

Buprenorphine for the Treatment of Opioid Dependence

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Buprenorphine has been available as a prescription opioid in Canada since 2008. It is marketed as *Suboxone*® by RB Pharmaceuticals in combination with naloxone in a sublingual tablet. In Canada, it is indicated for maintenance treatment of opioid dependence.

Buprenorphine treatment provides an important alternative to methadone maintenance treatment in Canada. It has been shown to be a valuable strategy in helping to address the consequences of the prescription opioid crisis in Ontario, perhaps particularly so in areas where there are few methadone treatment providers.¹ As with methadone treatment, patients prescribed buprenorphine should be carefully monitored within a framework of medical, social, and psychosocial support as part of a comprehensive opioid dependence treatment program.²

Pharmacist involvement in buprenorphine treatment can include the supervision of drug administration, monitoring patients, communicating with the treatment team, providing encouragement and support, and dispensing take-home doses ("carries").

Involvement in the treatment of opioid-dependent patients with buprenorphine, has the potential for pharmacists to expand their scope of practice and provides a satisfying professional opportunity to participate in the recovery of individuals dependent on opioids. This area of practice may be of particular interest to those pharmacists already involved in the provision of methadone maintenance treatment. Opioid dependence is a complex disorder; therefore pharmacists who take training specific to buprenorphine therapy and other treatment options will be best able to provide pharmacy services to these patients.

With buprenorphine maintenance treatment, as with methadone maintenance treatment, patients benefit from physicians and pharmacists working collaboratively to provide optimal treatment. This includes communicating clinical observations, missed doses, and, in particular now, warnings in response to the Narcotic Monitoring System (NMS). Pharmacists need to monitor and manage messages that appear through NMS for patients on buprenorphine treatment, since alerts may have special significance in this population who have already been diagnosed with a substance use disorder.

Clinical practice guidelines have been developed by the Centre for Addiction and Mental Health (CAMH) to support the initiation, maintenance and discontinuation of buprenorphine/naloxone maintenance treatment in the ambulatory treatment of adults and adolescents with opioid dependence in Ontario. The Guidelines³ are available from the CAMH, OCP or CPSO websites, and should be reviewed before dispensing buprenorphine. (<https://www.porticonetwork.ca/documents/507864/0/buprenorphin+guideline+2012/ef7d9c7a-d1b4-46b7-b566-7207c31ac1b7>)

KEY MESSAGES FOR BUPRENORPHINE

- Suboxone® is an opioid prescription medication containing buprenorphine 2 mg and 8 mg (in *sublingual* tablets) in fixed combination with naloxone 0.5 and 2 mg respectively (to deter injection drug use).
- Sublingual dissolution of Suboxone® tablets usually takes 2 to 10 minutes.
- Buprenorphine:
 - is efficacious as maintenance

therapy in the treatment of opioid dependence.⁴⁻⁶

- is an alternative to, but not a substitute for, methadone maintenance treatment.⁷
- acts primarily as a partial agonist at mu-opioid receptors.²
- is considered safer in overdose than methadone, although if combined with other CNS depressant drugs (e.g., benzodiazepines) respiratory depression can occur.⁸ If clinical symptoms of overdose occur, higher doses of naloxone or other measures for treatment may be required.⁹
- may have a lower potential for abuse and dependence than pure agonists such as morphine¹⁰⁻¹¹, although abuse does occur.¹⁰⁻¹² The addition of naloxone to the Suboxone® product formulation is intended to further reduce the risk of injecting, but does not eliminate the risk.
- can be titrated to a stable dose within days, in contrast to methadone which typically may take weeks to achieve the optimum dose.
- prescribed at maximal doses, may not be sufficient for all patients. When the maximum daily dose does not stabilize a patient, consideration should be given to switching to methadone.
- may induce withdrawal in patients dependent on opioids if administered too soon after last use of full opioid agonists, e.g. oxycodone or fentanyl.
- has also been successfully used for medical withdrawal treatment (detoxification) from opioids^{8,13} and for the treatment of pain¹⁴ (both are unapproved indications in Canada).

REGULATORY FRAMEWORK FOR BUPRENORPHINE

Buprenorphine/naloxone does

not require a special prescribing exemption, unlike methadone, so prescriptions may be written by any practitioner licensed to prescribe narcotics. The College of Physicians and Surgeons of Ontario (CPSO) advises that they expect all physicians who wish to use buprenorphine to treat opioid-dependent patients will have training/education on this drug, and addiction medicine generally, prior to initiating buprenorphine treatment (www.CPSO.on.ca). In addition, the Ontario Drug Benefit LU codes for Suboxone® state that prescribers should complete an accredited course on opioid addiction and buprenorphine treatment before prescribing.

