

Buprenorphine: a potential new treatment option for opioid dependence

Although there are an estimated 60 000–90 000 illicit opioid abusers¹ in Canada, only about 25% are currently receiving treatment.² Methadone, a long-acting opioid agonist, is the treatment of choice for opioid dependence. However, although methadone is very effective, its use requires careful adherence to dosing guidelines and close monitoring because its long half-life increases the risk of overdose. Buprenorphine, a relatively newer treatment option, may increase safety and treatment access for opioid-dependent patients. It also has a long half-life, but it is a partial μ -opioid receptor agonist and thus may carry less risk of overdose. Currently, buprenorphine is being used in several countries for the treatment of opioid dependence, and it should soon be available in Canada as an additional treatment option to methadone.

Pharmacology: Buprenorphine is an opioid with high affinity for opioid receptors. It is a partial μ -receptor agonist as well as a kappa-receptor antagonist. μ -Opioid receptors mediate the common opioid effects such as analgesia, sedation, euphoria and respiratory depression. As a partial μ -receptor agonist, buprenorphine may result in less sedation than full μ -opioid agonists such as methadone and morphine while still decreasing cravings for other opioids and preventing opioid withdrawal. The clinical implication of the antagonist kappa receptor effect is not well understood, but it may result in buprenorphine having some mild antidepressant properties. As a partial agonist, buprenorphine has a “ceiling effect”: there is a plateau to its opioid agonist effects at higher doses.

Buprenorphine has a higher affinity for and lower intrinsic activity at opioid receptors than full μ -opioid agonists such as methadone, oxycodone and

heroin. Hence, buprenorphine displaces agonists from opioid receptors and may precipitate withdrawal in patients physically dependent on opioids. The effect of buprenorphine peaks at 1–4 hours after the initial dose.

Buprenorphine is metabolized mainly by cytochrome P4503A4 in the liver; its half-life is 24–60 hours.

Although it is not yet approved for use in pregnancy, initial studies have shown that buprenorphine is efficacious, well tolerated and safe in pregnancy. Neonatal withdrawal, as with other opioids, can occur. The current standard of care for opioid dependency in pregnancy is methadone treatment.

Effectiveness: Both buprenorphine and methadone are effective in the treatment of opioid dependence. In a Cochrane review,³ methadone was better at patient retention than buprenorphine, but both medications, when prescribed in flexi-

include nausea, vomiting and constipation. It is important to note that buprenorphine may precipitate opioid withdrawal symptoms if it is administered before other opioid agonist effects have subsided. Respiratory depression (and death) have been reported in the context of intravenous polysubstance, usually benzodiazepine, abuse.

Practical considerations: Buprenorphine therapy is initiated when the patient is experiencing opioid withdrawal symptoms (e.g., at least 4 hours after the use of a short-acting opioid, or 24 hours after the use of a long-acting opioid) because it may otherwise precipitate withdrawal.

Buprenorphine, which has poor oral bioavailability, can be administered in the form of sublingual tablets. Although the exact preparations that will be available in Canada are not yet known, buprenorphine hydrochloride (Subutex) is available in other countries in 0.4, 2 and 8 mg sublingual tablets. A sublingual formulation combined with naloxone (Suboxone) is also available: the addi-

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ble, high-dose regimens, decreased heroin use to the same extent: average daily doses ranged from 8 to 32 mg buprenorphine and from 54 to 150 mg methadone; study duration ranged from 6 to 26 weeks. Buprenorphine treatment is effective in primary care settings and specialized clinics, with equally improved social and medical status and treatment retention in both settings.⁴

Adverse effects: Adverse effects are similar to those of other opioids and

tion of the opioid antagonist naloxone should theoretically discourage intravenous use of the drug, although its effectiveness in this respect is not well proven. A starting dose of 2 mg has been used in most studies, but 4 mg has also been safely used. The dose may be increased by 2–4 mg daily until an effective dose, which is usually in the range of 8–24 mg daily, is achieved. Because of buprenorphine’s ceiling effect, daily doses above 32 mg, which is the maximum daily dose on the product mono-

graph, are unlikely to provide any further benefit. Buprenorphine's long duration of action may also allow for alternate day or thrice-weekly dosing.

Patients should be switched from methadone to buprenorphine only if methadone is ineffective at stopping opioid use or if the patient is experiencing adverse effects. Patients taking less than 30 mg of methadone a day may experience milder withdrawal when transferred to buprenorphine than those taking higher doses.

Exemptions to prescribe methadone are required by Health Canada but are administered through provincial medical colleges. Some provinces have an educational and practicum requirement. It is likely that attendance at an educational seminar will be required to prescribe buprenorphine.

Although buprenorphine has not yet been priced in Canada, in the United States the cost of a month's supply of the drug may be as much as 10 times that of the cost of a standard month's supply of methadone. However, in a 6-month cost-effectiveness analysis conducted at

specialist outpatient drug treatment centres in Australia,⁵ a methadone treatment program in this context was not significantly less expensive than a buprenorphine treatment program.

Withdrawal management: Opioid tapering is often preferred by patients over opioid agonist maintenance, and it may be useful for those with a shorter and less severe history of addiction. In clinical trials, buprenorphine has been shown to be more effective than clonidine, the standard withdrawal management therapy, and, because it is a partial agonist, it is also safer to rapidly titrate the dose than that of a full μ -opioid agonist such as methadone. In addition, buprenorphine's slow dissociation from μ -opioid receptors results in diminished withdrawal symptoms upon discontinuation. In most withdrawal management protocols, buprenorphine is quickly increased to a therapeutic dose (8–16 mg), and the dose is then reduced by 2 mg every 1–3 days for inpatients, or 2 mg every week for outpatients. Adjuvant medications may be

used, such as antidiarrheals and anti-inflammatories. Patients should receive counselling and monitoring.

Summary: Buprenorphine should be viewed as an alternative to, but not replacement for, methadone for opioid agonist therapy in patients with opioid dependence. Buprenorphine is viable in the primary care setting, which enhances treatment accessibility, and may be a better initial choice for patients at greater risk of respiratory depression, such as elderly patients and those taking benzodiazepines. Choice of first-line treatment will depend on patient preference, expectations, past treatment experiences and side effect profile as well as availability, dispensing regulations, cost and government reimbursement schedules. However, regardless of choice of methadone or buprenorphine, patients with opioid dependence do best in a comprehensive program involving opioid agonist treatment, counselling and support.

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This article has been peer reviewed.

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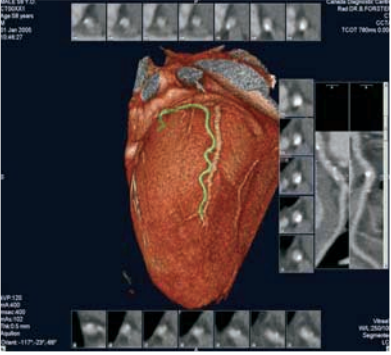
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