescribing buprenorphine for me. Repeatedly missing appointments may result in the reduction of my carry status and could interfere with the doctor/client relationship.

I understand that I will not be given a dose of buprenorphine if I:

1. Appear to be intoxicated or under the influence of some other substance. If this occurs, I may be requested to see a physician. For the sake of my own physical safety, I may be asked to wait before receiving my dose, or I may be refused a dose for that day.

2. Arrive late, after the clinic/pharmacy hours.

3. Exhibit threatening or disruptive behaviour toward any staff member or another patient.

4. Do not show proper identification.

5. Miss doses of buprenorphine such that in order to re-start, I would need to be assessed by a physician.

Regarding take-home buprenorphine dose(s):

1. Buprenorphine is a potent medication. A single dose taken by a patient who is not tolerant to opioids can be fatal, especially if taken by a child. For this reason, I agree to store any take-home doses in a locked container, in a location where they are unlikely to be stolen or accidentally taken by another person.

2. I agree that the number of take-home doses I receive will be decided by my physician, with input from therapists, nurses and pharmacy staff, as I progress in my treatment.

3. I agree not to give, lend or sell my take-home doses to anyone.

4. I agree that I will consume the buprenorphine on the dates specified on the medication label and in the appropriate manner.

5. I agree that take-home doses will *only* be given if I leave urine screens according to the schedule arranged with my doctor. I understand that if an appointment is missed and a prescription is sent to my community pharmacy directly, my prescription may not include my take-home dose(s).

Consents

- I allow the College of Physicians and Surgeons of Ontario or its designate to review my chart. This is done to assess the care provided by my physician and is not meant to judge my recovery.

- I allow my buprenorphine prescribing physician or dispensing pharmacist to speak to other doctors or other health care professionals about my care.

- I allow pharmacy and nursing staff to speak to pharmacists or other health care providers to verify any recent buprenorphine dose(s) that I may have received at another pharmacy or institution.

Confidentiality

- Everything that you tell the clinic staff is confidential, although it is important to realize that under exceptional circumstances we can be obliged to report something you tell us to the appropriate authority. This can occur under the following conditions:

- If we suspect that a child is at risk of emotional or physical harm or neglect, then, under the Child Welfare Act, it is the law that we report this information.

- If you become suicidal, homicidal, or are unable to take care of yourself due to a psychiatric

condition, you might be held to be assessed by a psychiatrist against your will.

- If you reveal to the staff that you intend to harm another person, we will be obliged to protect that person by notifying the appropriate authority.
- If a court subpoenas your chart, we must release it to the party that requests it.
- If it is suspected that you are unable to drive an automobile due to a medical condition (which includes intoxication from alcohol or drugs), we are obliged to notify the Ministry of Transportation of this situation.
- Certain infections must be reported to the local public health department (for example, tuberculosis, HIV).

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

My signature below indicates that I agree to follow the obligations and responsibilities outlined in this agreement. Should I fail to meet my responsibilities as a participant in this agreement, I understand that I may be asked to leave the buprenorphine program.

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

_____
Dated (dd/mm/yyyy)

_____	_____
Client/Patient (Print Name)	Witness (Print Name)
_____	_____
Client/Patient Signature	Witness Signature

Client/patient to initial each page of this agreement.
Copy of signed agreement to be given to client/patient.

Appendix K: Clinical Opiate Withdrawal Scale (COWS)

For each item in the list below, circle the number that best describes the patient's sign 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.

Score: 5–12 = mild withdrawal; 13–24 = moderate withdrawal;
25–36 = moderately severe withdrawal; more than 36 = severe withdrawal

Patient's Name: _____ Date and Time: ____/_____/____:_____

Reason for This Assessment: _____

_____

Resting Pulse Rate: _____beats/ minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81–100 2 pulse rate 101–120 4 pulse rate greater than 120	**GI Upset:** *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past ½ hour not accounted for by room temperature or patient activity* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flush or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor:** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness: *Observation during assessment* 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	**Yawning:** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute

Pupil Size: 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	**Anxiety or Irritability:** 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
Bone or Joint Aches: *if patient was having pain previously, only the additional component attributed to opiate withdrawal is scored* 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	**Gooseflesh Skin:** 0 skin is smooth 3 piloerection of skin can be felt, or hairs standing up on arms 5 prominent piloerection
Runny Nose or Tearing: *not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	**Total Score** _____ The total score is the sum of all 11 items. Initials of Person Completing Assessment: _____

From: Wesson, DR & Ling, WJ. *(2003).* *Psychoactive Drugs* 35(2): 253–9.

Supplements

Supplements: Table of contents

Please note: These supplements are provided to assist clinicians in their practice and were not developed using the same methodology as the main body of the guideline

Supplement 1:

Key concepts in addiction

Meldon Kahan MD CCFP FRCPC & Anita Srivastava MD CCFP MSc

Addiction: Definition from the American Society of Addiction Medicine (ASAM):

> *Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm and craving.*

Physical dependence refers to two related phenomena, tolerance and withdrawal. Although they sometimes coexist, physical dependence and substance dependence ("addiction") are *not* synonymous. Many patients on daily doses of opioids for the treatment of chronic pain are physically dependent without being psychologically dependent ("addicted").

Tolerance is due to compensatory changes in the number and sensitivity of CNS receptors. Clinically, this means that the patient needs to take more of the drug over time to achieve the same effect. Tolerance to the analgesic effects of opioids develops slowly, whereas tolerance to their mood-altering effects begins within days.

Withdrawal. For short-acting opioids, withdrawal symptoms start within 6-12 hours after the last use and peak at 2-3 days. Psychological symptoms include anxiety, craving, and insomnia. Physical symptoms include myalgias, cramps and diarrhea. Objective signs include restlessness, lacrimation, rhinorrhea, yawning, sweating, chills and piloerection. Physical symptoms largely resolve by 5 to 10 days, although insomnia and dysphoria may last for weeks or months afterwards. Opioid withdrawal does not have medical complications except during pregnancy, when it can induce spontaneous abortion,

premature labour and fetal distress. The greatest medical risk of opioid withdrawal is the accompanying loss of tolerance, putting patients at risk for overdose if they relapse following medical detoxification [1]. Some patients may become very dysphoric during acute withdrawal and patients should be asked about mood and depressive symptoms, in particular suicidal ideation.

Substance dependence ("addiction") occurs when users find the psychoactive effect of a drug so reinforcing that they are unable to control their use of the drug. It is characterized by the "four C's":

- **C**ontrol – loss of control over use
- **C**onsequences - continued use despite knowledge of harmful consequences
- **C**ompulsion to use
- **C**ravings.

DSM-IV CRITERIA FOR SUBSTANCE DEPENDENCE: [2]

At least three of the following in a 12 month period*:

- Tolerance
- Withdrawal
- Taking larger amounts than intended
- Unsuccessful efforts to reduce drug use
- Preoccupation with the drug – great deal of time spent acquiring and using it
- Reduction of important activities because of the drug
- Continued use despite knowledge of drug-related physical or psychological problems

* *This means that at least three of the criteria need to have been present in the same 12 month period. The criteria do not have to have been present for a duration of 12 months in order to make the diagnosis.*

Clinical features of opioid dependence ("addiction")

Opioid-dependent patients experience reinforcing psychoactive effects from opioid use, such as reduced anxiety and an increased sense of energy and well-being. Tolerance to these effects develops rapidly, forcing users to escalate the amount of opioid they consume in order to achieve the same effect. Over time, users begin to experience intensely uncomfortable and frightening withdrawal symptoms at the end of a dosing interval. Opioid-dependent patients are often depressed and anxious due to the dysphoric effect of

high opioid doses, recurrent withdrawal symptoms, concern regarding maintaining their opioid supply and/or social difficulties created by their drug consumption.

Opioid-dependent patients who receive opioid prescriptions from a physician often display aberrant drug-related behaviours, reflecting their need to overcome tolerance and experience euphoria while avoiding withdrawal symptoms (see Table below). They may chew, snort, or inject the drug rather than take it orally as prescribed. They may consume larger amounts than prescribed, running out of their medication early and repeatedly request fit-in appointments. They may access opioids from other sources (the 'street', friends, other prescribers). Physicians and other clinicians should monitor for these behaviours. The Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain [3] provides useful information and clinical tools that can assist the physician in diagnosing and managing prescription opioid misuse and dependence in clinical practice.

The physician should explain to the patient that with appropriate treatment of their opioid dependence, the patient's mood, relationships, and work performance will likely improve. Any concurrent pain problem will also likely improve because withdrawal-mediated pain will resolve with successful opioid tapering or agonist treatment. Consultation with an addiction medicine physician may be helpful.

