NACD

National Advisory Committee on Drugs

Report to the National Advisory Committee on Drugs on

Use of **Buprenorphine** as an intervention in the treatment of **Opiate Dependence Syndrome**

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"Use of Buprenorphine as an intervention in the treatment of Opiate Dependence Syndrome"

from the Working Party,
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Appendicies

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Glossary

ADRs	Adverse Drug Reactions
ALT	Alanine Transferase
AST	Aspartame Transferase
BPN	Buprenorphine
CI	Confidence Interval
Clon	Clonidine
db	double blind
dd	double dummy
EMCDDA	European Monitoring Centre for Drugs & Drug Addiction
ERHA	Eastern Regional Health Authority
EU	European Union
FDA	Food & Drug Administration
GP	General Practitioner
Hep C	Hepatitis C
I/V	Intravenous
I/M	Intramuscular
LAAM	Levo-alpha-acetyl-methadol
Meth	Methadone
Nalt	Naltrexone
NAS	Neonatal Abstinence Syndrome
NIDA	National Institute on Drug Abuse
NDA	New Drug Application
NDTRS	National Drug Treatment Reporting System
ns	not significant
OPPIDUM	Observation of Illegal Drugs & Misused Psychotropic Medications
RCT	Randomised Controlled Trial
S/L	Sublingual
SPC	Summary of Product Characteristics
SPESUB	Suivi Pharmaco-epidemiologique du Subutex®
SSRIs	Selective Serotonin Reuptake Inhibitors

Executive Summary

The physical, psychological and social implications of opiate dependency are well known. A variety of treatment approaches, including behavioural therapy, social skills and stress management have been used. The pharmacotherapeutic approach, using methadone maintenance therapy, has proved most beneficial to date and is the mainstay of treatment in the Irish setting.

A systematic review was undertaken in order to evaluate the potential usefulness of buprenorphine as an intervention in the treatment of opiate dependency. All available data were retrieved by means of a comprehensive search of the published literature and clinical trials databases. Authors of pivotal studies were contacted for further information, for inclusion in a meta analysis. Contact was made with experts in the UK and France, to evaluate the practical issues associated with buprenorphine in a clinical setting. Pharmacoeconomic data were retrieved from the GMS, ERHA and the manufacturer for the purposes of analysis.

The results of the clinical trials evaluation showed that buprenorphine appeared to have potential in the management of opiate dependence. It was shown to be at least as effective as other treatment regimens (clonidine and lofexidine) in treating managed opiate withdrawal (detoxification). Buprenorphine (at doses of ›8mg/day) was as effective as methadone as a maintenance treatment option. It was not possible to define the optimal dosage regimen for either indication, but treatment appeared to be most effective when dosage was titrated to the individual's needs. Because of its pharmacological profile, less than daily dosing (e.g. thrice weekly) is a possible dosing option.

Evaluation of its use in clinical practice showed that it was considered as effective as methadone for maintenance treatment, had a better safety profile but had more abuse potential. Accordingly, supervised dispensing was recommended by many experts, especially in the early months of treatment. Experience of its use in managed opiate withdrawal was more limited but was also favourable.

The review suggests that buprenorphine may be viewed as an effective treatment option in the management of opiate dependence syndrome, with an acceptable safety profile.

Chapter 1

Introduction

Opiate derivatives, including heroin, opium and morphine became available on the European illegal drug markets from the late 1960s. Illicit opiate use increased during the 1970s and became a major problem in the 1980s, because of its association with the HIV/AIDS epidemic (Farrell et al, 2000).

Current EU figures for problem drug use (defined as injecting drug use or long-duration/regular use of opiates, cocaine and/or amphetamines) range from 2-3:1,000 to 5-8:1,000 inhabitants, aged between 15 and 64 years (EMCDDA, 2001). Ireland's rate is intermediate at 3-5:1,000. Heroin is the main substance of problem drug use in the EU (National Drugs Strategy, 2001).
It is estimated that about one quarter of people who have ever used heroin develop dependence (Ward et al, 1999).

Many countries have introduced drug treatment programmes. However, the nature and extent of these programmes vary considerably from country to country. In 2000, it was estimated that over 300,000 drug users in the EU were receiving substitution treatment, compared with 110,000 in the USA and 20,000 in Australia (Farrell et al, 2000).

Methadone substitution is the most widely available maintenance treatment. There are, however, certain disadvantages associated with methadone therapy, including (a) the risk of fatal respiratory depression in overdose, because of its full agonist properties (b) the inconvenience of daily dosing and daily attendance at clinics, which makes it unattractive to some patients and (c) the risk of diversion of take-away doses (Mattick et al, 1998). Levo-alpha-acetyl-methadol (LAAM) has been used in several EU countries and in the USA in recent years. It has the advantage of thrice weekly dosing. However, in 2001, the EU Committee for Proprietary Medicinal Products (scientific committee of the European Medicines Evaluation Agency – EMEA) suspended the marketing authorisation for LAAM, on safety grounds (EMEA Public Statement, 2001).

Buprenorphine was introduced into the maintenance treatment programmes of several EU countries since 1996 and France, in particular, has extensive clinical experience with its use in both primary care and specialist clinic settings. Other agents, such as heroin and slow release morphine have been used, under trial conditions only, in some countries.

Illicit opiate use became a public health problem in Dublin in the early 1980s. Methadone treatment was available during the l980s but only in a limited fashion. Following a series of government initiatives in the 1990s, the availability of methadone maintenance treatment was extended (Barry, 2000). The Drug Misuse Research Division of the Health Research Board is responsible for operating the National Drug Treatment Reporting System (NDTRS), which is the main source of information on drug misuse in Ireland. In its statistical bulletin for 1997 and 1998 (NDTRS, 2000), it noted that 85% of all clients receiving treatment for drug misuse were in the former Eastern Health Board area and of these, heroin was the main drug of misuse in approximately 70% of cases.

As of December 2000, 5,032 individuals were registered on the Central Drug Treatment List (which is compiled by the Eastern Regional Health Authority and is the only methadone maintenance register at present) to avail of methadone maintenance therapy (National Drug Strategy, 2001). The figure for the end of February 2002, was 5,958 (personal communication, Central Drug Treatment List). This constitutes a large treatment cohort and therefore any initiative, which would improve or extend availability of treatment, would be of benefit.

In June 2001, Mr Eoin Ryan, the Minister of State for Local Development with special responsibility for the National Drugs Strategy, asked the National Advisory Committee on Drugs (NACD) to undertake "research on the effectiveness of buprenorphine as a form of treatment for opiate addiction". As a result, the NACD commissioned this review.

This review will evaluate the usefulness of buprenorphine as an intervention in the treatment of opiate dependence syndrome, in terms of effectiveness, safety in use, and practical and pharmacoeconomic implications. Where appropriate, comparison will be made with methadone, the mainstay of treatment, in order to more clearly define its potential role in the Irish setting.

Chapter 2

Aims and Objectives of the Review

The aim of this review was to evaluate the effectiveness of buprenorphine as an intervention in the treatment of Opiate Dependence Syndrome.

The objectives of the review were to

1. identify all sources of information (both published and unpublished) relating to buprenorphine and in particular to its use in the management of opiate dependency,
2. retrieve all relevant information for the purposes of formal evaluation, including those in languages other than English,
3. undertake a review of the pharmacology of buprenorphine, including its potential for interaction, using both preclinical and clinical data,
4. undertake a systematic review and if possible, formal meta-analysis of the clinical trials, which evaluate the efficacy of buprenorphine, in the management of opiate dependency,
5. evaluate the safety of use of buprenorphine, including the abuse potential, using data from preclinical and clinical studies and from real life usage,
6. investigate the usefulness of buprenorphine in certain sub-groups of opioid-dependent subjects, including its potential use during pregnancy,
7. undertake a pharmacoeconomic analysis to evaluate the cost-benefit of use of buprenorphine in the management of opiate dependence syndrome and,
8. assess the implication of the use of buprenorphine as an intervention in the treatment of opiate dependence in Ireland.

Chapter 3

Research Methodology of the Review

Primary and review articles, abstracts and other published information on buprenorphine were identified using the following sources –

- Medline, Pharmline, Micromedex, Iowa Drug Information Service, (computerised indexing and retrieval systems)
- Inpharma, Drugs and Therapy Perspectives (abstracting and current awareness publications)

Review journals (such as Drugs) and reference textbooks (Martindale 32nd edition, "Pharmacological Basis of Therapeutics" Goodman and Gilman 10th Edition) were also searched for background pharmacology.

Clinical Trials registers in the UK and USA (www.controlled-trials.com; www.clinicaltrials.gov) were searched to get information on ongoing studies with buprenorphine, and the manufacturer was asked to provide (a) all adverse drug reaction data collected from post-marketing surveillance studies in order to evaluate the safety profile with real life usage and (b) information on pre-clinical studies from the drug development dossier.

The search terms used were as follows – buprenorphine, opiate, opioid, addiction, therapeutic, maintenance, withdrawal, methadone and heroin. These were employed separately and in combination with one another. The reference lists of relevant articles and reviews were examined for further reports.

No time limit was put on the earliest date for acceptability of data and studies were evaluated from 1978 onwards. The data lock point for inclusion in the review was the 31st December 2001. Articles that became available after that time were taken into account if they were judged to provide additional information, which might influence the outcome of the review.

Once identified, all papers were evaluated for relevance to the review. Papers in languages other than English were included if they were considered to be relevant to the review.

Data from randomised controlled clinical trials were pooled and included, if appropriate, in a meta analysis to compare the efficacy of sublingual buprenorphine with oral methadone in the management of opiate dependence. A meta analysis is a statistical technique for combining the results of independent studies, to present an objective and quantitative measure of effectiveness of an intervention. It reduces the chances of Type II errors by pooling the data across several smaller studies and therefore increases the confidence with which the efficacy of an intervention can be assessed (Sutton et al, 1999; Chalmers & Altman, 1995).

The data were systematically reviewed to determine the optimal dosing regimen for buprenorphine and to see if it might be more effective for specific sub-groups of patients. Safety was assessed using preclinical data as well as pharmacovigilance data from clinical usage.

Articles, reviews and other papers relating to the economic impact of buprenorphine were retrieved for evaluation. The manufacturer was asked to provide data on pharmacoeconomics relating to its specific product Subutex®. Information on current cost estimates for the treatment of opiate dependence was sought from the Eastern Regional Health Authority (ERHA) and the General Medical Services (GMS). These data were used in the pharmacoeconomic evaluation.

