EDITORIAL

Buprenorphine for the treatment of heroin dependence

In November 2000 the Therapeutic Goods Administration approved the registration of buprenorphine in Australia for the treatment of heroin dependence. The product, Subutex®, will be launched in early 2001. This is an important leap forward in heroin treatment options for Australia.

The demand for pharmacotherapies has been increasing, and is likely to continue as new products enter the market. In Victoria, the average increase in methadone clients from 1993 to 1996 was 33% and it has continued to rise, although at a slower rate, since then. Importantly, however, this rise has not been commensurate with new treatment options—we would expect that with the introduction of buprenorphine as a maintenance treatment option, greater demand for maintenance treatment will ensue.

Buprenorphine is a partial mu opiate agonist that has been widely used as an analgesic. In Australia, low-dose buprenorphine is registered as Temgesic® as an analgesic, not for the treatment of heroin dependence. The doses of Temgesic® are insufficient to produce adequate treatment outcomes in heroin dependent individuals. High-dose sublingual buprenorphine tablets, marketed as Subutex®, come in three doses (0.4 mg, 4 mg and 8 mg). Subutex® has been registered for treatment of heroin dependence in France since 1993, and has recently been registered in the United Kingdom and seven other European countries.

Like other opiate substitution medications, buprenorphine prevents or relieves withdrawal symptoms associated with heroin use, reduces cravings for heroin use and blocks or reduces the ‘high’ of additional heroin use. Buprenorphine exhibits ceiling opiate effects on a range of physiological and subjective measures. Although high buprenorphine doses can cause sedation, they very rarely cause respiratory depression. These ceiling effects suggest that even at high doses, buprenorphine is safer than other substitution maintenance treatments. It should be noted, however, that cases of death as a result of combined benzodiazepines and buprenorphine have been reported in France [1]. Buprenorphine has a long duration of action, with high affinity to the mu receptors and slow dissociation. Thus it can be administered on alternate days, while maintaining its effects over the 48-hour period [2,3].

In the context of heroin withdrawal, buprenorphine has a mild withdrawal syndrome with rebound withdrawal upon cessation uncommon. Thus buprenorphine can be used both as a withdrawal treatment and a maintenance treatment. A brief examination of the safety and efficacy research on buprenorphine maintenance treatment will be followed by a brief summary of its efficacy in treating heroin withdrawal.

Buprenorphine has a good safety profile, without serious adverse events attributable to the drug. There is a range of side effects that are similar if not identical to those derived from the opiate class of drugs. These include headache, constipation, insomnia, asthenia, nausea, dizziness and sweating [4,5]. Tolerance tends to develop rapidly to these side effects and symptoms are generally transient. The ceiling effect diminishes the risk of respiratory depression which markedly enhances buprenorphine’s safety profile.

A number of randomized controlled trials have examined the efficacy of buprenorphine maintenance compared to methadone maintenance. In summary, the majority of studies found that between 8–12 mg daily of buprenorphine had similar rates of opiate positive tests as methadone 50–65 mg daily [4,6–8]. However, high-dose methadone (65–80 mg) had the lowest rates of positive heroin use [9]. The exception has
been the work of Fischer et al. [10], reporting lower heroin use rates in the buprenorphine group compared to the methadone group. Similarly, Johnson et al. [11] reported a non-significant difference in illicit drug use rates.

As with heroin use outcomes, retention outcomes have varied between studies. A number of studies reported equivalent retention rates between patients on buprenorphine (8–12 mg) and those on medium-dose methadone (30–60 mg), but overall lower retention than high dose methadone [9,10,12]. However, others have reported non-significant differences [8,11].

One could conclude, therefore, that buprenorphine maintenance is equivalent to medium-dose methadone. However, the research evidence has some caveats. First, the majority of studies were fixed-dose studies, with maximum buprenorphine doses of 8 mg. More recent Australian research [13,14] has demonstrated that under open label conditions, clients have maintenance doses which range between 8 mg and 32 mg. Hence the interpretation of lower efficacy compared to high-dose methadone may well be a function of the research trial designs, and further comparative research with higher doses of buprenorphine is required.