Clinical Features of Prescription Opioid Dependence

Feature	Examples
Unsanctioned use	Recurrent prescription losses
	Multiple unsanctioned dose escalations
	Binge rather than scheduled use
Alters the route of delivery	Injects, bites or crushes oral formulations
Accesses opioids from other sources	Purchases the drug from the 'street'
	Double doctors
	Goes to walk-in clinics and emergency departments
	Drug seeking
	Dose high or rapidly escalating despite stable pain condition
	Aggressive complaining about the need for higher doses
	Harassing staff for faxed scripts or fit-in appointments
	Nothing else 'works'
Accompanying conditions	Currently addicted to alcohol, cocaine or other drug
	Underlying mood or anxiety disorders not responsive to treatment
Repeated or severe withdrawal symptoms	Marked dysphoria, myalgias, GI symptoms, craving
Social Features	Deteriorating or poor social function
	Concern expressed by family members

Patient's views on their opioid use	Sometimes acknowledges being addicted
	Strong resistance to tapering or switching to a different opioid
	Admit to mood-leveling effect or distressing withdrawal symptoms

Treatment options

Medical detoxification

Medical detoxification refers to medically supervised withdrawal from opioids in order to help support the transition from a physically dependent state to a non-dependent state. It can be carried out in an inpatient or an ambulatory setting. Medical detoxification generally has low success rates and the rate of relapse following medical detoxification is high [4, 5, 6]. Nevertheless, it is frequently preferred by patients and families, and may be recommended for certain patients with better prognostic factors, for example those patients who:

- are dependent only on opioids, and in particular oral opioids
- have a brief duration of dependence (i.e., less than one year)
- are a younger age
- have no major psychiatric comorbidity
- are socially stable with a supportive network.

The most common medications used to alleviate opioid withdrawal symptoms are alpha-adrenergic agents such as clonidine. Other symptom-relieving medications can be used for insomnia (e.g. trazodone), myalgias (e.g. NSAIDS), diarrhea (e.g. loperamide) and nausea (e.g. ginger tablets or dimenhydrinate). In some settings, opioid agonists such as methadone and buprenorphine are employed to assist medical detoxification. Regardless of the withdrawal treatment modality relapse rates are high, especially if the patient does not participate in a formal psychosocial treatment program. Physicians and other clinicians need to educate patients and families that relapse to opioids following detoxification increases overdose risk due to loss of tolerance. Studies have found sustained-release naltrexone to be efficaceous in preventing relapse following opioid withdrawal management. This product is not currently available in Canada.

Psychosocial treatment programs

Psychosocial treatment programs offer comprehensive assessment, group and individual therapy, patient education and long-term follow-up. Overall, inpatient and outpatient programs have similar effectiveness. Inpatient programs might be preferred for patients who have failed at outpatient therapy, have concurrent medical or psychiatric illnesses, experience protracted opioid withdrawal symptoms such as dysphoria and insomnia, or have a socially unstable home environment. The Ontario Drug and Alcohol Helpline website at http://www.drugandalcoholhelpline.ca/. can inform the patient and physician

about treatment programs in Ontario, including a program description, admission criteria, waiting lists and application procedures.

Opioid agonist treatment

Opioid agonist treatment refers to the use of a substitution opioid to manage opioid dependence. Methadone and buprenorphine are both long-acting opioids that are used in opioid agonist treatment. Opioid agonist treatment programs are usually comprehensive and structured [7], dispensing long-acting opioid medications with graduated take-home doses, along with urine drug testing, concomitant psychosocial counselling and medical care. As discussed in this guideline, buprenorphine and methadone maintenance treatment have been shown to reduce mortality, drug use and retain patients in treatment.

Supplement 2:

Pharmacology of buprenorphine

Meldon Kahan MD CCFP FRCPC & Anita Srivastava MD CCFP MSc

Buprenorphine is a partial mu receptor agonist with lower intrinsic activity at the receptor site compared to full mu opioid agonists such as heroin, oxycodone or methadone. Clinically this means that buprenorphine has a "ceiling effect": Once a certain dose is reached, the opioid agonist effects plateau. This dose will differ between individuals. This phenomenon reduces its risk of overdose compared to methadone and other full mu agonist opioids. Buprenorphine is rapidly absorbed sublingually and reaches a peak serum level and peak effect in about one to four hours. Buprenorphine has a high affinity for opioid receptors, attaching tightly to the receptors and dissociating slowly from them. Buprenorphine's half-life is 24-60 hours (average around 32 hours) [8]. Because of its slow onset and long duration of action, opioid-dependent patients do not experience sedation or euphoria at the appropriate sublingual dose. There can be large variations between individuals with respect to buprenorphine's absorption and duration of action [9]. Because of its high receptor affinity, buprenorphine acts as an opioid antagonist by displacing other opioids from opioid receptors. For example, buprenorphine 8 mg completely attenuates the effects of hydromorphone 4 mg IM for 72 hours [10]. This pharmacological property has two clinical implications: first, the reinforcing effects of other opioids are blocked and second, patients who are physically dependent on opioids may experience precipitated withdrawal if they ingest buprenorphine while they still have opioids in their system.

Drug interactions

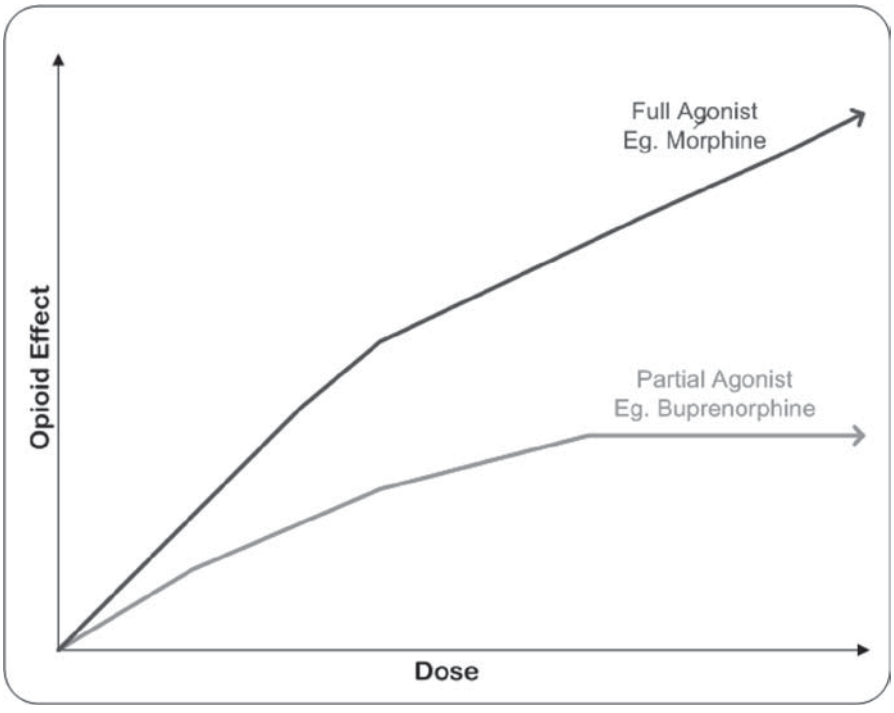
Because buprenorphine is metabolized via cytochrome p450 3A4 enzyme there is the potential for interactions with 3A4 inducers and inhibitors [11]. Generally there have not been a significant number of clinically significant drug interactions with buprenorphine

described in the literature. Nevertheless, one would educate the patient and monitor them closely when starting or stopping a known 3A4 inducer or inhibitor in a patient maintained on buprenorphine. Good communication between providers and good patient education are important.

Cytochrome P4503A4 Inducers	Cyotchrome P4503A4 Inhibitors
carbamazepine, phenytoin (divalproex does not interact) rifampin efavirenz, nevirapine lopinovir, nelfinavir, amprenavir, abacavir barbiturates St John's Wort cocaine use ethanol (chronic use)	fluconazole (possibly ketoconazole and itraconazole) fluvoxamine (less so sertraline, fluoxetine, paroxetine, buproprion) grapefruit juice urinary alkalinizers omeprazole disulfiram ethanol (acute use) delavirdine ciprofloxacin erythromycin, clarithromycin, (azithromycin does not interact) diltiazem, verapamil, amiodarone ritonavir, indinavir

Classification of opioids

Figure 1: Classification of opioids – dosing effect



Buprenorphine-naloxone combination (Suboxone)

In Canada, buprenorphine is available as a combination product of buprenorphine: naloxone in a 4:1 ratio (Suboxone). The buprenorphine monoproduct (buprenorphine alone, without naloxone) is not available in Canada, except for pregnant patients where it may be obtained from the manufacturer through a special access program. Naloxone is an opioid antagonist and is added to buprenorphine to deter injection abuse of buprenorphine. Naloxone has a poor sublingual bioavailability, but will precipitate withdrawal in opioid-dependent patients [12] when used intravenously. The extent to which naloxone reduces injection abuse is not known. However, in controlled trials, the mono and combination products were equally effective in reducing opioid use [13]. The addition of naloxone appears to be harmless as it does not interfere with the pharmacokinetics of buprenorphine [8, 14].

Summary of Buprenorphine Pharmacology

Feature	Result
SL & IV absorption Poor oral absorption	· Can be abused intravenously
Very tight binding (affinity) to opioid receptors	· Competes with and displaces other opioids from opioid receptors · Triggers withdrawal in physically dependent patients who have recently taken opioids · Blocks the analgesic action of other opioids
Slow dissociation from opioid receptors	· Long duration of action · Relieves withdrawal and cravings for 24 hours or more
Partial agonist with ceiling effect	· Very low risk of overdose when used on its own · May be less effective than higher doses of methadone
Buprenorphine is combined with naloxone	· When injected, naloxone will trigger withdrawal in patients physically dependent on opioids · Acts as a deterrent to IV use

Supplement 3:

Clinical assessment prior to buprenorphine/naloxone therapy

Meldon Kahan MD CCFP FRCPC & Anita Srivastava MD MSc CCFP

A comprehensive assessment is necessary to make an accurate diagnosis, identify concurrent medical, psychiatric and social problems and formulate a treatment plan. A clinical assessment should include the following:

Substance use history. Physicians should document the amount, pattern and duration of opioid use, route of administration, and time of last use. Since polysubstance use is common among opioid users, the physician should also ask about alcohol, cocaine, cannabis, benzodiazepine, tobacco and methamphetamine use.

