There is an alternative Buprenorphine maintenance

Led by one of the world's most respected authorities on drug-based treatments, a team of US experts assesses the evidence for a drug emerging as the most promising alternative to methadone for the treatment of opiate dependence.

by **Walter Ling**,
Alice Huber & **Richard A. Rawson**
Department of Psychiatry and Biobehavioral Sciences,
University of California, Los Angeles

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Background text

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Available worldwide for several decades as an analgesic, buprenorphine's (available in Britain under the trade names Subutex and Temgesic) potential for the treatment of heroin addiction was recognised in the late 1970s when studies showed that it substituted for heroin and suppressed opiate withdrawal but itself caused relatively minor withdrawal symptoms.[1]

The drug's advantages and its limitations both arise from the fact that though it acts at the same μ neuronal receptor sites as heroin, morphine and methadone, these are *full* opiate 'agonists' (drugs which produce opiate effects) while buprenorphine is best described as a *partial* agonist. This creates a ceiling effect beyond which dose increases prolong its action but do not intensify opiate-type effects, and confers on it a high safety profile, limiting the degree to which it causes respiratory depression and also euphoria.[2,3] It also means that when it is substituted for high doses of one of the full agonists, the result can be a degree of opiate withdrawal. The drug's high affinity for the μ receptor provides it with a long duration of action, allowing for flexible dosing schedules.

Dr Walter Ling, Dept. of Psychiatry and Biobehavioral Sciences, UCLA, 11075 Santa Monica Blvd., Suite 200, Los Angeles, California 90025, USA, fax 001 310 312 0552, e-mail lwalter@ucla.edu.

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Laboratory studies on human beings showed that buprenorphine suppresses heroin self-administration[4,5] and early clinical observations supported its utility and safety in opiate addiction treatment.[6,7,8] Here we focus on its potential in substitution therapy, playing the role usually associated in the UK and the USA with methadone.

Rivals methadone but harder to start

During the past decade controlled clinical trials involving over 1000 subjects have established buprenorphine's safety and efficacy in the treatment of opiate addiction. Trials varied in length from several weeks to a year, and used such common outcome measures as illicit opiate use (measured by urinalysis and self-report), retention, craving, and global assessment of improvement.

In an early trial, 8mg a day of buprenorphine was superior to 20mg a day of methadone and comparable to 60mg on measures of retention and illicit opiate use.[9] Continued illicit drug use was common across all groups, suggesting that a higher dose of buprenorphine might be needed. In a one-year, double-blind randomised trial involving 225 patients, 80mg a day of methadone performed better on measures of retention, opiate use, craving and global assessment than 30mg of methadone or 8mg buprenorphine, which were comparable to each other.[10] Individually adjusted doses of buprenorphine and methadone were compared in a study of 164 patients.[11] After adjustment, doses averaged 8.9mg daily of buprenorphine and 54mg of methadone. No significant differences were noted in treatment compliance, use of illicit opiates or retention to week 16.

These US studies used liquid buprenorphine, but tablets have been used in Europe for several years. Both are absorbed under the tongue ('sublingual'). In a Swiss study of 58 patients at three clinics, those allocated to buprenorphine started on 4mg a day increasing to up to 16mg by day 15.[12] Methadone was started at 30mg a day and similarly adjusted up to 120mg. Doses were maintained for the next 21 days averaging 10.5mg of buprenorphine and 69.8mg of methadone. No significant differences were seen in the proportion of positive urines. The large number of early dropouts on buprenorphine was attributed to inadequate induction.

In Vienna, buprenorphine was compared to methadone in a double-blind, 24-week randomised trial involving 40 patients.[13] At average doses of 7.3mg a day and 63mg a day respectively, there were no significant differences in illicit drug use, but retention was poorer on buprenorphine. The same investigators conducted an 'open' trial with 60 patients randomised to buprenorphine or methadone but who knew which drug they were on.[14] Retention was better among patients treated with up to 80mg a day of methadone than those treated with up to 8mg a day buprenorphine, but among patients who completed the study those on buprenorphine had significantly lower illicit opiate use. Another study also found that 8mg a day buprenorphine had lower retention than variable dose methadone.[15] In a 72-patient study in Italy, illicit drug use, craving and retention were comparable between 8mg a day buprenorphine and 60mg a day methadone, with a trend towards greater retention on methadone.[16]

Overall, these studies show that once a maintenance dose is reached, buprenorphine and methadone perform comparably. However, with highly dependent patients, getting to this point appears somewhat more difficult with buprenorphine, and more patients drop out during induction.