Finally, in order to identify the practicalities of use of buprenorphine, healthcare professionals, experienced in the use of buprenorphine for the management of opioid dependence, were identified in the UK, France and Australia and contacted for further specific data on the advantages and disadvantages of buprenorphine use in clinical practice.

Chapter 4

Review of Clinical Pharmacology

4.1 Introduction

Buprenorphine hydrochloride (Subutex®, Buprenex®, Temgesic®) C_{29} H_{41} NO_4. HCL.

[5α, 7α, (S) – 17 – (Cyclopropylmethyl) –α– (1,1-dimethylethye) – 4, 5 – epoxy – 18, 19 – dihydro – 3 – hydroxy-6 – methoxy – L – methyl – 6, 14 – etheno – morphinan – 7 – methanol.

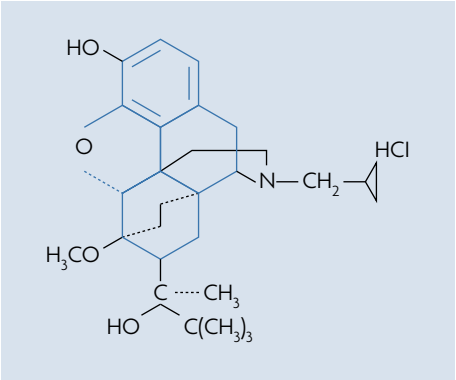


Figure 1

Buprenorphine is a partial opiate agonist analgesic. It acts as a partial agonist at the opioid μ receptor, which mediates analgesia, respiratory depression and reduced gastrointestinal motility. It acts as an antagonist at the k opiate receptors. As a partial agonist, buprenorphine displays a bell shaped dose response curve, with subjective opiate-like effects reaching a maximum at a dose of about 1mg (subcutaneously) in man (Heel et al, 1979). Experimental evidence suggests a ceiling on the ability of the drug to depress the respiratory system following overdose, which may reflect a combination of extensive drug metabolism and the basic pharmacology outlined above. Walsh et al (1994) administered single sublingual doses of up to 32mg buprenorphine (equivalent to 1000mg of oral methadone) to non-opioid dependent volunteers and noted only marginal effects on respiratory function, as measured by respiratory rate and oxygen saturation. This represented a dose of 70 times the recommended analgesic dose at the time. This supported the safety of buprenorphine.

Buprenorphine associates with opioid receptors slowly but with high affinity and dissociation from the receptor site is (pseudo) irreversible (Lewis, 1985). Therefore, its effects may be prolonged with potential implications in relation to frequency of administration e.g. alternate days. The study by Walsh et al outlined above (1994) recorded plasma levels comparable to "therapeutic" maintenance levels (8mg/day) at 96 hours, after the 32mg dose. Furthermore some of the opioid agonist effects (such as pupillary constriction) also lasted for 48 – 96 hours, in a dose-related manner. This supported the feasibility of less than daily administration as the lower toxicity noted with buprenorphine allowed for the administration of larger doses, which would have a long duration of action. The tight binding also makes it difficult for opioid antagonists to displace buprenorphine. However, since the opioid effect of respiratory depression is relatively mild with buprenorphine, it is safer than other opioid full agonists such as methadone. The tightness of binding is thought to be one of the possible reasons for the low level of withdrawal symptoms, associated with the abrupt discontinuation of chronic administration of buprenorphine, when compared with other opioids. However, its partial agonist properties may also be involved in this phenomenon.

4.2 Pharmacokinetics

Pharmacokinetics may be defined as the study of the time course of absorption, distribution, metabolism and excretion of drugs. It is essential to consider the pharmacokinetic profile of buprenorphine, as this may have potentially clinically relevant implications in the area of drug interactions.

4.2.1 Absorption

After oral administration, buprenorphine is relatively ineffective because there is an efficient first-pass metabolism by the liver. However, it is reasonably well absorbed sublingually – the absolute bioavailability of buprenorphine from a sublingual solution dose

in ethanol was recorded at approx 30% by Mendelson et al (1997). This study, undertaken in healthy volunteers, also noted equivalent bioavailability for 3 and 5 minutes sublingual exposure to the ethanol solution. It is estimated that absorption from the oral route is 15% of that from the sublingual route.

Although most of the studies reported in the Clinical Trials Section (see Chapter 5) used an ethanol solution for sublingual administration, buprenorphine has been formulated into a tablet for sublingual use for commercial presentation. Schuh and Johanson (1999) compared plasma concentrations after doses of 2, 4, 8mg buprenorphine solution and the 8mg tablet. Each dose was administered to 14 opioid dependent patients for a total of 7 days, at a time. Blood samples were collected over the next 3 days, before changing to the next dosage regimen. Although there was considerable individual variability, the mean plasma concentrations were significantly lower for the 8mg tablet than those of the 8mg solution at the 120 minute time point. The plasma concentrations produced by the 8mg tablet were 55% of those produced by the 8mg solution. Similar results were reported by Nath et al (1999). Finally, workers have noted that the buprenorphine tablet is easily crushed and injected and therefore has the potential for abuse (Mattick et al, 1998).

4.2.2 Metabolism (including drug interaction)

The metabolism of buprenorphine is shown in Figure 2.

Patients prescribed buprenorphine are likely to receive other medications, therefore it is important to consider the issue of drug interactions. There are few data in the literature documenting formal pharmacokinetic studies with buprenorphine. However, knowledge of its kinetic profile may help to identify potential drug interactions.

The two main routes of metabolism include glucuronidation to buprenorphine 3-0-glucuronide (80-90%) and N-dealkylation to N-dealkyl buprenorphine (10-20%). Although the N-dealkylation pathway represents less than

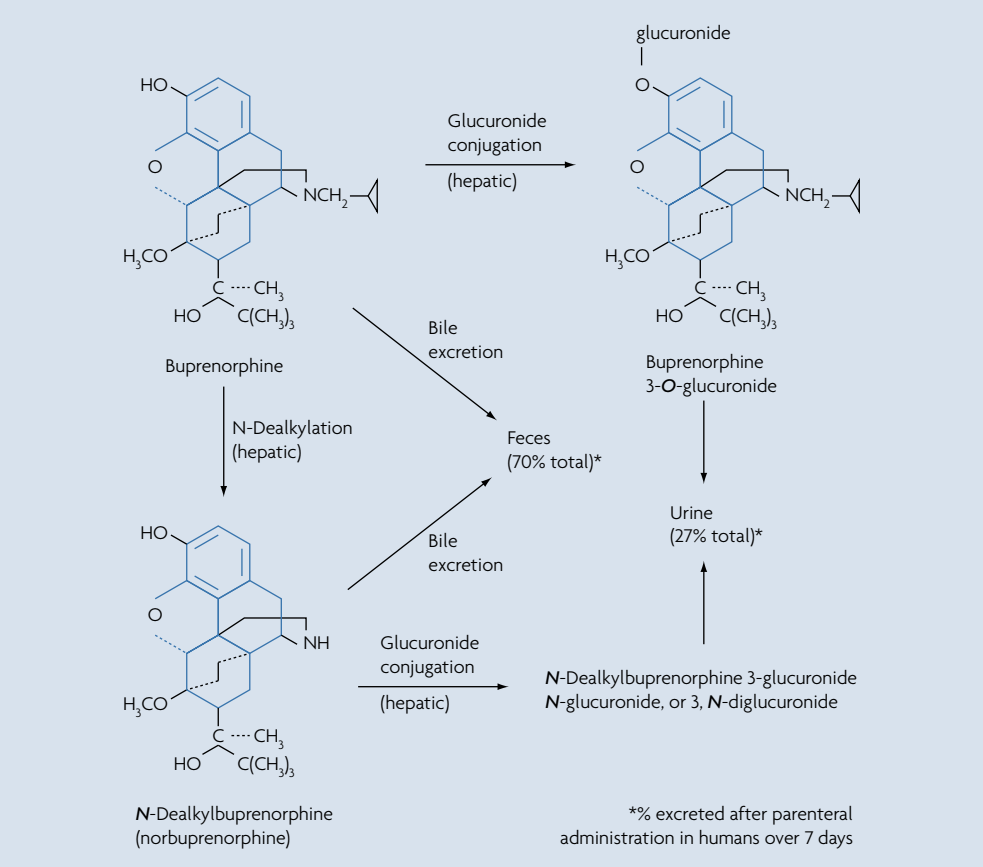


Figure 2: Metabolism of buprenorphine

20% of the metabolism it is important to note that this pathway is mediated by cytochrome P450 3A4. As this enzyme is involved in the oxidative metabolism of over 50% of the drugs used in humans the potential for drug interactions is evident. The combination of buprenorphine and benzodiazepines has resulted in respiratory depression (see Chapter 6, Drug Safety). This results from a pharmacodynamic and possibly a pharmacokinetic interaction. Therefore, buprenorphine should be used with caution in the presence of benzodiazapines. Review of their kinetic profiles suggests that certain benzodiazepines are more likely to interact e.g. lorazepam, temazepam and oxazepam and therefore these may be best avoided. In addition, caution is advised when co-prescribing neuroleptics where the potential for interaction may result from a pharmacodynamic and/or pharmacokinetic mechanism.

Drugs such as haloperidol, chlorpromazine, pimozide and clozapine are metabolised by similar enzymes mediating buprenorphine metabolism i.e. cytochrome P450 3A4 and glucuronyl transferase (GT). Potential interactions may also result from combination with some of the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac®) and fluvoxamine (Faverin®), which inhibit CYP3A4 and sertraline (Lustral®), which is metabolised by this enzyme. Citalopram (Cipramil®) and paroxetine (Seroxat®) are less likely to interact, however all SSRIs may potentiate the central nervous system depressant effects of buprenorphine.

Some tricyclic antidepressants amitriptyline, desipramine, imipramine and clomipramine are metabolised by CYP 3A4 and GT hence the potential for interaction. Nortriptyline and dothiepin are less likely to result in a kinetic interaction but all of these drugs have the potential to enhance the central depressant effects of buprenorphine through a pharmacodynamic mechanism. Other agents that enhance the central nervous system depressant effects of buprenorphine include other opioid derivatives, sedative H_1 receptor antagonists, clonidine and related substances. Monoamine oxidase inhibitors (MAOIs) may also exaggerate the effects of buprenorphine. Injection drug use is the more common risk factor for the acquisition of HIV infection in Ireland, with drug users representing 42% of the total HIV positive cohort (HIV/AIDS Statistics, 1999). Drugs used in the treatment of HIV disease and associated opportunistic infections may interact with buprenorphine. With respect to anti-HIV drugs, the nucleoside analogues are unlikely to interact with the exception of zidovudine (AZT). As both drugs are metabolised predominantly by glucuronidation, buprenorphine could potentially increase the toxicity of AZT by inhibiting its metabolism (and vice versa).