DSM criteria for opioid dependence. To be eligible for buprenorphine/naloxone maintenance therapy, patients should meet DSM criteria for opioid dependence (see Supplement 1)

Previous treatment episodes. A patient's history of previous treatment is useful in treatment planning. For example, relapse shortly following abstinence-based treatment supports the need for agonist treatment. If possible, the physician should obtain information from previous treatment providers to determine how well the patient responded and the reasons for drop-out or discharge.

Social history. Social factors can affect treatment plans and outcomes, including current living arrangements, parenting arrangements and the safety of children at home. Substance use among family members may have a major impact on the patient's treatment and prognosis.

Psychiatric history. Opioid users have a high prevalence of mood and anxiety disorders, and suicidal ideation commonly accompanies dependence on opioids, cocaine, alcohol and sedatives (See Supplement 6).

High-risk behaviours. High-risk behaviours such as unsafe sex and needle sharing are common among injection opioid users. It is important to remember that even one episode of injection several years prior is still a risk factor for blood-borne virus infection. Sharing of crack pipes and intranasal straws also present a risk for transmission of viruses.

Reporting obligations. It is also important to assess for any reporting obligations such as Ministry of Transportation and Children's Aid.

A focused **physical examination** should be performed, with special attention to hepatosplenomegaly, cardiovascular and respiratory status, and needle track marks. A well- documented baseline mental status examination is also important.

Baseline laboratory tests include CBC, MCV and GGT (to detect heavy alcohol consumption), AST, ALT (viral or alcoholic hepatitis), hepatitis B, C, and HIV serology, and B-HCG for women in the reproductive age group. At least one urine drug test should be taken and interpreted prior to treatment. TB skin testing should also be done for patients at risk for developing TB disease.

Example Buprenorphine Patient Assessment Checklist

History
• Establish DSM diagnosis of opioid dependence • Amount, pattern and route of opioid use. Assess degree of tolerance • Withdrawal symptoms • Other drug use (alcohol, cocaine, opioids, benzodiazepines, cannabis, nicotine) • Consequences of use (physical, social, occupational, legal, financial) • Social situation, including safety of children living at home • Depression, anxiety, psychosis, suicidal ideation • Spousal, child abuse • Previous treatment attempts • If injection drug use: sharing of injection equipment; history of hepatitis B, C, and/or HIV • High-risk sexual activity (involvement in the sex trade, or sexual activity while impaired) • Driving • Possibility of pregnancy
Physical
• Mental status examination • Vital signs • Track marks • Liver, spleen • Cardiovascular, respiratory
Laboratory
• CBC, MCV • GGT, AST, ALT • B-HCG • Hepatitis B, C, HIV • TB skin testing if high-risk • Urine drug test

Supplement 4:

Ordering and interpreting urine drug tests

Meldon Kahan MD CCFP FRCPC, Anita Srivastava MD MSc CCFP

Rationale of urine drug testing [15]

An excellent Review of Urine Drug Testing for the primary care clinician can be found at the following link: http://www.familydocs.org/files/UDTMonograph_for_web.pdf.

Urine drug testing (UDT) is an important objective tool for the clinician to further evaluate their patient following a detailed history and physical examination. When used in the context of opioid agonist treatment it serves a few key functions. First, it can be used to confirm the presence of a problematic drug in the patient presenting for opioid dependence treatment and in doing so reinforce their eligibility for opioid agonist treatment. Second, it can be used to detect other drugs in the patient's urine that would affect the dosing of the opioid agonist agent (for example the presence of benzodiazepines). Third, when the patient is stabilizing on buprenorphine, UDTs can corroborate his or her self report of abstinence from problematic drugs, allowing the clinician to make more confident decisions about frequency of follow-up, treatment of other co-existing conditions and the initiation and maintenance of buprenorphine take-home doses.

Urine drug tests should be requested and interpreted as with any other diagnostic test, namely with the clinical justification and pre-test likelihood of a certain result in mind. In taking this approach to urine testing, the clinician will be more likely to view this form of testing in a patient-centered manner, be purposeful about interpreting the results and reflecting the results to the patient and adjusting the treatment plan as necessary.

Point of care testing versus standard lab testing

Point of care testing utilizes urine reagent sticks ('dip sticks'), each containing several immunoassays. The most commonly used sticks contain assays for cocaine, opioids, oxycodone and benzodiazepines. Point of care testing is useful for providing immediate feedback to the patient on their drug use, and making prompt decisions about take-home doses.

Point of care testing has more false positives and false negatives than standard laboratory testing using chromatography. The sensitivity and specificity of the tests varies between companies. Interpretation of the results requires precision in timing; the tests must be read a certain number of minutes after dipping in the urine. These tests are "subjective" (presence or absence of a faint coloured line on the stick). Also, immunoassays are more prone to invalidation by adulteration or tampering than chromatographic techniques. Point-of-care reagent sticks are ordered from private companies. In Ontario, physicians are reimbursed by OHIP for interpreting point of care urine tests. To ensure accuracy of the results, the physician should periodically send a sample to the lab for chromatography testing. This is particularly important if there is a discrepancy between the patient's self report and the point of care test result, and if there are legal implications for the test (eg involvement with a child protection agency).

Detection of different classes of drugs

Buprenorphine

Buprenorphine is not detected on a routine opioid immunoassay, but buprenorphine-specific immunoassay sticks are available from private labs.Laboratories have a specific chromatographic assay for buprenorphine. On the laboratory requisition, the physician should specifically request testing for buprenorphine and buprenorphine metabolites in the urine.

Opioids

Immunoassay techniques detect opioids for 3-5 days after last use, but cannot distinguish between specific opioids. Semi-synthetic opioids such as oxycodone are often not reliably detected, and synthetic opioids such as methadone, buprenorphine and fentanyl are reliably undetected. Substances such as poppy seeds and fluoroquinolone antibiotics can cause false positive opioid immunoassay results.

Chromatography techniques only detect opioids for 1-2 days after last use, but will distinguish between different types of opioids and are more reliable for semisynthetic and synthetic opioids. Codeine is metabolized to morphine, so both will be detected in a

patient on prescribed codeine. Codeine may also result in small amounts of hydrocodone in the urine. Morphine can be metabolized to small amounts of hydromorphone.

Benzodiazepines

Immunoassay techniques will reliably detect diazepam and benzodiazepines structurally similar to diazepam. Because diazepam has a very long half-life and is highly lipid soluble, it is detected for up to three weeks after use. Intermediate acting agents such as lorazepam, clonazepam and bromazepam have poor sensitivity and are often undetected. Clonazepam in particular is poorly detected unless used in high doses. Chromatography is not routinely performed to distinguish between the different benzodiazepines.

Cocaine

The cocaine metabolite benzoylecgonine (BEG) is detected by both immunoassay and chromatography. The parent compound (cocaine) is detected by chromatography for only a few hours after use. The cocaine metabolite (BEG) immunoassay is highly specific for cocaine ingestion. It does not cross-react with local anaesthetics, and second-hand smoke will not cause a positive UDS for cocaine or BEG.

Cannabis

The immunoassay for THC is both sensitive and specific. Regular use of cannabis is detected by UDS for up to 28 days, while occasional use is detected for 3-4 days.

Summary: Urine Drug Screening

	Immunoassay	Chromatography
Opioids	• Detection window 3-5 days • Can't distinguish different opioids. Misses synthetic opioids eg oxycodone, fentanyl, methadone. • A specific immunoassay is available for oxycodone	• Detection window 1-2 days • Identifies specific opioids, including synthetic opioids. • Codeine metabolized to morphine • Monoacetylmorphine (MAM) very specific for heroin use
Cocaine/BEG	• Detection window for BEG is 3-5 days • Very specific for cocaine use	• Detection window for cocaine 1-2 days • Very specific for cocaine use
Benzodiazepines	• Regular diazepam use detected for up to 30 days. • Lorazepam & other intermediate-acting benzos often missed • Clonazepam poorly detected at moderate doses	
Cannabis	• Regular daily use: Can detect up to 10-28 days	

Supplement 5:

Buprenorphine/naloxone dispensing

Satinder Sanghera RPh, BScPhm

Pharmacists have an integral role in the provision of substance abuse treatments, including buprenorphine/naloxone. Being the health care providers who see patients most often, pharmacists have the opportunity to provide support and encouragement, and to assist patients with day to day challenges. With regular patient contact, pharmacists can monitor and contribute important feedback on patient progress during their communication and collaboration with physicians.

Buprenorphine/naloxone does not require a special prescribing exemption, unlike methadone, so prescriptions written by any practitioner licensed to prescribe narcotics in Ontario are valid. The physician regulatory bodies expect prescribers of buprenorphine/naloxone to be knowledgeable in this field.

Pharmacists offering buprenorphine/naloxone dispensing services must be aware of the unique characteristics and the specific issues that exist in dispensing medications for the maintenance treatments of substance dependence. Pharmacy managers, in accordance with NAPRA (National Association of Pharmacy Regulatory Authorities) Model Standards of Practice for Canadian Pharmacists, must take initiative to thoroughly understand these issues and ensure that all staff pharmacists and technicians possess the skills and training to offer these services safely and effectively.