Prescriptions for Suboxone® have the same requirements as other "straight" Narcotic Drugs (Schedule N drugs); however, in addition, it is best practice to also indicate:

- start and stop dates
- days for supervised administration
- days for take home doses

As with other opioids, dispensing procedures for buprenorphine/naloxone must comply with the *Narcotics Safety and Awareness Act, 2010*, and requirements of the Narcotics Monitoring System.¹⁵

The Guidelines highly recommend that pharmacists who provide buprenorphine services undertake training. Pharmacists must be aware of the unique nature of buprenorphine dispensing and specific issues that exist in dispensing medications for the maintenance treatment of substance dependence. Some training resources are provided at the end of this article.

HOW BUPRENORPHINE WORKS

Buprenorphine is a synthetic opioid with a unique profile: it is a partial

mu-opioid receptor agonist.² Buprenorphine has a lower intrinsic activity at the mu-opioid receptor than a full agonist (e.g. methadone or oxycodone). This means that there is a "ceiling effect" to its opioid agonist effects at higher doses,¹⁶ making it safer in overdose and reducing its potential for abuse. There may be little increase in efficacy by increasing doses above 16 to 32 mg daily (Note: the maximum approved daily dose for Suboxone[®] in Canada is 24 mg). Although it is a partial agonist, buprenorphine has a very high affinity for the mu receptor. This tight binding means that buprenorphine can diminish the effects of other opioid agonists (e.g. methadone or oxycodone). It can precipitate withdrawal in those physically dependent on full opioid agonists by displacing them from opioid receptors.² The tight binding is also associated with a slow dissociation from the mu receptor resulting in a long duration of action.² This is why buprenorphine is associated with a milder withdrawal syndrome and has been used to assist in detoxification from other opioids.^{8,13}

Buprenorphine's partial mu-opioid agonist activity is beneficial in the treatment of opioid dependence because:

- It reduces craving for opioids.
- It may diminish the effects of other opioids (e.g. morphine, oxycodone, heroin).
- It can attenuate opioid withdrawal.

PHARMACOKINETIC CHARACTERISTICS SPECIFIC TO BUPRENORPHINE¹⁷

Buprenorphine's pharmacokinetic properties allow it to be utilized as a feasible maintenance treatment for opioid dependence. Buprenorphine has poor oral bioavailability due to extensive metabolism by intestine and liver. Sublingual administration

allows absorption through the oral mucosa and thus prevents breakdown via first-pass metabolism. Suboxone[®] tablets are formulated to be dissolved under the tongue. The onset of action is slow, with peak effects from sublingual administration occurring 3 – 4 hours after dosing. Buprenorphine is converted in the liver primarily by cytochrome P450 (CYP) 3A4 to an active metabolite (norbuprenorphine) with weak intrinsic activity. Both norbuprenorphine and buprenorphine are subject to hepatic glucuronidation. The mean elimination half-life is indicated as 37 hours in the product monograph², with evidence in the literature of large inter-individual variation (24 to 69 hours) following sublingual administration.¹⁷ Most of the dose is eliminated in the feces, with approximately 10 – 30% excreted in urine.

The slow onset of action and extended duration of action are both desired features in a treatment for opioid dependence. It is possible that buprenorphine can be given on an alternate day or three times weekly dosing schedule once

the patient has been stabilized on a daily buprenorphine dose. However, this may be a theoretical advantage, since many patients may have difficulty adhering to alternate day schedules and may benefit from daily contact with a pharmacist.

CLINICAL ASSESSMENT CONSIDERATIONS

"Opioid dependence" in the context being discussed in this article, can be considered the same as "addiction" which is characterized by a loss of control over opioid use, continued use despite knowledge of harmful consequences, compulsion to use and/or cravings. Many patients on chronic opioid therapy become physically dependent but not necessarily "addicted". Physical dependence (the development of tolerance and appearance of withdrawal symptoms after dose is lowered or stopped) alone does not indicate a diagnosis of opioid dependence.

