

**APPLICATION FOR INCLUSION OF BUPRENORPHINE IN THE
WHO MODEL LIST OF ESSENTIAL MEDICINES**

**PROPOSAL FOR
THE INCLUSION OF BUPRENORPHINE IN THE
WHO MODEL LIST OF ESSENTIAL MEDICINES**

**DEPARTMENT OF MENTAL HEALTH AND SUBSTANCE ABUSE
Management of Substance Abuse**

HIV/AIDS DEPARTMENT



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APPLICATION FOR INCLUSION OF BUPRENORPHINE IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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Summary of the proposal

The scope and relevance of buprenorphine in the management of opioid dependence is demonstrated through a review of *epidemiological data* on the extent of opioid dependence worldwide, the burden of disease due to opioid dependence and the role of opioid dependence in HIV/AIDS epidemics. Most illicit opioid use is heroin use, mainly through intravenous injecting. Heroin users have a mortality risk 13 times higher than the average in the same age group, even without taking into consideration increased mortality associated with HIV epidemics and other blood-borne infectious diseases. In some parts of Europe, heroin injecting accounts for 25-33% of deaths in young adult males. Worldwide, it is estimated that there are 12.6 million injection drug users (IDUs) and that around 10% of HIV infections are associated with injecting drug use. In 2003 injecting drug use (IDU) directly accounted for approximately 420 000 new HIV infections globally. HIV seroprevalence rates as high as 60 to 90% are seen among injecting heroin user populations in various countries of Eastern Europe, South-East Asia and Western Pacific regions.

Buprenorphine is a synthetic opioid that is being increasingly used for substitution therapy of opioid dependence. The global number of persons with opioid dependence receiving prescribed buprenorphine is estimated to be close to 200 000, and to be on the increase in practically all regions of the globe.

Buprenorphine's mechanism of action, like morphine, is mediated by the activation of opioid receptors, principally of the μ type. The *pharmacology* of buprenorphine is well researched and documented. Four properties of buprenorphine's pharmacology make it an important drug to be included in the repertoire of drugs available for the provision of opioid agonist treatment worldwide. First, buprenorphine has less intrinsic activity at the opioid receptor and thereby lacks significant reinforcing properties when compared to full opioid agonists used for treatment (e.g. methadone) or illicitly (e.g. heroin) (Johnson & McCagh, 2000; Walsh et al., 1994). Second, buprenorphine exhibits a ceiling effect in its opioid receptor activity and thereby exhibits a greater margin of safety than full agonists such as methadone (Walsh et al., 1994). Third, buprenorphine can be delivered as thrice weekly therapy under direct observation, allowing for supervised dispensing and decreased risk for diversion (Fiellin et al., 2002; Amass et al., 2000). Finally, the limited available literature indicates that there are fewer documented interactions between buprenorphine and HIV antiretroviral therapies than have been documented with methadone and HIV medications (Carrieri et al., 2000; McCance-Katz et al., 2003; Rainey et al., 2002).

Clinical research data on the effectiveness of substitution maintenance therapy of opioid dependence with methadone are well documented in clinical trials, large prospective long-term observational studies, and special research on cost and cost-effectiveness. A number of controlled studies have compared buprenorphine and methadone and showed that buprenorphine and methadone had similar efficacy in the management of opioid dependence. The results of several major randomized trials of buprenorphine against methadone and against placebo treatment suggests that buprenorphine is as effective as methadone as a maintenance agent in the therapeutic doses which have been used in the trials. Recently completed Cochrane review of buprenorphine against methadone (Mattick et al., 2003) confirms the results of the major trials of buprenorphine and shows a dose-response relationship for buprenorphine in reducing illicit opioid use and in retaining patients in treatment. However, when compared with methadone, the results of the meta-analysis indicate that methadone is statistically significantly better able to retain patients and to suppress heroin use than buprenorphine in flexible dosing approaches, especially if high-dose methadone is used. Similar conclusions have been reached by other recent meta-analytic reviews of these treatments (Barnett et al., 2001; West et al., 2000).

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The *safety* and efficacy of buprenorphine has been compared with that of methadone in a number of clinical studies (Ling et al., 1996; Ling et al., 1998; Johnson et al., 2000; Petitjean et al., 2001; Mattick et al., 2003; Digiusto et al., 2004; Giacomuzzi et al., 2003). These studies found that there were no serious adverse effects from buprenorphine treatment and that the frequency and severity of side effects was similar for both methadone and buprenorphine patients. Buprenorphine patients reported slightly better quality of life than methadone patients after 24 weeks of treatment (Giacomuzzi et al., 2003).

Buprenorphine is more costly than methadone to purchase as a medication, but it is a cost-effective option for the management of opioid dependence within a maintenance program operated over sufficient duration to achieve health gains and drug-free lifestyle. Results of the largest randomized controlled trial of methadone to date (Mattick et al., 2003) showed no significant difference in *cost-effectiveness* when methadone was compared to buprenorphine (Doran et al., 2003), and potential cost-effectiveness for combined buprenorphine/naloxone formulation was shown to be greater than methadone due to reduced costs of treatment delivery in certain settings compared with methadone (Rosenheck & Kosten, 2001).

During the last two decades, scientific evidence has accumulated that buprenorphine maintenance, in addition to being an effective treatment for opioid dependence, has a supportive function to enhance *HIV/AIDS prevention, treatment and care*. Buprenorphine maintenance treatment programs provide opportunities for expanded HIV prevention among injecting drug users and a platform for implementation of directly observed antiretroviral therapy for opioid dependent people with HIV/AIDS as well as therapy for opportunistic infections such as tuberculosis (WHO, UNODC, UNAIDS, 2004).

The accumulated data demonstrate that treatment of opioid dependence with buprenorphine is a major public health tool in the management of opioid dependence and in HIV/AIDS prevention and care for opioid dependent injecting drug users.

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1. Summary Statement of the proposal for inclusion, change or deletion

Buprenorphine is proposed for the inclusion in the World Health Organisation (WHO) Model List of Essential Medicines for the management of opioid dependence, including opioid dependence co-occurring with HIV/AIDS, and for HIV prevention and care among opioid dependent individuals.

2. Focal points in WHO for application

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3. Name of Organisation(s) consulted and/or supporting application:

Joint United Nations Programme on HIV/AIDS
College on Problems of Drug Dependence (CPDD), USA

4. International Nonproprietary Name (INN, generic name) of the medicine:

Buprenorphine hydrochloride

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the WHO Model List of Essential Medicines as an individual medicine under section 24 (Psychotherapeutic medicines) and new subsection "Medicines used in substance dependence". A square box symbol is not required.

6. Information supporting the public health relevance (epidemiological information on the disease burden, assessment of current use, target population)

6.1 *Epidemiology of opioid dependence*

6.1.1 *Prevalence of opioid dependence*

Even though non-medical opioid use is prohibited by international law, such use occurs in many countries of the world. Table 1 gives an overview of estimated prevalence of "problematic" opioid use in different regions of the world (Degenhardt et al., 2001; WHO, 2000). By the operational definition used by Degenhardt et al (2001), "problematic" opioid users are dependent on opioids as defined by ICD-10 (WHO, 1993). These prevalence rates were estimated based on the UN Drug Control Program's (UNDCP, 2000) Global Illicit Drug Trends for persons over the age of 15 years and the additional assumption that 28% of all users in the past year were "problematic" users or opioid dependent users, the latter fraction being derived from an Australian national survey (Hall et al., 1999). It must be noted that prevalence estimates of use were not available for all countries in all WHO regions. In making estimates for countries which had no reported prevalence estimates, WHO regional estimates of prevalence were used by deriving a weighted average prevalence rate from the data that were available from countries in the region. These estimates have to be considered as rather conservative, because other estimates, e.g.

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from EMCDDA, tend to be higher than those reported above (e.g. Kraus et al., 2003; EMCDDA, 2003a). Also recent data from the U.S. National Survey on Drug Use and Health study demonstrated that in 2003 in USA 57.4 percent of past year heroin users (0.2 million) were classified with dependence on or abuse of heroin (Substance Abuse and Mental Health Services Administration, 2004).

Table 1: Prevalence (%) of opioid dependence in the past 12 months among persons 15 years and above according to 14 WHO regions for the year 2000.

Regions	Population ('000s) over 15 years	Prevalence of opioid dependence	Population ('000s) with opioid dependence
Europe A (e.g., France, Germany, Italy, Netherlands, Spain, UK)	339,446	0.11	373
Europe B (e.g., Bulgaria, Poland, Romania, Turkey)	161,213	0.09	145
Europe C (e.g., Russia, Ukraine)	152,432	0.19	290
America A (e.g., Canada, USA)	255,420	0.13	332
America B (e.g., Argentina, Brazil, Chile, Costa Rica, Mexico)	297,625	0.03	89
America D (Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru)	44,658	0.07	31
Eastern Mediterranean B (e.g. Islamic Republic of Iran, Jordan, Libyan Arab Jamahiriya, Saudi Arabia, Tunisia)	86,853	0.55	478
Eastern Mediterranean D (e.g., Afghanistan, Egypt, Morocco, Pakistan, Sudan)	204,039	0.41	837
South East Asia B (Indonesia, Sri Lanka, Thailand)	206,870	0.04	83
South East Asia D (e.g., Bangladesh, India)	818,521	0.15	1,228
Western Pacific A (e.g., Australia, Japan)	129,888	0.04	52
Western Pacific B (e.g., China)	1,131,503	0.02	226
Africa D (e.g., Algeria, Niger, Nigeria)	159,577	0.09	144
Africa E (e.g., Congo, Ethiopia, Uganda, South Africa)	190,152	0.01	19
Total	4,178,197		4,327

Letters A-E are based on level of child and adult mortality with A indicating the lowest levels, and E the highest (WHO, 2000)

Prevalence of opioid dependence seems to be concentrated mainly in younger age groups, and higher in men compared to women (Degenhardt et al., 2001; WHO, 2001; 2002). In many countries,

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especially in developed nations, non-medical opioid users are more concentrated in cities (Bless et al., 1994; Garfield, Drucker, 2001).

In terms of types of opioid substances used, heroin is the most used opioid, but there are countries or regions where opium or other forms of opioids are more prevalent. Even though the above estimates mainly reflect injecting drug use, there are other forms like smoking or inhaling, some of them more prevalent in developing countries.

6.1.2 Disease Burden

Long-term heroin users as one significant population of non-medical opioid users have a substantially increased risk of premature death from drug overdoses, violence, suicide and infectious disease-related causes (Darke & Ross, 2002; English et al., 1995; Hulse et al., 1999). Cohort studies of the mortality of heroin users treated before the advent of HIV indicated that they were 13 times more likely to die prematurely than their age peers (English et al., 1995; Goldstein & Herrera, 1995; Hser et al., 1993). In countries with a high prevalence of HIV infection among IDUs, deaths from AIDS are a major contributor to premature death among heroin users (EMCDDA, 2003b; UNAIDS, 2002).

The risk of fatal opioid overdose is higher among opioid dependent heroin injectors who are male and increases with the duration of opioid dependence. It is also higher among those who use heroin with cocaine, alcohol and benzodiazepines and those returning to heroin use after a period of abstinence (Darke & Zador, 1996; Tagliaro et al., 1998; Warner-Smith et al., 2001).

In large parts of North America, Asia, and Eastern Europe, sharing contaminated needles, syringes and other injecting equipment accounts for a substantial proportion of HIV infections related to non-medical opioid use (Cohen, 2004; EMCDDA, 2003b; UNAIDS, 2002). The prevalence of hepatitis C virus (HCV) is even higher among IDUs, in some countries up to 90% (EMCDDA, 2003a). Chronic infection has been estimated to occur in 75% of infections, and 3-11% of chronic HCV carriers will develop liver cirrhosis within 20 years (Hepatitis C Virus Projection Working Group, 1998).

Heroin-related deaths (irrespective of the aetiology, i.e. whether by overdose or HIV/AIDS) which primarily occur among young adults males account for a substantial number of life years lost in some developed societies (World Health Organization, 2002). In some parts of Europe, namely, Scotland and Spain, opioid-related deaths account for as many as 25%-33% of deaths in young (15-39 years) males (EMCDDA, 2003b).

Degenhardt et al. (Degenhardt et al., in press) estimated mortality attributable to illicit opioid use in two ways: (1) applying estimated mortality rate from all causes (derived from cohorts of illicit opioid users) to data on the prevalence of illicit opioid use in each WHO region; and (2) summing the separately estimated annual mortality rate from AIDS, drug overdose, suicide and trauma among the estimated number of dependent opioid users in each region. In 2000, the median estimated global number of deaths from opioid use derived using the all-cause method was 197,383 while the equivalent number of deaths derived by adding the separate mortality rates was 240,483. Both estimates had wide uncertainty intervals around them (82,365 to 407,689 for the sum of the four causes of death and 101,751 to 322,456 for the all-cause estimates). When crude estimates of morbidity attributable to illicit drug use were added to mortality, illicit opioid use accounted for 0.7% of global disability adjusted life years.