Higher doses are better

As with methadone, higher doses of buprenorphine have been found more effective than low doses.[17,18] Our 16-week, double-blind, randomised trial involved 736 patients at 12 sites across the United States and Puerto Rico and compared 1, 4, 8, and 16mg a day of buprenorphine.[19] The focus was the difference between outcomes from 1 and 8mg. The 8mg group performed significantly better on measures of retention, drug use, craving and global rating of outcome. Almost 90% of patients who completed the study stayed for a further 36 weeks during which blind dose adjustments up to 32mg a day were allowed. The results suggested that liquid buprenorphine up to this level is safe for extended periods.

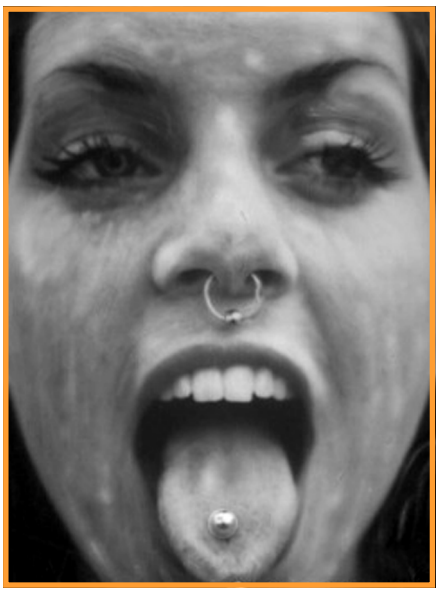
The only truly double-blind study comparing buprenorphine with an identically presented placebo involved 150 patients randomly assigned to 2mg or 8mg a day of buprenorphine or to placebo for the first six

days of a 14-day trial.[20] On day seven, they could change to an alternative dose. Irrespective of dose, patients treated with buprenorphine stayed on the initial dose longer (10–11 days versus 8 days), requested fewer dose changes, used illicit opiates less and rated medication adequacy higher than those treated with placebo. The results indicate that buprenorphine is superior to placebo, at least during initial treatment.

Suitable for primary care

France has the most extensive experience of buprenorphine. There 0.4, 2, and 8mg tablets have been available since 1996, dispensed from pharmacies under minimum control with a 28-day limit on takeaway doses. In one study buprenorphine was supplied daily by a pharmacy, administered under close supervision, and provided in concert with individualised treatment including twice-weekly visits to a psychiatrist for the first two weeks and weekly thereafter.[21] Opiate use and symptoms of depression declined dramatically during the first months of treatment. The benefits persisted up to 12 months, and quality of life (psychological, social, employment, legal and medical) improved.

Shortly after its introduction into the French outpatient health system, a national survey of 1785 randomly selected GPs assessed their attitudes to treating heroin addicts with buprenorphine.[22] Only 24% had treated drug injectors during the past 12 months and of those, only 31% felt prepared to prescribe buprenorphine. A positive attitude to buprenorphine was associated with prior experience with treating injectors, tolerance of drug use, and prescribing opiates for pain. However, allowing buprenorphine to be prescribed by all GPs quickly resulted in its more widespread acceptance. The number of patients treated with the drug rose from about 100 in 1996 to 30,000 six months after its approval. Currently, about 63,000 patients are treated with buprenorphine and another 8000 with methadone, with an associated decline of about 50% in overdose deaths, a marked decrease in drug use and improvements in health and quality of life.



One drawback with buprenorphine – it has to be taken under the tongue.

A comparison of 69 patients treated in France with buprenorphine either in the flexible general practice environment or in the more structured environment of an addiction clinic, showed significant medical and social improvement in both groups at three months continuing to six months.[23] Moreover, 65% were still in treatment after 180 days, demonstrating the effectiveness of buprenorphine in addicts with different social and medical backgrounds, regardless of clinical setting.

A survey of 2763 pharmacists, 200 GPs and 749 patients in a French treatment programme found the most common buprenorphine dose to be 6–8mg a day.[24] Some intravenous injection was found and illicit resale was suspected in a few cases, but overall outcomes and retention at six months were good. Patients felt positive about their treatment and reported few adverse effects. Communication between GPs and pharmacists was still not considered ideal, though relationships between patients and these practitioners had improved.

In the United States, 78% of 23 buprenorphine patients treated on a thrice-weekly schedule in primary care were retained for 12 weeks compared to 52% out of 23 at a traditional addiction clinic.[25] Fewer primary care patients used illicit opiates (63% v. 85%) and more achieved at least three consecutive weeks of abstinence (43% v. 13%).