Contraindications to buprenorphine/ naloxone in Canada² are:

- Allergy to buprenorphine/

NOTES ABOUT NALOXONE:

Naloxone, a pure opioid antagonist, is contained in Suboxone[®] tablets in combination with buprenorphine, with the intention of deterring patients from dissolving and injecting the tablet. When injected, naloxone may attenuate the effects of buprenorphine or cause opioid withdrawal effects in opioid-dependent individuals. However, the effect may be limited by the short half-life of naloxone and the relatively stronger binding by buprenorphine to the receptors.

When Suboxone[®] is used sublingually, naloxone is largely unabsorbed and does not exert pharmacological activity.¹⁷

Naloxone in Suboxone[®] tablets does not appear to influence the pharmacokinetics of buprenorphine.¹⁷

naloxone

- Use in opioid naïve patients.
- Breast feeding
- Severe respiratory insufficiency
- Severe hepatic insufficiency
- Acute alcohol dependence, or delirium tremens

DOSING INFORMATION

The product monograph states that Suboxone® must be given daily with supervised dosing by a health professional (e.g. a pharmacist) for a minimum of 2 months.² The exception to this is in circumstances in which the pharmacy is not open on weekends, in which case suitable patients may receive take-home doses for Saturday and/or Sunday and/or holidays.² However, the CAMH Guidelines, state that additional take-home doses earlier than two months could be provided if the physician decides that a patient would benefit from this and that the patient has a degree of clinical stability that would make them eligible for take-home doses. The patient must be made aware that this is against the Health Canada label, as well as all of the possible additional risks of receiving take-home dosing early in treatment such as overdose, consequences of careless storage and unintended ingestion by others, injection and diversion. Physicians document their rationale for the early take-home doses and their discussion with the patient about the risks. The number of take-home doses should be increased gradually and the patient carefully monitored. Refer to the Guidelines for further information.

INDUCTION

Therapy is initiated when the patient is **experiencing at least moderate opioid withdrawal symptoms:**

- at least 6-12 hours (preferably 12 hours) after use of short-acting

opioids (e.g. heroin, oxycodone)² or

- at least 12-24 hours (preferably 24 hours) or longer after the use of a long-acting opioid (e.g. oxycodone controlled-release formulations when swallowed whole).
 - For methadone maintenance patients wanting to switch to Suboxone®, waiting 3 days or more after the last dose of methadone before starting buprenorphine/naloxone is recommended. The methadone dose should be tapered down to 30 mg or less before buprenorphine treatment is initiated to minimize the possible precipitation of intense withdrawal symptoms.
 - At least 48 hours may be needed for patients discontinuing fentanyl patch use.

Initially a single dose of 2 to 4mg is given under supervision. An additional 4 mg may be administered later on in the same day depending on the individual patient's requirement.

Initial doses may be:

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

Precipitation of opioid withdrawal symptoms may occur when the patient is initiated on buprenorphine/naloxone if they are not yet in sufficient opioid withdrawal. Frequently, a Clinical Opiate Withdrawal Scale (COWS) score of 13 or greater is used to help determine this. The scale can be found in the Guidelines. If someone is not in sufficient withdrawal, buprenorphine, the high affinity partial mu agonist, displaces the

full mu agonist opioid from the mu receptors triggering a decrease in receptor activity which leads to a worsening of opioid withdrawal symptoms. If buprenorphine is taken when a patient is in sufficient opioid withdrawal, the partial agonism will produce relief of the withdrawal symptoms. Consideration should be given to reassessing the patient one hour after the first dose of buprenorphine to assess for possible precipitated withdrawal. Additional doses of buprenorphine are not recommended for precipitated withdrawal, rather, symptomatic management of withdrawal symptoms is preferred. The prescriber should be notified of the situation and buprenorphine induction rescheduled, typically for the next day. Abstinence from other opioids should be encouraged during this time.

MAINTENANCE

The dose should be increased progressively according to the individual patient's needs and should not exceed a maximum daily dose of 24 mg according to the Canadian product monograph.² Average maintenance doses have generally been found to be 8-12mg per day.³ The dose is titrated according to reassessment of the physical and psychological status of the patient.³ Stable doses of buprenorphine can be reached in a few days.

Once a patient has been stabilized on a maintenance dose, there is the option to reduce the frequency of administration for suitable patients (e.g. if doses have not been missed or when an alternative to take-home doses is needed for work or travel).^{18,19} Alternate day doses are given at double the daily dose (e.g. 16 mg q2days for a patient maintained on 8 mg per day). An example of three times weekly administration for a patient maintained on 8 mg per day would be: Monday and Wednesday doses

given at twice the daily dose (i.e. 16 mg) and a Friday dose at 3 times the daily dose (i.e. 24 mg). The dose given on any given day should not exceed 24 mg. In practice however, alternate day dosing may not be an effective strategy since many patients benefit from daily contact with the pharmacist or other health care providers, and some find it difficult to track days on which to take the medication.

