Update on the clinical use of buprenorphine

In opioid-related disorders

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Abstract

Objective To review the current evidence on buprenorphine-naloxone for the treatment of opioid-related disorders, with a focus on primary care settings.

Quality of evidence MEDLINE and the Cochrane Database of Systematic Reviews were searched. Evidence is mainly level I.

Main message Buprenorphine is a partial μ-opioid agonist and κ-opioid antagonist with a long half-life and less abuse potential than methadone. For detoxification, buprenorphine is at least equivalent to methadone and is superior to clonidine. For maintenance treatment, buprenorphine is clearly superior to placebo. Methadone has a slight advantage in terms of retention in treatment, but a stepped approach with initial use of buprenorphine-naloxone is as efficacious. Use of buprenorphine in the primary care setting is feasible, safe, and effective. Authorization to prescribe buprenorphine can be obtained after completing online training.

Conclusion Buprenorphine is a safe and effective agent for detoxification from opioids. It can be used as a first-line agent in maintenance programs, owing to its lower abuse potential relative to other opioids. Its effectiveness in primary care settings makes it a useful therapeutic tool for family physicians.

Dependence on opioids represents a considerable health issue, with an estimated 90 000 to 125 000 intravenous drug users in Canada.[1,2] These numbers are of concern given the high prevalence of hepatitis C (40% to 90%) and HIV (10% to 35%) in this population.[1,3,4] In addition, there is an increasing prevalence of prescription opioid drug abuse.[1,5,6]

Given the high rates of medical and psychiatric comorbidities among patients with addiction, family physicians are often confronted with this devastating disorder.[7,8] One of the difficulties for front-line clinicians has been the complexity of prescribing methadone, which requires a special licence in Canada.[9] In the United States, buprenorphine-naloxone was approved by the Food and Drug Administration in 2003 as an office-based maintenance treatment that could be used by primary care physicians.[10-13] In 2007, Health Canada approved Suboxone, a buprenorphine-naloxone combination for the treatment of opioid-related disorders.

Given buprenorphine-naloxone's lower potential for abuse relative to other opioids, general practitioners working in the community would benefit from having the capacity to prescribe it.[14] However, evidence is accumulating rapidly, making it difficult for physicians unfamiliar with this topic to obtain appropriate knowledge. This article reviews the evidence for and appropriate clinical use of buprenorphine.

KEY POINTS Given the high rates of medical and psychiatric comorbidities among patients with addiction, family physicians are often confronted with opioid-related dependence problems. One of the difficulties for front-line clinicians has been the complexity of prescribing methadone, which requires a special licence in Canada. Buprenorphine-naloxone was approved by Health Canada in 2007 for treatment of opioid-related disorders. Buprenorphine is an effective detoxification agent for opioid dependence; it is at least equivalent to, if not better than, methadone for this purpose. The literature demonstrates that buprenorphine is effective for longer-term opioid maintenance, although methadone remains a slightly superior substitution treatment. Physicians who wish to prescribe buprenorphine must complete a 60- to 90-minute online training program.

Quality of evidence

The Cochrane Database of Systematic Reviews and MEDLINE (Ovid) were searched using the key word *buprenorphine* for all articles published as of July 2010. The search was limited to human studies published in English. It yielded a total of 2004 potential articles. Studies related to pain control were eliminated, and the abstracts of all other articles were reviewed. Relevant studies with

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adequate methodology, mainly randomized clinical trials and meta-analyses, were selected and reviewed in depth. Evidence is mainly level I.