Due to the unique nature of buprenorphine dispensing and substance abuse treatment, pharmacists need to be familiar with optimal practice standards in buprenorphine/naloxone induction, maintenance, and tapering, and have an understanding of the risk of precipitated withdrawal specific to buprenorphine. Usual standards of patient care must also be provided, for example, to assess for drug therapy problems (including drug interactions – see *Supplement 2: Pharmacology of Buprenorphine*) and to provide patient

specific medication information and advice. One way to achieve this is to take a course (see Appendix I),

Observed dosing by pharmacists can be a valuable tool to help ensure patients take medications as prescribed, thereby leading to positive outcomes with patients in substance dependence treatment programs, or with patients experiencing problematic use of prescribed medications. Pharmacists providing observed dose dispensing services can offer physicians a method for bringing patients into a structured framework in cases where there may be suspected problematic medication use, or a loss of control over use. Observed dosing ensures adherence and can offer an effective mechanism to stabilize patients. This not only applies to buprenorphine/naloxone, but also when prescribing other narcotics or psychiatric medications. Physicians may also find utility for observed dosing frameworks for assessment of effect of dose adjustments. Observed dose administration in pharmacies requires special considerations, such as the impact on dispensary workflow. Also, pharmacists and pharmacy staff must be prepared for special situations that may arise, including a patient presenting intoxicated or after having missed doses.

For seamless and safe medication dispensing, effective communication between the physician and pharmacist is imperative. Pharmacists who make the decision to dispense buprenorphine/naloxone and provide observed dosing services are encouraged to take the opportunity to establish an effective working relationship with the prescribing physician. Communication channels, clearly established at the start of treatment, will be invaluable in providing safe and comprehensive patient care. In the substance dependent population, very specific issues arise in the pharmacy, and planning for this in advance allows for more effective patient care.

Pharmacists and physicians should be prepared to communicate at the initiation of treatment and on an ongoing basis regarding situations, such as:

- Changes during induction phase
- Missed doses, or missed take-home pick up days
- Changing patient condition, including intoxication
- Change of prescription, dose or take-home directions
- Drug Utilization Review warnings (double doctoring, polypharmacy)
- Transitions in care (for example, admission or discharge from hospital or correctional facilities, or when changing pharmacies)

The physician and pharmacist should agree upon suitable ways to share information with each other regarding their patient's progress in treatment, including ways for the pharmacist to contact the doctor for urgent communications during busy office hours as well as after hours.

The value of open and clear communication with patients cannot be overstated. In embarking on the provision of buprenorphine/naloxone dispensing services, pharmacists should discuss all pharmacy routines and expectations in a clear and direct manner and allow patients to seek clarification prior to consenting to receipt of services. In addition to dialoguing, having an information sheet to give to the patient that describes daily

pharmacy routines and expectations also helps to explain questions that may arise later. Some pharmacies utilize a treatment agreement format to deliver this information and achieve the necessary clarity in communication. *(Refer to sample treatment agreement below)*.

Pharmacists should communicate with patients at the initiation of treatment and on an ongoing basis regarding the following points:

- Usual pharmacy routines, including observed dosing and pharmacy hours
- Procedure after missed doses, lost take-home doses, missed clinic appointments, or lost prescriptions
- Protocol if patient presents intoxicated, or engages in inappropriate behaviour
- Buprenorphine/naloxone information, including drug interactions (e.g., highlighting the risk of concurrent consumption of alcohol or sedatives)
- Expectations for possible withdrawal symptoms or craving during induction
- Chronicity of treatment
- Review of information provided by physician to clarify any misconceptions, and to reinforce treatment goals and provide encouragement
- Appropriate patient behaviour in the pharmacy to maintain a safe treatment environment for all patients and for pharmacy staff
- Commitment by pharmacy staff to provide professional and respectful delivery of services to maintain a safe treatment environment for patients and for pharmacy staff.

Recommendations for patient initiation to pharmacy services

At physician's office

Select pharmacy location based on:

- Patient choice or current pharmacy services
- Pharmacy access and convenience of hours and location
- Buprenorphine/naloxone availability, and observed dosing services
- Pharmacy currently able to accept new patients
- Confirm ongoing affordability of buprenorphine/naloxone due to long-term nature of therapy

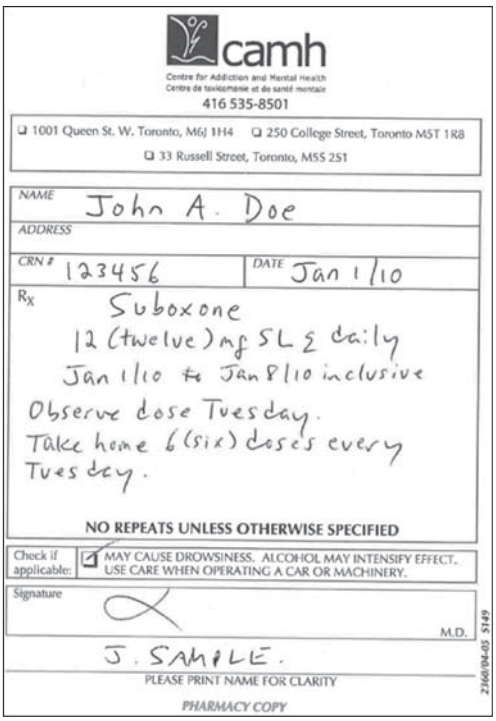
Physician to make contact with pharmacist prior to initiation of patient

Provide patient with written prescription, or fax directly to pharmacy (keeping original in chart, marked "faxed").

Prescription should indicate all of the following

- Pharmacy name
- Date prescription written
- Drug name and dose (mg dose in words and numbers)
- Start date and end date, stated as inclusive
- Dosing regimen (daily, alternate day or thrice weekly)
- Observed dose days
- Take home dose days
- Induction: dosing schedule, and clear instruction for induction process

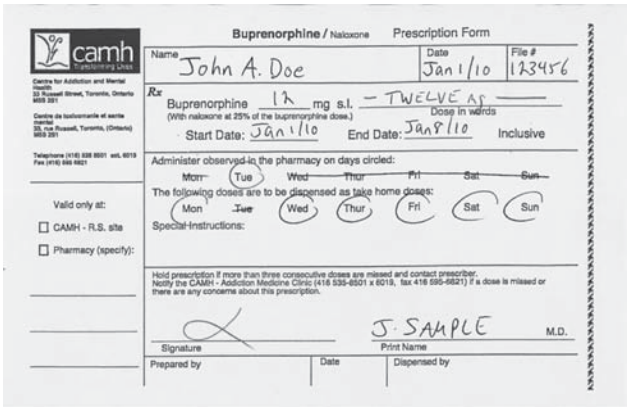
Sample prescriptions



camh
Centre for Addiction and Mental Health
Centre de toxicomanie et de santé mentale
416 535-8501
1001 Queen St. W. Toronto, M6J 1H4 250 College Street, Toronto M5T 1R8
33 Russell Street, Toronto, M5S 2S1

NAME John A. Doe
ADDRESS
CRN # 123456 DATE Jan 1/10
Rx Suboxone
12 (twelve) mg SL ξ daily
Jan 1/10 to Jan 8/10 inclusive
Observe dose Tuesday.
Take home 6 (six) doses every Tuesday.

NO REPEATS UNLESS OTHERWISE SPECIFIED
Check if applicable: MAY CAUSE DROWSINESS. ALCOHOL MAY INTENSIFY EFFECT. USE CARE WHEN OPERATING A CAR OR MACHINERY.
Signature
M.D.
J. SAMPLE.
PLEASE PRINT NAME FOR CLARITY
PHARMACY COPY
2366104-05 5149



camh
Buprenorphine / Naloxone Prescription Form
Name John A. Doe Date Jan 1/10 File # 123456
Rx Buprenorphine 12 mg s.l. — TWELVE AS —
(With naloxone at 25% of the buprenorphine dose.) Dose in words
Start Date: Jan 1/10 End Date: Jan 8/10 Inclusive
Administer observed in the pharmacy on days circled:
Mon Tue Wed Thur Fri Sat Sun
The following doses are to be dispensed as take home doses:
Mon Tue Wed Thur Fri Sat Sun
Special Instructions:
Valid only at:
CAMH - R.S. site
Pharmacy (specify):
Hold prescription if more than three consecutive doses are missed and contact prescriber. Notify the CAMH - Addiction Medicine Clinic (416 535-8501 x 6019, fax 416 595-6821) if a dose is missed or there are any concerns about this prescription.
Signature
J. SAMPLE M.D.
Print Name
Prepared by Date Dispensed by

At patient's first visit to pharmacy

Confirm ID, compare with information provided by physician during initial verbal contact, and establish method for ongoing identification.

Ask about allergies and current medications.

Provide information on buprenorphine/naloxone:

- Route of administration: buprenorphine/naloxone absorption sublingually, naloxone

absorption by other routes of administration
- Timeframes and expectations during induction phase, especially potential for withdrawal and craving
- Adverse effects: precipitated withdrawal, sedation
- Safety: drug interactions (especially other opioids, alcohol, sedatives).

Provide pharmacy and dosing routine information:

- Hours and usual protocols for observed dosing
- Procedure in case of missed doses, lost medication, or lost prescription
- Consequences of attending intoxicated, diversion attempts.

Discuss issues of double doctoring and explain that buprenorphine/naloxone prescription changes will require a new written prescription.

Discuss mutual respect and appropriate behaviour to maintain pharmacy as a respectful, professional service environment, and "safe place for treatment."

Discuss drug coverage, or payment issues if patient has no coverage.

Establish consent, including consent to communicate with all health care providers involved in buprenorphine prescribing or substance abuse treatment.