Secondly, the early research was conducted with liquid solution (in 30% aqueous ethanol), which does not have equivalent bioavailability to the sublingual preparation [15]. Lastly, the context within which the research trials were conducted is important. For those randomized to buprenorphine, the only treatment option if they dropped out was methadone. For those in methadone, there was no other treatment option (as they were not eligible for buprenorphine). This may have inadvertently biased buprenorphine towards higher dropout rates.

These points notwithstanding, in some ways buprenorphine is less appealing to heroin users. As a partial agonist it is less sedating than a full agonist and it blocks the high from additional heroin use. These features may account for lower heroin use with buprenorphine maintenance, but greater treatment dropout rates.

In summary, buprenorphine has a good safety profile, with features indicative of significantly less likelihood of respiratory depression. Other side effects are consistent with opiate medication. Efficacy research in maintenance treatment has demonstrated equivalent efficacy between buprenorphine and medium-dose methadone, with lower retention than high-dose methadone. Interpretation of this evidence requires caution due to a number of design features, such as fixed-dose protocols, use of liquid buprenorphine solution and artificial constraints upon treatment options. Some more recent research has demonstrated equivalent efficacy between buprenorphine and higher-dose methadone.

The use of buprenorphine for heroin withdrawal has also been subject to research enquiry. While the designs and control conditions have differed, the trials have consistently demonstrated superior outcomes for buprenorphine [16–19]. Australian research by Lintzeris and colleagues [20] compared buprenorphine with clonidine for out-patient heroin withdrawal. Buprenorphine demonstrated better retention, lower heroin use, lower withdrawal severity and most importantly greater post-withdrawal retention.

This latter finding has led to the development of the 'gateway' model of treatment [20]. The gateway model suggests that buprenorphine is a superior front-line option, with heroin-dependent treatment seekers easily inducted onto buprenorphine, for the commencement of a withdrawal episode. For those patients not able to sustain the withdrawal, they can be easily transferred to maintenance buprenorphine or other maintenance options. Those completing the withdrawal are more likely to link into appropriate post-withdrawal counselling options. One of the post-withdrawal options is transfer to naltrexone. Patients can do so during or very soon after buprenorphine cessation, without precipitating a withdrawal syndrome.

Part of the appeal of the 'gateway' model lies in the easy transition between buprenorphine and the various other treatment options. The reverse is not the case. For example, the transfer from methadone maintenance to buprenorphine does produce withdrawal, depending upon the original dose of methadone, and the time delay between last methadone dose and first buprenorphine dose.

With the introduction of buprenorphine in Australia, practitioners and heroin users require accurate information and education in relation to buprenorphine and the treatment options. The National Expert Advisory Committee on Illicit Drugs has developed nationally endorsed treatment guidelines for buprenorphine, which cover both withdrawal and maintenance treatment options. These will provide a sound footing for buprenorphine's introduction. As with other treatments for heroin dependence, little is known about patient selection. Based on the existing research and clinical experience gained as part of the Australian trials of buprenorphine heroin withdrawal, those motivated maintenance treatment methadone are likely maintenance. Those during maintenance drop out of bupren because of bupren client and clinician outcome plays an practitioners to be withdrawn—tions—such that a provision of this new to Australia, maximizing.

References

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phine; those motivated towards abstinence, seeking maintenance treatment and with poor responses to methadone are likely to respond well to buprenorphine maintenance. Those who continue to use heroin during maintenance treatment appear more likely to drop out of buprenorphine maintenance treatment, because of buprenorphine's blocking effects. Lastly, client and clinician expectancy regarding treatment outcome plays an important role. It behoves all practitioners to be well informed regarding buprenorphine treatment—its advantages, uses and limitations—such that a sensible and controlled introduction of this new treatment option is achieved in Australia, maximizing patient outcomes.

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References

[19] Bickel WK, Sitzer ML, Bigelow GE, Liebson IA, Jasienski DR, Johnson RE. A clinical trial of buprenor-