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6.1.3 *Opioid dependence and HIV/AIDS*

Although people with opioid dependence constitute only a small proportion of the population, because opioids are predominantly used by injection, the contribution of opioid use to the transmission of human immunodeficiency virus (HIV) is significant. IDU is one of the leading modes of HIV transmission globally (UNODC, 2004; UNAIDS, 2004). In the United States of America in 1999 injecting drug users accounted for 18% of the reported HIV cases classified by a specific risk and for at least 36% of all reported AIDS cases (Centers for Disease Control and Prevention, 2001). Between 1990 and 1998, IDUs were the largest group among diagnosed AIDS cases in Western Europe, since 2001 the second largest group in Central Europe and by far the largest group in the Eastern European Region (EuroHIV, 2003). HIV seroprevalence rates of 60 to 93% among injecting heroin users are seen in some countries of Eastern Europe, Eastern Mediterranean, South-East Asia and Western Pacific regions (UNODC, 2004; UNAIDS, 2004). Worldwide, it is estimated that there are 12.6 million IDUs and that around 10% of HIV infections are associated with IDU. Therefore, IDU directly accounted for approximately 420,000 new HIV infections in 2003 (UNAIDS, 2004).

IDU continues to drive HIV epidemics in many countries. Explosive HIV epidemics among injection drug users (with HIV prevalence among IDUs increasing from 0% to 30-50% within a period of one to two years) have been witnessed in most regions, starting with New York City around 1980, followed by epidemics in such cities/regions as Edinburgh in 1984, Bangkok in 1988, Manipur (India) in 1989, Myanmar in 1992, Odessa (Ukraine) in 1994, Ho Chi Minh City (Viet Nam) in 1995, Svetlogorsk (Belarus) in 1996, Yunnan Province (China) in 1996, Kaliningrad (Russian Federation) in 1997, Temertau (Kazakhstan) in 1997, Moscow in 1999 and Narva (Estonia) in 2000. In the past few years new HIV epidemics have emerged among IDU populations in such diverse countries as Argentina, China, Indonesia, Islamic Republic of Iran, Libyan Arab Jamahiriya, Malaysia, Nepal and Uzbekistan. In many regions there is significant overlap of drug using and sex worker populations, providing a bridge for the transmission of HIV to the general population (Ball A. et al., 1998; UNAIDS, 2004; UNODC, 2004).

It has become an international public health priority to reduce the risks of HIV transmission associated with injecting drug use. Buprenorphine is an increasingly commonly used medicine for substitution maintenance therapy of opioid dependence that provides an opportunity for expanded HIV prevention among injecting drug users and a platform for HIV/AIDS treatment and care, including the implementation of antiretroviral therapy for opioid dependent people with HIV/AIDS and treatment of opportunistic infections such as tuberculosis (WHO, UNODC, UNAIDS, 2004).

6.2 *Assessment of current use of buprenorphine*

The global number of persons with opioid dependence receiving prescribed buprenorphine is estimated to be close to 200 000, and to be on the increase in practically all regions of the globe.

The greatest level of experience with buprenorphine has occurred in France where buprenorphine treatment for heroin dependence has been widely available through general practitioners since 1995. By 1998 approximately 65,000 patients per year were in buprenorphine treatment in France and by 2001 this had increased to 74,000, while 9,600 were treated with methadone (Auriacombe et al., 2004). In Australia buprenorphine was registered for the treatment of opioid dependence in 2001 and there were 8, 641 patients registered as receiving buprenorphine maintenance treatment at 30th June 2003. Buprenorphine maintenance treatment (BMT) is currently available in 29 countries: Australia, Austria, Belgium, China (Hong Kong), Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, India, Indonesia, Israel, Italy, Lithuania, Luxembourg, Malaysia, Netherlands, Norway, Portugal, Singapore,

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Slovak Republic, Slovenia, South Africa, Sweden, Switzerland, Ukraine, United Kingdom, United States of America.

6.3 Target population

Buprenorphine treatment is indicated for those who are dependent on opioids and can be used as a substitution maintenance treatment or for detoxification and the management of opioid withdrawal. The target population for buprenorphine includes opioid dependent people with HIV/AIDS. The largest group receiving buprenorphine for treatment of opioid dependence are heroin dependent persons. The majority of them are injectors, a minority use heroin by smoking or sniffing, however, in a few countries, such as the Netherlands, the majority are non-injectors. In the European Union Member States it is estimated that sixty percent of opioid dependent drug users are drug injectors (EMCDDA 2003). There is a large body of research providing strong evidence that substitution maintenance treatment of opioid dependence reduces injection-related risk behaviour among injecting opioid users and enrolment in opioid maintenance treatment protects against HIV infection (Gowing et al., 2004a).

Four properties of buprenorphine's pharmacology make it an important drug to be included in the repertoire of drugs available for the provision of opioid agonist treatment worldwide. First, buprenorphine has less intrinsic activity at the opioid receptor and thereby lacks significant reinforcing properties when compared to full opioid agonists used for treatment (e.g. methadone) or abused (e.g. heroin) (Walsh et al., 1994; Johnson & McCagh, 2000). Second, buprenorphine exhibits a ceiling effect in its opioid receptor activity and thereby exhibits a greater margin of safety than full agonists such as methadone (Walsh et al., 1994). Third, buprenorphine can be delivered as thrice weekly therapy under direct observation, allowing for supervised dispensing and decreased risk for diversion (Fiellin et al., 2002; Amass et al., 2000). Finally, the limited available literature indicates that there are fewer documented interactions between buprenorphine and HIV antiretroviral therapies than have been documented with methadone and HIV medications (Carrieri et al., 2000; Rainey et al., 2002; McCance-Katz et al., 2003).

7. Treatment details

7.1 Indications for use

7.1.1 Opioid dependent people and goals of treatment

Buprenorphine treatment is indicated for those who are dependent on opioids, including those with HIV/AIDS, and who have had an extended period of regular opioid use, for the management of opioid withdrawal (detoxification) or as a substitution maintenance treatment. The goals of substitution maintenance treatment with buprenorphine are to reduce or eliminate illicit opioid use, improve the health and wellbeing of those in treatment; facilitate the social rehabilitation of those in treatment; reduce the spread of blood borne diseases including HIV/AIDS, associated with injecting opioid use; facilitate the treatment and care of opioid users living with HIV/AIDS (including those on antiretroviral therapy); reduce the risk of death; and reduce involvement in crime associated with opioid use (WHO/UNODC/UNAIDS, 2004).

7.1.2 Detoxification

The use of buprenorphine in detoxification and management of opioid withdrawal is an important aspect of the use of the medication in management of opioid dependence. The goal of detoxification

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treatment is to ensure that withdrawal from opioids is completed safely and with minimal discomfort. Buprenorphine appears to produce a milder withdrawal syndrome than methadone and to be more effective than symptomatic medications such as clonidine and benzodiazepines in managing detoxification from heroin (Lintzeris et al., 2001; Ford et al., 2003; Gowing et al., 2004b).

7.1.3 Maintenance therapy

Buprenorphine maintenance treatment is an important component of strategies to manage opioid dependence and prevent the spread of HIV/AIDS among injecting drug users through reductions in illicit drug use and high risk injecting and sexual behaviours. The provision of substitution maintenance treatment to opioid dependent individuals who are already infected with HIV improves adherence to treatment for HIV/AIDS and contributes to slowing the progression of the disease (WHO/UNODC/UNAIDS, 2004).

Buprenorphine maintenance or substitution treatment should be restricted to people who meet the clinical criteria for opioid dependence (WHO/UNODC/UNAIDS, 2004). Regulations in some countries prescribe that patients must also be aged 18 years or older, be able to give informed consent to commence treatment, and present proof of identity (Lintzeris et al., 2001; National Drug Strategy, 2001; McNicholas, 2004).

7.2 Dosage regimens

The appropriate dosing for buprenorphine treatment is divided into the *induction phase* of dosing involving the initial starting dose and the *stabilization dose*, and then dose adjustment for ongoing *maintenance therapy* or dose reduction for *detoxification*. In comparison with management of withdrawal from heroin or other short-acting opioids, detoxification from buprenorphine stabilisation or maintenance uses a slower dose reduction regime which usually takes place over several weeks.

7.2.1 Dosage regimens for detoxification

Detoxification from heroin or other short acting opioids with buprenorphine has been reported to be more effective than standard detoxification procedures in a recent review (Gowing et al., 2004b), citing a number of primary studies (Cheskin et al., 1994; Lintzeris et al., 2002; O'Connor et al., 1997). Detoxification with buprenorphine can be undertaken using a five to ten day program of reducing buprenorphine doses in either outpatient or inpatient settings (Lintzeris et al., 2001; Centre for Substance Abuse Work Group, 2002; Ford et al., 2003).

Doses should be titrated according to the patient's experience of withdrawal severity, cravings, side effects and other drug use. A number of dosage regimens have been proposed. Product information for buprenorphine recommends a ten day regime and a five day regime as shown in Tables 2 and 3.

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Table 2: Buprenorphine detoxification - ten day regime

Day	Buprenorphine dose
1	8 mg
2	6 mg
3	6 mg
4	4 mg
5	4 mg
6	2 mg
7	2 mg
8	1 mg
9	1 mg
10	0 mg

Table 3: Buprenorphine detoxification - five day regime

Day	Buprenorphine dose
1	6 mg
2	10±2 mg
3	10±2 mg
4	8±2 mg
5	4 mg

Table 4: Buprenorphine detoxification - four to eight day regime

Day	Proposed regime	Recommended upper and lower limits
1	6 mg	4-8 mg
2	8 mg	4-12 mg
3	10 mg	4-16 mg
4	8 mg	2-12 mg
5	4 mg	0-8 mg
6		0-4 mg
7		0-2 mg
8		0-1 mg

Australian guidelines propose a four to eight day regime as shown in Table 4 (Lintzeris, 2001).

Detoxification from buprenorphine stabilisation or maintenance uses a slower dose reduction regime which usually takes place over several weeks. US guidelines suggest 2 mg reductions every two to three days (Centre for Substance Abuse Treatment, 2004). Australian and UK clinical guidelines propose the following gradual dose reduction schedule (Lintzeris, 2001; Ford, 2003).

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Table 5: Gradual buprenorphine detoxification.

Daily buprenorphine dose	Reduction rate
Above 16mg	4 mg every 1-2 weeks
8-16 mg	2-4 mg every 1-2 weeks
2-8 mg	2 mg every 1-2 weeks
Below 2 mg	0.4-0.8 every 1-2 weeks.

7.2.2 Dosage regimens for maintenance therapy

Induction

The goals of induction are to achieve an adequate, clinically effective, maintenance dose as quickly as possible in order to prevent opioid withdrawal symptoms. At the same time, induction should not be so rapid as to lead to precipitated withdrawal. In order to reduce the risk and severity of precipitated withdrawal the starting dose should not be given for at least 6 hours following the last use of short acting opiates such as heroin and at least 24 hours following the last use of long acting opioids such as methadone. It is preferable to wait until mild withdrawal symptoms appear before administering the initial dose (Lintzeris et al., 2001; Ford et al., 2003; Centre for Substance Abuse Treatment, 2004).

The initial dose of buprenorphine should be determined for each patient based on the severity of dependence; the level of tolerance to opioids and the likelihood of concurrent polydrug use. The recommended starting dose is 4 mg in the morning with the option to administer an additional 2-4mg later in the day. Australian clinical guidelines recommend that the initial dose should be between 2 and 8 mg and should not exceed 8mg (Lintzeris et al., 2001), while other guidelines suggest a starting dose of between 4 and 8mg (Ford et al., 2003; Centre for Substance Abuse Treatment, 2004).

Stabilisation

The maintenance dose needs to be tailored to the patient's response to buprenorphine. Patients should be reviewed regularly for the first few weeks of treatment and the dose adjusted as indicated. For patients on doses less than 16mg/day, dose increments of 2-4mg should have a significant effect, while for those on doses > 16mg/day dose increments of 4-8mg are more effective (Lintzeris et al., 2001). Increases up to 4mg per day are possible (Ford et al., 2003; Centre for Substance Abuse Treatment, 2004).

Maintenance

Doses should be determined for individual patients but generally a higher dose is required for maintenance than is required for initial stabilisation. Early studies suggested that the efficacy of an 8mg dose of buprenorphine was equivalent to that of 60 mg of methadone and may be an optimal dose (Johnson et al 1992), however, later research concluded that 8mg was not a sufficient maintenance dose and that higher doses may be needed (Ling et al 1996, 1998). Some have suggested that 32 mg of buprenorphine thrice weekly may be equivalent to 100 mg methadone (Johnson et al., 2000). Effective maintenance doses, which reduce heroin use and improve treatment retention are typically achieved with buprenorphine doses in the range 12-24 mg/day (Ford et al., 2003; Johnson et al., 2000; Lintzeris et al., 2001; Petitjean et al., 2001)). The maximum maintenance dose recommended is 32mg/day (Ford et al., 2003; Lintzeris et al., 2001; Centre for Substance Abuse Treatment, 2004).

