

# **BUPRENORPHINE THERAPIES FOR THE TREATMENT OF OPIOID DEPENDENCE - SUBUTEX AND SUBOXONE\***

**Chris B Chapleo**  
**Director of Buprenorphine Business**  
**Reckitt Benckiser Healthcare (UK) Limited**

## **Introduction**

Drug addiction is a worldwide problem and opioid dependence, notably on heroin, is a major component. Strongly associated with drug addiction is the spread of infectious blood borne diseases such as HIV, Hepatitis C and tuberculosis, which are associated with the shared use of needles amongst intravenous drug users. Drug-seeking behaviour accounts for much crime and violence as addicts steal to buy more drugs, and the physical and psychological problems caused by the drugs give rise to unstable behaviour and a breakdown in normal interpersonal relationships. The high health service costs for the treatment of addiction related diseases as well as the high cost to society of drug related behaviour has prompted research to find new medications and treatment strategies for opioid dependence.

Opioid dependence treatment programmes vary between countries but underpinning the different strategies is the concept of harm reduction - a minimisation of the damage resulting from the addiction and drug-seeking behaviour, to both the patients and to society. This includes a range of measures including needle exchange and drug therapy with the overall objective of treatment being the rehabilitation and reintegration of heroin users into society with the ideal goal of achieving a drug free state.

## **Treatment Approaches**

There are two main treatment approaches: maintenance (also referred to as substitution) and detoxification. Maintenance treatment focuses on transferring patients from heroin to a pharmaceutical grade opioid with a longer duration of action on which they are maintained for periods of months to years with the objectives of weaning them off self-administration of illicit drugs, especially by the injectable route, and stabilising their life style. Methadone has been the most widely used maintenance agent, following the pioneering work of Nyswander and Dole<sup>1</sup>, and has been the mainstay of treatment therapy for many years and has contributed significantly to harm reduction and prevention policies. As once a day oral therapy, it reduces self-administration of intravenous heroin, limiting the spread of infectious diseases, and suppresses drug-seeking behaviour and the associated antisocial consequences. However, methadone has two disadvantages: like heroin it may produce dependence which often leads to increased doses with time and subsequent detoxification may be more difficult than from heroin. Methadone is a full agonist at mu-opioid receptors and can therefore lead to severe respiratory depression. Overdose with methadone can be fatal; accidental fatalities include children<sup>2</sup> having ingested their parent's medication and patients who increase their dose too quickly on initiating methadone therapy<sup>3</sup>. LAAM, a longer acting methadone-like agent that could be taken just three times a week, received marketing approval in the European

Union in July 1997 but was withdrawn in March 2001 because of cardiovascular problems<sup>4</sup>.

Detoxification is the process which eventually leads to the addict achieving a drug free state through the gradual or abrupt withdrawal of the illicit or prescribed drug. Short-term detoxification is when subjects are taken from heroin to a drug free state in 5-10 days. Generally however relapse is high because of the marked physiological and subjective symptoms that accompany withdrawal from the drug. Attenuation of some of the withdrawal symptoms is possible through the use of medications such as clonidine or lofexidine<sup>5</sup> and benzodiazepines. Detoxification schedules are often labour intensive and addicts require significant psychosocial support to get them through the difficult withdrawal period. Although relapse rates are high, detoxification is a good strategy for addicts who are highly motivated; whatever the outcome the process is valuable since it brings the addict into a caring environment often with provisions of psychosocial support. Once an addict has been successfully detoxified, abstinence from illicit opioids can be encouraged (relapse prevention) by daily administration of an opioid antagonist such as naltrexone which effectively blocks the effects of any subsequently administered heroin.

### **Buprenorphine**

The clinical utility of buprenorphine in the treatment of opioid dependence was first recognised as early as 1978<sup>6</sup> when it was shown to block the effects of heroin and block the withdrawal effects associated with the cessation of heroin. Subsequently, many clinical studies have confirmed that buprenorphine reduces drug-seeking behaviour shown by retention of patients in treatment and by increased number of urine samples free from opiates. The versatility of buprenorphine has been demonstrated through comparison studies with methadone and LAAM, successful detoxifications comparing it with clonidine, transference onto naltrexone following detoxification within a short timeframe and less than daily dosing schedules such as three times a week dosing. Buprenorphine is classified as a mu-opioid partial agonist and has very slow receptor dissociation kinetics; for this reason it has a number of advantages over methadone. Only a low level of dependence results from its repeated use, it produces lower subjective opioid agonist effects, there is no evidence of tolerance development in the treatment of opioid dependence and, importantly, there is a ceiling to its respiratory depressive effects. It is therefore safer in overdose compared to the full agonists heroin and methadone, and is easier to withdraw from than full agonists.