OBSERVED DOSING

Water can be provided to patients **before** their dose to moisten the mouth and potentially decrease the time it takes for tablets to dissolve. The 8 mg tablets, although not scored, may be split to speed up dissolution. Observed dosing includes checking under the tongue to ensure dissolution of the SL tablet.

A pharmacist can provide take-home doses or portions of doses only if it is indicated on the prescription.

Supervised dosing by pharmacists ensures patient adherence with buprenorphine therapy and that it is being taken appropriately. This may help achieve positive outcomes for patients in opioid dependence treatment programs, and especially for those with a history of aberrant medication-related behaviours. Observed dose dispensing services are part of a structured opioid treatment program and can act as an effective mechanism to stabilize patients.

RECOMMENDED DISPENSING PROCEDURE FOR PHARMACISTS:

- Confirm identity of patients using photo identification, especially when the patient is not known to the pharmacist.
- Assess patients for intoxication

and compliance prior to dosing. It is good practice to note the time of observed doses.

- It is recommended that pharmacists employ some form of dose tracking sheet/tool (e.g. a patient calendar) to aid assessment of adherence and missed doses.
- Dosing is best done in a private area of the pharmacy where the patient can sit undisturbed by other patients, yet still be observed by the pharmacist.
- It is recommended that tablets are pushed through foil wrapping into a medication cup to minimize handling.
- If the Suboxone® dose consists of more than one tablet, all tablets can be placed under the tongue at the same time.
- Tablets may be split to speed up dissolution if needed. Sometimes this strategy is also used to minimize diversion of observed doses. Crushing of tablets is discouraged.
- Dissolution of Suboxone® tablets is not immediate and may require up to 10 minutes to completely dissolve under the tongue. After 1–3 minutes, pharmacists should check under the tongue to assess for dissolution; this is the most important time for reducing the possibility of dose diversion, e.g. once the tablet begins to dissolve it becomes more difficult to divert (although it should be noted that diversion of this pulpy mass has occurred).
- Drinking water or other fluids immediately prior to taking Suboxone® may moisten the mouth and enhance dissolution of tablets and speed up the dosing administration process.
- While the tablets are dissolving, patients should be instructed to do their best not to swallow their saliva. Patients should not suck on the tablets.
- Patients should refrain from drinking fluids or eating for approximately 5 minutes or more,

after tablets have dissolved in order to ensure that the full dose of medication has been absorbed.

- If the patient vomits after taking the sublingual dose, a replacement dose is not required as there is no effect on buprenorphine absorption once the tablet has dissolved. This is in contrast to methadone treatment, when under certain circumstances, a replacement dose might be prescribed.
- Finally, pharmacists should consider using a treatment agreement with the patient. This helps to communicate information regarding practical issues pertaining to pharmacy routine and services, as well as expectations of the patient and pharmacy staff.
 - Refer to the CAMH Guidelines Supplement 5: Buprenorphine/ Naloxone Dispensing for more information, including a sample treatment agreement.

TAKE-HOME DOSES

Take-home dosing can be considered based on the assessment of clinical stability, length of time in treatment and the patient's ability to safely store the drug. The pharmacist can help to inform this decision by sharing with the prescriber information gathered in the course of providing pharmacy care. Examples of useful information include missed doses, Narcotic Monitoring System alerts, concerns regarding patient self-care, and incidents of intoxication. The risks and benefits of take home doses for a patient should be re-assessed on a regular basis. (See also Dosing Information section above.)

Pharmacists are encouraged to have an initial pharmacy/patient treatment agreement, and also a separate agreement for patients starting take-home doses to include more information on safety issues.

Take home doses should be kept in the original strip foil packaging, removed from the original box and placed in vials with childproof closures. There have been reports of overdoses involving children taking tablets.²⁰ Take home doses need to be securely stored.

MANAGEMENT OF MISSED DOSES

Pharmacists need to track missed doses of buprenorphine and be able to easily retrieve this important information; use of a tracking tool/record of dose administration is advised.

Compliance with buprenorphine treatment **needs to be monitored by the pharmacist**. All missed doses should be communicated to the prescriber, since they can be important indicators of client instability. The pharmacist should consult the prescriber to develop a plan on how to continue with buprenorphine treatment after more than 5 consecutive days missed. Recommendations for new starting doses are available in the CAMH Guidelines³ (Table 1) based on the patient's buprenorphine dose and number of consecutive doses missed.