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Dosing schedule

Buprenorphine is a long acting medication and is usually administered on a daily basis. However, recent studies have indicated that many patients who have been stabilized on buprenorphine can be maintained on alternate day or three times per week dosing schedules (Amass et al., 1994; Johnson et al., 1995; Amass et al., 1998; Bickel et al., 1999; De los Cobos et al., 2000; Schottenfeld et al., 2000; Mattick et al., 2003).

The dose dispensed for a 48 hour period is initially double the normal daily dose to a maximum of 32mg administered at any one time. For a three times a week schedule three times the daily dose is administered if the daily dose is less than 12mg. If the daily dose is greater than 12 mg then the maximum dose of 32mg is administered for the 72 hour period. Patients should be carefully monitored and doses titrated as necessary (Lintzeris et al., 2001).

7.3 Duration of substitution maintenance therapy with buprenorphine

Length of time in substitution treatment is predictive of an improved treatment outcome (Ward et al., 1998b). It is recommended that patients be encouraged to remain in treatment for at least 12 months to achieve enduring lifestyle changes (Gowing et al., 2001; WHO/UNODC/UNAIDS, 2004).

7.4 Reference to existing WHO and other clinical guidelines

The World Health Organization, United Nations Office on Drugs and Crime and The Joint United Nations Programme on HIV and AIDS Position paper on substitution maintenance therapy is an important international statement on the role of substitution maintenance treatment, including buprenorphine maintenance treatment, in the management of opioid dependence and HIV/AIDS prevention, treatment and care (WHO, UNODC, UNAIDS, 2004) (http://www.who.int/substance_abuse/publications/en/PositionPaper_English.pdf).

The WHO Expert Committee on Drug Dependence in its 30th Report acknowledged that there was "widespread adoption in many countries of the use of methadone and other similar substances for the management of opioid dependence" and that this treatment "is supported by ample scientific evidence of its benefits when delivered in well-controlled settings conforming to high standards" (WHO, 1998) (http://whqlibdoc.who.int/trs/WHO_TRS_873.pdf).

WHO Guidelines "Scaling up antiretroviral therapy in resource-limited settings" affirms that "opioid agonist pharmacotherapies, such as buprenorphine maintenance treatment, have the advantage of allowing direct observation of the concomitant administration of ART" and recommends that "where feasible, countries promote and support the development of integrated programmes involving the direct observation of therapies for management of both drug dependence and HIV infection among IDUs (WHO, 2002, 2003).

The Australian *National Clinical Guidelines and Procedures for the use of Buprenorphine in the Treatment of Heroin Dependence* were published in 2001 (Lintzeris et al., 2001). The guidelines have been translated into Italian for use in Italy. They have informed the development of the Royal College of General Practitioners' publication *Guidance for the use of buprenorphine for the treatment of opioid dependence in primary care* in the UK (Ford et al., 2003). The guidelines have also been used in international training workshops conducted in East Asia under the auspices of the World Health Organization.

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In the United States of America, *Model Policy Guidelines for Opioid Addiction Treatment in the Medical Office* (Centre for Substance Abuse Work Group, 2002) have been published. These guidelines detail the regulatory framework and requirements for buprenorphine treatment but do not include guidelines on dosage or other clinical management issues. In 2004, the US Department of Health and Human Services published a very thorough set of *Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction* (Centre for Substance Abuse Treatment, 2004). Additionally, the international peer-reviewed journal *Drug and Alcohol Dependence* has recently provided a guide for clinicians (Fudala & Bridge, 2003), although the guidelines are not consensus-based or based on a systematic review.

The Commission on Narcotic Drugs at its 47th Session in March 2004 invited WHO to develop guidelines on pharmacological therapy of opioid dependence, including therapy with buprenorphine, and these guidelines are in the process of development in WHO and are expected to be published in 2005.

WHO guidelines on "Comprehensive Treatment and Care of HIV-infected Injection Drug Users" is currently under development and will be published in early 2005. The guidelines will address issues related to opioid agonist pharmacotherapy, including treatment of opioid dependence with buprenorphine.

7.5 *Need for special diagnostic or treatment facilities and skills*

There is no need for special diagnostic facilities per se, but clinical skill in the diagnosis of drug dependence and the recognition of opioid dependence as a diagnosis separate from occasional opioid use or other illicit drug use is required (Bell et al., 1992; Lintzeris et al., 2001; Mattick & Hall, 1993; Ward et al., 1992; Ward et al., 1998d). In view of frequently observed psychiatric and somatic comorbidity in need of treatment, the respective clinical diagnostic screening also must be assured.

There are different formats for the dispensing of buprenorphine, especially related to daily versus alternate day or thrice weekly dosing and a record of doses received would be helpful to efficiently manage the patients dosing and ensure appropriate doses are administered.

Urine drug testing can be a useful tool in diagnosis of drug dependence (Ward et al., 1998c) and for monitoring treatment adherence and effectiveness (Ward et al., 1998d). Facilities for collecting and testing urine samples would be of benefit, but are not necessary for the adequate delivery of opioid replacement therapy (Ward et al., 1998c). In fact, in settings with constrained economic resources there would be an argument for testing urine samples only during the induction period. However, the presence of heroin metabolite (morphine) in urine can be a trigger for counselling and dose adjustment upwards to reduce ongoing illicit opioid use. For some settings, urine drug screening is an integral part of clinical treatment of opioid dependence. It is important, particularly in some developed nations (e.g. United States of America and parts of the European Union) to screen for opioids other than morphine and codeine (the standard opioids assayed for in a urine drug screen).

Clients may need to be registered in a central register of patients in opioid substitution therapy. This register can assist clinicians and others to oversee the functioning of the program, the extent and duration of patient enrolment, and to ensure patients do not register twice to receive buprenorphine from more than one source.

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8. Summary of comparative effectiveness

8.1 *Updated review of randomised clinical trials in a variety of clinical settings*

8.1.1 *Search strategy*

This search strategy was developed based on a Cochrane Review search strategy developed in consultation with a drug and alcohol research information specialist, and included a number of search strategies:

1. Search of the Cochrane Drugs and Alcohol Review Group Register for trials of buprenorphine and methadone maintenance therapy to September 2004.
2. Search of the Cochrane Controlled Trials Register for trials of buprenorphine and methadone maintenance therapy to September 2004.
3. Search of databases for published articles without language restrictions. MEDLINE (1966-2004) was searched using the Cochrane Collaboration optimised search strategy used to identify randomised trials, in conjunction with the following to identify studies comparing buprenorphine and methadone maintenance therapy.

MEDLINE (OVID)

#1 exp buprenorphine/or buprenorphine. ti, ab,rw, sh.

#2 exp methadone/ or methadone. ti, ab, rw, sh.

#3 exp opioid related disorders

#4 1 and 2 and 3

EMBASE (OVID) (1980-2004) was searched using the following terms:

#1 exp buprenorphine/ ct (limit to clinical trials)

#2 exp methadone/ ct

#3 exp drug dependence or exp substance abuse or exp drug abuse or #4 1 and 2 and 3.

As several drug and alcohol journals are not indexed on the main electronic databases, the following databases were searched up until 2001: Current Contents, Psychlit, CORK [www.state.vt.su/adap/cork], Alcohol and Drug Council of Australia (ADCA) [www.adca.org.au], Australian Drug Foundation (ADF -VIC) [www.adf.org.au], Centre for Education and Information on Drugs and Alcohol (CEIDA) [www.ceida.net.au], Australian Bibliographic Network (ABN), and Library of Congress databases were also searched for studies and book chapters with the key terms: buprenorphine, methadone, clinical trial, and randomised control trial. Available NIDA monographs and the College on Problems of Drug Dependence Inc. proceedings were searched for studies with the key terms: buprenorphine, methadone, clinical trial, and randomised control trial.

4. The references of all identified studies and published reviews were inspected for more trials.
5. Authors of identified RCT's were consulted to find out if there were any other published or unpublished RCT's comparing the efficacy of buprenorphine and methadone maintenance as therapies for opioid dependence.

Studies were excluded if not randomized, or if there was no control group included.

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8.1.2 *Place of buprenorphine in the management of opioid dependence*

Buprenorphine is a partial agonist at mu-opioid receptors and has been used extensively in many countries for the management of acute pain. Its use in management of opioid dependence has only occurred recently although its potential has been recognised from the late 1970s (Jasinski et al., 1978). The particular advantages that buprenorphine appear to potentially provide in the management of opioid dependence are several. The medication has a very good margin of safety (Walsh et al., 1994), and its partial agonist effect stops buprenorphine from causing the fatal respiratory depression which is associated with ingestion of other full agonist opioids (Umbricht et al., 1998). This margin of safety allows multiples of the daily dose to be dispensed less than daily rather than being dispensed as a daily dose (Amass et al., 1998; Amass et al., 1994; Johnson et al., 2000; Johnson et al., 1995b). This potential provides an advantage over the existing treatment option of methadone, which could not be safely administered in multiples of the daily dose due to fatal overdose risk.

The elimination of buprenorphine in humans is biphasic comprising a relatively short distribution half-life of 3 – 5 hours (Jaffe & Martin, 1990) and a long terminal elimination half-life of around 32 hours or more (Kuhlman et al., 1998). The medication appears to have the property of binding very tightly to receptor sites causing a very slow release from opioid receptors and this property produces the kinetics that are important in bringing about the long duration of action (Lewis, 1985). This strong binding to opioid receptor sites has also been observed in studies of pure opioid antagonists which show that it is quite difficult to displace buprenorphine from receptors (Kreek, 1996; Lehmann et al., 1988).

The tightness of binding of buprenorphine to, and slow dissociation from opioid receptor sites has been one explanation put forward for the very low level of withdrawal symptoms associated with abrupt cessation of chronic dosing with buprenorphine compared with other opioids such as morphine (Lewis, 1985). Others have considered whether the partial agonist effect of buprenorphine may reduce the extent of significant physical dependence (or neuroadaptation) and that this may be the mechanism whereby less severe withdrawal symptoms occur (Jasinski et al., 1978).

These features of buprenorphine make it a unique medication in the management of opioid dependence. It is a medication which can be given to heroin dependent individuals who are ambivalent about entering methadone treatment as it can be discontinued without the severe abrupt withdrawal symptoms associated with discontinuation of methadone, heroin or other full agonists (Fudala et al., 1990). In that sense, buprenorphine treatment is an important treatment modality that broadens the range of treatment options for opioid dependence and can reduce the gap between those in need and those in treatment (Institute of Medicine, 1990; National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998; National Drug Strategy, 2001).

The studies reviewed below are of two types, earlier studies often utilizing fixed doses. Fixed dose studies were conducted early in the process of investigating the medication, before investigators knew how buprenorphine could be best used and investigators were very cautious in using a new opioid. On the other hand, flexible dosing reflects clinical reality, and a number of studies have been completed with flexible dosing and are discussed below.

8.1.3 *Clinical trials comparing buprenorphine solution and methadone*

There are existing narrative reviews of the studies of methadone versus buprenorphine in the management of opioid dependence published elsewhere (Mattick et al., 1998), as well as quantitative reviews (West et al., 2000; Barnett et al., 2001; Mattick et al., 2003). Methadone is an effective treatment

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for the management of opioid dependence, and methadone is an appropriate comparison treatment in these trials. The trials reviewed in this section have all used an ethanol-based solution of buprenorphine (see Appendix 1), which has a slightly higher bioavailability than the tablet preparation. The section following this section reviews trials which have focussed on the tablet preparation, which is the marketed formulation.

Bickel et al. (1988)

The first randomised double-blind-trial comparing buprenorphine with methadone was conducted by Bickel and colleagues (Bickel et al., 1988). That study reported on 45 “male opiate addicts” who were stabilised either on 2 mg per day of buprenorphine or 30 mg per day of methadone for three weeks followed by a reduction regimen for four weeks and placebo administration for six weeks. There were no differences observed between the buprenorphine and methadone groups with respect to retention in treatment, symptom report or reduction of illicit opioid use. However, the 2 mg dose of buprenorphine was less effective than the 30 mg of methadone in its ability to attenuate the physiological and subjective effects of a six mg hydromorphone challenge.

Johnson, Jaffe and Fudala (1992)

In a longer randomised double blind trial, Johnson and colleagues (Johnson et al., 1992) recruited 162 individuals seeking treatment for opioid dependence. They were aged between 21 and 50 years with a self-reported duration of their current dependence on opioids of approximately three years, on average. Two thirds of the patients were male and the majority were described as “whites” with a small number of African Americans. Three treatment groups were used: 8 mg per day sub-lingual buprenorphine in an ethanol solution (n=53), 20 mg per day oral methadone (n=55), and 60 mg per day oral methadone (n=54). This study was conducted over 180 days, including 120 days of induction and maintenance therapy and 60 days of dose reduction and placebo dosing.