Subutex (buprenorphine alone) has been available for the treatment of opioid dependence in France since February 1996. Subutex has now received marketing authorisation for this indication in over 30 countries around the world, including most of Europe, and it is marketed in 25 countries<sup>7</sup>. Suboxone (buprenorphine + naloxone) was recently approved in the US where it is now available; the product is expected to receive European regulatory approval within the next 2 years. Buprenorphine is extensively metabolised in the small intestine and liver and is therefore unsuitable for oral administration - however sublingual administration provides an acceptable alternative. Suboxone has been developed with the objective of having the same sublingual effectiveness and safety as Subutex but with a lower intravenous abuse potential. Naloxone is very poorly absorbed sublingually and has no effect on

buprenorphine absorption. Intravenously naloxone has a faster onset of action than buprenorphine and being an antagonist it will produce rapid and intense opioid withdrawal symptoms in opioid dependent subjects; this will deter the intravenous misuse of Suboxone.

Evidence from the many studies on buprenorphine in the treatment of opioid dependence has been increasingly debated amongst physicians and policy-makers and the introduction of a new medication in the context of existing therapeutic approaches, in this case predominantly methadone, naturally leads to caution regarding change. There is a need therefore for data to allow new and existing medications to be directly compared and not surprisingly recent meta-analyses assessing the clinical effectiveness and safety of buprenorphine compared to methadone have been reported. Data from nine comparative trials using urinalysis as the common outcome measure lead to the conclusion that "for all practical purposes" buprenorphine and methadone can be used with equal success, but other aspects, such as the superior safety profile of buprenorphine and its milder withdrawal syndrome, may influence physician's choice of treatment<sup>8</sup>. The most recent analysis<sup>9</sup> focused on methadone but included 6 buprenorphine studies, which classified doses of buprenorphine of >8mg/day as "high dosage", and found a non-significant difference between this and high dose methadone in terms of both positive urines and retention in treatment; both agents showed a dose response relationship. Additionally it was concluded that buprenorphine has certain advantages over methadone, including alternate day dosing, the possibility of less social stigma, only mild withdrawal symptoms following abrupt discontinuation and a theoretically lower risk of overdose.

### **Early experience with Buprenorphine**

The earlier comparison studies of buprenorphine with methadone used slow matched dose induction schedules due to the safety concerns of methadone and the well-established evidence that increasing the methadone dose too quickly can lead to fatalities<sup>3</sup>. They also tended to use less than maximal doses of buprenorphine again due to safety considerations especially as buprenorphine was a new, untried opioid in this indication. Some of the early studies therefore used buprenorphine suboptimally and this was reflected in the results leading investigators to question the slow inductions and the low dose levels used. Increased usage of buprenorphine however leading to higher doses and shorter induction schedules have demonstrated its utility in treatment. To our knowledge there have been no fatalities reported during induction onto buprenorphine. Although buprenorphine is an agonist with high affinity for the mu-opioid receptor, a ceiling on its ability to cause respiratory depression has been clearly demonstrated. The "respiratory effect" reaches a plateau at doses between 2 and 16mg whether administered sublingually<sup>10</sup> or intravenously<sup>11</sup>. There is very strong evidence of buprenorphine's safety superiority over methadone in overdose based on the experiences in France since 1996<sup>12</sup>; also in dosing regimen studies patients have received up to four times their normal daily dose without experiencing any significant opioid agonist effects compared to their daily dose<sup>13</sup>. A number of the early fixed dose comparison studies compared 8mg buprenorphine as the maximum dose with methadone doses up to 80mg - in most countries Subutex is approved up to 32mg/day based on more recent clinical data demonstrating its safety and efficacy and in reality 8mg buprenorphine is probably only equivalent to 40-60mg methadone. There is now strong evidence supporting a more rapid dose induction schedule than the traditional 7 day or longer protocols - in a one year study with 472

heroin subjects 8mg buprenorphine was safely administered on day 1. Subsequent clinical titration of dose permitted up to 16mg to be administered on day 2<sup>14</sup> and in an open label phase of this study up to 24mg was administered on day 3<sup>7</sup>.

It is clear that buprenorphine provides a lower level of "reinforcement" to a patient especially at lower doses and additionally patients experience a "different feel" than they are accustomed to with methadone or heroin - this itself can lead to anxiety in a patient who is fearful of withdrawal. It is important therefore that patient's maintenance doses are clinically titrated quickly and that patients are prepared for the new medication with a "different feel" to prevent early drop out from treatment.