Prior to first dose, ensure patient is in withdrawal (refer to section 3. Initiation, maintenance and discontinuation of buprenorphine maintenance treatment, in Guideline Recommendations).

Pharmacy dispensing routine at each visit

Confirm identity.

Interpret prescription to confirm that a dose is available.

Check if dose is on daily, alternate day, or three times per week regimen.

Check for any authorized take-home doses.

Confirm date and amount of last ingested dose, taking special note of missed doses and dose increases.

Confirm patient is not intoxicated.

Ensure privacy and patient comfort to full extent possible.

Ensure patient does not have personal belongings on the dispensing counter (to minimize ease of diversion).

Dispense dose:

- Prior to giving tablets, for patients with dry mouth, give some water to moisten mouth.
- Remove SL tab from foil but do not touch (skin contact to be avoided).
- For higher doses, may cut into half or quarters to reduce dissolution time, and place in clear plastic dispensing cup.
- Do not grind or crush tablets as they may coalesce into a single mass with a reduced surface area thereby reducing dissolution.
- Ask patient to place contents of cup under the tongue, and not to suck on tablet while it dissolves.
- Patients could keep their head tilted slightly forward to reduce saliva collecting at the throat and being swallowed.

After around 1 minute, ask patient to show oral cavity for dissolution and expect patient to remain within close view of the pharmacy area until satisfied the entire dose has been administered. A chalky residue may remain even after drug has been sufficiently absorbed.

Advise patient to refrain from drinking fluids and eating for approximately 5 minutes to allow for sublingual absorption to be maximized.

Ask patient to sign/initial for receipt of dose after pharmacist is satisfied that dose has been administered.

Dispense take-home dose: (supply quantity until next observed dose day only).

- Dispense tablets in child proof vial inside original foil packaging.
- Individual daily doses should be uniquely identifiable and labelled with directions, consumption date, and dosage.
  - » Although observed doses may be administered on alternate days or thrice weekly, take-homes are typically consumed daily. Pharmacists must ensure this is labeled clearly.
- Affix appropriate warning labels.
- Asking patient to count tablets with pharmacy staff and sign is optimal practice, and will eliminate any chance of future disagreements.

Practical considerations

Missed doses

As part of education and training for provision of opioid substitution therapy, pharmacists are expected to have become familiar with potential risk for toxicity after a series of doses

has been missed, and tolerance to the opioid has diminished. Pharmacists must be prepared to manage this occurrence whenever a patient presents at the pharmacy after one or more days of unexpected absence. For more specific details in the approach after missed doses of buprenorphine/naloxone, pharmacists can refer to section 3. Initiation, maintenance and discontinuation of buprenorphine maintenance treatment, in Guideline Recommendations).

It must be understood also that dose authorizations do not carry forward if a dose was missed, meaning that the intended end of the prescription interval be preserved even if this means that a quantity lesser than total authorized will be dispensed. Further, there is utility in informing the prescriber when a patient is routinely missing doses. This information is valuable to the prescriber for assessment of clinical stability. Pharmacists are encouraged to keep physicians informed when a patient has missed one or more observed doses, or appears one or more days late to pick up take-home doses.

Last dose confirmation

In any circumstance where the patient was not seen for any number of days, and may have received care from another pharmacy or institution, it is the responsibility of the pharmacist to make contact with the other dispensing pharmacist to establish last ingested dose, date last observed, and any take-homes that were given. This is an essential step that must be taken prior to administering a dose, because after several days of missed doses, tolerance to opioid is reduced, and the administration of a previously prescribed dose could result in toxicity. There is also the possibility of overlapping prescriptions, thus a possibility of double dosing.

Patient intoxication

Patients who arrive for an observed dose of buprenorphine/naloxone should not present intoxicated. In cases where substance use continues to be problematic, the possibility of a patient arriving intoxicated does exist. Familiarity with substance abuse treatment will enable pharmacists to make a judgment on the degree of intoxication, and any potential for adverse effects upon buprenorphine/naloxone administration. In some cases, for patient safety, pharmacists will need to hold or delay administration. If this course of action is required, communication with the physician should occur to make a collaborative decision on how to proceed with dosing the patient. Safety risks of buprenorphine/naloxone, especially when alcohol or sedatives are used concurrently, should be reinforced to the patient.

Drug diversion

Buprenorphine/naloxone, like other opioids, is known to be diverted to illicit use and to be abused by oral, intranasal, or intravenous routes. Pharmacists must remain aware of the risk of diversion, and ensure that the protocols established for observing doses allow for adequate control and observation. Pharmacy managers must provide effective

adjustments to usual pharmacy dispensing workflow to accommodate requirements for observation of sublingual administration and tablet dissolution time.

Professional practice

The pharmacist's role in dispensing buprenorphine/naloxone for the treatment of substance dependence, in many cases, brings them into daily contact with patients. This places them in an important position to impact positively and significantly on patient outcomes. This can also bring challenges, especially in the face of inappropriate patient behaviour, or unforeseen difficult situations. Maintaining privacy in a busy community pharmacy setting can present a challenge also, and pharmacists must remain mindful of the sensitive circumstances facing patients in treatment for substance dependence. Pharmacists should be knowledgeable about local support services and refer patients as appropriate. As is in all practice environments, pharmacists must continually strive to maintain the highest standards of professionalism and mutual respect in their interactions with patients and all health care providers, with whom effective communication is essential to provide optimal care.

SAMPLE BUPRENORPHINE/NALOXONE (SUBOXONE) MAINTENANCE TREATMENT PHARMACIST-PATIENT AGREEMENT

You can expect this pharmacy to give you excellent and professional service. Our goal is to provide you with the best pharmacy care possible in an environment that is safe and respectful for you, our other patients and pharmacy staff.

Please read, sign and date the Suboxone Treatment Pharmacist-Patient Agreement below.

Suboxone is a medication that is regulated by a number of legal and medical guidelines. I understand that I need a **prescription** to receive Suboxone. To have a prescription, I have to keep my appointments with my doctor.

I will come for my Suboxone dose during regular pharmacy hours (specify below):

I agree to place the Suboxone tablet under my tongue and let it dissolve. I understand this may take up to 10 minutes and that I have to **stay in the pharmacy** until the tablet(s) has dissolved completely.

I agree **not to swallow** the tablet(s). I agree to let the pharmacist check to make sure the tablet(s) has dissolved before I can leave the pharmacy.

I understand that I need to present to the pharmacist a **valid photo ID** each time before I can receive my Suboxone dose.

I know that I will not be given Suboxone if I am intoxicated with alcohol or other drugs because of concerns about my safety.

If I don't take Suboxone for five consecutive days, I will have to see my doctor for a **new prescription**.

I understand that the pharmacy needs to be a safe place for patients and staff. I may no longer be served here if I ever threaten anyone or act violently while I am in the pharmacy.

I agree not to take part in any illegal activity, which includes selling or distribution of any kind of drugs in the surrounding vicinity of the pharmacy.

I agree to pay for my Suboxone tablets promptly.

I understand that some drugs are not safe to take while I am on Suboxone. I will tell the pharmacist if I am taking any other prescription or non-prescription (i.e. over-the-counter) drugs or herbal medicines.

I agree to let the pharmacist discuss my treatment with other health care providers, including doctors, nurses, therapists, pharmacists or anyone else who may be involved in my care. If I have to go to the hospital or any other institution, I also agree to let the pharmacist give the hospital or institution information about my medications.

I understand that I have to pick up my take-home doses myself. No one else can pick up my take-home doses. I also understand that I am responsible for the safe transport and storage of my take-home doses.

Before I can receive more take-home doses, I agree to bring back to the pharmacy the container in which my carries were given to me.

I know that if I lose my take-home doses, my doses will not be replaced unless I get a **new** prescription from my doctor.

If any doctor or dentist plans to prescribe me any opioid drugs, I will tell him or her that I am taking Suboxone. I know that it is **dangerous and illegal** not to do so.

Patient's signature: _____

Date: _____

Pharmacist's signature: _____

Date: _____

Supplement 6:

Concurrent disorders

Curtis Handford MD CCFP MHSc

Concurrent Disorders in this supplement refers to the co-existence of a substance use disorder and a primary psychiatric disorder [16]. The primary psychiatric disorder is not exclusively substance-related, though substances may exacerbate the condition. Substance use disorders and psychiatric illness occur very commonly together, most commonly mood, anxiety, personality and eating disorders [16].

Concurrent disorders are an important area for the clinician to be aware of as an untreated/undertreated psychiatric condition may frustrate attempts to stabilize the substance use disorder. Often a patient may be continuing to use a particular substance to "self-medicate" their psychiatric symptoms as an attempt to improve their ability to cope with those symptoms [17]. It is important for the clinician to be aware of the high prevalence of trauma in the substance dependent population and to consider this when patients continue to have persistent psychiatric symptoms and/or drug use despite optimal buprenorphine maintenance treatment.

One challenge for a clinician when confronted with a patient with a possible concurrent disorder is to establish whether the co-existing psychiatric symptoms are substance-related or are actually independent of the substance. Some clinical clues that support a primary psychiatric illness are: a clear history of psychiatric symptoms pre-dating the initiation of substance abuse; the persistence or worsening of the symptoms following a period of several weeks of abstinence and/or a strong family history of mental illness.

In general, for mild to moderate psychiatric symptoms it is appropriate for the clinician to work with the patient to achieve abstinence from the problematic substances and then carefully monitor the patient over the next 2-3 weeks to see if the psychiatric symptoms improve significantly or resolve [18]. If the symptoms resolve, it makes the diagnosis of a substance-induced psychiatric disorder much more likely and the treatment would be continued abstinence.