The primary outcome measures were retention in treatment and illicit opioid use. The percentage of subjects retained in treatment for the 25 weeks of the study were 30 per cent, 20 per cent and 6 per cent for buprenorphine, methadone 60 mg and methadone 20 mg, respectively. The methadone 20 mg group showed significantly poorer retention than either the buprenorphine or methadone 60 mg groups. There was no difference between the buprenorphine or the methadone 60 mg groups on the retention measure. For the second primary efficacy variable, the analysis showed that buprenorphine-maintained subjects produced an average of 53 per cent of urine samples negative for opioids, methadone 60 mg an average of 44 per cent, and methadone 20 mg an average of 29 per cent urine samples negative for opioids. When the data was analysed for the patients who completed the maintenance phase only, buprenorphine was associated with significantly more urines negative for opioids than either methadone 20 mg or 60 mg. The authors concluded that buprenorphine 8 mg per day was at least as effective as methadone 60 mg per day and both were superior to methadone 20 mg per day in reducing illicit opioid use and maintaining patients in treatment. The results were indicative of buprenorphine being as effective as methadone at the fixed doses given.

Kosten et al. (1993)

Kosten and his colleagues compared sublingual buprenorphine (2mg or 6mg/day) with methadone maintenance (35mg or 65mg/day) in a 24-week double-blind, double-dummy, randomised clinical trial (Kosten et al., 1993). The 125 subjects received fixed doses of both an oral syrup and sublingual ethanol solution (active and placebo). Comparison of the two buprenorphine groups revealed

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that there was less illicit opioid use in the 6mg group than in the 2mg group, as demonstrated by fewer opioid positive urines and self-reported illicit opioid use. Continued opioid withdrawal symptoms were also associated with the 2mg group, suggesting that this is not an adequate dose, on average.

Treatment retention was better in the methadone groups (20 weeks) compared to the buprenorphine groups (16 weeks), and opioid-free urines were higher for methadone than for buprenorphine (51% vs 27%), as was abstinence for at least 3 weeks (65% vs 27%). The authors concluded that both buprenorphine doses were clearly less effective than methadone, and that comparison studies of buprenorphine and methadone need to utilise doses of buprenorphine which are higher. Again, the suggestion of a dose-response relationship is clear, and others have been critical of the low doses used (Newman, 1994). It is unfortunate that most researchers have used fixed dose rather than flexible dose regimens, as there is a lack of information about the relative dose equivalence of buprenorphine and methadone.

Strain et al. (1994a)

The assessment of possible dose-equivalence was undertaken in a 26 week study in which the dose received by 164 subjects was varied to obtain optimum response, after initial stabilisation, at doses of 8mg/day sublingual buprenorphine or 50mg/day methadone (Strain et al., 1994b). Participants were randomly assigned to one of two treatment groups: sublingual buprenorphine in ethanol solution or oral methadone. The first four days comprised the induction phase of treatment. Subjects received daily doses of 2, 4, 6, and 8mg buprenorphine or 20, 30, 40, or 50mg methadone, in a double-blind and double-dummy dosing regimen, until stabilised. From weeks 3 to 16, subjects could receive double-blind dose increases and decreases (in increments of either 10mg methadone or 2mg buprenorphine) to a maximum of 4 increases (90mg methadone or 16mg buprenorphine) spaced at least 1 week apart. During the last 10 weeks doses were tapered by 10% per week to placebo. Outcome measures included retention in treatment, attendance & opioid positive urines.

The mean doses during the stable dosing period were 8.9mg/day buprenorphine and 54mg/day methadone. There were no group differences in the number of subjects requesting or receiving dose increases. Fifty-six per cent of subjects in each group completed the 16-week induction/maintenance phase. No differences were observed between the two groups with respect to retention time in treatment or to urine samples found to be positive for opioids. Buprenorphine and methadone were also equally effective in sustaining compliance with medication & counselling. These data suggest that a dose of 8mg buprenorphine is equivalent to a moderate dose of methadone.

Strain et al. (1994b)

The next major study by Strain reported on a comparison of buprenorphine and methadone in the management of patients who were using both opioids and cocaine (Strain et al., 1994a). Fifty-one opioid dependent patients were enrolled in a 26-week treatment program and received either 8 mg of sublingual buprenorphine or 50 mg of oral methadone with dose increases given up to a maximum of 16 mg of buprenorphine or 90 mg of methadone. On average, the patients were 32 years of age, the majority were male, 43 per cent were “white” and few were either married or employed, having on average 11 years of education. All the patients met criteria for opioid dependence under the DSM-III. Average doses were 11.2 mg of buprenorphine in an ethanol-based solution and 66 mg of methadone with half the patients receiving the maximum dose possible.

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Urine samples were collected three times each week. Both methadone and buprenorphine improved outcomes by reducing illicit opioid use and they were equally effective on measures of retention in treatment and compliance with the attendance and counselling. Both groups showed decreases which were significant in the extent of cocaine-positive urines but there was no differential effect between the two interventions.

Ling et al. (1996)

Ling and colleagues reported on a trial comparing 30mg methadone, 80mg methadone and 8mg buprenorphine (in ethanol solution) doses with 225 opioid dependent individuals (Ling et al., 1996). The results showed that 80mg methadone was superior to both 30mg methadone and to 8mg buprenorphine in retaining patients in treatment, reducing illicit opioid use, and decreasing craving for opioids. The 30mg methadone and 8mg buprenorphine were largely equivalent to each other in their effects on these variables, and there were no differences in the occurrence of adverse events or serious adverse events. Ling and colleagues noted the 8mg of buprenorphine in ethanol solution was not an optimal dosage, and that higher doses would probably provide a better outcome. They also noted the discrepancy between their results and those of earlier research (Johnson et al., 1992), and pointed out the need for research to address the dose levels of buprenorphine which are effective, rather than pre-determined doses. The flexible dose studies of Strain and colleagues (see earlier) and the large RCT conducted in Australia (see below) address the issue of appropriate dose more adequately than this study.

Schottenfeld et al. (1997)

Schottenfeld, and his colleagues compared buprenorphine and methadone at either 12 or 4 mg or 65 or 20 mg, respectively, in a 24 week double blind clinical trial (Schottenfeld et al., 1997). They enrolled 116 patients into each one of these four conditions and the patients were in their early 30s, mainly “white”, working and they had been using heroin for six or seven years on average. They reported no significant differences in retention rates or cocaine use. They did find the rates of opioid-positive toxicology tests were lowest for treatment using 65 mg of methadone (45 per cent positive) followed by 12 mg of buprenorphine (58 per cent positive), 20 mg of methadone (72 per cent) and 4 mg of buprenorphine (77 per cent positive).

Oliveto et al. (1999)

This study randomized 180 opioid dependent cocaine users in a study where subjects were allocated to desipramine hydrochloride (a tricyclic antidepressant) or placebo as well as 12 mg/day buprenorphine solution or 65 mg/day methadone in a 2x2 factorial design (Oliveto et al., 1999). The study lasted 13 weeks including a 3 week induction period and the medications were administered double blind. Weekly group therapy and monthly individual therapy were also provided. There were no significant differences in retention between the four treatment groups. Opioid abstinence increased faster with methadone treatment and cocaine abstinence increased faster with buprenorphine treatment. Opioid abstinence also increased faster in patients with high plasma desipramine levels regardless of opioid medication type. Buprenorphine was considered not more effective than methadone in reducing opioid use, and the authors suggested that more flexible dosing levels would assist in optimizing abstinence.

Johnson et al. (2000)

This 17-week randomised study compared thrice weekly buprenorphine (16 to 32 mg on Mondays and Wednesdays, 24 to 48 mg on Fridays), thrice weekly levomethadyl acetate (LAAM) (75 to

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115 mg), high dose daily methadone (60 to 100 mg) and low dose daily methadone (20 mg) maintenance treatment in 220 subjects (Johnson et al., 2000). The number of days subjects remained in the study was significantly higher for those receiving either LAAM (89 ± 6), buprenorphine (96 ± 4) or high dose methadone (105 ± 4) in comparison to low dose methadone (70 ± 4), and LAAM, buprenorphine and high dose methadone all significantly reduced illicit opioid use in comparison to low dose methadone. Similar side effects were reported among the different treatment and no toxic interactions associated with illicit drug use were reported. Buprenorphine and high dose methadone clients showed a trend towards higher rates of continuous abstinence than low dose methadone treatment. Thrice weekly buprenorphine dosing showed approximately equivalent outcomes to daily methadone treatment (in abstinence outcomes) or thrice weekly LAAM (in study retention outcomes).

8.1.4 Clinical trials comparing buprenorphine tablet with methadone

All the studies reviewed above were conducted with the buprenorphine sublingual solution formulation, while the product marketed is usually a sublingual tablet. A number of controlled studies have compared buprenorphine tablets and methadone (see Appendix 2). One study, conducted in Australia (Mattick et al., 2003), was a flexible dose, double-blind, double-dummy study and showed that buprenorphine and methadone had similar efficacy in the management of opioid dependence. Similar conclusions were also drawn from a number of European studies conducted comparing methadone and buprenorphine.

Eder et al. (1998) and Fischer et al. (1999)

An interim analysis of a study of buprenorphine tablet versus methadone was reported by Eder and colleagues (Eder et al., 1998) and these authors have recently published the final report of this study with a sample of sixty patients (Fischer et al., 1999). This Austrian study employed a maximum dose of 8 mg buprenorphine tablet but there was “no upper limit” set for the methadone dose. Thirty-four patients were enrolled in the study, 16 received buprenorphine and 18 receiving methadone. Patients in the buprenorphine group provided a greater proportion of negative urine samples (in particular cocaine-negative samples) compared with the methadone group although the difference was not statistically significant.

Retention in the buprenorphine group, however, was significantly less than in the methadone group. This difference was thought to be due to the maximum dose of the buprenorphine tablet being set too low, especially given the somewhat lower bio-availability of the tablet preparation compared with the ethanol-based solution which has been used in most of the trials in Northern America.

The final report with the full sample provided similar conclusions to those of the interim report (Fischer et al., 1999). This study was an open label study of 60 subjects randomized to daily buprenorphine or methadone maintenance treatment over 24 weeks following a 6-day induction period (Fischer et al., 1999). Maximum buprenorphine dose were fixed at 8 mg daily, while subjects receiving methadone had a maximum of 80mg daily. Retention rates were significantly better in the methadone group (71% completed the study versus 38% of buprenorphine subjects). When the drug use of those subjects completing the study was analysed, it was found that those receiving buprenorphine had significantly lower levels of opioid consumption than those receiving methadone.

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Uehlinger et al. (1998)

These Swiss researchers studied the effectiveness of the buprenorphine tablet formulation versus methadone (Uehlinger et al., 1998). This double-blind study conducted over a six week period employed a maximum dose of 16 mg buprenorphine tablet and 120 mg of methadone. Fifty-eight patients were enrolled in the study, 27 received buprenorphine and 31 received methadone. Patients in both groups provided a similar proportion of opioid-negative urine samples, but the buprenorphine patients had a slightly lower rate of cocaine-positive samples compared with the methadone patients. The difference in urine results was not statistically significant. Retention in the buprenorphine group, however, was significantly less (50 per cent) than in the methadone group (90 per cent). Many of the drop-outs from the buprenorphine patients occurred during the induction phase which was relatively slow compared with other studies. When commenting upon the discrepancy between their retention rates and those reported by others, the authors concluded that the “doses [of buprenorphine] used in the present study may have been too low in the induction phase and not increased quickly enough to retain the addicts” (p. 17).

Pani et al. (2000)

This multicentre double blind study enrolled 72 subjects and randomized them to either 60 mg methadone or 8 mg buprenorphine for six months (Pani et al., 2000). No significant differences were found in the urinalysis results of heroin use between groups or in treatment retention (47% retention in buprenorphine and 64% in methadone at 6 months), but there appeared to be a trend towards greater retention in the methadone group. No significant differences between groups were noticed in the reporting of adverse events, and there were no deaths or cases of hospitalization in the study. The non-significant trend to lower retention in buprenorphine group might be explained by insufficient buprenorphine dosage or too slow an induction period, however the result relevance was limited by low recruitment to the study.

Petitjean et al. (2001)

Petitjean and colleagues used double blinding and a flexible dosing regimen in their study of buprenorphine versus methadone maintenance (Petitjean et al., 2001). The study only lasted for 6 weeks (of which the first 3 weeks was a stabilization period) and recruited 58 subjects in three Swiss outpatient clinics. Mean doses of buprenorphine received were 10.5 mg per day and mean methadone doses were 69.8 mg per day. Similar proportions of subjects were dependent on cocaine or receiving other medications in each group.