The potential interactions with the second group of anti-HIV drugs – the non-nucleoside reverse transcriptase inhibitors e.g. nevirapine, efavirenz and delavirdine – are complex. Nevirapine and efavirenz are potent enzyme inducers and might be expected to increase buprenorphine metabolism thereby reducing its efficacy. Delavirdine may inhibit buprenorphine metabolism and therefore enhance its toxicity. The third group of anti-HIV drugs includes the protease inhibitors ritonavir, saquinavir, indinavir, nelfinavir and amprenavir. These drugs inhibit CYP 3A4 and therefore would be expected to increase buprenorphine levels. As ritonavir is a potent enzyme inhibitor, affecting the function of many isoenzymes, it should not be prescribed with buprenorphine until more data are available.

Drugs used in the treatment of opportunistic infections may also interact with buprenorphine. The macrolide antibiotics erythromycin and clarithromycin inhibit CYP 3A4 but azithromycin would not be expected to inhibit this enzyme and therefore would be the drug of choice. Similarly, the azole antifungal agents inhibit CYP 3A4 e.g. ketoconazole, intraconazole and to a lesser extent fluconazole. Enzyme inducing drugs will enhance buprenorphine metabolism and therefore reduce its efficacy. Recognised inducers are phenytoin, carbamezapine and phenobarbitone (anticonvulsants) and the antituberculous agent rifampicin.

To date, there are no reports of a significant interaction with cocaine, one of the agents most frequently used by polydrug users in association with opioids. This is likely due to the fact that cocaine is metabolised by different enzymes i.e. hydrolysis by serum

and hepatic pseudocholinesterase (90%) and hepatic N-demethylation. Ecstasy (MDMA) is metabolised by CYP 2D6, which is not involved in buprenorphine metabolism. Acute alcohol intake may impair the metabolism of buprenorphine, in addition to the enhancement of the central depressant effects, therefore acute alcoholism is a contraindication, as is delirium tremors.

The situation is further complicated by the incidence of hepatitis C co-infection in this patient population, which may be as high as 90% (Smyth et al 1995). The long-term treatment of choice for hepatitis C involves combination therapy with ribavirin and interferon. Although formal interaction studies have not been completed it is unlikely that a significant interaction between these drugs and buprenorphine would occur.

Finally, the presence of liver disease may be expected to alter buprenorphine kinetics. The metabolism of morphine (also glucuronidated) is altered significantly in the presence of hepatic cirrhosis where clearance may be reduced by 60%. Therefore caution is required when prescribing buprenorphine in the presence of liver disease. Frequent monitoring of liver function tests is advisable in view of the reported increase in AST and ALT following the introduction of buprenorphine therapy. Severe hepatic insufficiency is a contraindication to buprenorphine use (see Chapter 6).

4.2.3 Elimination

The main pathways of elimination include biliary excretion, hepatic glucuronidation and N-dealkylation. Elimination also occurs via the urine. In single dose studies, most of the dose (50 – 70%) was eliminated in the faeces over the first 4 days. Both unchanged drug and metabolites were detected (Walter and Inturrisi, 1995).

4.3 Preclinical studies

Buprenorphine has been evaluated in a number of standard rodent assays, which confirmed its dual agonist – antagonist activity, characteristic of a partial agonist (Rance, 1979). In terms of pharmacokinetic evaluation, the oral bioavailability in the dog was low (mean 7.4%) but parenteral administration gave better results – 70% bioavailability after intramuscular administration in the baboon (Walter and Inturrisi, 1995). The sublingual route gave a bioavailability of 30-50% of the dose (thought to reflect the human situation) but was slower compared to the parenteral routes.

Buprenorphine was widely distributed after absorption (Heel et al, 1979). Brain levels were higher than plasma levels at all time points in the rat. Only unchanged buprenorphine was present in the brain. In studies, in pregnant rats, radioactivity readily reached the placenta following oral parenteral dosing of radiolabelled buprenorphine. It appeared to accumulate in the foetal gastrointestinal human, thought to be due to biliary excretion, in the absence of a developed entero-hepatic circulation.

Excretion in the rat, dog and rhesus monkey was primarily via the faeces, following biliary excretion of conjugated unchanged drug and metabolites. Small amounts were noted in the urine (Walter and Inturrisi, 1995). A study in rats, using radiolabelled buprenorphine administered intramuscularly showed that drug-related material was excreted in the milk of rats and that concentrations of unchanged buprenorphine in milk were at least equal to that in plasma (Heel et al, 1979).

A series of animal toxicological studies was undertaken with buprenorphine by the manufacturer in the 1970s, when it was being developed as an opioid analgesic temgesic®. These included acute and chronic dose administration studies, reproduction toxicological studies and carcinogenicity studies. The findings showed no major tissue or biochemical toxicity after continuous subcutaneous administration for periods of up to 6 months (SPC, 2001). However injection site reactions were noted in many studies. It was found to be non-carcinogenic in mice after 86 weeks of administration, in rats after 99 weeks of administration at dosages of up to 2mg/kg/day. (unpublished data – company report 1997). The proposed sublingual dose range of buprenorphine for the management of opioid dependence is 2mg-32mg/day. This corresponds to 0.03mg/kg-0.45mg/kg per day, based on a 70kg man. There was no apparent effect on fertility and no teratogenicity in rats and rabbits but there was a slightly increased risk of parturition difficulties and increased neonatal mortality at the 5mg/kg/day dosage (Heel et al, 1979) probably due to maternal toxicity.

4.4 Summary and conclusions

Buprenorphine has been shown to be a partial opioid agonist. Its metabolic pathway suggests that there might be difficulties with drug interactions either with co-prescribed medications or co-administered illicit drugs. The clinical relevance of this will be discussed in the following sections. An extensive battery of tests has been undertaken in several animal species, evaluating the pharmacological and toxicological profiles of buprenorphine. Many of these were undertaken by the manufacturer in support of its application to license buprenorphine as an analgesic in the 1970s. Results show that buprenorphine's pharmacodynamic and pharmacokinetic profiles are consistent across animal species and are similar to those seen in man. The toxicological studies show an acceptable margin of safety for use of buprenorphine in the management of opioid dependence

Chapter 5

Review of Clinical Studies with buprenorphine

5.1 Use of buprenorphine for the management of opioid withdrawal

Managed opioid withdrawal (detoxification) is thought to be an important component of an effective treatment system for opioid dependency (Gowing et al, 2001). It is used to bring about drug-free status within a period of weeks/months. If used as a treatment entity in its own right, it is associated with a high rate of relapse once the "withdrawal" period is completed (Mattick & Hall, 1996). Therefore, it is usually used as part of a treatment programme. In those EU countries which have favoured drug-free treatment (as opposed to substitution treatment) programmes, detoxification is also associated with psychosocial/rehabilitation programmes (EMCDDA, 2001; Farrell et al, 2000). It may also be used as a first step for other forms of treatment or at the end of an extensive period of substitution therapy (Gowing et al, 2001).

There are no standard/established detoxification regimens and therefore review of the literature provides diverse information regarding medications used, regimens followed and patient management. The largest body of data comes from a systematic review undertaken by the Cochrane collaboration and published in 2001 (Gowing et al), which assessed the effectiveness of short-term use of buprenorphine in the management of the acute phase of opioid withdrawal. As with all Cochrane reviews, a thorough search of electronic databases, with subsequent retrieval of all relevant references was undertaken. It is not stated in the protocol what time limits were placed on the search, but it is noted that the references encompass a time period from 1982 up to 1999.

Studies were considered for the meta-analysis if (a) they were randomised or quasi-randomised controlled clinical trials or prospective controlled cohort studies, (b) they involved administration of buprenorphine over a short period (up to 10 days maximum) to ameliorate the signs and symptoms of opioid withdrawal and (c) they compared buprenorphine with another form of treatment or placebo.

It is important to mention that the cut-off point of 10 days was selected as it was judged by the reviewers to most accurately reflect the typical duration of the acute phase of opioid withdrawal. Studies, which were not suitable for inclusion in the formal meta-analysis, were also considered if they provided information not available in the meta-analysis studies (e.g. data on subgroups). The outcomes to be measured in the meta-analysis were (1) intensity of signs and symptoms and overall withdrawal syndrome experienced, (2) duration of treatment, (3) completion of withdrawal and (4) nature and incidence of adverse effects. Because it might be difficult to differentiate between (1) and (4), the reviewers defined adverse effects as those typical of opioid withdrawal (such as vomiting and diarrhoea) and incidents not typical components of opioid withdrawal (such as hypotension and dry mouth).

The review also aimed to look at the influence of subgroups on the outcomes, the drug of dependence, severity of dependence, polydrug use, concurrent illness, effect of the treatment setting and adjunctive treatment (such as psychosocial counselling etc).

After an extensive search of the literature, together with contact with researchers in the particular area, a total of 22 reports covering 20 studies were identified. Five of the studies met all of the inclusion criteria for systematic review. Nine were excluded because they entailed administration of buprenorphine for more than 10 days (n=8) or provided limited data on the participants (n=1). The remaining studies were used to provide supplementary data. The studies included in the systematic review are summarised in Table 5.1

There was variability in the characteristics of participants in the five included studies in terms of numbers of injectors and employment rates. Moreover, two of the studies were judged to be subject to bias (small numbers, possibility of attrition bias).

Table 5.1: Studies included in the Cochrane systematic review of "Buprenorphine for the management of Opioid withdrawal", Gowing et al, 2001.