If a substance-dependent patient presents severe symptoms (i.e., frank psychosis or depression with suicidal ideation), then it may be appropriate to initiate treatment for the psychiatric symptoms prior to achieving abstinence from substances. These patients may also require urgent psychiatric consultation or hospitalization [18]. Caution should be exercised in prescribing psychopharmacologic treatment that is sedating or that carries the risk of overdose or abuse. If the patient is admitted with a frank psychosis and is also opioid dependent, buprenorphine may be required to manage opioid withdrawal symptoms

Patients with primary mental illness on opioid agonist treatment require additional care when being prescribed sedating antidepressants or anticonvulsants. There is also the need for careful dispensing of all medications if suicidal ideation is present. Existing benzodiazepine therapy may require rationalization and possible tapering. Psychosocial counselling is very important in this population [16].

Any uncertainty regarding diagnosis or treatment options should be referred to a concurrent disorders psychiatrist.

Supplement 7:

Buprenorphine/naloxone prescribing for adolescents and young adults

Sharon Cirone MD CCFP(EM) ASAM(Cert)

Prevalence and scope of adolescent alcohol and substance use

The 2009 Ontario Student Drug Use Survey (OSDUS) [19] found that in the preceding year 58.2% of students in grades 7 through 12 reported use of alcohol, 25.6% used cannabis and 2.6% used cocaine. . The OSDUS survey trends demonstrate an overall decreasing rate of illicit drug use in the past decade. However, this is not the case for opioid use. In this survery, 17.8% of Ontario students reported non-medical use of prescription opioids (ie use without a prescription) in the preceding year. Opioids were the second most commonly used illicit substance, exceeded only by the use of cannabis. More students had used opioids than tobacco. Of note, the OSDUS does not survey street youth, incarcerated, or first-nation youth on-reserve, all of whom likely have higher rates of substance use and use disorders than the general adolescent population [20]

The increased use of heroin by adolescents that was reported in jurisdictions across the United States and Australia in the 1990s [21, 22] has now been overshadowed by the increasing non-prescription use of pharmaceutical opioids.

Risk factors

A number of risk factors [23, 24] have been associated with substance use among young people. The markers and population variables that may predict adolescent substance use include:

- Concurrent mental health disorders [25]
- Family history of substance abuse and/or mental health disorders
- Family dysfunction
- Either excessively permissive or conversely overly rigid parenting styles
- Childhood sexual abuse
- Street involvement (homelessness or significant engagement in street income or activities)
- Gay, lesbian, bisexual, transgendered youth, or those struggling to identify their sexuality.

Screening and identification in the primary care setting

Primary care physicians have a unique opportunity to engage youth and initiate conversations about alcohol and drug use. However, many primary care physicians do not routinely screen adolescents for substance use and the associated risk factors. One study found that 35% of adolescents reported discussing substance abuse with their primary care physicians, although 65% of the sample said they wanted to. [26]

Developing rapport should be the priority of the physician in initiating any conversations about alcohol anddrug use as well as any other social behaviours of adolescence, such as sexuality or peer relations. Interactions that attempt to "be where the patient is at" allow the adolescent or young person to feel validated for their stance and concerns [27]. Motivational interviewing is suggested as a way to open dialogue, to develop rapport with the adolescent and to enhance conditions for positive change. Recognition of the patient's preparedness for change allows for appropriate matching of motivational dialogue.

Confidentiality is an essential consideration in the treatment of adolescents. Age 16 is the age of consent for medical treatment in Ontario. At this age, patients have the same rights to confidentiality as any other adult patient. Between the ages of 14-16 years, the emancipated adolescent who displays full insight and appropriate judgement for the treatment plan and the risks involved, as deemed by the physician, may be treated as an adult. Despite this, involvement of parents and guardians, where possible, can be very helpful [23].

Screening tools may be helpful in the primary care setting. The CRAFFT questionnaire, a screening tool that resembles the CAGE questionnaire, asks 5 questions that relate to the consequences of alcohol and drug use. A score of 2 or more indicates possible alcohol or substance use disorders. If the screening indicates the youth is at risk, the physician

can conduct a more in-depth interview in the office or refer the patient to an addictions assessment/counselling service or an addiction medicine physician.

Screening and thorough assessment for all alcohol, tobacco, over the counter and prescription drug use, and illicit substance use should precede any treatment of opioid use disorders. Screening for process addictions (gambling, internet, and sex addictions) should be included, as well as screening for emotional and mental health disorders. Referral, where necessary, should follow and treatment options should be considered.

CRAFFT screening tool [28]

C	Have you ever ridden in a CAR driven by someone (including yourself) who was "high" or had been using alcohol or drugs?
R	Do you ever use alcohol or drugs to RELAX, feel better about yourself, or to fit in?
A	Do you ever use alcohol or drugs while you are by yourself, ALONE?
F	Do you ever FORGET things you did while using alcohol or drugs?
F	Do your family members or FRIENDS ever tell you that you should cut down on your drinking or drug use?
T	Have you ever gotten into TROUBLE while you were using alcohol or drugs?

2 or more "yes" answers indicate a potential substance use problem and the need for further assessment.

Treatment

The treatment modalities available to youth with alcohol or substance use disorders include individual counselling and therapy, group counselling, 12 step groups, day treatment programs, and residential treatment. Pharmacotherapy can also be considered for adolescent substance use disorders. The resources for assessment and treatment programs in Ontario are available on the Drug and Alcohol Helpline website at http://www.drugandalcoholhelpline.ca/.

Identification of opioid use disorders in adolescents should be followed by a referral to a physician with experience in the treatment of opioid dependence. This may include primary care physicians, addictions focused practice physicians, or psychiatrists with addictions experience.

Pharmacotherapy for adolescents and young adults with opioid use disorders

Compared to adult populations, there is less in the literature regarding opioid substitution therapy in adolescents (13-18 years) and young adults (18-25 years). A few studies from the 1970s address the use of methadone for detoxification and substitution therapy in adolescents [29, 30].

Buprenorphine's partial mu agonist profile and decreased overdose risk may make it a desirable choice in younger patients. Buprenorphine may also have improved withdrawl profile compared to full mu agonists. Concerns about inducing opioid tolerance with methadone is another reason why the availability of the partial agonist buprenorphine has been seen as a useful treatment alternative for younger opioid users. Younger patients who present for treatment of opioid dependence often have a shorter history of drug use than treatment-seeking adults. Reflections from Australian experience include:

> *In treating young people with relatively brief histories of heroin use, and often with significant polydrug use, it is sometimes easier to recognize quite severe drug related problems than to be confident that the person is using opioids regularly enough to produce neuroadaptation. [31]*

A recent study concludes that "buprenorphine with behavioural interventions is significantly more efficacious in the treatment of opioid-dependent adolescents than clonidine and behavioural interventions". [32]. There have been other recent studies demonstrating the use of buprenorphine in adolescents and young adults [31, 33] Canadian experience with buprenorphine treatment of adolescents with opioid dependence is sparse at this time. The increasing rates of non medical use of prescription opioids, however, suggests that more adolescents and youth will be seeking treatment both in the primary care and addictions medicine settings.

For adolescent and youth who are diagnosed as opioid dependent, treatment options should be offered including medically supported withdrawal management, opioid assisted withdrawal management, and opioid substitution therapy. Buprenorphine for acute opioid withdrawal management would at present be an off label use in Canada.

Induction, stabilization, and maintenance dosing of buprenorphine is similar to that in adults. The pharmacotherapy decisions are similar to adults, including the structure and safety measures of substitution programs. The psychotherapeutic approaches however, may differ. Treatment approaches should include non confrontational techniques, the expectation of erratic attendance and treatment retention, motivational interviewing for risk reduction, appropriate involvement of family or other significant supports, referral or sessions to address other needs of adolescents (eg educational, vocational, housing, STD, HIV, and pregnancy prevention, and skills training needs), and appropriate referral for counselling, psychiatric assessment , or psychotherapy.

Summary

The neurodevelopmental issues of adolescents and young adults must be taken into consideration when treating opioid dependence in this population. The treating physician must have a sound understanding of the patterns of drug use in adolescents, the risk factors, and the medical, social, and mental health issues that complicate substance use disorders in young people. Screening tools, assessment and diagnosis, and treatment settings and modalities must consider the unique needs of this population. There is evidence supporting the use of buprenorphine for maintenance treatment in adolescent and young adult populations. In fact, some Australian authors have argued that buprenorphine be considered the first line pharmacotherapy for opioid substitution treatment in this particular group of patients. [31].

PRACTICE POINTS

1. The physician should observe an appropriate level of confidentiality for the adolescent during assessment and treatment. [23]

2. The clinical assessment of adolescents requires routine screening questions about the use alcohol and other substances. If screening raises concerns about the possibility of a substance use disorder, the clinician should conduct a more formal evaluation to determine the quantity or frequency of use and consequences of use for each substance used. [23]

3. Adolescents with substance use disorders (SUDs) should receive specific treatment for their substance use. They should be treated in the least restrictive setting that is safe and effective. [23] Options for treatment settings include outpatient, day treatment programs, Chemical Withdrawal Units ('detox'), and residential treatment programs.