Retention rates were significantly better in those subjects treated with methadone (90%) compared to buprenorphine (56%), possibly due to inadequate induction doses of buprenorphine. Survival analysis confirmed the significant difference in retention, and almost all of the buprenorphine patients who dropped out did so within the first 10 days, 67% of them reporting withdrawal symptoms. Both treatment groups had similar illicit opioid and cocaine use, measured through urine samples. Patients were excluded after missing three consecutive days of treatment, or medical reasons such as medication toxicity or illness. The frequency of most adverse events was not different between treatment groups, although methadone recipients reported significantly more sedation than buprenorphine recipients. 33% of buprenorphine group reported headaches was not significantly different from the 23% of the methadone group. No serious adverse events occurred.

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Mattick et al. (2003)

Mattick and colleagues performed a randomized, double blind, double dummy study of buprenorphine versus methadone maintenance in 405 subjects in three Australian methadone clinics (Mattick et al., 2003). The formulations of medications (buprenorphine in commercial tablet form), flexibility in dose levels for each medication, and criteria for discontinuation from the study (after 5 to 7 days of non-attendance) were all comparable to what would occur in clinical practice. Of the 13 weeks study duration, the first six weeks consisted of daily dosing for all subjects, then buprenorphine subjects were transferred to alternate day dosing for the remainder of the study. No significant differences were noted in completion rates at 13 weeks but methadone treatment was significantly superior to buprenorphine when survival analysis was used. This difference was not sustained when survival analysis was performed separately for daily and alternate day dosing periods. It was suggested that low doses during the buprenorphine induction phase could lead to earlier drop-out of patients, but it is important to note that retention between buprenorphine and methadone was only significant on one of four analyses. No differences in illicit drug use were found between methadone and buprenorphine treatment groups, 85% of buprenorphine subjects transferred to alternate day dosing were maintained on this dosing schedule, and both methadone and buprenorphine maintenance were considered effective in treating opioid dependence.

Ahmadi et al. (2003)

This Iranian, 24-week study compared three treatments in 204 male dependent intravenous buprenorphine users; 50 mg p/day naltrexone, 50 mg/day methadone and 5 mg/day buprenorphine (Ahmadi, 2003). The doses of methadone and buprenorphine were chosen because they are the usual maximum doses in Iran. Retention in methadone (84%) was found to be significantly better than both buprenorphine (59%) and naltrexone (21%) groups, and retention in buprenorphine was also better than in the naltrexone group. No significant side effects were reported for any of the medications.

Gerra et al. (2004)

This Italian, 12-week study (Gerra, 2004) compared a mean dose of 81.5mg methadone with 9.2mg of buprenorphine in the maintenance treatment of 154 heroin dependent patients and found similar retention at 12 weeks (61.5% versus 59.2%) but more illicit opioid use in the methadone group compared with the buprenorphine group (32.1% versus 25.6%).

8.1.5 Placebo-controlled studies

There have been three placebo controlled studies reported (see Appendix 3).

Johnson et al. (1995)

Johnson and colleagues were the first to compare buprenorphine treatment with a placebo control condition, rather than with methadone (as in previous studies) (Johnson et al., 1995a). This was a 2 week (14 day) double-blind study, which was part of a 20 week study. Participants were randomly assigned to one of 3 treatment conditions in a 2:2:1 ratio: placebo (n=60), sublingual buprenorphine 2mg (n=60), or buprenorphine 8mg (n=30). On days 6-13 patients could request to change to another dose condition, which would be randomly chosen from the two to which they had not been originally assigned. Outcome measures included the percentage of patients on initial dose, percentage of opioid positive urines, and

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dose adequacy, as measured by patients' responses to questions as "How well has this dose of medicine been holding you?".

Analyses showed that subjects given buprenorphine showed greater time on initial dose, requested fewer dose changes, used less illicit opioids, and rated dose adequacy higher than those on placebo, but that the two active medication groups did not differ from each other. This result is somewhat surprising given other results suggestive of a dose-response relationship for buprenorphine, but the failure to detect differences between the two buprenorphine dose levels may have been due to the short duration of the study period.

Fudala et al. (2003)

A second major placebo controlled trial was reported by Fudala et al. (Fudala et al., 2003). In this study, patients were randomly assigned to receive 16 mg of buprenorphine or placebo medication. The patients were recruited from a population of opioid dependent individuals and 326 were randomised to treatment, 110 to receive the combination therapy of the buprenorphine and naloxone, 106 to receive the monotherapy of buprenorphine alone and 110 to receive placebo. All the patients were opioid dependent and had used heroin for an average of 84 months at the time of entry into the study.

The majority of patients were "white" males and they were in their mid 30s. The double blind phase of the trial ran over a four week period and patients received 14.1 mg per day of buprenorphine, respectively. The number of urines negative for opiates were similar in the two active treatment conditions at 17.8 per cent negative for the buprenorphine/naloxone combination and 20.7 per cent negative for the buprenorphine mono-therapy. The placebo group had only 5.8 per cent of urines negative for opioids and both the active treatment groups performed significantly better than the placebo group in terms of samples of urine negative for opiates.

These authors then continued with an open phase wherein they examined the combination therapy for adverse events across a 52-week period in total including the double blind phase. They found few and mild treatment related adverse events which were most commonly headache and constipation but there was little evidence of any significant changes in liver function tests or haematology tests. These authors concluded that buprenorphine appeared to be a safe intervention to administer on an out-patient basis to opiate dependent individuals.

Kakko et al. (2003)

Another longer term trial of buprenorphine and placebo studied a small group of forty patients over twelve months and showed 75% retention in the buprenorphine group and 0% retention in the placebo group, a result consistent with the other placebo-controlled trials. Urinalysis results also favoured the active treatment.

Ling et al. (1998)

Although not strictly placebo controlled, as all groups had received buprenorphine (Ling et al., 1998), this study treated 1 mg buprenorphine as a placebo dose and showed active treatment was superior with 4 mg, 8 mg and 16 mg buprenorphine in retention and use of illicit opioids.

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8.1.6 *Relevance and generalisability of the trial results*

One important consideration is the generalisability of the results of the trials, especially those from the USA. One major issue relates to the bio-availability of the ethanol-based sublingual solution formulation of buprenorphine which has been used in all of the North American trials of buprenorphine versus methadone. There is evidence that the bioavailability of this ethanol-based solution is greater than the bioavailability of the buprenorphine contained in the tablet formulation, which is the marketed formulation (Mendelson et al., 1995). Results from a recent 24 subject comparative bioavailability study showed that the bioavailability of buprenorphine from the tablet formulation was 70% of that from the ethanol based solution used in many of the original trials (Ling et al., 1998), and other studies have reported similar results (Strain et al., 2004; Schuh & Johanson, 1999; Nath et al., 1999). Additionally, there is a combined buprenorphine/naloxone tablet which is available in some countries and this preparation is designed to reduce injection of the crushed-up tablet by potentially causing a withdrawal reaction if injected by opioid dependent patients not in regular buprenorphine treatment. Additional information on a combined buprenorphine/naloxone formulation is available at http://www.fda.gov/cder/drug/infopage/subutex_suboxone/default.htm or from the manufacturer.

There are no other issues to do with the generalisability of the North American data to the international context. The patients in the trials which have been conducted in the USA are remarkably similar to patients in treatment in many parts of the world for opioid dependence. Approximately two-thirds are male, they are generally in their early 30s, they have a history of opioid use of a number of years typically between 5 and 7 years on average, they tend to be unemployed, and they tend to use other drugs. It is important to recognize that to the extent that an individual is dependent on opioids, the most important clinical feature is the dependence, and differences across countries become much less important than the fact that the individual is opioid dependent. Similar observations have been made in the context of the trials of methadone maintenance treatment where that intervention was studied against no treatment, placebo medication, withdrawal detoxification, or intensive psycho-social interventions. These studies were conducted in quite different settings by different researchers and all came to the same conclusion, that methadone maintenance was more effective than these other interventions in reducing opioid use and in reducing criminal activity.

8.2 *Quantitative review*

There has been a recently completed Cochrane review of buprenorphine against methadone, and the essential results of the review are set out below (Mattick et al., 2003).

8.2.1 *Flexible dose buprenorphine versus flexible dose methadone*

The flexible dose studies reported probably provide the best estimate of the likely impact of methadone and buprenorphine in day-to-day clinical practice, as they mirror clinical practice in terms of dose adjustments and in terms of the doses employed in the studies. The six studies (Fischer et al., 1999; Johnson et al., 2000; Mattick et al., 2003; Petitjean et al., 2001; Strain et al., 1994a, 1994b) included in the flexible dose buprenorphine versus flexible dose methadone analysis (837 participants) showed that methadone was more likely to retain patients than buprenorphine (six studies, 837 participants; RR= 0.82; 95% CI: 0.69-0.96) (Figure 1). The chi-square test for heterogeneity was not significant. Inspection of the relative risks for retention in treatment for these six flexible dose studies showed two studies had significant poor retention for buprenorphine, but the other four studies showed no statistical significant difference.

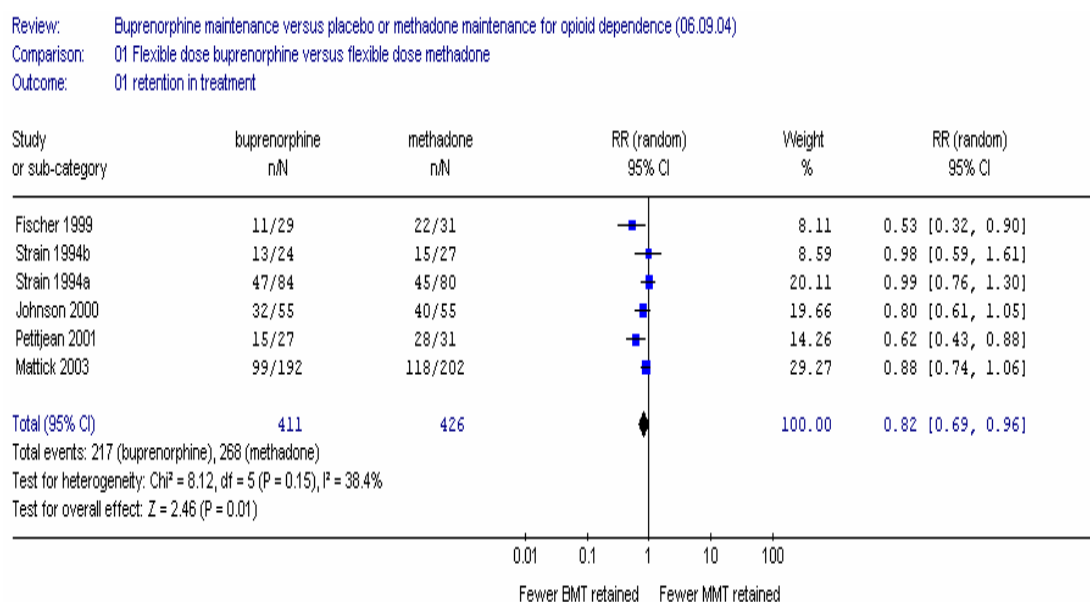
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While there was a difference in retention favouring methadone, turning to the effect of buprenorphine and methadone on drug use, the flexible dose studies showed no significant difference between the two interventions in terms of heroin use, based on results of morphine urinalysis (six studies, 837 participants; SMD= -0.12; 95% CI: -0.26- 0.02) (Figure 2), or in terms of self-reported heroin use (two studies, 326 participants; SMD= -0.10; 95% CI: -0.32- 0.12).

Similarly, there was no statistically significant difference between the flexible dose methadone and buprenorphine trials in terms of cocaine positive urines (five studies, 779 participants; SMD= 0.11; 95% CI: -0.03 - 0.25) or benzodiazepine positive urines (four studies, 669 participants; SMD= 0.11; 95% CI: -0.04-0.26).

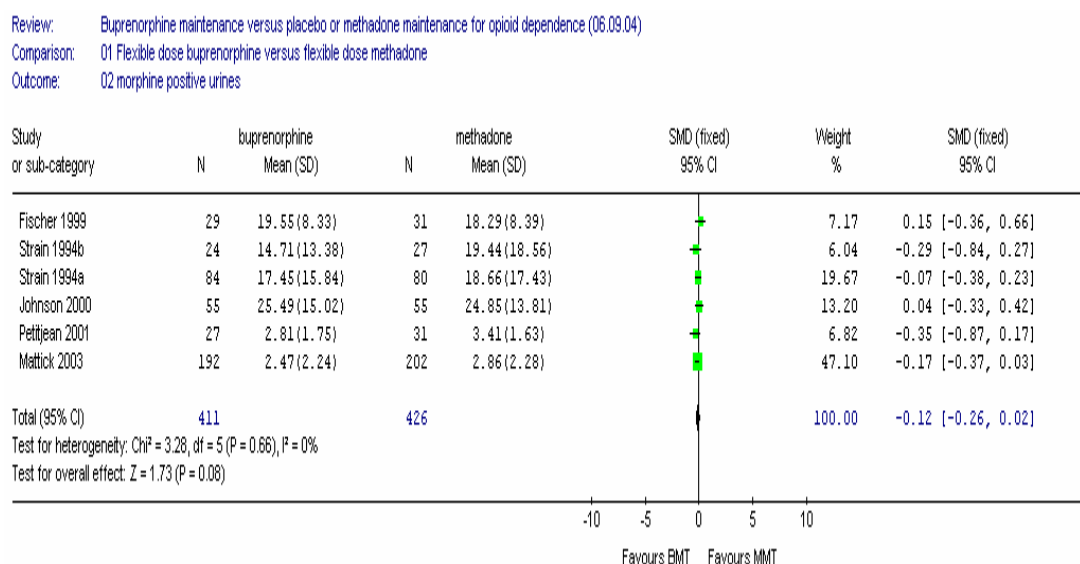
In the one study that reported on criminal activity, there was no statistically significant difference between the buprenorphine and methadone groups (SMD= -0.14; 95% CI: -0.41- 0.14).