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

Level III: Expert opinion or consensus statements

Main message

Pharmacology. Buprenorphine is a partial μ-opioid agonist and κ-opioid antagonist.[15,16] It has less abuse potential than other opioids because the intensity of the rewarding effect is milder and plateaus at higher doses.[16,17] This "ceiling effect" is due to the partial agonistic action on opioid receptors, and possibly to agonistic action on the opioid receptor-like (ORL1) receptor.[18] Buprenorphine's partial agonist action (characterized by low intrinsic activity and high binding affinity) can induce withdrawal in opioid-dependent patients who are using full agonists (eg, methadone, heroin) by displacing opioids from the receptor.[19] It tends to produce a normalizing effect in individuals with heroin addiction already in withdrawal, as opposed to classic symptoms of opioid intoxication in control subjects.[20] Sublingual buprenorphine has a long half-life (24 to 60 hours, mean 37 hours) and is highly bound to plasma proteins (96%). It is metabolized by CYP 3A4 to various metabolites, including the active norbuprenorphine.[15,21-23] The μ blockade can last for up to 5 days owing to slow dissociation from the receptor.[24]

Despite these properties, there have been some reports of abuse and opioid withdrawal upon acute discontinuation of buprenorphine.[17,25,26] To counteract potential misuse, Suboxone was formulated as a combination with the opioid antagonist naloxone in a ratio of 4 to 1, for sublingual administration. Naloxone has poor bioavailability in the sublingual form; therefore, buprenorphine's effect predominates.[15,27] However, if buprenorphine-naloxone is taken inappropriately via subcutaneous, intramuscular, or intravenous administration, sufficient naloxone is absorbed to induce some withdrawal symptoms in opioid-dependent users.[28-30]

Buprenorphine is a safe treatment with expected side effects of sedation, constipation, headache, nausea or vomiting, and dizziness, and it carries a lower risk of respiratory depression than full opioid agonists do.[15,31] There are rare reports of hepatoxicity, in addition to a few cases of death when combined with benzodiazepines.[31,32] Liver function should be periodically monitored. Buprenorphine is associated with less QT interval prolongation than methadone is.[33,34]

Detoxification. The main features of opioid withdrawal are nausea, vomiting, diaphoresis, yawning, fatigue, aches and pain, diarrhea, mydriasis, and piloerection.[35] Subjective symptoms are much greater than objective signs.[36,37] Cravings begin 4 to 6 hours after the last dose of short-acting opioids, leading to active drug-seeking behaviour. This is followed by anxiety, diaphoresis, and agitation after 8 to 12 hours and the other symptoms after 12 to 24 hours. Peak withdrawal discomfort is usually experienced after 36 to 72 hours and decreases thereafter.[35] All these symptoms are delayed with long-acting opioids such as methadone. Consciousness is usually unimpaired, and opioid withdrawal is not life-threatening in itself, even if untreated. In both outpatient and inpatient settings, the therapeutic goal of using a long-acting agent like buprenorphine is to eliminate illicit opioid use, control the rate of taper, reduce withdrawal symptoms, and improve retention in treatment.

The best evidence for the efficacy of buprenorphine in acute detoxification comes from a 2009 Cochrane meta-analysis by Gowing et al.[38] In studies comparing buprenorphine to clonidine (an α_2 agonist), buprenorphine was clearly superior in mean peak and overall withdrawal scores. Completion rates were significantly higher with buprenorphine (relative risk 1.64, $P<.001$, number needed to treat 4[38]), with no difference in adverse reactions.[38-40] More important, in the 5 studies comparing buprenorphine with methadone, completion rates were similar, with a trend in favour of buprenorphine. There were no differences in the intensity of withdrawal symptoms or in adverse reactions. Initial studies yielded conflicting results about the optimal duration of tapers.[41-43] A recent large randomized trial demonstrated that, after a month of stabilization with active treatment, a 7-day taper was equivalent to a 28-day taper in terms of the number of opioid-free urine samples.[44] However, another comparative study suggested that a 30-day taper enhanced participation in longer-term treatment compared with a 5-day taper.[45]

For the induction phase, patients can be started on buprenorphine (maximum 8 mg on day 1, as per the drug monograph, in single or divided doses) 12 to 24 hours after the last opioid dose. Dosage can then be adjusted based on clinical symptoms.[12,15,46] Patients should be observed medically for at least 2 hours after the initial dose.[47] Among opioid-dependent patients, it is important to observe withdrawal symptoms before starting buprenorphine because the partial μ-agonist action could abruptly precipitate withdrawal. Monitoring symptoms with an opioid withdrawal scale, such as the Clinical Opiate Withdrawal Scale (COWS) or the Clinical