4. Family therapy or significant family/parent involvement in treatment should be a component of treatment of substance use disorders. [23]

5. Interventions and treatment plans should attempt to incorporate services in other domains (e.g., vocational, educational. recreational, medical, family, and legal). [23]

6. Adolescents with SUDs should receive thorough evaluation for comorbid psychological, emotional, and psychiatric disorders. Comorbid disorders should be appropriately treated. [23]

7. Pharmacotherapy for opioid use, abuse, and dependence may include symptomatic treatment of withdrawal, opioid assisted withdrawal management, opioid substitution therapy or antagonist treatment.

8. Non-opioid treatment options should be strongly considered for opioid-dependent adolescents who are new to treatment.

9. Adolescents and young adults who use opioids and meet the DSM criteria for abuse or dependence should be considered for medically assisted detoxification. The pros and cons of inpatient versus ambulatory and symptomatic versus opioid-assisted treatment of withdrawal should be discussed. The optimal duration of long acting opioid-assisted withdrawal management is not yet established. The goal is to provide a transition from physical dependence on opioids to a drug-free state while minimizing withdrawal symptoms.

10. Substitution treatment with opioid agonists should be considered in young patients who meet the DSM criteria for opioid dependence. Patients that do not have a history of daily use, do not use opioids IV, or do not have consistent use greater than one year duration may still meet the criteria for opioid dependence.

11. Buprenorphine may be preferred in this population over methadone [31]. Buprenorphine prescribing in adolescents follows the same principles of prescribing as in adults. Failure to stabilize with buprenorphine maintenance treatment could result in consideration of methadone maintenance treatment.

12. Physicians who care for adolescents with opioid use disorders should ensure that they are capable of providing psychosocial services, either in their own practices or through referral to community counselling or therapy services.

Supplement 8:

Buprenorphine use in pregnancy

Alice Ordean MD CCFP, MHSc

A. Management of opioid dependence

Neonatal effects

Opioid replacement therapy has been documented to improve maternal and neonatal outcomes when used in pregnant opioid-dependent women [34-37]. Methadone reduces fetal exposure to repeated cycles of intoxication and withdrawal and thus, leads to increased fetal growth and less neonatal morbidity and mortality than continued opioid abuse. Currently, methadone maintenance therapy is the standard of care for pregnant opioid-dependent women.

Buprenorphine represents an alternative opioid replacement treatment. In non-pregnant individuals, buprenorphine maintenance has been shown to be as effective as methadone in reducing illicit opioid use and retaining patients in care [38]. Due to greater availability of buprenorphine, women will be getting pregnant while on buprenorphine maintenance.

There is a small body of evidence regarding the use of buprenorphine in pregnancy consisting of just over 300 buprenorphine-exposed neonates. A recent systematic review of over 30 studies has documented that buprenorphine is as efficacious and as safe as methadone during pregnancy [39-40]. To date, buprenorphine has not been associated with any teratogenic effects. In addition, babies born to buprenorphine-maintained pregnant women had birth outcomes including birth weight and Apgar scores within normal range and similar to those exposed to methadone. A buprenorphine-related neonatal abstinence syndrome (NAS) has also been observed with some significant differences [39-43]. On

average, NAS symptoms and signs were noted within 12-48 hours, peaked within 72-96 hours and lasted approximately 120-168 hours. The most frequent symptoms consisted of tremors, hyperactive moro, hyperreflexia and sleep less than 3 hours after feeding [44-45]. Overall, approximately half of neonates exposed to buprenorphine in pregnancy required medical treatment for NAS. However, NAS symptoms and signs secondary to buprenorphine exposure were reported to be milder and of shorter duration. This has recently been duplicated in a large double-blind, double-dummy randomized trial [46]. These positive short-term outcomes help to support the use of buprenorphine as an alternative treatment of opioid dependence in pregnancy.

Buprenorphine has been shown to cross the placental barrier to the fetal circuit [47]. Approximately <10% of the buprenorphine dose was transferred to the fetus and the remainder was retained by the placental tissue. Furthermore, there have been no adverse effects documented on placental tissue viability and function. The low transplacental transfer of buprenorphine to the fetus may explain the moderate neonatal abstinence syndrome in the limited number of published studies.

Long-term effects

The long-term effects of in utero exposure to buprenorphine are uncertain. At the present time, there is little published data on developmental outcomes for these children. One such report followed four children until ages 3 to 5 years old and reported to be "well" [48]. Another study reported normal development of two infants at 6 and 12months [49]. The largest study followed 13 neonates using the Denver Development Screening Tests II at ages 6 and 9 months [50]. Seven infants demonstrated transient motor abnormalities such as hypertonia in both lower and upper limbs and jerky movements from age 3-9months. Organic causes were ruled out and developmental milestones were reached within normal limits for eleven of these infants.

Dose adjustments

Buprenorphine should be clinically titrated until other opioid use is discontinued. Similar to methadone maintenance treatment, buprenorphine dosing may need to be adjusted in the third trimester. Limited pharmacokinetic data is available. There was no association found between the daily buprenorphine dose and severity of NAS [41, 43-44].

B. Management of obstetrical care

Pregnant women on buprenorphine maintenance therapy should be considered at high-risk and should be followed by a physician with expertise in the management of substance dependence. The frequency of visits depends on individual needs. Biweekly visits can be considered due to limited experience with buprenorphine use in pregnancy and then, weekly visits in the third trimester. Third trimester tests of fetal well-being are also recommended for these high-risk pregnancies.

C. Breastfeeding

The use of buprenorphine by breastfeeding women remains controversial. Currently, there are no controlled clinical studies addressing the use of buprenorphine while breastfeeding. Both buprenorphine and its main metabolite, norbuprenorphine, were measured at low concentrations in breast milk [51]. In this case report, the amount of buprenorphine ingested by the noenate was low and seemed to have no effect when breastfeeding was discontinued abruptly with no evidence of withdrawal symptoms or signs in the neonate. In contrast, another study demonstrated a breast milk to plasma ratio of ~1 [45]. Since buprenorphine has poor oral bioavailability, neonates would be exposed to a small proportion of the total amount of buprenorphine in the breast milk. More research is needed to determine the neonatal effects of buprenorphine exposure through breast milk.

Breastfeeding rates have not been frequently reported in studies. One controlled study reported that 50% of mothers nursed their neonates [43]; however, there was no further information provided.

Summary

There is limited data to determine whether buprenorphine is a better pharmacological agent for the treatment of opioid dependence during pregnancy. Based on this preliminary data, buprenorphine use during pregnancy does not expose these women and their fetus to a greater risk than expected with methadone. A multi-site randomized controlled trial is currently in progress to compare the severity and duration of neonatal abstinence syndrome secondary to methadone and buprenorphine exposure in pregnancy. Until the results of this study become available, preliminary studies have demonstrated the safety of buprenorphine in pregnancy and thus, buprenorphine maintenance treatment can be considered as an option for the management of opioid dependence during pregnancy.

SUMMARY: USE OF BUPRENORPHINE IN PREGNANCY

1. Methadone maintenance treatment is the current standard of care for the treatment of opioid dependence in pregnancy. However, pregnant opioid-dependent women may be considered for induction to buprenorphine after a review of the risks and the benefits of this treatment in comparison to methadone maintenance therapy. The optimal treatment during pregnancy remains to be determined.

2. Pregnant women already maintained on Subutex (buprenorphine) can continue on buprenorphine monotherapy for the duration of the pregnancy after a discussion of the risks associated with continued buprenorphine use based on the current available literature. Women may also consider a transfer to methadone maintenance therapy.

3. Pregnant women on Suboxone (combination of buprenorphine and naloxone) should be switched to buprenorphine monotherapy since the safety of naloxone in pregnancy is yet to be determined.

4. Buprenorphine has been measured in maternal breast milk. Breastfeeding by women on buprenorphine maintenance treatment can be considered after weighing the risks and benefits of buprenorphine exposure.

5. The long-term of effects of in utero exposure to buprenorphine remain to be determined.

Supplement 9:

Buprenorphine maintenance therapy and HIV, hepatitis infection

Curtis Handford MD CCFP MHSc

Buprenorphine and HIV Infection

Injection drug use (IDU), including injection of opioids, is one of the leading risk factors to acquire human immunodeficiency virus (HIV) infection. In the first half of 2007, 22.8% of new positive HIV tests in Canada were attributed to IDU [52]. 41.1% of women who tested positive for HIV in the first half of 2007 were injection drug users (IDUs), making IDU the leading risk factor for HIV infection among Canadian women [53]. The prevalence of HIV infection among IDUs in Toronto is estimated to be 5.1% [54][2]. The prevalence of HIV among IDUs has been estimated to be 14.7% in certain regions of Ontario[3] and as high as 23% in Vancouver although some say the rate of new HIV infections among IDUs in that city is now decreasing [55].

The relatively high prevalence of HIV among IDUs can largely be explained by risky behaviours associated with IDU. For example, in one study, 27.6% of IDUs reported needle sharing in the past 6 months. This included 20.2% of HIV positive IDUs [56]. Unsafe sexual practices are also highly prevalent amongst IDUs [57]. In one study, 4.8% of HIV-negative IDUs had an HIV-positive sexual partner at the time of the study [58]. An important consideration is that 40% of drug users are in a sexual relationship with a non-user. These non-using partners are often women of child-bearing age [59] who could potentially put unborn children at risk of HIV infection.

A recent systematic review of 28 mostly observational studies concluded that entry into opioid substitution treatment resulted in a statistically significant decrease in drug

injection, sharing of injecting equipment, sex with multiple partners and HIV infection amongst opioid-dependent injecting drug users [60]. It should be noted that all the included studies in this review involved methadone as the substitution agent. However, given the relative equivalence of efficacy between methadone and buprenorphine [61], it is at least reasonable to assume that similar benefits would also be accrued in buprenorphine maintained patients.