Figure 1: Retention in treatment in flexible dose studies



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Figure 2: Morphine positive urines in treatment in flexible dose studies



8.2.2 Low dose buprenorphine versus low dose methadone

The comparison of low dose buprenorphine and low dose methadone (two studies, 121 participants) indicated no statistically significant difference in retention in treatment ($RR = 0.74$; 95% CI: 0.52-1.06), nor was there evidence of differences in morphine positive urines and cocaine positive urines based on one trial. There was no difference in self-reported heroin use (one study with 44 participants; $SMD = -0.28$; 95% CI: -0.35- 0.90).

8.2.3 Low dose buprenorphine versus high dose methadone

When low dose buprenorphine is compared to high dose methadone (2 RCTs, 120 participants) there was no statistical difference in retention in treatment ($RR = 0.69$; 95%CI: 0.45-1.06). The trials involved did not show heterogeneity. The results show that low dose buprenorphine is not more effective than high dose methadone in retaining patients in treatment, and it is not superior to high dose methadone in suppressing heroin use as indexed by the extent of morphine positive urines (one study, 57 participants; $SMD = 0.88$; 95% CI: 0.33 - 1.42). However, the overall effect is only based on one study, as data from the second study (Kosten et al., 1993) concerning the urine results were not available for this review. There was, also, no statistically significant difference of the effect of low dose buprenorphine and high dose methadone beyond the effect on cocaine, as shown from data on cocaine positive urines (one study, 57 participants; $SMD = -0.08$; 95% CI: -0.60- 0.44).

There was no statistically significant difference in self-reported heroin use (one study, 38 participants; $SMD = -0.06$; 95% CI: -0.70- 0.58). However, the results from Schottenfeld et al (1997) on self-reported heroin use, which could not be included in this meta-analysis, did show a significant advantage for high dose methadone (65mg) over low dose buprenorphine (4mg).

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8.2.4 *High dose buprenorphine versus low dose methadone*

When comparing high dose buprenorphine there was one study which favoured high dose buprenorphine in terms of retention, one study that favoured low dose methadone, and two studies showed no statistically significant difference. The test for heterogeneity was significant for the retention data (chi-square=11.47, df=3, p=0.0095) therefore no summary measure is provided. However, high dose buprenorphine was superior to low dose methadone in terms of heroin use as shown from morphine positive urines (three studies, 317 participants; SMD= -0.23; 95%CI: -0.45--0.01), but again the chi-square test for heterogeneity was significant (p=0.041), even though direction of the estimates were homogeneous. In terms of cocaine positive urines, no benefit was shown for high dose buprenorphine compared with low dose methadone, based on only one study (59 participants).

There was no difference in self-reported heroin use (one study, 37 participants; SMD= -0.64; 95% CI: -0.06- 1.33).

8.2.5 *High dose buprenorphine versus high dose methadone*

Comparing high dose buprenorphine and high dose methadone, the data on retention in treatment (5 RCTs, 449 participants) showed no statistical difference between the two interventions (RR=0.79; 95% CI:0.62-1.01), but suggest that high doses of buprenorphine are less likely to retain patients than high dose methadone. The trials involved in this comparison (Johnson et al., 1992; Kosten et al., 1993; Ling et al., 1996; Pani et al., 2000; Schottenfeld et al., 1997) did not show any evidence of heterogeneity. High dose buprenorphine was also significantly less able to suppress heroin use as shown by morphine positive urines (3 studies, 314 participants: SMD=0.27; 95%CI: 0.05-0.50) while no statistically significant difference was found in terms of cocaine use based on the cocaine urine analysis results of only one study (57 participants).

There was no difference in self-reported heroin use (two studies, 74 participants; SMD= -0.02; 95% CI: -0.48- 0.45). This lack of significance is consistent with the results from Schottenfeld (Schottenfeld et al., 1997) on self-reported heroin use, which could not be included in this meta-analysis, and which did not show a significant advantage for high dose methadone (65mg) over high dose buprenorphine (12mg).

8.2.6 *Low dose buprenorphine maintenance versus placebo*

Turning to the results on the two trials (487 participants) comparing low dose buprenorphine (2mg or 4 mg) versus placebo medication (0mg or 1mg, respectively) (Johnson et al., 1995a, Ling 1998), the results showed a benefit for low dose buprenorphine above placebo in terms of retaining patients in treatment (RR=1.24; 95% CI: 1.06-1.45). However, low dose buprenorphine patients had no less heroin use as indexed by morphine positive urines, cocaine positive urine results, and benzodiazepine positive urines, although these latter two results came from only one of the two trials (Johnson et al., 1995a).

8.2.7 *High dose buprenorphine maintenance versus placebo*

The results on the two trials (463 participants) comparing high dose (8mg) buprenorphine versus placebo medication (Johnson et al., 1995a, Ling 1998), the results showed a benefit for buprenorphine above placebo in terms of retaining patients in treatment (RR=1.21; 95% CI: 1.02-1.44). Not only were patients better retained by buprenorphine but they had less heroin use as indexed by morphine positive urines. There was an advantage for placebo in terms of cocaine positive urine results, but this is based on

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only one study (Johnson et al., 1995a). By way of contrast, buprenorphine was superior to placebo in terms of its ability to suppress benzodiazepine use, again this result coming from one trial (Johnson et al., 1995a).

8.2.8 *Very high dose buprenorphine maintenance versus placebo*

Finally, turning to the one trial (366 participants) comparing very high dose (16mg) buprenorphine versus buprenorphine 1 mg day (Ling et al., 1998), the results showed a benefit for high dose buprenorphine above very low dose buprenorphine in terms of retaining patients in treatment (RR=1.52; 95% CI: 1.23-1.88). Not only were the patients in this single trial better retained by buprenorphine, but they had less heroin use when receiving 16mg of buprenorphine than placebo patients as indexed by morphine positive urines.

Other measures (e.g. use of other drugs, physical health, and psychological health) were too infrequently and irregularly reported in the literature to be usefully integrated in the quantitative part of this review.

8.3 *Summary of comparative efficacy in treatment of opioid dependence*

The results of the pivotal and other major trials of buprenorphine against methadone and against placebo treatment suggests that buprenorphine is as effective as methadone as a maintenance agent in the therapeutic doses which have been used in the trials. Specifically, randomized research has demonstrated that buprenorphine is as effective as methadone as maintenance medication in reducing illicit opioid use and in retaining patients in treatment. Buprenorphine is superior to placebo in terms of retention based on the large study by Ling (Ling et al., 1998), the study by Kakko (Kakko et al., 2003) and the study by Johnson (Johnson et al., 1995), and it is superior in terms of its ability to suppress heroin use (Fudala et al., 2003). Although the effect is not always reported (Montoya et al., 2004), the evidence from the review overall shows a dose-response relationship for buprenorphine.

When compared with methadone, the results of the meta-analysis indicate that methadone is statistically significantly better able to retain patients than buprenorphine in flexible dosing approaches, the difference being in favour of methadone. Methadone is better able to suppress heroin use than buprenorphine, especially if high-dose methadone is used (and vice-versa). Similar conclusions have been reached by other recent meta-analytic reviews of these treatments (Barnett et al., 2001; West et al., 2000). One explanation which has been advanced by authors in some of the studies included here for the poorer retention in buprenorphine treatment (Fischer et al., 1999; Petitjean et al., 2001) is that they inducted patients too slowly onto buprenorphine and this was the cause of the poorer retention in that medication group. It is possible that retention is affected by too slow induction, and given the apparent relative safety of buprenorphine it may be possible to induct people to higher doses at a more rapid rate and to overcome the problem of slightly poorer retention for buprenorphine compared with methadone. However, there are a number of other possible explanations for the poorer retention on buprenorphine than methadone. In particular, it may well be that buprenorphine, being a partial agonist, does not retain people because it does not have a full opioid effect and is less satisfying to patients. Another possibility is that patients in the initial stages of dosing who have recently ingested heroin suffer a mild withdrawal syndrome by virtue of buprenorphine (a partial agonist) displacing heroin (a full agonist) from opioid receptors in the central nervous system, and this mild withdrawal may lead patients to leave treatment. A further possibility is that buprenorphine is simply easier to withdraw from and, on that basis, patients are more at liberty to leave treatment without the severe withdrawal syndrome that can accompany methadone withdrawal. Of course, these factors may all act together to cause buprenorphine to have a

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slightly poorer outcome in terms retention than methadone. Future research should be undertaken to address this particular issue.

8.4 *Buprenorphine's role in preventing HIV transmission and HIV/AIDS treatment and care*

8.4.1 *Prevention of HIV risk behaviours*

There is a large body of research providing strong evidence that opioid substitution/maintenance treatment using methadone reduces injection-related risk behaviour among injecting opioid users and this reduction in risk behaviour is reflected in the findings of a number of independent researchers on different continents that enrolment in opioid maintenance treatment protects against HIV infection (Abdul-Quader et al., 1987; Blix & Grönbladh, 1991; Blix & Grönbladh, 1988; Brown et al., 1989; Chaisson et al., 1989; Marmor et al., 1987; Metzger et al., 1993; Schoenbaum et al., 1989). Given the evidence of similar effects from methadone and buprenorphine, the protective effect should also be exerted by buprenorphine maintenance treatment (Ward et al., 1998a). Indeed, there is a literature on the role of buprenorphine in HIV infected patients showing buprenorphine may protect against sero-conversion to HIV. One randomized trial (Mattick et al., 2003) and one observational study (Carrieri et al., 2003) have reported a decrease in the frequency of injecting, and one reported decrease in overall HIV risk behaviours (Mattick et al., 2003). Two observational studies have demonstrated low rates (0.4-0.8% over 2 years) of HIV seroconversion in patients receiving buprenorphine (Fhima et al., 2001; Duburcq et al., 2000). However, the role of buprenorphine in preventing HIV risk behaviour and HIV transmission has not yet been as systematically or rigorously evaluated as that of methadone. On an international level, a large-scale clinical trial of the efficacy of buprenorphine as HIV prevention is planned by the HIV Prevention Network in the USA.

8.4.2 *Role in HIV/AIDS treatment and care*

The majority of the literature on the use of buprenorphine in HIV seropositive patients comes from France where the medication has been available since 1995. Between 1995 and 1998 a prospective observational study, the Manif 2000 cohort, enrolled 467 HIV seropositive patients who had been infected through injection drug use. Patients were 18 years old or older with CD4+ cell counts > 300/mm, no opportunistic infections, and met criteria for CDC stage A or B. A portion of these patients were actively injecting opiates and a subset of these received buprenorphine treatment in the period during which the cohort was followed. Evaluation of 167 patients in this cohort who received highly active antiretroviral therapy (HAART) for a median of 5.3 months revealed that the likelihood of non-adherence to these medications was highest in the patients who were actively using injecting drugs (58%) compared to those who were former injection drug users (35%) and those who were receiving buprenorphine treatment (22%) (Moatti et al., 2000). Active drug users not receiving buprenorphine treatment were 5.1 times (OR 1.3-20.1) more likely to be non-adherent to their HAART medication than those who were receiving buprenorphine (Moatti et al., 2000).

A second report from the same cohort revealed that HIV seropositive patients receiving HAART along with buprenorphine were able to achieve clinical outcomes with respect to biological markers (e.g. clinically significant rise in CD4 cell counts and decrease in HIV viral load) similar to those patients not receiving buprenorphine, after a median of 3.7 months of exposure to the antiretroviral medications (Carrieri et al., 2000).

The final report from this group tracked treatment retention in the 114 patients in the cohort who received buprenorphine during the entire follow-up period. Forty-six (40%) patients discontinued

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treatment during the follow-up, with 23 (44%) of these dropping out of treatment within 9 months and 25 (54%) of these indicating reversion to injection drug use (Carrieri et al., 2003). The implications of this level of treatment retention on HIV risk behavior, HIV disease status, and viral resistance patterns is not known. Notably, thirty-two of the 114 patients (28%) who received buprenorphine during the follow-up period reported injecting buprenorphine. This practice, expected to be more likely with the buprenorphine only preparation compared to the buprenorphine/naloxone combination, has been reported in those countries in which this preparation is available.