Study	Type	Numbers	Doses	Comparator	Result
Cheskin et al 1994	RCT/db	25 recruited (18 in analysis). All heroin users	BPN S/L 2mg/ dose to a max of 17mg over 3 days	Clon 0.3mg/dose to a max of 2.7mg over 5 days	Lower withdrawal symptoms & higher completion rates for BPN
Janiri et al 1994	RCT/db	39 (13 per group) 22 Meth users; 17 meth/heroin users	BPN 1/M 0.9mg days 1 + 2 and then 0.45mg on day 3 + 0.15mg on day 4	Clon 0.3-0.9mg/ day X 6 days or Lefetamine 60 – 240mg / day X 6 days	Withdrawal scores better with BPN. Completion rates equal for all groups
Nigam et al 1993	RCT	72 recruited (44 in analysis – 22 per group). 90% heroin users. Rest opium users. No I/V users.	BPN S/L 0.6 – 1.2mg/day X 10 days (3 divided doses)	Clon 0.3-0.9mg/ day X 10 days (3 divided doses)	Subjective & Objective withdrawal scales better with BPN. 65% v 50% completion rates BPN v Clon
O'Connor et al 1997	RCT/db	162 recruited (53 BPN & then 54 Clon + nalt; 55 Clon). All heroin users	BPN S/L 3mg / day X 3 days & then Clon & Nalt	Clon 0.1 – 0.2 every 4 hours X 7 days + Nalt 50mg on day 8; Clon as above plus Nalt 12.5mg – 50mg on days 1-3	Higher withdrawal scores for BPN on days 1-4 but lower thereafter. Completion rates equal.
Umbricht et al 1999	RCT	60 recruited (32 on BPN – Nalt; 28 on BPN followed by Nalt). Heroin users – only 30% injectors	BPN S/L 12mg day 1; 8mg day 2; 4mg day 3; 2mg day 4	Nalt given either in combination or after BPN 12.5 – 50mg per day to day 8	Withdrawal scores declined with BPN. Completion rates 76% v 56% BPN + then Nalt

Legend for Table 5.1

RCT = Randomised Controlled Trial
db = Double Blind
BPN = Buprenorphine
Clon = Clonidine
Nalt = Naltrexone
S/L = Sublingual Administration
I/V = Intravenous Administration
I/M = Intramuscular Administration

Heroin was the main opioid of abuse in four of the five studies (n=290). The other study had participants withdrawing from methadone (n=22) or methadone and heroin (n=17). A small number of patients were opium smokers. The inhalation route is thought to result in lower levels of dependence (Strang et al, 1999).

Clonidine is an alpha-adrenergic blocking agent, originally developed as an anti-hypertensive treatment. It has also been shown to be effective in suppressing the opioid withdrawal syndrome (Gossop, 1988). Four of the studies compared buprenorphine with clonidine, but each study's treatment regimen was vastly different, in terms of dosage and timing of buprenorphine and clonidine and also in the manner of use of concomitant medications. The fifth study compared buprenorphine administered with 2 different regimens of naltrexone. The studies differed greatly in terms of the way "completion of withdrawal" was determined and in the evaluation of withdrawal severity. In addition, different preparations and routes of administration of buprenorphine were used in the various studies.

The results showed that where buprenorphine was compared with clonidine, the results tended to favour buprenorphine in terms of alleviating the symptoms of opioid withdrawal. However, because varying treatment regimens were used in all studies, an overall evaluation of dose response and relative efficacy was not possible. Information on the usefulness of buprenorphine in participants withdrawing from methadone was sparse but suggested that it was as effective as clonidine. It is important to note that the dose of methadone had been reduced to 10mg/day before entry into the withdrawal programme.

One of the supplementary studies (Banys et al, 1994) suggested that there might be racial differences in the metabolism of opioids, which might account for differences in the efficacy of buprenorphine but the numbers were small (n=15). Although the study from Bickel et al (1988) was described as a detoxification study, it involved administration of buprenorphine or methadone for 7 weeks in a randomised controlled double blind trial and therefore was classified as one of the supplementary studies. The results in this study were similar, in terms of retention in treatment and illicit opioid use for buprenorphine 2mg or methadone 30mg given daily. But buprenorphine was less able to attenuate the effects of opioid challenge (hydromorphine 6mg administered intramuscularly). This was the first randomised controlled trial to compare buprenorphine and methadone in opioid dependent patients.

Because of the wide variability in the study limits between the five included studies, it was not considered appropriate to undertake formal meta-analysis in the review. However, the reviewers' overall conclusion was that short-term use of buprenorphine appears to have potential as an approach in the management of withdrawal from opioid dependency. It was not possible to provide recommendations on an appropriate treatment protocol (in terms of dosage or duration of treatment).

Clonidine, used at the dosage needed to suppress opioid withdrawal syndrome is associated with a number of adverse effects (such as hypotension and sedation) and therefore patients require close medical supervision (Ward el al, 1998). Lofexidine is a structural analogue of clonidine but with less side effects and it has been used widely in the UK for opioid detoxification since it was authorised in 1992. An open label study was published recently (White et al, 2001), which compared buprenorphine with lofexidine in the management of withdrawal in a community setting. The results showed that subjects receiving buprenorphine were more likely to complete detoxification and had a less severe withdrawal syndrome than lofexidine. The efficacy of buprenorphine was dose-related. Although this study was not randomised and involved retrospectively reviewed subjects as well as prospectively followed subjects, the result supports the use of buprenorphine in the management of opioid withdrawal. The design of the study precluded conclusions regarding relative efficacy, however the investigators found that matching the dose of buprenorphine to the subject's daily opioid use prior to treatment resulted in a less severe withdrawal syndrome and greater chance of completion of treatment.

Summary

Although managed withdrawal has been recognised as an important treatment option in the management of opiate dependency for many years, no established treatment regimens exist to date. A systematic review of the use of buprenorphine for the management of opioid withdrawal has recently been undertaken by the Cochrane Collaboration group. The studies identified were found to be too heterogeneous to allow formal meta-analysis to be undertaken. However buprenorphine was evaluated using a number of dosage regimens, and was shown to be at least as effective as clonidine (the treatment option most widely reported) in terms of reduction of severity of withdrawal syndrome and completion of withdrawal. The authors concluded that "buprenorphine has potential as a medication to ameliorate the signs and symptoms of withdrawal from heroin and possibly methadone" (Gowing et al, 2001). There was insufficient information for the authors to be able to recommend the appropriate dosage regimen, but the importance of titration of the dose to the individual subject was highlighted in some reports.

5.2 Use of buprenorphine as substitution therapy in the management of opiate dependency

Examination of all data sources (outlined in Chapter 3) has recovered a large body of data pertaining to the use of buprenorphine in the treatment of opioid dependence. In addition, the search identified that the Cochrane Collaboration is currently undertaking a systematic review of the use of buprenorphine maintenance (versus placebo or methadone) for opioid dependence (Mattick et al, 2001). This is due to be published shortly but the published protocol was taken into account when undertaking the current review. Problems have been identified with these data and these are discussed below.

Evaluation of the clinical trials has been divided into separate sections – randomised controlled trials (with or without an active comparator), sub-group analysis including use in pregnancy, dose-ranging studies, and non-randomised open label studies.

5.2.1 Randomised controlled trials with an active comparator

A summary of all identified randomised controlled trials of buprenorphine versus an active comparator is given in tabular form in Appendix III.

Two meta-analyses have been identified from the literature (Barnett et al, 2001 and West et al, 2000), which compare buprenorphine with methadone. There is a good deal of overlap between the two (5 randomised controlled comparative studies from the 1990s are common to both), but Barnett et al (2001) appears to be the more statistically sound. A brief summary of the evaluation of these meta-analyses follows:

West et al (2000) provide a meta-analysis of 9 separate trials comparing buprenorphine to methadone. This meta-analysis is considered inferior to that by Barnett et al (2001) as it includes very different types of studies, and does not use the original data but attempts to extract the information from the published articles (weaker methodology). For these reasons only the meta-analysis of Barnett et al is considered in detail.

Barnett et al (2001) provides a comprehensive meta-analysis of four of the five randomised trials comparing buprenorphine and methadone published up to 1998 (Table 5.2), using "high dose" buprenorphine i.e. daily doses of at least 6mg per day (range 6-12mg per day), and "high dose" methadone i.e. average daily doses of 60mg per day (range 50-80mg per day). Patients in the included studies are followed up for 16-24 weeks, and two summary statistics are extracted from each study and combined in the meta-analysis. These are:

a) Proportion of positive urinalysis tests (out of all possible tests). Missing tests are handled in one of two ways (i) treated as positive and (ii) excluded from the analysis.

b) Hazard ratio (or relative risk of discontinuation in buprenorphine group compared with methadone group) calculated using Cox proportional hazards model.

Overall, the authors found a significant difference, with an average 8.3% (p=0.002) more positive urinalysis tests with buprenorphine than methadone. Although statistically significant, the result is not of particular clinical significance or importance. The overall rate of discontinuation was 1.26 times greater in the buprenorphine group than in the methadone group (p=0.019). This reduces to 1.17 (p=0.087) if one study, based On a lower dose of buprenorphine, is excluded. In a sub meta-analysis of three trials (Barnett et al), found that those on buprenorphine have 8.4% (95% CI 1.2-5.6%) *fewer* positive urinalysis tests and lower rate of discontinuation than low dose methadone.

Some of the included studies reported other secondary outcomes, such as self-reports of illicit drug use, withdrawal symptoms, but as these were not reported in all studies they are not considered further in the meta-analysis.

Since this analysis was performed, a further 4 randomised trials have been identified. Petitjean et al (2001) compared the safety and efficacy of sublingual buprenorphine tablets with oral methadone in a population (n=58) of opioid-dependent individuals in a double blind, randomised, six-week trial using a flexible dosing procedure. This study reported better retention rates for methadone, although the high attrition rate with buprenorphine occurred in the induction phase and therefore was thought to be due to inadequate induction doses. There was no difference between the groups in terms of positive urine samples, withdrawal symptoms or concomitant ingestion of cocaine.

Pani et al (2000) enrolled 72 subjects from 9 treatment units in a randomised controlled double blind study to receive either sublingual buprenorphine (8mg/day) or oral methadone (60mg/day) for 6 months. There was no significant difference between the groups at the end of the study. A non-significant trend in favour of methadone was noted in respect of retention in the study, but the investigators reported that the subjects on buprenorphine who dropped out differed significantly from those who stayed, in terms of a higher level of psychopathological symptoms and a lower level of psychosocial functioning.

Johnson et al (2000) compared LAAM (75–115mg), buprenorphine (16–32mg) and high-dose/low dose methadone (60–100mg/20mg respectively) in a 17-week randomised study of 220 subjects (55 per group). Methadone was administered daily and the other medications were administered thrice weekly. Results showed that LAAM, buprenorphine and high-dose methadone were superior to low-dose methadone in terms of treatment retention, urine toxicology and withdrawal symptomatology. It also showed that thrice weekly administration of buprenorphine was comparable with daily methadone treatment (see also **5.2.5**).