MANAGEMENT OF INTOXICATED PATIENTS

Prior to dosing, pharmacists should assess patients for possible intoxication. For purposes of

patient safety, patients should not receive a dose of buprenorphine/naloxone if they appear intoxicated or sedated. Pharmacists will need to hold or delay administration. It is recommended that the prescriber be contacted to make a collaborative decision on patient management. Patient safety is paramount. Due to the long duration of action of buprenorphine/naloxone, it is reasonable to hold one day's dose and reassess the next day. Education should be provided to the patient to reinforce safety risks of buprenorphine/naloxone, especially when used in combination with alcohol (or sedatives).

To help prevent such a situation, it is recommended that pharmacists communicate with patients at the initiation of treatment and on an ongoing basis to discuss what to expect should they present to the pharmacy for their dose while intoxicated. Pharmacists should be familiar with signs and symptoms of intoxication.

Information about intoxicated patients and course of action in the pharmacy needs to be shared with the prescriber.

CONTINUITY OF CARE

Communication must occur among pharmacists and other health care providers (as with

methadone maintenance treatment) to ensure that there are no omissions or overlaps in buprenorphine dosing. This is important when a patient is switching pharmacies, or is admitted or discharged from institutions such as hospitals or jails.

UNAPPROVED USES FOR SUBOXONE

WITHDRAWAL TREATMENT

Although not officially approved for opioid detoxification/medical withdrawal, buprenorphine treatment has been shown to be well accepted by patients and effective for this purpose.²¹

PAIN TREATMENT

Suboxone® has been prescribed (off-label in Canada) in the context of treatment of pain and chemical dependence.¹⁴ Similarly to methadone, when buprenorphine is prescribed for this indication, it is frequently given as a split dose.

ADVERSE EFFECTS

It is important to distinguish adverse effects from *withdrawal symptoms* that can be precipitated by buprenorphine.

As discussed above, after the first

TABLE 1: SUGGESTIONS FOR MANAGING MISSED DOSES³

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

dose of buprenorphine there may be some precipitated opioid withdrawal symptoms if the patient was not in sufficient withdrawal prior to first administration, such as headache, gastrointestinal upset, nausea, diarrhea, runny nose, sweating.

Adverse effects during buprenorphine treatment may be dose related and similar to other opioids. Most common are constipation, headache, CNS depression (e.g. sedation) euphoria, sweating, nausea, insomnia and orthostatic hypotension.

Toxic effects can be caused by buprenorphine alone or in combination with other CNS depressants. Since buprenorphine is a partial agonist, there is a ceiling effect on respiratory depression; however, very high doses of buprenorphine in some individuals have been associated with severe symptoms. Respiratory depression, when it occurs, may be delayed in onset and more prolonged than with opioids such as morphine, and reversal with naloxone is more difficult due to buprenorphine's very tight binding to opioid receptors. Other treatment approaches may be necessary (e.g., assisted ventilation).

DRUG INTERACTIONS

Serious respiratory depression has occurred when buprenorphine has been combined with CNS depressants including other opioids, alcohol, benzodiazepines, certain antidepressants, sedating antihistamines, and barbiturates.²

Special caution is recommended with the use of benzodiazepines and buprenorphine as this combination has resulted in respiratory depression, coma and death.²

Medications with CNS depressant effects should be avoided whenever possible and patients counselled regarding the risks associated with alcohol and benzodiazepine use.²

Buprenorphine is primarily metabolized by CYP3A4. Inducers (e.g. phenytoin, carbamazepine, rifampin) or inhibitors (e.g. ketoconazole, fluvoxamine, erythromycin, indinavir, saquinavir) of this enzyme would be expected to interact with buprenorphine. Ketoconazole, a powerful inhibitor of CYP3A4, has received particular attention and it has been reported to significantly increase peak plasma concentrations of buprenorphine.¹⁷ Careful patient monitoring and adjustment of buprenorphine dose when necessary, is recommended. Pharmacists may find the following link useful: <http://www.opioiddruginteractions.com/>

SPECIAL PATIENT POPULATIONS:

PREGNANT PATIENTS

The role of buprenorphine in pregnancy has not been clearly elucidated and Suboxone® is not approved for use in this population.² However there are studies which have shown buprenorphine to be efficacious, well tolerated and safe in pregnancy.^{22,23} Neonatal withdrawal can occur, although some sources indicate that symptoms are mild or absent in many cases.^{8,24} Although buprenorphine may prove to be a suitable option for the treatment of opioid dependence during pregnancy, the role and safety of naloxone in this context is not known. Buprenorphine without naloxone (Subutex®) may be an option through Health Canada's Special Access Programme. The current standard of care for the treatment

of opioid dependence in pregnancy is still methadone maintenance treatment.