There is evidence of the role of buprenorphine in HIV-infected patients showing ease of withdrawal (Montoya et al., 1995; Umbricht et al., 2003).

In the USA, the National Institute of Drug Abuse (NIDA) is planning a randomized clinical trial of buprenorphine in HIV seropositive patients. In addition, demonstration projects designed to incorporate buprenorphine into HIV primary care settings are to be initiated in the USA, funded by the Health Resources Service Administration.

Buprenorphine's pharmacokinetic and pharmacodynamic interactions with antiretroviral agents indicate that buprenorphine may be preferable to methadone for the treatment of comorbid opioid dependence and HIV disease.

In the international system of control of dependence producing substances, buprenorphine has been placed on Schedule III of the 1971 Convention, while methadone is a Schedule I drug in the Single Convention on Narcotic Drugs, 1961, and as such can only be prescribed through highly regulated mechanisms of prescription and often only in specialized drug dependence treatment programs. Buprenorphine, being a Schedule III drug in the 1971 Convention on Psychotropic Substances, may be available by prescription from qualifying physicians, and, as a result, can be used as a treatment for opioid dependence in multiple practice and treatment program settings, having the potential to increase access to treatment for this population and to simplify treatment by making it possible for a single provider to render care for both substance use disorder(s) and HIV disease.

8.5 Conclusion

During the last three decades, the scientific evidence has accumulated that substitution maintenance is an effective treatment for opioid dependence that has a supportive function to enhance HIV/AIDS prevention, treatment and care. In conjunction with evidence for a capacity of buprenorphine maintenance therapy for recruiting opioid-dependent injecting drug users into treatment, retain them in treatment and reduce risky behaviours associated with HIV transmission, treatment of opioid dependence with buprenorphine is a major public health tool in the management of opioid dependence and in HIV prevention, treatment and care among opioid dependent drug users. Buprenorphine as the added potential to increase access to treatment through provision of treatment in multiple practice and treatment program settings.

9. Summary of comparative evidence on safety

9.1 Estimate of total patient exposure to date

The greatest level of experience with buprenorphine has occurred in France where buprenorphine treatment for heroin dependence has been widely available through general practitioners since 1995. By 1998 65,000 patients per year were in buprenorphine treatment in France and by 2001 this had increased to 74,000, while 9,600 were treated with methadone (Auriacombe et al., 2004).

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Buprenorphine was registered in Australia for the treatment of opioid dependence in 2001 and there were 8, 641 patients registered as receiving buprenorphine maintenance treatment at 30th June 2003. Buprenorphine is available for treatment of opioid dependence in other 27 countries, but the number of patient treated in these countries is not yet known. However, based on the available data, currently the global number of persons with opioid dependence receiving prescribed buprenorphine is estimated to be about 180 000.

9.2 *Description of adverse effects/reactions*

Buprenorphine has similar adverse effects to those of other opioids. The most common adverse effects include drowsiness, sedation, constipation, headache and other pain, nausea, insomnia, and sweating. Patients appear to experience less sedation on buprenorphine than on methadone (Lintzeris et al., 2001; Ford et al., 2003). Tolerance to most of these effects develops with ongoing use of opioids and most heroin dependent patients will have developed tolerance to them prior to commencing buprenorphine treatment. Recently, a large patient series was reported on and rates of adverse events were similar in the buprenorphine active-treatment and placebo groups (Fudala et al., 2003).

In patients with marked drug dependence, or who have recently used other opioids, the initial dose of buprenorphine can produce a precipitated withdrawal effect similar to that produced by opioid antagonists. This is usually transient and disappears once patients are stabilised on buprenorphine (Lintzeris et al., 2001).

The French experience suggests that buprenorphine patients experience fewer side effects than methadone patients. Since 1995, reported adverse events associated with buprenorphine use have been very rare – approximately 130 per year which is less than 1% of all adverse drug events. Some complications associated with injection of buprenorphine have been reported and there have been 53 cases of cytolytic hepatitis. This appears to be more likely if the patient has Hepatitis C or is being treated with other medications metabolised by the liver (Auriacombe et al., 2004).

Studies of the safety of buprenorphine at different doses and different dosing schedules found that there were no significant differences in adverse events between groups and that buprenorphine can be administered safely by doubling the dose on alternate days or by tripling the daily dose every three days (Amass et al., 1994; Johnson et al., 1995; Amass et al., 1998; Johnson et al., 2000; Montoya et al., 2004).

9.3 *Variation in safety due to health systems and patient factors*

Safety in overdose

Buprenorphine is a partial opioid agonist with high affinity and low intrinsic activity at the μ -opioid receptor and is considered to be much safer in overdose than full opioid agonists such as methadone. Buprenorphine is well-tolerated even by individuals who are not opioid dependent (Johnson & McCagh, 2000; Walsh et al., 1994).

Buprenorphine displays ceiling effects at high doses where effects reach a plateau beyond which larger doses produce little or no additional effect (Walsh et al., 1994). Buprenorphine causes slight depression of respiratory rate and oxygenation at doses up to 16mg, with no additional effect at higher doses up to 32mg. Consequently, buprenorphine alone is very unlikely to cause fatal respiratory depression even in non opioid dependent individuals (Walsh et al., 1994).

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Mortality

Deaths due to buprenorphine have been reported rarely outside of France (Boyd et al., 2003), however, widespread availability and minimal regulation of buprenorphine does not appear to have been associated with high numbers of buprenorphine-related deaths typically associated with alcohol consumption and with benzodiazepine use especially benzodiazepine injection. French monitoring shows a steady decline in opioid overdose deaths since 1994 (Auriacombe, 2001; Auriacombe et al., 2004; Gueye et al., 2002; Pirnay et al., 2004). Between 1994 and 1998, there were 1.4 times as many deaths related to buprenorphine than methadone related deaths, however, when death rates were calculated, the estimated annual death rate related to methadone was at least three times greater than the rate for buprenorphine related deaths (Auriacombe et al., 2001).

Polydrug use, particularly involving benzodiazepines, is a significant factor in buprenorphine related deaths (Auriacombe et al., 2004; Gueye et al., 2002; Pirnay et al., 2004). From 1996 to 2000, buprenorphine was associated with 137 deaths in France, however, all but one of these also involved benzodiazepines and or other central nervous system depressants and the role of buprenorphine as the cause of death is questionable (Auriacombe et al., 2004). Pirnay and colleagues (Pirnay et al., 2004) reviewed 60 consecutive opioid related deaths which occurred in Paris between 1997 and 2002. Buprenorphine was detected in 34 cases, all of which also involved other drugs. Buprenorphine was considered to be directly responsible for the death in only five cases, however, four of these also had non toxic levels of other drugs which may have contributed (Pirnay et al., 2004). Gueye et al. (Gueye et al., 2002) investigated 40 opioid related deaths in north east Paris between 1995 and 1999 of which 13 involved buprenorphine. In all of these cases, other drugs were also involved, most commonly benzodiazepines, alcohol and cannabis.

9.4 Use of buprenorphine in pregnancy

Buprenorphine is not approved for use in pregnancy in many countries, being classified as a Category C drug for use in pregnancy (no adequate well-controlled studies in pregnant women). However, there is increasing interest and research in buprenorphine as a medication that has great potential for decreasing the neonatal abstinence syndrome and enhancing neonatal health (Comer & Annitto, 2004; Fischer et al., 2000; Johnson et al., 2001; KayembaKays & Lacyde, 2003; Lacroix et al., 2004).

9.5 Drug interactions

Buprenorphine is metabolized by several isoforms of the cytochrome P450 family, mainly by P450 3A4, and co-medications that are inhibitors or inducers of these isoforms can increase or decrease, respectively, buprenorphine plasma levels. Subjects receiving buprenorphine should be closely monitored and may require dose-reduction if inhibitors of CYP 3A4 are co-administered, such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) and HIV protease inhibitors (see below). The interaction of buprenorphine with CYP 3A4 inducers has not been studied and it is recommended that patients receiving buprenorphine should be closely monitored if inducers of CYP 3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

While buprenorphine alone has been documented to demonstrate a ceiling to respiratory depressant effects in clinical pharmacological testing (Walsh et al., 1994), the interaction with other CNS depressants

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such as benzodiazepines and alcohol may be potentially serious or lethal, especially if administered to non-tolerant individuals (Walsh & Eissenberg, 2003).

Buprenorphine's pharmacokinetic and pharmacodynamic interactions with antiretroviral agents has been studied and, unlike methadone which has an adverse interaction with zidovudine (McCance-Katz, 1998), buprenorphine does not increase zidovudine concentrations (McCance-Katz, 2001). Patients with HIV managed with efavirenz-containing highly active anti-retroviral therapy (HAART) regimens frequently suffer a severe opioid withdrawal syndrome (McCance-Katz, 2002). This withdrawal apparently occurs as a result of efavirenz induction of cytochrome P450 3A4, which is chiefly responsible for methadone metabolism. However, buprenorphine treatment is not associated with opioid withdrawal when efavirenz is administered concomitantly (McCance-Katz, in press), nor does buprenorphine appear to markedly alter efavirenz plasma concentrations (Pade, in press), thereby simplifying the treatment of opioid-dependent patients with HIV disease requiring efavirenz treatment. Similarly, methadone has been associated with opioid withdrawal symptoms when administered in combination with lopinavir/ritonavir (McCance-Katz et al., 2003). Ongoing studies examining interactions between buprenorphine and (a) nelfinavir, (b) lopinavir/ritonavir, (c) ritonavir, and (d) delavirdine have revealed no adverse events in study subjects, despite the observation of significant pharmacokinetic interactions predicted based on the known clinical pharmacology of each of the antiretroviral agents in terms of their effects on cytochrome P450 3A4 which is principally responsible for the metabolism of buprenorphine (McCance-Katz, unpublished data).

9.6 *Summary of comparative safety against comparators*

The safety and efficacy of buprenorphine has been compared with that of methadone in a number of clinical studies (Ling et al., 1996; Ling et al., 1998; Johnson et al., 2000; Petitjean et al., 2001; Mattick et al., 2003; Digiusto et al., 2004; Giacomuzzi et al., 2003). These studies found that there were no serious adverse effects from buprenorphine treatment and that the frequency and severity of side effects was similar for both methadone and buprenorphine patients. Buprenorphine patients reported slightly better quality of life than methadone patients after 24 weeks of treatment (Giacomuzzi et al., 2003).

10. Summary of available data on comparative cost and cost-effectiveness

10.1 *Range of costs of proposed medicine*

The cost of buprenorphine per patient/year vary from USD\$300-600 for generic substance from BUFA B.V. (the Netherlands) to approximately USD\$1750-3500 from Rusan Pharma Ltd. (India) and Reckitt Benckiser Pharmaceuticals Inc. (USA) for an average dose per patient/day of 8mg to 16mg for the lower and upper dollar figure. These costs appears to be heavily influenced by an international pricing policy by the company holding a patent on buprenorphine in many countries. Buprenorphine combinations with naloxone are more expensive.

10.2 *Results of cost-effectiveness analysis*

In a comparator analysis, Barnett showed that buprenorphine may almost always be less cost-effective than methadone as a maintenance agent (Barnett et al., 2001). However, analysis of data from the largest randomised controlled trial of methadone to date (Mattick et al., 2003) showed no significant difference in cost-effectiveness when methadone was compared to buprenorphine (Doran et al., 2003). This latter article presents the cost-effectiveness of buprenorphine versus methadone in the management of heroin dependence. The trial used a flexible dosing regime that was tailored to the clinical need of the

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patients, with high maximum doses, using the marketed tablet formulation, under double-blind conditions. A total of 405 subjects were randomised to treatment at one of three specialist outpatient drug treatment centres. The costs included both direct patient costs and operating (facility) costs. The primary outcome measure used in the economic analysis was change in heroin-free days from baseline to the sixth month of treatment. Mean costs of methadone and buprenorphine treatment over a 6-month period were \$1,415 and \$1,729 respectively.

The incremental cost-effectiveness ratio of –\$201 per additional heroin free day in the sixth month implies that it cost \$201 more to achieve an additional unit of outcome for buprenorphine. However, while methadone was less costly than buprenorphine treatment, the difference in cost and cost-effectiveness of the treatments was not statistically significant. The data generated by this study provided evidence that the use of methadone and buprenorphine in the management of opioid dependence are equally cost-effective.

In withdrawal, buprenorphine delivered in specialist settings compared with GP or family physician delivered treatment showed similar cost-effectiveness (Gibson et al., 2003). Additionally, at least one analysis saw greater potential cost-effectiveness for buprenorphine/naloxone than methadone due to reduced costs of treatment delivery in certain settings compared with methadone (Rosenheck & Kosten, 2001). These authors suggested, at worst, equal cost effectiveness, but provided sensitivity analyses to suggest buprenorphine/naloxone had a greater cost-effectiveness ratio than methadone with mean costs of \$3211-\$6742 for buprenorphine compared with \$5927-\$8849 for methadone in the first year of treatment, and even greater cost-effectiveness than methadone in subsequent years (Rosenheck & Kosten, 2001).

