The occasional treatment of opioid use disorder

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INTRODUCTION

Opioid use disorder (OUD) has become common in many regions of Canada, particularly in rural northwest Ontario.[1,2] In the past, addicted patients had to access methadone-dispensing physicians if opioid agonist therapy was indicated. This generally took patients out of a primary care setting and away from their community, where robust addiction services were absent.[3,4] Rural physicians who decide that opioid agonist therapy is a good option for their patient may now consider initiating sublingual buprenorphine/naloxone combination therapy in the office setting or even offer home induction.[5–12] Rural physicians may encounter patients who mismanage their opioid prescriptions and are subsequently found to have OUD. Treating the addiction locally can help patients eliminate much of their dysfunctional behaviour and allow them to identify underlying life issues.

Buprenorphine/naloxone combination therapy was approved for the treatment of opioid dependence in 2003 in the United States and in 2007 in Canada. Numerous cases of safe office-based and home induction of buprenorphine/naloxone therapy have been documented. [5–12] This combination agonist–antagonist medication has a demonstrated safety profile (see "Pharmacologic characteristics") and can be used for managing opioid withdrawal or for opioid substitution maintenance therapy.[13]

In northwest Ontario, where an epidemic of OUD has been observed since 2009,[14] rural clinicians are becoming familiar with inducing buprenorphine/naloxone therapy and maintaining patients on this treatment.[14,15] This article reviews the medication and describes induction and maintenance therapy.

OPIOID USE DISORDER

The terminology now used by the American Psychiatric Association is "opioid use disorder," and clear criteria have been established for diagnosis. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5),[16] OUD "includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition." Specific criteria can be found in DSM-5.[17]

TREAT THE WHOLE PERSON

In almost all cases, the underlying cause for OUD is pain — physical, emotional, spiritual and/or mental. Suffering in any of these realms may be the root cause for a person's initial use of opioids and the subsequent development of OUD. A patient receiving opioid agonist (substitution) therapy will no longer experience the euphoric effects of illicit opioids, thereby losing a key coping mechanism. In addition to opioid agonist therapy, supports (typically called after-care) will be needed to assist the patient in dealing with his or her underlying issues. Although studies differ in their findings regarding the

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benefits of psychosocial supportive programs in the treatment of addictions,[18,19] there is general consensus that opioid agonist therapy should be accompanied by psychosocial supportive therapy.[16] Furthermore, fear of withdrawal symptoms can be a powerful driver of ongoing addictive behaviours; buprenorphine/naloxone therapy works well to mitigate those symptoms.

PHARMACOLOGIC CHARACTERISTICS

At first glance it may seem an odd combination: an opioid agonist and an antagonist. The opioid component, buprenorphine, is a semisynthetic opioid derived from the opium poppy that is 40 times more potent than morphine.[13] It binds strongly to the body's opioid receptors (particularly the μ receptor) and acts very much like methadone, by competing with other opioids for access to these receptors. As with methadone, its long half-life provides relief from withdrawal symptoms. Compared to methadone, which is a full μ-opioid receptor agonist, buprenorphine is a partial μ-opioid receptor agonist and has a better safety profile, with minimal respiratory depression and associated morbidity and mortality.[13]

When used as a single component, buprenorphine has limited euphoric effect when administered sublingually, but if administered intravenously, it can become a drug of abuse. When combined with naloxone, the risk of such diversion is decreased, as intravenous use may lead to withdrawal. Naloxone has almost no bioavailability when taken sublingually or orally. Hence the naloxone component of buprenorphine/naloxone allows the buprenorphine component to be safely used as agonist replacement therapy, with a built-in deterrent against diversion to intravenous use.

Precipitated withdrawal at induction must be avoided by ensuring the patient is in some opioid withdrawal. Because of buprenorphine's higher affinity for the μ-opioid receptor, it displaces other opioids from the receptor. Given that most opioids are full agonists, this creates sudden withdrawal symptoms as the expression of full agonist activity is replaced by partial agonist activity.[13] Another disadvantage of this strong receptor binding is that, should the patient require emergency analgesia, much higher dosages of opioids must be used to overcome the buprenorphine that is bound to the receptors.

The safety profile of buprenorphine notwithstanding, concurrent administration of other respiratory depressants such as alcohol, illicit opioids and benzodiazepines should be avoided.