PATIENTS WITH RENAL OR HEPATIC FAILURE

The dose of buprenorphine does not have to be significantly adjusted in renal impairment.¹⁷ It is possible that the dose may need to be modified in chronic liver disease.¹⁷

PATIENTS WITH ONTARIO DRUG BENEFIT COVERAGE

Both strengths of Suboxone are currently covered by the Ontario Drug Benefit plan under two Limited Use (LU) codes:

- 437: For the treatment of opioid dependence in patients who have failed, have significant intolerance, have a contraindication to, or who are at high risk for toxicity with methadone
- 438: For the treatment of opioid dependence when a methadone maintenance program is not available or accessible (i.e. No methadone maintenance programs available in the area, or waiting list is 3 months or longer).

For both codes, ODB indicates that physicians should complete an accredited course on opioid addiction and buprenorphine treatment before prescribing.

ABUSE OF BUPRENORPHINE

Buprenorphine is considered to have a lower potential for abuse due to its pharmacological properties (i.e. partial opioid agonist activity) compared to opioids which are full agonists, e.g. oxycodone or morphine. However, abuse has been reported in countries where both buprenorphine alone, and in combination with naloxone are available.⁹⁻¹¹ There have been increasing reports of misuse from

the US involving buprenorphine.^{25,26} Some have suggested that abuse may occur in the context of attempting to alleviate withdrawal rather than for the purpose of seeking euphoria.²⁷

Buprenorphine tablets have been abused by crushing and then administration by snorting or by the intravenous route.

In the US, buprenorphine is also available in a sublingual film formulation. Concerns have also been

expressed about the diversion and abuse of this dosage form.²⁸

Supervised daily dosing in the first 2 months of buprenorphine treatment helps to reduce the risk of diversion. Pharmacists may minimize diversion through careful dispensing and dose monitoring, paying special attention to Narcotic Monitoring System alerts, watching for “double doctoring” and communicating possible diversion (e.g. lost or stolen carries) to the physician.

Use of diverted buprenorphine by opioid-naïve people can result in overdose, particularly when combined with alcohol, benzodiazepines or other CNS depressants. Diversion for use in a person dependent on methadone or other opioids can cause them to experience precipitated withdrawal.

Conclusion

Buprenorphine is available as Suboxone®, approved for the treatment of opioid dependence. This sublingual formulation is combined with naloxone to deter intravenous use. Pharmacists in Ontario have an opportunity play an important role in the management of Suboxone® treatment with other members of the treatment team.

Opioid substitution therapy, whether with buprenorphine or methadone, has been shown to be far more effective than detoxification in improving outcomes in the treatment of opioid dependence.²⁴ Buprenorphine has several advantages when compared to methadone: it is safer in overdose, optimal dosing can be achieved quickly, it may be associated with less abuse and diversion, it may be easier to taper, it may be associated with less stigma and may be more convenient for the patient. Clinical practice guidelines are available on the use of buprenorphine/naloxone for opioid dependence. They provide evidence-based clinical recommendations developed by

a multidisciplinary committee, and are available from the CAMH, OCP or CPSO websites.³ Pharmacists providing care to patients on this treatment should have this resource on hand.

Buprenorphine may be considered a first line therapy, especially in those with a shorter history of opioid dependence and/or lower levels of opioid agonist needs. However, those that do not do well on maximum doses of Suboxone® (24mg daily) may need to switch to methadone with its greater dosage range.

There had been a growing problem of prescription opioid abuse in Ontario.²⁹ The number of individuals seeking treatment^{30,31} has increased, as has the number of inadvertent deaths associated with opioid overdoses.^{32,33} Although OxyContin is no longer available, new generic formulations have been approved requiring caution. Pharmacists are vital health-care team members, and are well positioned to address the increasing problem of prescription opioid abuse and addiction.

The profession needs to take a lead role and actively engage in being part of the solution to this problem.³⁴ The Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain (<http://nationalpaincentre.mcmaster.ca/opioid/>) provides guidance for pharmacists in managing patients on chronic opioid therapy. Developing expertise in the pharmacological treatment of opioid dependence is also an important component.