To place the cost-effectiveness of buprenorphine maintenance in a context, it is relevant to understand the evidence on the cost-effectiveness of methadone. Methadone is a cost-effective option. For instance, Goldschmidt reported methadone maintenance to be as effective as a therapeutic community intervention, but with cost of providing methadone one-quarter the cost of therapeutic communities, methadone treatment was found to be twice as cost-effective (Goldschmidt, 1976). More recently, a cost-effectiveness analysis of methadone maintenance treatment using life-years of survival (Barnett, 1999) has showed an incremental cost-effectiveness ratio of \$5915 per life year saved. This study included all costs of treatment provision in the analysis, based on a separate analysis of costs from 600 methadone maintenance programs. Subsequently, Barnett and Hui drew on this earlier work and have found that methadone maintenance treatment to be cost-effective with an incremental cost-effectiveness ratio of less than \$1100 per quality-adjusted life year. They reported this ratio to be more cost-effective than many widely used medical therapies (Barnett & Hui, 2000). Additionally, they found the use of low doses of methadone were less cost-effective than adequate doses and that short episodes of methadone treatment of less than six months are not likely to be cost-effective compared to other options.

Taken together, the evidence suggests that buprenorphine is more costly than methadone to purchase as a medication, but it is a cost-effective option for the management of opioid dependence within a maintenance program operated over sufficient duration to achieve health gains and drug-free lifestyle.

11. Summary of regulatory status of the medicine

Buprenorphine is defined as a psychotropic drug under international control in the United Nations Drug Control Conventions of 1961, 1971 and 1988 and is included in Schedule III of the 1971 International Convention on Psychotropic Drugs. In the UK, buprenorphine is classified as a Schedule 3

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drug under the Misuse of Drugs Regulations 1985 and is approved for instalment prescribing (i.e. daily dispensing) for the treatment of drug dependence (Department of Health, 2001). In Australia, buprenorphine is classified as a Schedule 8 (controlled) drug and is licensed for detoxification and maintenance treatment for opioid dependence. In the USA, buprenorphine is classified as a Schedule III Narcotic under the Controlled Substances Act and is approved for use in office-based opioid substitution treatment (Department of Justice Drug Enforcement Administration, 2002; Resnick, 2003).

Australia and the USA are examples of countries with strict regulation of buprenorphine prescribing. In Australia, buprenorphine can only be prescribed by authorized prescribers and drug users receiving prescriptions must be registered with a central authority. Regulations also include training for prescribers, specific criteria for entry to BMT, supervised dosing and regular attendance at the dispensary, regular urine checks, and limitations on take-away doses (Lintzeris et al., 2001). In the USA, access to buprenorphine was extended beyond accredited drug treatment programmes to private medical practitioners in office based practice in 2002. Physicians intending to prescribe buprenorphine must notify the central regulatory authority that they have completed a training course, undertake to treat no more than 30 opioid dependent patients and to refer suitable patients for psychosocial therapy (Resnick, 2003). US model policy guidelines also specify requirements for assessment, record keeping, informed consent, treatment monitoring, and adjunct treatments (Centre for Substance Abuse Work Group, 2002).

There is considerable variation in Europe in the regulation of buprenorphine treatment. France has the least restrictive regulation of buprenorphine and has allowed all registered medical doctors to prescribe buprenorphine without special license or education since 1995 (Auriacombe et al., 2004) while in a number of other countries (e.g. Denmark, Finland, Greece, Norway, Sweden, Netherlands, and Portugal) buprenorphine prescribing is restricted to specialised treatment services. In some of those countries limitations are also placed on the number of patients who can receive buprenorphine maintenance treatment (EMCDDA, 2002).

12. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

Buprenorphine hydrochloride

OS: *Buprenorphine Hydrochloride USAN*

IS: *CL 112302 (Lederle, USA), NIH 8805, RX 6029-M (Reckitt & Colman, Great Britain), UM 952*

PH: *Buprenorphine Hydrochloride Ph. Eur. 3, USP 24*

PH: *Buprenorphinehydrochloride Ph. Eur. 3*

PH: *Buprénorphine(chlorhydrate de) Ph. Eur. 3*

Formulations of buprenorphine

- Buprenorphine Hydrochloride, Sublingual Tablets ^{a,b}
- Buprenorphine Hydrochloride Combinations (with Naloxone Hydrochloride), Sublingual Tablets
 - ^a US Pharmacopoeia
 - ^b British Pharmacopoeia

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13. Proposed text for the WHO Model Formulary

Buprenorphine hydrochloride

Drug subject to international control under the Convention on Psychotropic Substances (1971)

Sublingual Tablets, buprenorphine hydrochloride 2 mg, 8 mg

Uses: detoxification and maintenance therapy in opioid dependence; therapy of opioid withdrawal state.

Contraindications: acute respiratory depression; known hypersensitivity to buprenorphine.

Precautions: severe impairment of hepatic or pulmonary function; increased intracranial pressure; myxedema or hypothyroidism, adrenocortical insufficiency; CNS depression, toxic psychoses; severe inflammatory bowel disease, prostatic hypertrophy or urethral stricture; renal impairment (Appendix 4); **interactions:** Appendix 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving, especially during induction phase and dose adjustment.

When the fixed combination preparation containing buprenorphine and naloxone is used, the usual precautions and contraindications associated with naloxone should be considered.

Overdosage: naloxone may not be effective in reversing any respiratory depression produced by buprenorphine, and the primary management should be re-establishment of adequate ventilation with mechanical assistance or respiration, if required.

Dosage: Doses should be titrated according to the patient's experience of withdrawal severity, cravings, adverse effects and other drug use. For *management of opioid withdrawal state*, start with 4-8 mg a day, *sublingually*, with subsequent reduction of dosage by 1-4 mg over four to ten days. For *detoxification* from buprenorphine stabilisation or maintenance, a slower dose reduction regime should be used over several weeks.

For *maintenance therapy* of opioid dependence. *Induction phase:* initial dose of buprenorphine hydrochloride, *sublingually*, 2-8 mg a day. The recommended starting dose is 4 mg in the morning with the option to administer an additional 2-4mg later in the day. Patients should be carefully monitored during this time and should be observed daily for signs of intoxication or withdrawal. *Stabilisation phase:* patients should be reviewed regularly for the first few weeks of treatment and the dose adjusted as indicated with recommended dose increments of 2-4mg per day. *Maintenance phase:* doses should be determined for individual patients but generally a higher dose is required for maintenance than is required for initial stabilisation. Effective maintenance doses, which reduce heroin use and improve treatment retention are typically achieved with buprenorphine doses in the range 12-24 mg/day. The **effects:** respiratory depression; anorexia, nausea, vomiting (particularly in initial stages), constipation; euphoria, hallucinations, dizziness, drowsiness, confusion, insomnia, headache; dry mouth, spasm of urinary or biliary tract; hypotension, postural hypotension, vertigo, bradycardia,

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tachycardia, palpitations, headache, sweating, miosis, hypothermia; decreased libido; rash, facial flushing, urticaria, pruritus.

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Appendix 1 – Outcome of buprenorphine maintenance (using the liquid ethanol-based solution) compared with methadone maintenance in opioid dependence

Study	Subjects	Treatment conditions	Treatment duration and dosing details	Outcome for opioid abuse	Retention in treatment
Bickel (1988)	45 male opiate addicts	1. buprenorphine 2 mg 2. methadone 30 mg	3 weeks maintenance and 4 weeks reduction with fixed doses	No between-group difference	No between-group difference
Johnson et al. (1992)	162 patients seeking treatment for opioid dependence	1. buprenorphine 8 mg 2. methadone 20 mg 3. methadone 60 mg	120 days maintenance 60 days dose reduction/ placebo with fixed doses	1. 47% urines positive 2. 71% urines positive 3. 56% urines positive	1. 30% retained 2. 6% retained 3. 20% retained
Kosten et al. (1993)	125 opioid dependent patients	1. buprenorphine 2 mg 2. buprenorphine 6 mg 3. methadone 35 mg 4. methadone 65 mg	24 weeks with fixed doses	1. & 2. 49% urines positive 3. & 4. 73% urines positive 1. & 2. 27% abstinent 3. & 4. 65% abstinent	Methadone (20 weeks) had better retention than buprenorphine (16 weeks)
Strain et al (1994a)	164 opioid dependent patients	1. buprenorphine 8.9 mg 2. methadone 54 mg	26 weeks flexible dose study	No between-group difference	No between-group difference
Strain et al (1994b)	51 opioid dependent patients	1. buprenorphine 11.2 mg 2. methadone 66 mg	26 weeks flexible dose study	No between-group difference	No between-group difference
Ling et al. (1996)	225 opioid dependent patients	1. buprenorphine 8 mg 2. methadone 30 mg 3. methadone 80 mg	24 weeks with fixed doses	3. > 1. or 2. in reducing illicit opioid use and cravings	3. > 1. or 2. in retaining patients in treatment
Schottenfeld et al. (1997)	116 patients who had used heroin for 6-7 years	1. buprenorphine 4 mg 2. buprenorphine 12 mg 3. methadone 20 mg 4. methadone 65 mg	24 weeks with fixed doses	1. 77% urines positive 2. 58% urines positive 3. 72% urines positive 4. 45% urines positive	No significant between group differences in retention
Olivetto et al. (1999)	180 opioid dependent cocaine abusers	1. buprenorphine 12 mg 2. methadone 65 mg	13 weeks with fixed doses	Opioid abstinence increased faster with methadone than buprenorphine	No significant between group differences in retention
Johnson et	220 opioid	1. buprenorphine	17 weeks thrice	1., 3, and 4. > 2.	1., 3, and 4. > 2: -

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al. (2000)	dependent patients	16-32 mg 2. methadone 20 mg 3. methadone 60-100 mg 4. LAAM 75-115mg	weekly buprenorphine, daily methadone and thrice weekly LAAM within dose ranges shown	in reducing illicit opiate use	1. 96 days on average 2. 70 days on average 3. 105 days on average 4. 89 days on average
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Appendix 2 – Outcome of buprenorphine maintenance (using a marketed tablet) compared with methadone maintenance in opioid dependence

Study	Subjects	Treatment conditions	Treatment duration and dosing details	Outcome for opioid abuse	Retention in treatment
Fischer et al. (1999)	60 opioid dependent patients	1. buprenorphine 8 mg 2. methadone no upper limit on daily dose	24 weeks flexible dosing of methadone, but fixed buprenorphine doses	No between-group difference	1. 38% retained < 2. 71% retained
Uehlinger et al. (1998)	58 opioid dependent patients	1. buprenorphine 16 mg 2. methadone 120 mg	Six weeks with 16 mg and 120 mg maximum doses	No between-group difference	1. 50% retained < 2. 90% retained
Pani et al. (2000)	72 opioid dependent patients	1. buprenorphine 2 mg 2. methadone 60 mg	Six months with fixed doses	No between-group difference	1. 47% retained = 2. 64% retained
Mattick et al (2003)	405 opioid dependent outpatients	1. buprenorphine 10.1 mg 2. methadone 52.1 mg	13 weeks flexible dose study, with alternate day dosing of buprenorphine	No between-group difference	1. 52% retained < 2. 58% retained
Ahmadi et al. (2003)	204 male opioid dependent patients	1. buprenorphine 5 mg 2. methadone 50 mg	24 weeks flexible dose study	No between-group difference	1. 59% retained < 2. 84% retained
Gerra et al. (2004)	154 patients with severe heroin addiction	1. buprenorphine 9.2 mg 2. methadone 81.5 mg	12 weeks flexible dose study	1. 25.6% positive < 2. 32.1% urines positive for illicit opioid use	1. 61.5% retained = 2. 59.2% retained

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**Appendix 3 – Outcome of buprenorphine maintenance compared with placebo
maintenance in opioid dependence**

Study	Subjects	Treatment conditions	Treatment duration and dosing details	Outcome for opioid abuse	Retention in treatment
Johnson et al. (1995)	150 opioid dependent patients	1. buprenorphine 2 mg 2. buprenorphine 8 mg 3. placebo	2 weeks fixed dosing of buprenorphine or placebo	1. & 2. > 3., using less illicit opioids than placebo participants	1. & 2. = 78% retained < 3. 67% retained
Fudala et al. (1998)	326 opioid dependent patients	1. buprenorphine 16 mg 2. buprenorphine/nlx 16 mg 3. placebo	Four weeks fixed dosing of buprenorphine or placebo	1. 82% urines positive 2. 79% urines positive 3. 96% urines positive	Study terminated early due to poor performance of placebo patients
Kakko et al. (2003)	40 opioid dependent patients	1. buprenorphine 16 mg 2. placebo	12 months	1. 25% urines positive 2. not stated, but presume ongoing drug use; & 4 placebo patients died compared with no deaths in the buprenorphine group	1. 75% retention 2. 0% retention at 12/12

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