Liquid versus tablets

The buprenorphine tablet was developed after the liquid was found to discolour with time and was suspected of becoming unstable with long-term storage. Given as a single dose, the bioavailability of the tablet varied from 25 to 80% that of the liquid, averaging about 50%.[26] However, the implication that tablets may need to carry twice the dose to achieve an equivalent effect may be unfounded. In our as yet unpublished study of 24 patients assigned to one formulation for ten days followed by ten on the alternate formulation, we found that blood levels on the tablets approached 65–70% of levels on the liquid. In a subsequent chronic dosing study over 16 weeks, the levels achieved by the two formulations approached parity.

Abuse can be reduced

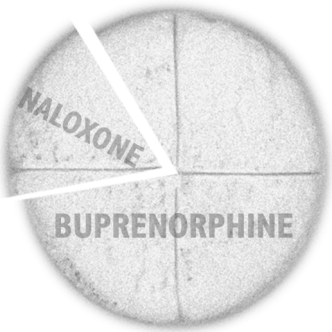
Buprenorphine abuse has been noted in some parts of the world, especially India (where methadone is not available)[27,28] and also in Britain when heroin was in short supply.[29,30] In France, several buprenorphine-related deaths have been reported since the drug became legally available, all linked to concomitant use of benzodiazepines.[21]

Intravenous misuse of buprenorphine in New Zealand became significant after the tablet was introduced in 1982.[31] In 1990, 81% of patients seen at the Wellington Alcohol and Drug Clinic reported misuse of buprenorphine tablets over the previous four weeks and 65% had buprenorphine in their urine. To counter this trend, a combination tablet consisting of 0.2mg buprenorphine and 0.17mg naloxone was introduced in 1991. Naloxone has little impact when the tablet is taken as intended under the tongue, but counters buprenorphine's opiate effects if the tablet's contents are injected, in theory reducing its attractiveness to injectors. A repeat survey found that 57% (down from 81%) reported misuse of the combination tablet and 43% (down from 65%) tested positive in urinalyses. A third of the patients reported withdrawal symptoms with the combination tablet and though it retained potential for misuse at the dosages employed, it was less attractive to misusers than the

Golden Bullets

Key practice points from this article

- Clinical observation and controlled clinical trials have established the safety and efficacy of buprenorphine as a an opioid maintenance or detoxification agent.
- Compared to methadone, more patients may drop out especially during induction but after that, given equivalent doses, performance is roughly comparable.
- Sublingual tablets with buprenorphine alone, or with the addition of naloxone which appears to reduce abuse potential, have been shown to produce comparable clinical effects to liquid buprenorphine at appropriate doses and to be acceptable to patients.
- Dosing strategies ranging from several times a day to two or three times a week appear feasible, reducing both clinic workload and inconvenience for patients without the risk of diversion entailed in take-home doses.
- Buprenorphine seems safe in pregnancy and minimises neonatal withdrawal.



Safety
Especially when combined with naloxone to deter injection

+

Convenience
Alternate day or less frequent dosing works well

=

Buprenorphine
a promising alternative to methadone for suitable patients

buprenorphine-only tablet.

In laboratory studies, combining buprenorphine with naloxone in a 4:1 ratio made the product less desirable for misuse. This tablet has recently been undergoing clinical evaluation in the United States.[26] A pilot study found induction on to the tablet was easily accomplished and that it was well accepted by patients.[32] In another US study, the first 29 of 47 patients were inducted on to combination tablets.[33] Seven complained of withdrawal symptoms, four of whom had transferred from methadone with an average daily dose of 48mg. The remaining 18 were inducted on buprenorphine-only tablets, including three patients who had transferred from methadone averaging 39mg daily. Two of the 18 – neither methadone transfers – complained of withdrawal.

A newly completed large, multi-centre study sponsored by the US National Institute on Drug Abuse found combination and buprenorphine-only tablets clinically comparable and superior to placebo.[34]

No need for the daily grind

Buprenorphine's high receptor affinity suggests the feasibility of less than daily dosing. An alternate-day schedule was initially trialed among opioid-dependent inpatients treated with 8mg buprenorphine daily or every other day, with placebo on intervening days.[35] No differences in opiate effects or withdrawal symptoms were observed, but opiate craving and unpleasant feelings were worse on placebo days. A later study confirmed that the two schedules produced comparable retention and illicit drug use reductions.[36]

Another US study tested the comparability of individually adjusted doses at different intervals. Daily buprenorphine doses for 13 patients were adjusted over 13 days. For the next 21 days they continued on their daily dose or on double this on alternate days with placebo in between.[37] The only significant difference was that on alternate-day dosing, patients' ratings of opiate effects were considerably lower. The two schedules were equivalent with regard to withdrawal suppression, retention and treatment compliance. Later, the same investigators showed that while symptoms of withdrawal were slightly lower with daily than with alternate-day dosing, most patients preferred only having to attend every other day.[38]

Less frequent dosing was tested on 16 patients randomly assigned after a 10-day stabilisation period to daily buprenorphine, twice the daily dose every two days, or triple every three days, with placebo on intervening days.[39] Opiate effects and withdrawal symptoms were greater on the triple dose but there were no adverse reactions and opiate intoxication never become excessive. The results suggest that buprenorphine can safely be administered every three days by tripling the daily dose with only minimal complaints, and that thrice weekly clinic attendance without take-homes may be possible.