Involvement in buprenorphine treatment provides pharmacists with increased opportunities to provide pharmaceutical care to patients with opioid dependence. Pharmacists who already provide methadone services may be in a position to expand their scope of practice and further participate in the recovery of their patients with opioid dependence. Pharmacists in most cases see the patient more frequently than the prescribing physician. This means that direct open communication between the physician and pharmacist is essential for the optimal care of patients receiving buprenorphine

TABLE 2: COMPARISON OF BUPRENORPHINE TO METHADONE

	BUPRENORPHINE	METHADONE
Formulation	Sublingual tablet	Oral liquid
Effective treatment for opioid dependence?	Yes	Yes
Physician exemption required to prescribe?	No	Yes
Pharmacology at opioid receptors	<i>Partial</i> mu-agonist	<i>Full</i> mu agonist
Onset of action	Slow sublingually	Slow orally
Duration of action	May be longer	Long
Titration time to stable dose	Days (to weeks)	Weeks
Supervised doses	Yes	Yes
Take-home doses possible?	Yes	Yes
Need for extemporaneous preparation by pharmacist	No	Yes
Time to ingest dose	Minutes (needs to dissolve under tongue)	Seconds (swallowed)
Alternate day dosing possible?	Yes	No
Ceiling dose for opioid substitution effects?	Yes	No (can titrate dose higher for patients who require it)
Ceiling dose for respiratory depressant effects?	Yes (may be safer in overdose)	No
Sedation	May be less	May be more pronounced
Physical dependence/withdrawal	May be less/milder	May be more difficult
Is abuse possible?	Yes (naloxone included to ↓ IV abuse)	Yes (juice added to ↓ IV abuse)
Concern of added toxicity when combined with CNS depressants?	Yes	Yes
CYP3A4 interactions	Yes	Yes
Stigma	May be less	Possibly more
Does counselling improve treatment outcomes?	Yes	Yes
Ontario Drug Benefit Coverage	Not a general benefit, but available through Limited Use (see above)	Yes
Need to provide discreet seating area in pharmacy for dosing?	Preferable	Seating not required (but may be best to have discreet area to medicate)

treatment. Possible barriers for patients to access treatment include the cost of Suboxone®, although the ODB Limited Use codes have now made this product more available. Another challenge is the ability to provide a suitable, confidential area in the pharmacy where patients can wait while the

buprenorphine dose is dissolving under the observation of the pharmacist.

Pharmacists who take buprenorphine training are best able to provide support and encouragement and to help prevent, identify and resolve drug-related problems

in their patients on buprenorphine treatment. Good communication between the pharmacist, physician and patient will result in optimal patient care before, during and throughout buprenorphine treatment.

Case Examples

CASE: MR. M



Mr. M arrives at the pharmacy Tuesday morning for his first scheduled dose of Suboxone® 4mg. He has recently stopped his chronic opioid therapy and reports that his last dose of oxycodone controlled-release was approximately 12 hours prior. The pharmacist confirms that he is showing/experiencing signs of opioid withdrawal, including mild headache and some mild nausea. The pharmacist observes Mr. M take his Suboxone® 4mg sublingual dose as prescribed and ensures that the SL tablets have dissolved completely. The pharmacist dispenses two additional Suboxone® 2mg tablets, as prescribed, for Mr. M to take home in case his withdrawal symptoms re-appear in the evening. Approximately 45 minutes later that same day, Mr. M returns to the pharmacy and reports worsening symptoms including sweating, increase in his headache, runny nose, abdominal upset with increased nausea, as well as diarrhea. Due to the timeframe of Mr. M's worsened symptoms of withdrawal, the pharmacist counsels Mr. M that is likely experiencing symptoms of precipitated opioid withdrawal from his first dose of buprenorphine. Mr. M admits that he actually had his last dose this morning, since he was worried about how long he would have to wait for his Suboxone® dose to "kick in".

CASE: MR. Y

Mr. Y is a 54 year-old male with a history of opioid dependence, who is maintained on buprenorphine/naloxone (Suboxone®). He has a history of opioid-taking behaviours that are associated with an increased risk of overdose, including taking more opioid analgesics

than prescribed when he was using oxycodone controlled-release, and stock-piling his previously prescribed methadone carries. According to his pharmacy records his buprenorphine had been prescribed as 8 mg SL on Monday, Wednesdays, and 12mg on Fridays. During a visit with his physician 4 weeks after starting Suboxone®, Mr. Y reports he is actually taking $\frac{1}{2}$ of an 8mg tablet every day. He stated that his pharmacy permits him to take $\frac{1}{2}$ of the tablet home for the days he does not have observed dosing.