PATIENT ASSESSMENT

A clinical assessment is needed to confirm the diagnosis of OUD, identify concurrent disorders and clarify the patient's treatment goals. Screening blood tests are beneficial for diagnosing bloodborne infections and other health issues in a high-risk population. Investigations should include a pregnancy test, complete blood count, liver function tests, screening for hepatitis B, hepatitis C and HIV infection, a urine drug test and screening for sexually transmitted infections. Useful resources are available through the Centre for Addiction and Mental Health for this initial assessment.[20] Since opioid agonist therapy is a harm-reduction strategy, the patient with OUD must have adequate harmful effects to warrant therapy. It is also important to recognize that chronic pain is a common comorbidity in patients who have opioid addiction. Adjunctive therapies (e.g., anticonvulsives, antidepressants, nonsteroidal anti-inflammatory drugs) may be required to manage pain while the patient is receiving opioid agonist therapy.

STARTING BUPRENORPHINE/ NALOXONE THERAPY

Starting the treatment is typically referred to induction. Induction and maintenance therapy can be given in outpatient settings including the office,[5–10] unsupervised at home[11,12] or as direct observed therapy.[21] Induction instructions are similar in all 3 settings. Provinces have different prescribing requirements (Table 1).

Since buprenorphine/naloxone binds powerfully to opioid receptors, it displaces any illicit opioids present. The patient must therefore be in moderate

Table 1: Provincial and territorial buprenorphine/ naloxone prescribing requirements

Methadone exemption required	No methadone exemption required*
Saskatchewan	British Columbia
Manitoba	Alberta
Newfoundland and Labrador	Ontario
Northwest Territories	Quebec
	New Brunswick
	Nova Scotia
	Prince Edward Island
	Yukon Territory
	Nunavut

*Some jurisdictions require online continuing medical education.

withdrawal before therapy is started. Measuring withdrawal has been standardized by use of the Clinical Opioid Withdrawal Scale (COWS), available online (https://www.naabt.org/documents/COWS_induction_flow_sheet.pdf).[22] Moderate withdrawal is generally identified by a COWS score of 12 or greater.[22] Patients in moderate withdrawal can safely receive induction therapy with buprenorphine/naloxone without great risk of precipitating increased withdrawal symptoms.

USE IN PREGNANCY

There are 3 published articles regarding patients who were incidentally or purposefully exposed to buprenorphine/naloxone prenatally (including induction therapy during pregnancy).[23–25] No adverse outcomes were observed in the total of 71 patients exposed for months to buprenorphine/naloxone.

If buprenorphine/naloxone is diverted to intravenous or intranasal use, however, it can cause severe withdrawal and pose a risk for the fetus.[26] For this reason, current recommendations are that women who become pregnant while taking buprenorphine/naloxone should continue their present treatment but should transition to buprenorphine monotherapy when possible, owing to concerns about withdrawal if buprenorphine/naloxone is used improperly (i.e., injected).[27] Since the single component buprenorphine is available only by special access from the manufacturer, this process can take weeks to set up. The combination drug is available through pharmacies.

PRECIPITATED WITHDRAWAL

Precipitated withdrawal may occur when the first dose of buprenorphine/naloxone is provided to a patient who still has a significant amount of full-agonist opioid occupying the μ-opioid receptors. Precipitated withdrawal differs from the "typical" withdrawal to which patients are accustomed. Precipitated withdrawal has a sudden onset of full withdrawal symptoms within 30 to 60 minutes of the first dose of buprenorphine/naloxone. In addition, it is difficult to reverse because of the high affinity that buprenorphine has for opioid receptors. It is important to prevent precipitated withdrawal by ensuring the patient is in moderate withdrawal before starting buprenorphine/naloxone therapy (it is easier to avoid precipitated withdrawal than to treat it).

Recommended lengths of abstinence before the first dose of buprenorphine/naloxone are listed in Table 2.

Table 2: Recommended length of abstinence before first dose of buprenorphine/naloxone

Drug/route	Length of abstinence
Buprenorphine by any route	None
Methadone by any route	≥ 3–5 d (great individual variance), ideally from a dosage ≤ 30 mg
Other opioids	
Intravenously	≥ 12 hr
Intranasally (snorting), smoking, chewing, orally	≥ 24 hr

WITHDRAWAL SYMPTOMS

Be prepared to manage withdrawal symptoms and common side effects. Patients are typically still experiencing significant withdrawal symptoms for the first 2 days of induction therapy. Some physicians simply provide reassurance and remind patients that their withdrawal will be relieved within a couple of days (most patients have significant improvement by day 3).