Institute Narcotic Assessment (CINA),[48] can be helpful to ensure that patients are in withdrawal before buprenorphine induction. Initial dosing can be estimated using equivalencies (**Table 1**)[49]; however, clinicians must be aware that these equivalencies have not been developed for opioid-dependent populations and must therefore be used along with clinical judgment. Extrapolating from Mattick et al, 6 to 12 mg of buprenorphine would correspond roughly to 35 to 60 mg of methadone.[50] Once stabilization has been achieved, doses can be reduced by 10% to 20% every 1 to 2 days. However, there might be advantages to a slower taper, with the rate of reduction negotiated with the patient. The manufacturer recommends that dosing be observed for the first 2 months, if possible.[46,51]

Table 1. Approximate opioid equivalencies compared with 10 mg of parenteral morphine: *Equivalencies are approximations and should be used with clinical judgment; clinicians must be particularly careful when the total equivalent opioid dose is more than 100 mg of methadone.*

GENERIC NAME	EQUIVALENT DOSES, MG	POTENCY RATIO COMPARED WITH PARENTERAL MORPHINE
Oral morphine	20-30	Approximately 0.5
IV morphine	10	1
Oral methadone	20	0.5
Oral codeine	200	0.05
Oral oxycodone	20	0.5
IV hydromorphone	1.5	5
Oral hydromorphone	7.5	1.3
Heroin	5-10	1-2
Fentanyl	0.05-0.1	100-200
IM meperidine	75	0.13
Oral meperidine	300	0.03

IM—intramuscular, IV—intravenous.
Data from Knotkova et al.[49]

It is of interest to primary care physicians that induction with buprenorphine-naloxone can be conducted as an office-based procedure, and even as a home-based treatment with adequate outcomes.[52] This opens up the possibility for family physicians to do an initial outpatient detoxification with buprenorphine-naloxone, and refer patients who do poorly to specialized centres for either inpatient detoxification or methadone trials. Kahan and colleagues provide more details on the process of induction.[53]

Maintenance. Although detoxification can sometimes lead to total abstinence from opioids, relapse rates are high.[54] To improve outcomes, long-term maintenance treatments with opioid agonists were developed within the context of a harm-reduction approach.[55] The objective is to decrease illicit opioid use and to reduce injection behaviour and the concomitant harms, such as HIV and hepatitis C infection. Methadone has been widely employed in opioid substitution programs, with a long history of safety and effectiveness.

Studies comparing buprenorphine to placebo were overwhelmingly in favour of the active treatment.[56,57] Initial studies comparing buprenorphine to methadone for substitution yielded conflicting results.[58-61] Meta-analyses comparing these medications have generally supported a slight advantage of methadone maintenance.[50,62,63] The largest meta-analysis by Mattick et al included 24 randomized trials with 4497 patients.[50] For flexible doses of both medications, methadone was slightly more likely to retain patients in treatment (relative risk 0.80). Medium doses of buprenorphine (7 to 15 mg) were superior to low doses of methadone (20 to 35 mg), but not to methadone doses ranging from 50 to 80 mg. The authors hypothesized that the superiority of methadone might be the result of overly slow induction of treatment with buprenorphine.[50,64]

In 2007 Kakko et al published an interesting trial in which flexible doses of methadone were compared with a stepped treatment approach with buprenorphine-naloxone. Patients in the latter group initially received buprenorphine-naloxone, but were switched to methadone if they required more than 32 mg per day.[65] After a 24-day induction phase, patients were followed for 6 months with optimal adjustments of dosing. Both arms had a similar retention rate (78%). In the buprenorphine-naloxone group, 46% of those who completed the study had continued taking buprenorphine and 54% were switched to methadone. Although a proportion of the sample required methadone, the important point for family physicians is that a first-line trial of buprenorphine-naloxone can be effective, leading to similar overall outcomes compared with methadone. Given its better safety profile, buprenorphine is an interesting option to implement in outpatient primary care clinics, which tend to attract patients with different characteristics than specialized clinics do.[66,67]