A study of a small group of patients further extended the dosing interval to four times the daily dose every four days.[40] None of the higher doses induced greater opiate-type effects than daily dosing and subjective withdrawal effects increased only slightly with time since last dose, implying that a twice-weekly schedule may be safe and feasible. An attempt to extend the schedule to five or six times the daily dose every five days found that symptoms returned after four days, suggesting that this may be the limit to which the interval can be extended.[41]

More recently, this work has been extended to the buprenorphine/naloxone tablet.[42] In a US study, after induction 26 patients were stabilised on 8mg buprenorphine and 2mg naloxone daily for two weeks, then randomly allocated to three weeks on the same dose, the same dose every other day, or twice the dose every other day, with placebo on intervening days.[33] Just 14 patients completed the 11-week study, most dropping out during stabilisation. Among those who completed, the three regimes did not result in different withdrawal ratings or opiate effects. Drop out was (non-significantly) less on the double-dose regime and doubling did not cause adverse effects.

Finally, blood levels were monitored in ten patients on different thrice-weekly buprenorphine regimes. Regimes were maintained for three weeks and provided weekly total buprenorphine doses of 64, 84 and 112mg.[43] There was also one week of 16mg a day dosing. There were no significant differences in heroin use and withdrawal symptoms were similarly minimal across all the schedules. Blood levels 72 hours after the highest dose and 48 hours after the lowest were comparable to those at 24 hours following daily administration.

These studies indicate that an adequate dose of buprenorphine-only or combination tablets can be safely administered on alternate days or three times a week with good clinical results and patient acceptance.

Other potential advantages

Though our focus here has been on substitution treatment, buprenorphine seems an especially good candidate for use in opioid detoxification.[44,45] In short regimes of under a

week it has been found at least as effective as clonidine[46] and it can be integrated with naloxone to speed detoxification even further.[47] However, extending buprenorphine detoxification over a month or more has been found preferable to a 12-day schedule.[48] Contingency management techniques rewarding opioid-free urines and participation in therapeutic activities enhance detoxification outcomes.[49 50]

Buprenorphine can also be expected to decrease or eliminate the neonatal abstinence syndrome and improve pharmacotherapy for pregnant opioid-dependent women.[51 52]

OFFCUTS

As the most potent symbol of an accommodation with illegal drug use in the interests of harm reduction, **syringe exchange** continues to arouse controversy. Hastily interpreted findings from Canada seeming to cast doubt on their anti-HIV record, spread of hepatitis C, and a sometimes less than proactive stance on encouraging addiction treatment and medical care, have given ammunition to the critics. But in a broader perspective these can be seen as the trees obscuring the wood: syringe exchange could work better – but it works. Heavyweight support from the UN and the USA has lent credibility to its role as a crucial element in a strategy to prevent the spread of blood borne diseases, but in both cases the statements have received little publicity.

In a first position paper on preventing HIV among drug injectors, agencies across the UN agreed (❶) that "needle exchange programmes have shown reductions in needle risk behaviours and HIV transmission and no evidence of increase into injecting drug use or other public health dangers," though services could do more in the way of "AIDS education, counselling and referral to ... treatment". A statement (❷) seemingly omitted from the current US Surgeon General's web site records that former Surgeon General David Satcher (who left office in February 2002) and senior scientists at the US Department of Health and Human Services "unanimously agreed that there is conclusive scientific evidence that syringe exchange programmes, as part of a comprehensive HIV prevention strategy, are an effective public health intervention that reduces the transmission of HIV and does not encourage the use of illegal drugs." President George Bush remains opposed, and federal funding for syringe exchange continues to be blocked.

❶ United Nations. **Preventing the transmission of HIV among drug abusers. A position paper of the United Nations System.** 2000. Download from www.unaids.org/publications/documents/specific/index.html#drug

❷ US Surgeon General. **Evidence-based findings on the efficacy of syringe exchange programs: an analysis from the Assistant Secretary for Health and Surgeon General of the scientific research completed since April 1998.** March 2000.

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