Many patients experience at least some transient side effects from buprenorphine/naloxone (e.g., headache, nausea). Table 3 lists the most common side effects. Note that there is some overlap between the symptoms of withdrawal and the side

Table 3: Typical opiate withdrawal signs and symptoms, and common acute buprenorphine/naloxone side effects

Opiate withdrawal signs and symptoms	Buprenorphine/naloxone side effects
Nausea/vomiting	Headache
Diarrhea	Nausea/vomiting
Abdominal cramps	Hyperhidrosis
Diaphoresis	Constipation
"Bone pain" or arthralgia	Insomnia
Myalgia	Unmasking of chronic pain
Fever/chills	Somnolence
Yawning	Euphoria
Rhinorrhea	
Lacrimation	
Piloerection	
Tremors	
Anxiety	
Restlessness	
Irritability	
Insomnia	
Headache	
Fatigue, "feeling lazy"	
Mydriasis	

effects of buprenorphine/naloxone. Most of the side effects are transient and resolve within a few days, except for constipation, hyperhidrosis and any underlying chronic pain.

PROCEDURE

After OUD has been established as a diagnosis, a clinical assessment has been completed and the patient agrees to the treatment plan, induction therapy can be scheduled. The patient must be instructed to abstain from opioids according to the time frames suggested in Table 2; otherwise he or she may risk precipitated withdrawal. The goal of induction therapy is to determine the dosage of buprenorphine/naloxone that relieves symptoms of withdrawal for a full 24 hours, without overmedicating. In the case of office induction, during daily visits for the first 4 to 5 days, assess for signs of drowsiness. Excessive drowsiness may indicate that the dosage is too high and should be decreased by 2 mg (or more). Some mild drowsiness can be expected at first, and the patient should be cautioned against driving or using heavy equipment until this effect resolves, typically within a week.

Day 1

- Ask the patient about his or her last illicit opioid use (when, which opioid, how much and by what route). If the patient has used an opioid within the time frames listed in Table 2, it may be best to delay induction therapy by a few hours.
- Assess the patient's level of opioid withdrawal by using the COWS. A COWS score of 12 or greater is recommended, but lower scores may still be acceptable depending on how long it has been since the patient's last illicit opioid use.
- Buprenorphine/naloxone comes in 2 mg and 8 mg dosages of buprenorphine. The tablets can be divided and are applied under the tongue until dissolved (2–10 min). For most patients, 4 mg is an appropriate first dosage (a smaller dosage may be appropriate for some patients; a larger starting dosage is not recommended). This dosage is provided by direct observed therapy.
- The patient then returns for reassessment at least 3 hours later, at which time, if he or she is still experiencing withdrawal symptoms, another 4 mg dose (or less if appropriate) is given. **The maximum amount given on day 1 is typically 8 mg** (in 2 divided doses). However, a third dose of 4 mg (total 12 mg) can be given 2–3 hours later for certain patients (e.g., those who are pregnant or are at high risk for not completing induction therapy owing to severe withdrawal) to reduce withdrawal symptoms as quickly as possible.

Day 2

- Assess the patient's level of withdrawal. If he or she is still experiencing any withdrawal symptoms, more than the total dosage given on day 1 will be needed. A COWS score of 12 or greater was required only to avoid precipitated withdrawal on day 1; now the goal is to eliminate withdrawal. Typically, 4 mg is added to the previous day's total, but if the previous day's dose lasted almost the full 24 hours, 2 mg may be a more appropriate titration. Hence, the dosage given at the beginning of day 2 is [day 1 total dosage + 4 mg (or 2 mg)].
- If the patient is not experiencing any withdrawal symptoms on day 2, it may be that the total dosage given on day 1 is the appropriate dosage. In that case, the amount given on day 2 is the same as the total dosage that was given on day 1.
- If the patient seems excessively drowsy, the dosage from day 1 may have been too much, and less than the day 1 total dosage should be given.
- Patients can be given the option of returning later in the day for an additional dose if withdrawal symptoms return.
- **The recommended maximum total dosage for day 2 is 16 mg.**

Day 3

- Assessment and dosing continues as described for day 2.
- Typically only 1 dose is provided on day 3 (and beyond).
- **The recommended maximum total dosage for day 3 is 20 mg**.

Day 4

- **The recommended maximum total dosage for day 4 is 24 mg**.

To go above 24 mg of buprenorphine/naloxone is off-label use in Canada. However, some patients may require a higher dosage. In Europe and the US, the maximum dosage is set at 32 mg; beyond

this amount, there is no further benefit owing to the ceiling effect of buprenorphine.

STABILIZATION PHASE

The first 2 to 3 months of buprenorphine/naloxone therapy are referred to as the stabilization phase. The concept of stability in the treatment of opioid addiction generally refers to achievement of many or all of the following goals:

- Discontinuation of injection drug use
- Consistent attendance for direct observed therapy, with very few missed doses
- Improved function in activities of daily living
- Improved quality of life.