Finally, Fischer et al (1999) randomised subjects to receive either buprenorphine or methadone on a daily basis in an open comparative study for a period of 24 weeks. A total of 60 subjects with opioid dependence were enrolled.
The results showed that retention rates were significantly better in the methadone group but that the buprenorphine subjects who completed the treatment had significantly lower rates of illicit opioid drug usage.
This study is of interest in that it is the first comparative study to use the sublingual buprenorphine tablets (as opposed to the ethanol solution). The mean daily dose of buprenorphine used was 7.5mg (compared with 63mg of methadone). This study was included in the meta-analysis from West et al.

After detailed evaluation of these additional studies, the first two were not considered suitable for inclusion in a meta-analysis. Petitjean et al studied the subjects for a period of 6 weeks only, and this was not considered long enough to examine retention on treatment, while Pani et al used a fixed dosing rather than flexible dosing regimen used in the other studies. For the remaining studies (Fischer et al, Johnson et al), the main authors were contacted in relation to the use of their original data/statistics. This was to enable the results from their studies to be incorporated into a further meta-analysis, thereby updating the analysis of Barnett et al (2001) (see Table 5.2 below). The same statistical methods are used as Barnett et al (described in Appendix I) to update the analysis and these are based on weighting the primary outcome measures from each study by 1/variance of the outcome measure.

Data from both authors (Dr Fischer and Prof Johnson) were obtained and included in a further meta-analysis of all 6 studies. A summary of the findings from each of the studies by Fischer et al (1999) and Johnson et al (2000) are presented in Table 5.3 below. The subjects' mean proportion positive urinalysis for the study by Fischer et al is slightly higher than that from the other studies, and this is because all subjects had to have positive urinalysis in the week 1 induction period, which was included in the proportion positive urinalysis (~5-10% higher proportion because of this). As the present analysis focuses on the difference between the groups, this was not considered to be a problem. The retention rate for buprenorphine in the study by Fischer et al is considerably worse than for methadone, as indicated by the large relative hazard ratio of 2.58 (i.e. those on buprenorphine 2.58 times more likely not to be retained in treatment than the methadone group). This was explained to some extent by the slow induction and low upper dose of 8mg buprenorphine (tablet) during the first few weeks of the study, as well as reported 'undifferentiated dysphoria' and 'a state of clarity' during the induction phase on buprenorphine, and more severe withdrawal symptoms observed with buprenorphine. The bioavailability of the tablet formulation of buprenorphine has been reported to be half that of the ethanol formulation (Nath et al 1999; see also Chapter 4)

When the data from these studies were added to those from the 4 main studies already reported in Barnett et al (i.e. excluding Kosten et al), significant heterogeneity between studies was observed only in the case of the retention in treatment outcome (Cochrane's $Q=20.07$, $p<0.001$), attributed to Fischer et al for the reasons given above. The final meta-analysis of the 6 studies for positive urinalysis are shown in Table 5.4a below. The results indicate that those on buprenorphine had 8% more positive urinalysis than those on methadone. Although statistically significant ($p<0.05$), the result was not considered clinically significant.

The results from combining the 5 studies (i.e. excluding Kosten et al and Fischer et al) in relation to non-retention on treatment are given in Table 5.4b. They show that those on buprenorphine are 1.23 times more likely not to be retained on treatment than those on methadone, but this result is not statistically significant, and therefore it is concluded there is no difference between groups in retention rates. This is further illustrated, in Table 5.5, which outlines the completion rates in each of the six studies. Only one study (Fischer et al, which was described above and was not included in the retention analysis) showed significant differences between the buprenorphine and high dose methadone. Buprenorphine at 8mg/day was shown to have significantly higher retention rates than lower dose methadone (20-35mg) in Johnson et al (1992), but no statistically significant differences were noted between high dose buprenorphine (12mg) and low dose methadone (25mg) in the Schottenfeld et al (1997) study.

There is wide variability between the designs of the studies, doses of methadone and buprenorphine and types of non-pharmacological interventions and subjects in the various studies described, which means the results need to be interpreted with some caution.

Since the data lock point, another meta analysis has been identified (Farré et al, 2002). This compared the efficacy of methadone with that of buprenorphine and LAAM. The results showed that there was no significant difference between high dose buprenorphine (≥ 8mg/day) and high dose methadone (≥ 60mg/day) for both treatment retention and illicit opiate use. Methadone was more effective than lower dose buprenorphine (<8mg/day).

5.2.2 Placebo studies

Only one study has been identified here. This was undertaken to satisfy FDA guidelines on evaluations of new medicines and was part of a larger study undertaken by the research group (Johnson et al, 1995). It was a double blind randomised study, which involved 150 subjects who were randomised to receive 2 different dosage regimens of buprenorphine or placebo for 14 days. After day 6, it was possible to change to an alternative group. Participants also received daily one-to-one counselling. The results showed that actively treated patients scored significantly better on all outcomes (treatment retention, urinalysis, withdrawal symptoms) than the placebo group, but there was no difference between the 2 dosage groups of buprenorphine.

Table 5.2: Summary of meta-analysis by Barnett et al (2001)

Study	Methadone dose (mg/day)	Buprenorphine dose (mg/day)	Study numbers	Difference in mean proportion positive urinalysis	95% Confidence interval
Johnson (1992)	60	8	107	-0.022	-0.142, 0.097
Strain (1994)	50	8	164	0.051	-0.044, 0.146
Schottenfeld (1997)	65	12	57	0.155	0.001, 0.310
Ling (1996)	80	8	150	0.169	0.066, 0.273
Kosten (1993)	65	6	62	0.244	0.085, 0.404
Summary based on all 5 studies					Fails heterogeneity test
Summary based on excluding Kosten				0.083*	0.027, 0.140

Table 5.3: Summary of study characteristics and results from Fischer et al (1999) and Johnson et al (2000)

Study characteristics					Subjects mean proportion positive urinalysis for opiates				Non retention in treatment buprenorphine vs methadone	
Study	Methadone dose	BPN dose	Study length	Number of subjects	BPN	Methadone	Difference	95% Confidence Interval for the difference	Relative Hazard ratio	95% Confidence Interval
Fischer (1999)	63mg (mean)	7.5mg (mean) tablet form	24 weeks	60	0.734	0.677	0.057	-0.096, 0.210	2.58	1.21, 4.92
Johnson (2000)	60-100 mg	16-32mg (thrice weekly)	17 weeks	110	0.667	0.613	0.054	-0.069, 0.177	1.71	0.89, 3.28

Table 5.4a: Final meta-analysis of positive urinalysis results from 6 studies

	Difference (p-value)	Confidence Interval	Test for homogeniety
Difference in proportion positive urinalysis between buprenorphine and methadone	0.076 (p<0.05)	0.03, 0.12	Q=7.24, 5df P=0.203

Table 5.4b: Final meta-analysis of non-retention in treatment (relative hazard ratio) from 5 studies (excluding Fischer et al)

	Relative Hazard ratio	Confidence Interval	Test for homogeniety
Non-retention of buprenorphine vs methadone	1.23 (p=0.07)	0.98, 1.53	Q=5.5, 4df P=0.24

Table 5.5: Completion rates by dose of buprenorphine and methadone in randomised trials included in the meta analysis

Study (duration)	Dose (number of subjects)	Overall % retention in study	
		Study duration	Follow-up
Fischer 1999 (24 weeks)	BPN 7.5mg (29) tablet Meth 63mg (31)	38% 71%*	
Johnson et al 2000 (17 weeks)	BPN 16-32mg (55) Meth 60-100mg (55)	58% 73%	
Schottenfeld 1997 (24 weeks)	BPN 12mg (29) BPN 4mg (29) Meth 65mg (28) Meth 25mg (30)	55.2% 34.2% 64.3% 46.7%	
Strain et al 1994 (26 weeks)	BPN 8mg up to 16mg (mean 11.6mg) (24) Meth 50 up to 90mg (mean 66.6mg) (27)	**% days' attend clinic** 81% 88%	
Ling et al 1996 (26 weeks)	BPN 8mg (75) Meth 80mg (75)	**At 26 weeks** 35% 52%	**At 52 weeks** 20% 31%
Johnson 1992 (17 weeks + 8 week detoxification)	BPN 8mg (53) Meth 60mg (54) Meth 20mg (55)	**17 weeks** 42%Ö 32% 20%Ö	**25 weeks** 30%Ö 20% & 6%Ö &

* significantly different ($p<0.05$) – see text for details

Ö & significantly different ($p<0.05$) from one another (within the same study)

5.2.3 Subgroups of responders to buprenorphine

Few randomised or non-randomised studies have examined specific sub-groups of responders to buprenorphine treatment. A summary of those that have is given in Table 5.6 below.

One study already included in the meta-analysis of randomised controlled trials (above) is that of Schottenfeld et al (1998). Here the authors found significantly better rates of abstinence from opioids, and better overall retention rates in women compared with men, and this was particularly the case for those on buprenorphine 4mg. The authors attribute the gender differences to possible differences in central opioid neuronal pathways, with findings of increased mu receptor density in women, although they also comment on the limited power of the study due to the small numbers of women studied. Subjects with a history of sedative dependency had lower attrition from treatment in both buprenorphine groups (4mg and 12mg) compared with the methadone 65mg group.

Others (Pani et al, 2000 and Resnick et al, 1991) found that higher levels of psychosocial functioning resulted in better adherence and response to buprenorphine than those with lower psychosocial functioning, suggesting that those with higher psychosocial functioning would be more suitable for buprenorphine treatment. Kosten et al (1990) found that the effect of buprenorphine on signs of depression was short-lived, and that the rate of dropout on buprenorphine was marginally worse ($p=0.06$) in the depressed compared with non-depressed subjects during follow-up. Schottenfeld et al (1998) found no association between depression and outcomes of treatment (retention or illicit opioid use) in those on buprenorphine and methadone.