### **Buprenorphine in Maintenance**

In studies using flexible dosing schedules the daily maintenance doses used have been in the range 2-32mg but the average maintenance dose has usually been 10-12mg/day. Examples include a multicentre Australian study<sup>7,15</sup> which showed that the effective dose range was broad with some patients being adequately maintained on 4mg/day while others required 24mg/day but the mean daily dose was 10.9mg; in a Swiss study<sup>16</sup> where the maximum permitted daily dose was 32mg the mean dose was 10.5mg. In the US a study<sup>17</sup> was conducted with a development liquid product, that resulted in a mean daily dose of 8.9mg which is equivalent to 11.1-11.8mg of Subutex. This same US group repeated the study in opioid dependent cocaine users<sup>18</sup> and found that buprenorphine and methadone performed equally well in terms of study retention and urine toxicology. Both agents reduced the level of cocaine use, however the mean daily doses of both methadone and buprenorphine were higher than those needed to stabilise and maintain heroin users with the buprenorphine mean dose being 11.2mg of the liquid product which equates to 14.0-14.8mg/day of Subutex.

In a French study over 1000 patients who entered treatment with Subutex were followed for 6 months with 73% being retained in treatment<sup>19</sup>. There were significant reductions in the use of a range of psychoactive substances: heroin 83%, codeine 82%, cocaine 75% and benzodiazepines 48%. Other benefits included significant decreases in morbidity and mortality whilst employment increased.

One key efficacy study compared 16mg Subutex with matched placebo and matched 16mg Suboxone (16mg buprenorphine/4mg naloxone) under double blind conditions for the first 4 weeks of treatment. Urine toxicology and heroin craving assessments clearly demonstrated superiority of both buprenorphine products over placebo and that there was no difference between Subutex and Suboxone<sup>20</sup>.

A number of studies have reported that the efficacy of buprenorphine is not compromised when buprenorphine is dosed on alternate days<sup>21</sup> with double the established daily dose or three times a week dosing<sup>22</sup>. In one such study buprenorphine and LAAM, both administered three times a week were compared with daily administered low and high doses of methadone<sup>23</sup> with the conclusion that buprenorphine, LAAM and high dose methadone resulted in similar outcomes and all were superior to low dose methadone. Less than daily dosing of buprenorphine is of significant benefit when supervised dosing is mandatory and has a very obvious administration cost benefit compared with daily-dispensed methadone. It is also patient preferred; in a comparison of four different dosing regimes of buprenorphine

86% of subjects preferred either alternate day or every third day dosing to daily dosing<sup>13</sup>.

### **Buprenorphine in Detoxifications**

A Cochrane review<sup>24</sup> of many studies investigating buprenorphine's use in detoxifications concluded that buprenorphine appeared to be more effective than clonidine in reducing signs and symptoms of opiate withdrawal and in supporting the completion of withdrawal from heroin. This effectiveness and superiority over conventional detoxifications from heroin has been demonstrated in short-term detoxifications (5-10 days)<sup>25,26</sup>. An inpatient placebo controlled study<sup>25</sup> used a 5-day withdrawal schedule which resulted in 90% (n=63) of patients experiencing no or mild withdrawal symptoms and 61% experienced no side effects. In an open label outpatient study buprenorphine was compared to a group receiving symptomatic medication (clonidine, analgesics, benzodiazepines) - 86% of the buprenorphine group completed their withdrawal programme compared to 57% of the symptomatic group. Buprenorphine treatment was shown to have enhanced cost-effectiveness in achieving heroin free days during withdrawal with significantly less heroin use during the follow up period compared to the symptomatic group. Following long term maintenance therapy gradual dose tapering (over 28-36 days) appears to be associated with the best outcomes<sup>27</sup>. Three studies<sup>28</sup> have exploited buprenorphine's mild withdrawal profile to avoid difficulties of methadone withdrawal. Buprenorphine was used as an intermediate step between methadone and abstinence; three weeks of buprenorphine stabilisation after transfer from methadone was followed by a gradual dose reduction over 16 weeks which resulted in 78% of patients completing withdrawal and 35% were using neither heroin or methadone one month later. Once detoxified, patients are vulnerable to relapse yet transfer onto naltrexone from methadone is often delayed for up to 14 days because of potential precipitated withdrawal problems - this is when the patient is most vulnerable and relapse onto heroin is common. In contrast transfer onto naltrexone can be well tolerated within 24 hours of the last buprenorphine dose<sup>26,29</sup> thus greatly reducing the period of vulnerability.

### **Summary**

It is important for physicians to have flexibility when planning the ideal treatment for their patients and in buprenorphine they have a therapy that covers the full spectrum of opioid dependence treatment; a safe rapid induction to achieve maintenance doses and stabilisation with the ability (as and when appropriate) to detoxify through a dose tapering regimen. Alternatively buprenorphine offers probably the most efficient, convenient and cost effective way of directly detoxifying the patient from heroin. During maintenance the frequency of dosing can be flexible depending on the physician's and/or patient's preferences, for example dosing can be daily or on alternate days or three times a week. Once detoxified a quick transfer to naltrexone is possible thus minimising that period of vulnerability when relapse to heroin can often occur. In addition, in combination with naloxone buprenorphine offers significant non-divertable potential in take-home situations.

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