It has long been known that HIV-infected injection drug users are less likely than other HIV-infected patients both to have access to care or to receive antiretroviral (ARV) therapy [62-63]. IDUs are also known to have poorer adherence to ARV therapy [64]. Successful ARV therapy depends to a great extent on a high level of medication adherence and in order to maximize the likelihood of near-perfect medication adherence, many authorities consider the treatment of an active substance use disorder to be a prerequisite to initiating ARV therapy [65]. This view is somewhat controversial [66] as many active substance abusers taking ARVs are still able to maintain undetectable viral loads [67][16]. It has been shown that buprenorphine treatment improves adherence to ARVs among IDUs [64] without influencing the virologic response to ARVs [68].

A very important consideration for any buprenorphine-prescribing physician is the potential for drug interactions between buprenorphine and several antiretroviral medications. The biggest concern among HIV physicians around prescribing buprenorphine is the concern about possible drug interactions with ARV therapy [69]. Buprenorphine is metabolized to norbuprenorphine via the hepatic p450 system, in particular the CYP3A4 isoenzyme. Several antiretroviral medications also interact with the CYP3A4 enzyme pathway. Though only limited information is available regarding interactions between buprenorphine and ARVs [65] there are several potential interactions with ARVs that could result in either increased or decreased serum levels of buprenorphine. It is important for the physician to be aware that p450 inducers and inhibitors can theoretically influence buprenorphine metabolism both when they are initiated and when they are discontinued.

Nucleoside reverse-transcriptase inhibitors (NRTIs) do not have a clinically significant effect on buprenorphine metabolism[34]. Also, it appears that unlike methadone, buprenorphine does not appear to raise zidovudine (AZT) levels [70].

The non-nucleoside reverse-transcriptase inhibitors (NNRTIs) efavirenz and nevirapine are potent CYP3A4 inducers, and have been shown to decrease both methadone and buprenorphine levels [70]. However, unlike with methadone, where this interaction often results in the onset of opioid withdrawal symptoms and a need for the dose of methadone to be increased, the buprenorphine maintained patients on efavirenz generally do not experience opioid withdrawal symptoms, potentially making buprenorphine a superior choice for these patients [70]. Conversely, The NNRTI delaviridine inhibits CYP3A4 and increases patient exposure to buprenorphine, but without symptoms of opioid toxicity [71] or QT interval prolongation [72].

The situation with protease inhibitors (PIs) is slightly less straightforward. As a result of in vitro studies, certain protease inhibitors have generally been considered as CYP3A4 and 2D6 inhibitors, which in theory could result in increased levels of methadone or buprenorphine and cause opioid toxicity or overdose. However, in vivo studies have suggested that

the opposite may be true and that the PIs amprenavir, nelfinavir and lopinavir actually appear to somehow *decrease* methadone levels, potentially resulting in opioid withdrawal symptoms [70, 73]. Ritonavir alone does increase methadone levels, but in a modest and likely insignificant manner [70]. Ritonavir alone also increases buprenorphine levels but in a modest way that does not appear to be clinically meaningful [73-74] and without QT interval prolongation [72]. There have been case reports of possible opioid excess in buprenorphine-maintained patients receiving atazanavir/ ritonavir, leading the authors to suggest that buprenorphone should be initiated at lower doses in patients taking this particular combination of medications [75].

Drug	Effect on CYP3A4	Effect on serum buprenorphine levels	Clinically significant?
NRTIs	None	None	No
NNRTIs			
efavirenz	Potent inducer	Decease	No
nevirapine	Potent inducer	?	?
delaviridine	Inhibitor	Increase	No
PIs			
nelfinavir	inducer	Decrease	No
lopinavir/ritonavir	inducer	Decrease	No
ritonavir	inhibitor	Increase	No
atazanavir/ritonavir	inhibitor	Increase	Possible

Good communication between the HIV patient and buprenorphine-prescribing physicians is essential. It is also good practice to educate patients about drug-interactions, to monitor patients closely during medication changes and to adjust the buprenorphine dose based on the patient's response to the new medication(s). This wait-and-see approach is generally considered preferable to adjusting the dose of buprenorphine or ARVs in anticipation of a drug interaction [76].

There is exciting potential for buprenorphine therapy in the HIV-positive patient population as "flexible community-based HIV care sites" are essential to managing HIV-infected patients with substance use disorders [65], and buprenorphine offers "a new possibility of expanding the access of opioid treatment within the HIV primary care setting" [67].

Buprenorphine and hepatitis

There is a strong association between injection drug use (IDU) and hepatitis C infection. It appears that IDU is the route of transmission for about 70-80% of the recent HCV cases in Canada [77]. Hepatitis C infection can often be successfully eradicated with a long and complex medical treatment regimen involving pegylated interferon and ribavirin. Because of the length and complexity of this regimen, it has generally been accepted that

ongoing and untreated substance abuse is an absolute contraindication to treatment [77], though this view is becoming increasingly controversial. Much like the situation with antiretroviral therapy in HIV infection, the stabilization of an injection opioid use disorder with buprenorphine could be critical in preparing a hepatitis C-infected patient for interferon/ribavirin treatment.

The product monograph [74] for Suboxone (buprenorphine/naloxone) lists severe hepatic insufficiency as a contraindication to treatment with Suboxone. It also states that cautious titration of the dose of buprenorphine may be required for patients with mild to moderate hepatic dysfunction. The rationale for the above precautions is that impaired hepatic clearance may prolong the action of buprenorphine.

The product monograph also states that there have been rare case reports of hepatitis and hepatic necrosis associated with buprenorphine use. Examples of these case reports include patients who were taking prescribed sublingual buprenorphine at therapeutic doses [78-80] who developed increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels following initiation of buprenorphine therapy. All of the affected patients had underlying hepatitis B and/or hepatitis C infection. It appears that elevated liver enzymes were more likely to occur with a higher dose of buprenorphine. Liver enzyme levels normalized with decreased dose or gradual discontinuation of buprenorphine. There are also case reports of hepatitis among hepatitis C-infected patients who injected buprenorphine [81]. It is hypothesized that the hepatic effects of buprenorphine may be due to inhibited hepatocyte mitochondrial function.

Conversely, there have also been published case reports of hepatitis C-infected patients with markedly elevated baseline liver enzymes having their liver enzymes improve and normalize after starting on buprenorphine maintenance therapy [82].

There are clinical trials that are underway to further evaluate the effects of buprenorphine on hepatic function. For now, some people are recommending close monitoring of buprenorphine patients with known liver disease, including liver enzyme testing at baseline, one month post-treatment initiation, and quarterly thereafter [83]. Patients with marked baseline transaminases (3-5 times the upper limit of normal or greater) may want to delay buprenorphine initiation until these abnormalities have been further evaluated and/or corrected.

Supplement 10:

Acute and chronic pain in buprenorphine/naloxone maintenance

Curtis Handford MD CCFP MHSc

Management of *acute pain* in a patient on buprenorphine maintenance treatment

1. If able to anticipate the acute pain (e.g. surgical procedure), educate the patient about the possible risk of being triggered by the use of opioids and encourage them not to accept a prescription for an opioid they have previously abused. Patients should be reassured that their acute pain will be managed properly.

2. Employ non-opioid alternatives when possible.

3. If an opioid prescription is necessary, ensure that the patient is aware that it will be a short term prescription only.

4. Ensure only one prescriber

5. Only small amounts of opioid should be dispensed at one time.

6. Can prescribe an opioid analgesic while maintaining the patient on the same dose of buprenorphine [84]. Prescribers should be aware that the patient may require a larger amount of opioid analgesic and at more frequent intervals.

7. In some cases, the buprenorphine may need to be discontinued and an opioid analgesic started outright [85]. The prescriber needs to be aware that the absence of the buprenorphine will create an "opioid debt" which may require a larger dose of analgesic than usually expected. The prescriber should be aware that as buprenorphine is eliminated from the body over the subsequent 72 hrs, the amount of opioid analgesic required may in fact decrease.

8. Patient should be monitored closely during and following the use of opioids

9. If buprenorpine was discontinued outright, when the pain situation has resolved and the patient is ready to resume their buprenophine maintenance therapy they should present for induction as described in section 3. Initiation, maintenance and discontinuation of buprenorphine maintenance treatment, in Guideline Recommendations.

10. Alternatively, if a patient is clinically stable and receiving take-home doses of buprenorphine, one could divide the buprenorphine into BID or TID dosing and slowly titrate this to analgesic effect. It could then be tapered down and the doses consolidated as the pain problem resolves.

Management of *chronic non-cancer pain* in a patient on buprenorphine maintenance treatment

1. In general, chronic opioid analgesic therapy should not be started in a patient on buprenorphine maintenance treatment. Non-opioid alternatives should be aggressively optimized.

2. In these cases a referral to a reputable multidisciplinary chronic pain clinic regarding pharmacologic and non-pharmacologic non-opioid alternatives would be recommended.

3. If the decision to initiate opioid analgesics has been made, the patient should be monitored by or advice should be sought from a physician experienced in addiction medicine.

   Note: Buprenorphine-naloxone sublingual tablets are not currently approved in Canada as an analgesic agent. There is a transdermal buprenorphine product (BuTrans) recently approved in Canada for the treatment of moderate intensity chronic pain.

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