Laqueille et al (2001), in an observational study, followed 73 subjects on buprenorphine (mean dose 8.5mg/day) for 3 months and assessed response to treatment as remaining in the study and having more than 75% negative urine tests over the last month. They observed better response in those with: opiate addition less than 10 years, a high score on the Addiction Severity Index, an absence of depression, and a

Table 5.6: Sub-group analysis of randomised and non-randomised studies

Study	Subjects	Subgroups-findings
Schottenfeld et al (1998)	RCT – buprenorphine (4 or 12mg) versus methadone (20 or 65mg) to assess the effect of gender and psychopathology and interaction with treatment. 80 male : 36 Female	Found a significant gender effect i.e. better rates of abstinence of opioid use in women compared with men; within the 4mg buprenorphine group females also had better retention, and lifetime sedative use was also associated with better retention. No effect of depressive state on outcome.
Eder et al (1998)	RCT – 16 on buprenorphine (free dosing to a max 8mg); 18 on methadone (free dosing no upper limit)	Buprenorphine appeared more effective in the more motivated subjects and authors suggest further investigation here.
Pani et al (2000)	RCT – 72 patients on buprenorphine (8mg) or methadone (60mg) followed up for 6 months	Patients dropping out in the buprenorphine group differed significantly in their levels of psychosocial symptoms (serious symptoms of depression) from those not dropping out. Predictors of good adherence were good psychic state and psychosocial adjustment
Ahmadi (2001)	330 subjects randomised to 3 doses of buprenorphine (110 in each)	Addicts previously using <2mg opium daily had better outcomes on buprenorphine.
Johnson et al (1995)	Placebo controlled trial versus buprenorphine	Male subjects receiving buprenorphine had significantly fewer positive urine tests during days 3-7 compared with placebo than females (but small numbers in this group). Suggest early effectiveness may be gender-specific.
Resnick et al (1991)	16 heroin dependent subjects followed for 26-32 months with buprenorphine (non-randomised). Subjects asked to rate psychosocial functioning at baseline and follow-up.	Levels of psychosocial functioning and global assessment of functioning were significantly higher for those responding to buprenorphine compared with those not responding (i.e. relapsed to heroin).
Laqueille et al (2001)	Observational study 73 subjects on BPN (mean dose 8.5mg/day) for 3 months	Better response in those with: opiate addiction <10yrs; high score on ASI; absence of depression; low disinhibition rate (Zukerman scale)

RCT = Randomised controlled trial

ASI = Addiction severity Index

low rate of disinhibition (Zukerman's scale). The dose of buprenorphine did not affect the response.

In summary, the only sub-group which appears to perform best on buprenorphine and for which the results are replicated in more than one study is the group of subjects that have higher baseline levels of psychosocial functioning and global functioning, and less depressive illness. The effect of gender on the response to buprenorphine was found in only one study (Schottenfeld et al, 1998) and requires further validation in other studies.

5.2.4 Use in pregnancy

The published literature contains a series of case reports in which buprenorphine was used during pregnancy (Johnson et al, 2001). These retrospective reports involved women who became pregnant while on buprenorphine therapy and showed no particular problems during pregnancy for the mother, with a neonatal abstinence syndrome (NAS) in the infant of mild-moderate intensity (Reisinger 1997, Eder et al, 2001).

Jernite et al (1999) analysed the cases of 24 opioid-dependent pregnant women (and their offspring) who were treated with buprenorphine during pregnancy. Of these, 13 were reviewed retrospectively while 11 were followed prospectively and actively managed throughout pregnancy (medical and social support). The results showed that the prospectively followed group had much better outcomes, in terms of prematurity, foetal growth retardation and acute foetal distress. In addition, these women were more likely to bring their infants home (90.9% vs. 69% of retrospective group). However there was no difference in the level of NAS between the 2 groups (63% vs. 69%). This highlighted the need for total management of the opioid dependent subject, in addition to substitution treatment, during pregnancy.

A study, undertaken by Marquet et al (1997) measured the levels of buprenorphine and the metabolite norbuprenorphine, around the time of birth, in the serum of a mother (maintained on buprenorphine throughout pregnancy) and compared them with those found in the serum, urine and meconium of the infant. Levels of buprenorphine were 6 times higher in the infant's serum compared with the mother, with correspondingly low levels of the metabolite norbuprenorphine, probably due to immature hepatic metabolism in the infant. However, the infant experienced a mild NAS only, which did not require pharmacological intervention. Moreover, the infant was breast-fed for 6 weeks with no ill effect. The authors suggested that these findings supported the safety of buprenorphine during pregnancy.

Rohrmeister and workers (2001) enrolled all infants, born in the university hospital of Vienna to opioid-dependent mothers over a 4-year period (March 1995 to September 1999). A total of 88 infants were included with a median gestational age of 39 weeks. Overall, 72% had to be treated for NAS, but the incidence and duration of NAS with buprenorphine treatment was significantly lower than with other groups – 19% of the buprenorphine group of infants required treatment, compared with 76% of the methadone group and 93% of the slow-release morphine group. This study further supported the use of buprenorphine during pregnancy.

Two open-label studies have been undertaken in pregnant opioid-dependent women. Fischer and workers (1998; 2000) undertook an open-label study evaluating a flexible buprenorphine-dosing regimen in opioid-dependent pregnant women. A total of 15 women were enrolled – 14 were receiving either methadone or slow-release morphine maintenance treatment and one was on "street heroin" at enrolment. They received a mean of 8.4mg/day of buprenorphine and were entered into the existing pregnancy and drug addiction programme in the hospital.

All were delivered of healthy infants. NAS was mild in 4 (27%), moderate (requiring treatment) in 3 (20%) and absent in 9 (53%) infants. There was no correlation between the mother's dose of buprenorphine and risk of NAS.

The second open label study involved 3 opioid-dependent pregnant women in the USA (Johnson et al, 2001). All were admitted to a hospital based specialist treatment programme for pregnant drug-dependent women. Only one had been treated previously for opioid dependence. The women

completed induction successfully over 3 days and were maintained on doses of buprenorphine of between 8 and 12mg/day until delivery. Urinalysis was negative for opioids on all occasions with one exception.

All 3 women were delivered of healthy infants. Symptoms of mild NAS were reported in all infants. These peaked at 72 hours and returned to pre 12-hour levels by 120 hours. None of the infants required pharmacological intervention for withdrawal.

Although these two studies were limited in terms of design and numbers and give details on the infants around the time of birth, the results support the usefulness of buprenorphine during pregnancy and its safety in terms of reduced NAS for the infant.

5.2.5 Dose ranging studies with buprenorphine

The literature search has retrieved several reports of studies, which investigated various dosing schedules for buprenorphine. These studies are too heterogeneous to enable a formal meta-analysis to be undertaken. Therefore, they will be systematically reviewed on an individual basis in this section.

Studies identified may be divided into those which sought to confirm the optimum daily dose and those which evaluated the efficacy of various less than daily dosing regimens.

Daily administration studies

A large multicentre study was undertaken by Ling et al (1998) to evaluate the safety and efficacy of an 8mg/day dosage of buprenorphine, using a 1mg/day dose as comparator. It was undertaken in co-operation with the National Institute on Drug Abuse (NIDA) and was intended to provide pivotal information for a new drug application (NDA) to the Food and Drug Administration (FDA), in the USA. Therefore, it was designed according to FDA guidelines. It was a randomised clinical trial where the 1mg/day dose was adopted to serve as placebo. It was double blind in design and lasted for 16 weeks. Two other dose groups were included – 4mg/day and 16mg/day – but the results from these dose groups were evaluated as secondary outcomes for statistical reasons. Doses were administered under supervision every day for the duration of the study. Urines were collected three times weekly and analysed for opiates and cocaine. Subjects enrolled in the study were offered a 1 hour weekly counselling session, in addition to daily attendance at the clinic. Outcomes evaluated were (1) treatment retention time in the study, (2) urine toxicology, (3) self-reports of craving and global severity and (4) severity ratings by the research team.

A total of 736 subjects were enrolled at 12 specialist outpatient clinics. Approximately 180 were randomised to each treatment group. Overall, 51% completed the study. Results for the treatment retention for the 8mg and 16mg groups were statistically significantly better ($p<0.05$) than for the 1mg group (52% and 61% versus 40%).

The results showed a consistently better response for each outcome measure than the dose below it, although these differences did not always reach statistical significance. Urine toxicology results were significantly better for the 8mg group than those for the 1mg group for urine toxicology (32.9% versus 18.5% negative for opiates). The investigators evaluated the total number of negative urines contributed by each patient as another measure of treatment effectiveness (TES) and found that the 1mg group was significantly worse then the other dosage groups on this score (5.6, 9.6, 10.3 and 13.9 for 1, 4, 8 and 16mg respectively) where 48 is the maximum score i.e. maximum number of urines collected.

Significantly higher craving scores occurred in the 1mg group compared with the 8mg group up to week 12 only. As might be expected, the craving scores in the 1mg completer group were significantly worse than the 8mg and 16mg groups until week 8 only, after which the difference was not statistically significant. Staff ratings for the 8mg group were significantly better than for the 1mg group throughout the study, but patient self-ratings for these groups only showed a significant difference in favour of the 8mg dose at week 4.

This was not designed as a dose-response study but the results showed an apparent monotonic relationship between dosage and each outcome measure. The study confirmed that 8mg was statistically superior to 1mg for all outcomes measured and therefore confirmed that

buprenorphine showed efficacy in the management of opioid-dependent patients at this dose. However, the low scores on the TES and the low retention rates suggested that further work was needed to define the optimum dose for use in clinical practice.

Less than daily dosing

The need for daily administration of methadone has been reported as a limitation to the successful management of some heroin addicts because (1) there are problems of compliance with daily attendance and (2) daily attendance reduces the numbers of patients that can be treated. Buprenorphine's profile of high affinity binding to opioid receptors, (see Chapter 4) coupled with pseudo irreversible binding, implies a potential for a reduction in the frequency of dosing (e.g. alternate day/every third day).

Alternate day dosing

Several pilot studies, looking for the optimal dosing regimen have been reported. Fudala and workers (1990) evaluated a dose of 8mg of buprenorphine given either daily (n=9) or every second day (n=10). Subjects were all opioid-dependent and were initially stabilised on 8mg for 18 days. Results showed that alternate-day dosing was tolerated by the group but that they consistently reported a greater urge for opioid use and higher dysphoria scores on the placebo days. From day 37 to day 52, all subjects were put on placebo. No withdrawal signs were detected using the standard Himmelsbach scale but the subjects complained of mild to moderate opioid withdrawal symptoms lasting for up to 10 days. This preliminary study suggested that alternate day dosing was possible but that daily dosing provided greater control.

In a study undertaken in the USA in 1993 (Resnick et al) 31 opioid-dependent patients who were maintained on doses of 4-16mg/day for several months were given double their daily dose every 2 days and evaluated for withdrawal symptoms. The majority of patients experienced no symptoms after the alteration in dosing schedule although "restlessness and anergia" were noted in some at the end of the interval period. The dosage regimen was subsequently increased to triple the daily dose every third day and, on follow-up, 29 patients were maintained, heroin-free, on this regimen. Patients expressed satisfaction for the reduced clinic attendance associated with this schedule.