Another topic of interest is the amount of counseling required for cost-efficient treatment. In a 24-week randomized controlled trial in an office-based primary care setting, patients receiving weekly medication dispensing and standard medical visits (20 minutes) fared as well as those receiving extended medical management sessions (45 minutes) and 3 visits per week for medication dispensing.[68] This suggests that short medical counseling sessions are efficacious when appropriate pharmacologic treatment is instituted. Although this supports the feasibility of primary care treatment, one must not forget the importance of psychosocial interventions in the treatment of substance-related disorders.[69]

Doses and frequency of administration. It is well established that moderate to high doses (8 to 16 mg) have significantly higher efficacy ($P<.05$) than low doses (1 to 3 mg).[50,70,71] Although the maximum dose recommended by the manufacturer is 24 mg, doses of up to 32 mg have been used in some trials.[65] Buprenorphine's long half-life and slow dissociation from opioid receptors allows the possibility of less-than-daily dosing. Distribution 3 times a week can be as efficacious as daily dosing for all outcomes.[72,73] However, this should only be initiated after stabilization on a daily dose, and the dosage must be increased to maintain the same total amount of drug.[74,75]

Special populations. Primary care physicians are often confronted with chronic pain disorders.[6,76,77] According to the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain,[78] buprenorphine can be used for treatment of opioid addiction in chronic noncancer pain and could be preferable to other options in patients with higher risks of toxicity (eg, elderly patients, benzodiazepine users), adolescents, and young adults, or in communities where methadone is unavailable.

Methadone is the standard of care for pregnant women and has been shown to reduce illicit opioid use, enhance compliance with obstetric care, and improve neonatal outcomes.[79,80] In a small Cochrane meta-analysis of maintenance treatment in pregnancy, there were no differences in maternal or fetal outcomes between groups taking buprenorphine or methadone.[81] The authors concluded that there were insufficient data to support the superiority of either treatment. Recent trials have suggested buprenorphine to be superior in terms of fetal outcomes, with less severe neonatal abstinence syndrome.[82,83]

Intoxication with buprenorphine in children is relatively safe.[84] In a retrospective study, no severe effects occurred in children who ingested less than 4 mg, and there were no deaths.[84] Children should be referred to emergency care for all ingestions of greater than 2 mg or for any type of ingestion of more than a lick in patients younger than 2 years of age.

Conclusion

Buprenorphine is an effective detoxification agent for opioid dependence (level I), and it is at least equivalent to, if not better than, methadone for this purpose.[39] The literature demonstrates that buprenorphine is efficacious for longer-term opioid maintenance (level I), although methadone remains a slightly superior substitution treatment.[50] Its lower abuse potential and good safety profile make it particularly appealing for family physicians. Buprenorphine might be best used within a stepped-care approach, in which it is tried initially and those patients requiring higher dosages or those who fail to respond are then referred for methadone maintenance.[65] Moderate to high doses (8 to 24 mg) of buprenorphine are usually required. Use of buprenorphine-naloxone in primary care settings is efficacious, safe, and feasible within reasonable time constraints.[11,68]

Although a specific licence is required to prescribe methadone, physicians who wish to prescribe buprenorphine must only complete a 60- to 90-minute online training program (**www.SuboxoneCME.ca**). Once physicians have completed the 6 modules necessary to safely use buprenorphine, they obtain authorization to prescribe this medication. More exhaustive continuing medical education programs are available for physicians with less experience in treating opioid dependence. Given the available evidence, Canadian physicians working with this challenging patient population should take advantage of this new tool.

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Competing interests

Dr Fraser has previously received grants (speaking honoraria) from Pfizer, GlaxoSmithKline, and AstraZeneca, but has no link with the pharmaceutical industry currently. None of the authors has any relationship with Schering-Plough or Merck (distributor of Suboxone).

Contributors

All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

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