It is important to recognize that it is common for patients to still use illicit drugs during the stabilization phase, and some patients will continue to use illicit drugs throughout buprenorphine/naloxone therapy. In these cases, one should remember the overall goals of harm reduction. Abstinence may not be achieved for every patient, so consideration should be given to the benefits of therapy, such as

- Decreased or discontinued injection drug use
- Improved finances
- Improved nutrition
- Ability to maintain employment or to care for children
- Decreased risk of violent altercations
- Improved attendance for routine health care.

The following criteria are helpful in determining a therapeutic dosage for the patient:[16]

- No withdrawal symptoms for the full 24 hours between doses
- Reduced cravings (but cravings may still be present)
- Cessation of opioid abuse
- A slip or relapse to opioid use does not result in euphoria
- No sedation and minimal other side effects.

MAINTENANCE THERAPY AND BEYOND

The overall goal is to reduce harm caused by OUD that affect the individual, the family and the community. These harms include, but are not limited to:

- Transmission of blood-borne infections (e.g., HIV, hepatitis C) and sexually transmitted infections (e.g., hepatitis B, chlamydia, gonorrhea)
- Complications of intravenous drug use (e.g., soft tissue infections, deep vein thrombosis, pulmonary embolus, endocarditis, osteomyelitis, sepsis)
- Financial difficulties (e.g., selling necessary belongings, not buying adequate groceries)
- Prostitution
- Criminal activities, especially break and enter, and theft
- Physical assaults and altercations
- Pregnancy complications (e.g., spontaneous abortion, preterm labour)
- Neonatal abstinence syndrome among infants born to women with OUD
- Children being neglected
- Children being apprehended and placed into care by child protective services
- Poor school attendance by children
- Poor vaccination rates (with resulting risks of outbreaks of vaccine-preventable diseases)
- Suicide and homicide.

One of the primary goals of therapy is to retain the patient in treatment, as dropping out or sudden discontinuation of buprenorphine/naloxone therapy leads to high rates of relapse to opioid abuse. With this in mind, we need to consider the various barriers and events that might increase the risk of attrition.

The maintenance phase is the time to address various issues related to OUD, such as

- Psychiatric comorbidities
- Other drug and alcohol abuse
- Unstable relationships
- Parenting skills, education, employment
- Financial issues
- Health issues.

It is a time for long-term goal setting. Moving beyond OUD and avoiding future relapse requires that the patient has constructed a different life, with healthy coping mechanisms and strong social supports. Often, there is deep emotional trauma from which the patient needs to heal.

Some patients will therefore be in the maintenance phase for life. Others may be able to taper off after several months to a year. The length of maintenance therapy is very individual.

Patients who wish to stop buprenorphine/naloxone therapy should be counseled carefully, as the risk of relapse is very high. They may wish to attend a detoxification program to get through the final withdrawal from buprenorphine/naloxone, or medications for symptom management can be provided by the family physician. Slow tapering over several weeks is recommended.[28] If relapse occurs, the patient should be welcomed back to opioid ago-

nist therapy without judgement. Recovering from relapse may provide lessons and insights that could allow a successful discontinuation later.

Alternative dosing regimens

Once a patient has been maintained on a stable dosage for a period of time, an alternative dosing schedule might be preferred if the patient's dosage is appropriate to allow it. The long half-life of buprenorphine allows the option of longer dosing intervals of up to 2 or even 3 days, as long as the maximum dosage given on any one day does not exceed 24 mg. One caveat of alternative dosing regimens is that managing missed doses can become complicated.[19,29,30]

URINE DRUG SCREENING

The clinical utility of urine drug testing is as follows:

- To assess stability of the patient's condition
- To provide a starting point for discussion of triggers and coping strategies
- To assess for illicit nonopioid drug use and allow for additional treatment planning
- To enable the patient to participate in an incentive program
- To corroborate the patient's self-report of drug use or abstinence
- To detect substances that may be unsafe in combination with buprenorphine/naloxone (e.g., benzodiazepines)
- To document the presence of buprenorphine as a replacement therapy agent.

It is important to note that there is no evidence to support the use of punishment, or the threat of punishment, in the treatment of addictions. This means that buprenorphine/naloxone therapy should not be withheld as a consequence (punishment) for a positive urine drug test result. The fear of being "kicked off" buprenorphine/naloxone creates an unnecessary stress for patients who may still be struggling with drug use. Many patients have intense fear and anxiety regarding opioid withdrawal. Stress and anxiety are common triggers for drug use, and therefore any addiction treatment program should aim to decrease stress in a patient's life and assist with general stress management.

CONCLUSION

Buprenorphine/naloxone combination therapy is a safe and effective outpatient treatment strategy for OUD. Rural physicians can benefit from knowing about it. Even if they decide not to become involved in prescribing it, some of their patients may be taking it, and it is important to understand its pharmacologic characteristics and be comfortable with its use.

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