In a similar study, Amass and workers (1994) compared daily versus alternate day buprenorphine administration in 13 opioid-dependent subjects who were stabilised (over a period of 2 weeks) on either 2mg/70kg/day (n=2), 4mg/70kg/day (n=6) or 8mg/70kg/day (n=5). All medications were administered under double-blind conditions, using a flavour solution to mask the test dose. From day 14 onwards subjects were randomly assigned to receive their maintenance dose either daily or every second day (double dose) for 3 weeks, after which they were eligible to enter a crossover phase for the next 3 weeks. No difference was noted between the groups in terms of treatment retention, positive urinalysis or subjective ratings (self and staff ratings). There was a difference in the subjective "agonist effect" ratings when the treatment and placebo days were compared for the first 3 week cycle, which was not seen in the second cross-over phase. However, the treatment schedule was well tolerated by the group with 77% completion rates.

Although these studies involved small numbers of subjects, the results suggest that less than daily administration of buprenorphine may be possible from a safety and efficacy point of view and could lead to greater patient compliance. However, these findings need to replicated using much greater numbers of subjects.

Thrice weekly dosing

Chawarski (1999) undertook a double-blind trial in a group of 10 opioid dependent subjects. The study used a within-subject design with three different thrice-weekly dosing schedules of buprenorphine administered sublingually, under supervision, on Fridays, Sundays and Tuesdays. This dosing period was preceded by a week of induction (daily dosing) and followed by one week of daily administration at the end of the study. The different schedules were randomly assigned, with each schedule lasting 3 weeks. The same random allocation was repeated in each patient, for a total of 18 weeks.

Doses administered were as follows
Daily dose – 16mg/70kg. Thrice weekly
Regimen A – 16mg;16mg;32mg/70kg;
Regimen B – 22mg;22mg;40mg/70kg;
Regimen C – 34mg;34mg;44mg/70kg.
Each dose was based on bodyweight (70kg) and therefore it was adjusted on an individual basis. Subjects were evaluated by means of urinalysis, self-reports and staff reports of opiate withdrawal symptoms. In addition, plasma samples were collected during the second week of each thrice weekly regimen at 24, 38 and 72 hours post dose and at 24 hours after daily administration (on 3 occasions).

Only one patient dropped out of the study (at 13 weeks). The number of urine samples which was positive for opiates decreased from baseline, but there was no indication that higher doses were more effective. Both patient and staff scores showed low levels of withdrawal symptoms in each dosage group (no significant difference).

Plasma levels showed wide intra-patient variability but in general higher doses of buprenorphine resulted in significantly higher overall plasma concentrations. The plasma levels at 74 hours after the higher thrice-weekly regimen were comparable to the 24-hour level seen with the 16mg/70kg daily, supporting the feasibility of thrice-weekly buprenorphine for maintenance treatment.

Two recently published studies (Schottenfeld et al, 2000; de los Cobos et al, 2000) compared the efficacy of daily versus thrice weekly administration of buprenorphine in the management of opioid dependence. Both were randomised controlled double blind trials. Schottenfeld enrolled 97 patients (of whom 92 completed the 3 day induction period) who were randomised to receive buprenorphine at a total weekly dose of 112mg/70kg by either daily or thrice weekly dosing for 12 weeks, in an ethanol-based formulation.

Results showed treatment retention rates of 71% and 77% (daily v thrice weekly). Concomitant heroin use decreased significantly in each group, as evidenced by a reduction of approximately 50% in the number of opiate positive urines and a decrease in the number of self-reported days of heroin use per week.

Furthermore patients on thrice-weekly dosing did not report increased craving or illicit drug use during the "placebo" days. There was no difference in the pattern of reported side effects between the groups.

The study was undertaken in the USA, where cocaine abuse is a major problem. It noted an increase in the use of cocaine over the 12 weeks of study. This was judged to be important as cocaine use was an exclusion criterion and 70/92 baseline urines had tested negative. The authors suggested that this would need further evaluation.

The overall conclusions were that the study supported the clinical efficacy of thrice weekly dosing.

In contrast, the second study (de los Cobos, 2000) randomly assigned 60 opioid dependent subjects to receive a total 56mg buprenorphine per week, administered either daily or thrice weekly. Treatment was started after an inpatient induction phase. Buprenorphine tablets were used in this study.

Results showed similar retention rates of 63% and 70% for daily and thrice weekly dosing respectively. However illicit opiate use was greater in the thrice-weekly dose group and this became significant from week 3 onwards with only 13.3% of the thrice-weekly dose group achieving abstinence from opioids for at least 4 weeks, compared with 36.6% for the daily dose group. Cocaine abuse was equal for each group – 22.3% and 21.7% positive urines in the daily and thrice weekly dose groups. Self-reports of craving were also higher in the thrice-weekly dose group. Of interest is the fact that the plasma levels of buprenorphine were similar in both groups.

The authors concluded that the dosing schedule used was probably inadequate (8mg/day of the tablet calculated as being equivalent to 5.6mg/day of buprenorphine solution). However, they suggested that daily dosing should be continued until the patient is stabilised, before changing to a less than daily dosing regimen. This is in keeping with the Australian guidelines on buprenorphine use (Lintzeris et al, 2001; see also Chapter 7).

Greater than thrice weekly dosing schedules

Investigators have evaluated the potential of administering buprenorphine at even greater intervals (96 and 120 hour intervals). Petry and workers (1999) enrolled 26 opioid dependent subjects in a double blind placebo-controlled crossover trial, whereby each subject received, in a random order, the following dosing regimens for 5 repetitions each –

(a) a maintenance dose every 24 hours,
(b) a doubled maintenance dose every 48 hours,
(c) a tripled maintenance dose every 72 hours and
(d) a quadrupled maintenance dose every 96 hours. The maintenance dose was determined during a period of induction and was either 4mg/70Kg or 8mg/70Kg per day.

Only 14 of the subjects completed the study but, of these, only 5 were dismissed for continuing illicit opioid abuse. There was no safety concern with excessive opioid agonist effects with the quadrupled dose and opiate withdrawal symptoms were seen at the end of the dosing period in a similar fashion for each group (i.e. the magnitude of withdrawal experienced at 96 hours after the quadrupled dose was similar to that experienced at 48 hours after the doubled dose).

Although this study involved very small numbers and was undertaken under experimental conditions (and therefore could not be said to be representative of real life usage), the results suggest that it is possible from a safety and efficacy perspective to lengthen the interval between buprenorphine doses. This could be important for compliance and proper management of a treatment clinic – 4 of the subjects, initially enrolled in this study, had to drop out because of transportation problems.

Another study (Gross et al, 2001) has evaluated the efficacy of buprenorphine administered at intervals of up to 120 hours. Twenty-nine opioid-dependent subjects were enrolled and, after a period of induction and stabilisation on either 4mg/70kg/day or 8mg/70kg/day, 26 were randomised to receive either a quintuple maintenance dose every 120 hours or a sextuple dose every 120 hours. This was continued for 20 days, after which they had a 4-day placebo phase and then crossed over to the other treatment regiment for a further 20 days. A test dose of the top dose was given, in 3 divided doses, before the formal dosing schedule began to evaluate safety and all subjects tolerated the dose. Only 14 subjects completed the study. Seven were dismissed for illicit drug use and 5 left without notice. The completers experienced agonist effects 24 hours after dosing. Significant subjective withdrawal-related effects were noted in each dose, from 96 hours onwards.

This study involved limited numbers and had a high attrition rate, but it reinforced the safety of buprenorphine at high single doses (the highest single dose administered was 76.4mg to the opioid-dependent subjects) and suggested that the maximum dosing interval was 96 hours.

In summary, several studies have been undertaken to identify the optimal dosing regimen for buprenorphine in its use in the maintenance treatment of opioid dependency. These studies have methodological problems, either in terms of design, small numbers studied and/or study dosing. Furthermore, although several studies used a "flexible" dosing regimen, this did not involve individual titration of dose. However, the results support the usefulness of buprenorphine, but it is not possible to identify the optimal dose. The studies also showed that it was possible to use a less than daily dosage administration in this indication, which should be of use in clinical practice.

5.2.6 Other studies on the effectiveness of buprenorphine

Few non-randomised studies examining the effectiveness of buprenorphine in the management of opioid dependency have been reported. Strain et al (1996) performed a follow-up analysis of their clinical trial from 1994 that was included in the meta-analysis. This reported on the subset of 86 patients (from 164) who remained on treatment throughout the whole study period. They found similar effects on urine test results

between the two groups and a decreased trend in positive tests over time in the buprenorphine group, although this finding was non-significant.

O'Connor et al (1998) enrolled 46 subjects who were randomly assigned to receive thrice weekly buprenorphine either in a primary care clinic (affiliated with a drug treatment programme) or in a traditional drug treatment programme for 12 weeks. No comparator was used. The results were at least as good for the primary care group as for those in the traditional drug treatment setting. This study is interesting from the treatment setting point of view as retention times (78% and 52% for primary care/traditional treatment programmes) are similar to those seen in other studies with daily buprenorphine regimens.

Reisinger et al (1985) was the first observational study to examine buprenorphine, but there was no comparison arm. Thirty-one of the 65 participants enrolled into the study had abandoned treatment within 2 weeks, but this was related to the low initial dose (approximately 2mg/day)

5.2.7 Buprenorphine in combination with naloxone

Naloxone acts as a competitive antagonist at the opioid receptors in the central nervous system, reversing the effects of opioids. It has no opioid agonist activity of its own.

A combination of buprenorphine and naloxone (4.1 ratio) has been developed for use in opioid dependence and is currently under review by the Food and Drug Administration (Raisch et al, 2002, see also Chapter 6 Abuse Liability). The aim of the combination is to reduce the abuse potential of buprenorphine without affecting its efficacy as a maintenance treatment for opioid dependence.

Several preliminary studies have been reported which evaluated buprenorphine and naloxone in combination. Harris and workers (2000) investigated the effects of buprenorphine alone and in combination with naloxone (in 2:1 or 1:1 ratio) in opioid dependent volunteers who had been stabilised on buprenorphine for a week. There was no evidence of precipitated opiate withdrawal either after sublingual or intravenous doses of the combination. The ratio of the drug combination in this study was not the one chosen for the tablet formulation.

Fudala et al (1998) investigated the effects of a 4:1 combination of buprenorphine and naloxone administered intravenous to 10 opioid dependent subjects, stabilised on morphine. The combination produced opioid antagonist-like effects. The investigators concluded that these effects should limit its potential for intravenous abuse.

Amass and workers (2000) compared the efficacy of daily versus alternate day treatment with the buprenorphine/naloxone combination tablet in 26 opioid dependent outpatients. No difference was found in terms of treatment retention and positive urinalysis between the 2 dosage regimens.