The pharmacist reported to the physician that they had not given permission for him to take $\frac{1}{2}$ of the observed dose home, but did indicate that it takes a very long time to observe Mr Y taking the whole dose, and that it was possible that the client took the initiative to take a split portion of the dose home. Going forward, the pharmacist recommended that daily observed dosing be prescribed for this client and indicated that more care would be taken with observation of dosing in the future.

Nº 0928 camh <small>Centre for Addiction and Mental Health</small>		 *D0355A*	Client/Patient ID Label
PRESCRIPTION – BUPRENORPHINE			
Client/Patient Name: <u>John A. Doe</u> <small>(last name, first name)</small>			
Health Record #: <u>987654</u>			
Address: <u>15 Oak Street, Toronto</u>		Date of Prescription: <u>June 1, 2014</u> <small>(dd/mm/yyyy)</small>	
<input type="checkbox"/> Addition Medicine Service 100 Stokes Street Toronto, Ontario M6J 1H4 Tel: 416-535-8501 x 36019 Fax: 416-595-6821	<input type="checkbox"/> Medical Withdrawal Service 40 & 50 White Squirrel Way Toronto, Ontario M6J 1H4 Tel: 416-535-8501 x 7197 Fax: 416-425-5279	<input type="checkbox"/> Medication and Substance Program 455 Spadina Avenue, Suite 200 Toronto, Ontario M5S 2G8 Tel: 416-535-8501 x 77369 Fax: 416-971-7172	
<input checked="" type="checkbox"/> Valid <u>only</u> at the following pharmacy: <u>ABC Pharmacy</u> <u>123 Main St</u>		Rx BUPRENORPHINE SUBLINGUAL <u>12</u> mg <u>Twelve</u> mg <small>(With naloxone at 25% of buprenorphine dose)</small> Dose in words Start Date: <u>June 2/14</u> End Date: <u>2014</u> Inclusive	
I.D. Type: <input checked="" type="checkbox"/> OHIP Card <input type="checkbox"/> Other (specify): <u>0987654321</u>		Observed dosing in the pharmacy on days circled: Mon <u>Tue</u> Wed Thur Fri Sat Sun	
I.D. Number: NO REFILLS		The following doses are to be dispensed as take home doses : Mon Tue <u>Wed</u> <u>Thur</u> <u>Fri</u> Sat Sun	
		Special Instructions: <u>once daily</u>	
<ul style="list-style-type: none"> If any dose is missed, please notify the prescriber by fax or phone. In certain situations, e.g. stabilization or increasing dose, the prescription will need to be cancelled and modified. If 3 consecutive doses or more are missed, contact the prescriber. If 5 consecutive doses or more are missed, <u>cancel prescription</u> and contact prescriber For any concerns, please fax a copy of this prescription to the prescriber. 			
 Signature		<u>J. Sample</u> M.D. <u>12345</u> Print Name CPSO #	

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CASE: MS. P.

It is Friday evening and Ms. P arrives at the pharmacy for her observed daily dose of buprenorphine/naloxone. She has been maintained on Suboxone® 24 mg daily for the past 3 months. When the pharmacist greets her at the counter, she is wearing sunglasses and stumbling as she walks. After further assessment, the pharmacist notices that her eyes are reddened, she is slurring her words, and is slightly confused. With further questioning, the pharmacist confirms that Ms. P is intoxicated with alcohol. She received her last


dose of Suboxone® on the previous day. The pharmacist explained their concern to the patient and for safety reasons did not provide the dose to the patient. The pharmacist followed up with the prescriber according to their agreed upon process.

BUPRENORPHINE TRAINING RESOURCES

The CAMH Opioid Dependence Treatment Core Course now includes training on both methadone and buprenorphine.

http://www.camh.ca/en/education/about/AZCourses/Pages/odtcore_odt.aspx

The CAMH manual *Methadone Maintenance: A Pharmacist's Guide to Treatment* is currently being updated and the new edition will include buprenorphine maintenance treatment. It should be available later this year.

While waiting to take full training, pharmacists can access the Reckitt-Benckiser online Suboxone Education Program at <http://www.suboxonecme.ca>. 

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