Although these are just preliminary studies, the results suggest that a combination of buprenorphine and naloxone may be as effective as buprenorphine alone in the management of opioid dependence and that it will have less abuse potential.

5.3 Overall summary and conclusions

Many clinical trials have been undertaken to evaluate the use of buprenorphine in the management of opioid dependency. In terms of its use in managed withdrawal, the studies were too heterogeneous to enable formal meta analysis to be done but a systematic review suggested that buprenorphine had potential in this area.

Similarly, the studies investigating the use of buprenorphine as maintenance/substitution treatment used diverse protocols in terms of (a) dosage regimen (daily versus less frequent dosing), (b) dosage schedules (fixed versus flexible) (c) total dosage of buprenorphine (2-8mg/day or higher) and (d) the formulation of buprenorphine used. Moreover, studies varied in their non-pharmacologic treatment regimens, which could affect the endpoints and therefore introduce bias. Nevertheless the results of a formal meta-analysis performed on 6 randomised controlled trials, using methadone as comparator, showed that high

dose buprenorphine was similar to high dose methadone in terms of treatment retention with a small increase in positive urinalysis relative to methadone. Although the latter was statistically significant, it was not felt to be clinically relevant. It was not possible to determine the optimal dosing regimen although it was noted that less than daily dosing was feasible in clinical practice.

From the data available it was not possible to determine whether buprenorphine was more suitable for specific sub-groups. There is some evidence to suggest that those, with higher psychosocial and global functioning are more likely to respond to buprenorphine, but more studies are required to substantiate this. Data, available to date, on its use in pregnant women showed that buprenorphine was efficacious and safe for both women and infants but definitive recommendations on dosing regimens could not be deduced from the studies undertaken.

Chapter 6

Review of Drug Safety

6.1 Post-marketing data

Post-marketing safety data are available from the UK and France where buprenorphine is licensed for the treatment of opioid drug dependence, within a framework of medical, social and psychological treatment and has been in use since 1998 and 1996 respectively. In the UK, the product licence holder is undertaking a surveillance study, conducted under the guidelines for company-sponsored safety assessment of marketed medicines (SAMM). This is a non-randomised, non-interventional, observational study, comparing the safety of patients treated with Subutex® and methadone, over the first 6 months of treatment. The objective of this study is to evaluate the safety of high dose buprenorphine, used for substitution therapy.

The company plans to recruit 200 investigators in several settings – community drug teams, drug dependency units and general practice – and to enrol 5,000 opiate dependent patients, requiring opiate substitution therapy. Patients will be entered in the ratio of 4 Subutex®-treated patients for every 1 methadone patient. The number of subjects required is based on results from controlled studies, which showed retention in treatment for 6 months of 40 – 50%. A total population of 5,000 would be expected to result in the required number so that a 20% difference, if present, could be detected.

Data will be collected at baseline and at 6 months and the main outcomes to be measured are general health (assessed by the Opiate Treatment Index – OTI), details on opiate dependency, usage and employment status. In addition, details of "serious adverse events" occurring within the previous 6 months will be collected at the 6 months time-point. A serious adverse event is an experience by the patient that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, or is a congenital anomaly/birth defect, that occurs when the patient is on medication, irrespective of whether or not it is deemed drug-related or expected by the investigator.

The company has provided an interim report from this post-marketing study. Since April 2000, 175 sites have been enrolled and 107 of these have contributed data. A total of 846 patients have been enrolled. Approximately 800 report forms have been received and validated. Initial evaluation shows that 84 % of patients are receiving buprenorphine, 70% are male and the vast majority (97%) are Caucasian. So far, ten cases of "serious adverse events" have been reported by the investigators, including one death (suicide, judged to be unlikely to be associated with the treatment). Of these, 2 have been evaluated as being probably related – one relates to sensory disturbance, which was reclassified as not serious and from which the patient recovered completely with withdrawal of treatment. The second relates to "accidental injury" where the patient fell and injured himself. There was also evidence of a drug interaction in this case (concomitant use of benzodiazepines). The subject did not require hospitalisation and recovered completely but buprenorphine was withdrawn. Two of the remaining adverse events were thought to be possibly related to treatment (withdrawal syndrome and convulsions) and the remainder were thought unlikely to be due to the treatment.

There is preliminary information on the dropouts in the study. These are subjects who fail to complete 6 months of treatment. The biggest single reason for this appears to be failure to attend the clinic (no reason given), which was recorded in 26% of the dropout cases. A further 16% changed to detoxification regimens and the remaining causes (all at less than 10%) include adverse event, withdrawal symptoms, left the area, did not like/want treatment with buprenorphine, and returned to heroin use.

This study is limited in that it allows for the collection of minimal data only. Moreover, the results to hand are preliminary. However, they support the view that use of buprenorphine

for the management of opiate addiction in normal clinical practice has not produced any unexpected or unacceptable toxicity.

Information has been retrieved from the Adverse Drug Reactions Online Information Tracking (ADROIT) System of the Medicines Control Agency (MCA) in the UK. This provided information on all adverse drug reactions (ADRs) in its database for buprenorphine from 1977 – 15/05/01.

A total of 962 reports were received in that time, outlining 1,952 reactions. The commonest reported ADRs were nausea (191), vomiting (337) and dizziness (excluding vertigo n=202). The next commonest were hallucinations (63), headache (58) and vertigo (55). Respiratory depression was noted in only 39 cases and 4 cases of hepatobiliary disorders were recorded. Four deaths were reported (3 cardiac arrests and 1 acute circulatory failure) but there are no further details available for these reports. It is important to remember that the data relate to all dosage forms of buprenorphine (i.e. lower dosage temgesic® as well as Subutex®) and are not linked to drug usage figures. Although these data are non-specific, they are important in that the pattern of ADR reports is in line with the known pharmacologic profile of buprenorphine.

Finally, the product Subutex® was marketed in France from February 1996 and up until August 1997 21 liver/biliary system related adverse effects in 12 patients were reported (unpublished data – company clinical expert report, 1997). Most of these were "hepatitis" and were not fatal. There were 2 deaths reported, due to liver failure. One of these had pre-existing hepatitis B and C. The other presented with hepatitis and hepatocellular damage, which proved fatal. The summary of Product Characteristics (SPC) in France was amended in September l997 to include a warning about hepatitis and hepatic events. This warning is also included in the UK SPC as follows:

> HEPATITIS, HEPATIC EVENTS: Hepatic necrosis and hepatitis with jaundice, which generally have resolved favourably, have been reported in patients who use buprenorphine. Causality has not been clearly established. When a hepatic event is suspected and the causality is unknown, further evaluation is required. If Subutex® is suspected to be the cause of hepatic necrosis or jaundice it must be discontinued as rapidly as the patient's clinical condition permits. All patients should have liver function tests performed at regular intervals.

6.2 Fatalities with use

The published data on fatalities come from a series of case reports, primarily from France. A lot of work has been done by French researchers to develop suitable assays for measuring buprenorphine and its primary metabolite norbuprenorphine in blood and body tissues, in order to estimate the potential at-risk level for a fatal outcome. Reynaud and workers (1998) reported on a series of 6 deaths occurring in known drug abusers in France. Three of the cases had what were described as "normal" plasma levels of buprenorphine and norbuprenorphine, while the other three had high normal levels. All of the cases had evidence of therapeutic levels of benzodiazepines – demethyldiazepam and 7-amino flunitrazepam. No traces of other opiates were detected in the post-mortem blood, while a moderate ethanol level was found in 3 cases.

Tracqui et al (1998) reported on 20 cases of fatality in drug users from urban areas in France. All cases showed normal or slightly elevated plasma levels of buprenorphine. In addition, evidence of psychotropic agents (especially benzodiazepines) was found in all of the plasma samples. These workers also reported on the phenomenon of injecting the crushed tablets (designed for sublingual use) and felt that this contributed to the risk of a fatal outcome. Both Traqui and Reynaud recommended that the provisions for dispensing buprenorphine that pertained in France at that time should be reviewed.

In 2001, Kintz published a comprehensive compendium of French fatalities involving buprenorphine usage from 1996 – 2000. Toxicologists in France were notified and asked to provide data for the report. A total of 117 cases from 14 centres were identified and included in the analysis. This paper excluded the cases previously reported by Traqui.

In Kintz's report, evidence of drug-related fatality had been found at the site of death in 2/3 of cases – empty packages of tablets, spoons, straws, syringes, other psychotropics. In addition, half of the subjects showed needle marks suggestive of intravenous injection before death. All cases showed post-mortem signs consistent with death involving CNS depressants (especially seen in opiate-related deaths).

The mean plasma levels for buprenorphine and norbuprenorphine were normal although there was a wide variation within the group. All but one case had a concomitant intake of psychotropic agents. This case was diagnosed as Mendelson's syndrome – tracheobronchial inhalation. Table 6.1 shows the range of concomitant drugs.

The paper concludes that the risk of death with buprenorphine is associated with concomitant use of psychotropic agents and the intravenous injection of the tablet formulation, which gives immediate bioavailability of the tablet. It states that these cases probably represent an underestimation of the total number of buprenorphine-related fatalities because not all areas of the country were included in the survey and autopsies were not always requested in cases of drug-related death.

Finally, of interest is a case report of an intentional suicide from France (Gaulier et al, 2000) in which several drugs, including buprenorphine had been taken. High plasma levels of buprenorphine and norbuprenorphine were found and the site of death suggested that the drug had been taken orally. Therefore, it is possible to get toxic levels after oral intake.

It is important to note that in France, physicians may prescribe a supply of up to 28 days of buprenorphine for substitution treatment and many of the papers cite the ready availability of relatively large doses of buprenorphine as a contributory factor in buprenorphine-related death (see also Chapter 7).

6.3 Abuse liability

It has been known from its early development phase that buprenorphine has the potential for abuse, as it produces opioid-type effects in animals and humans (Jasinski et al, 1978; Mello et al, 1981). Since the 1980s a series of papers from various countries, including Ireland, (O'Connor et al, 1988) have reported on the misuse of buprenorphine (which was available as an analgesic) among problem drug users. In 1991, Lavelle and workers reported that buprenorphine was more frequently misused than heroin or other opiates among a group

Table 6.1:

Drug Class	Drug Name	No. of Patients (N=116*)
Benzodiazepines	nordiazepam others others	64 27
		total **91**
Neuroleptics	cyamemazine others	26 11
		total **37**
Antidepressants	tricyclics SSRIs	8 10
		total **28**
Narcotics	morphine (8 @ toxic levels) codeine methadone pethidine propoxyphene	12 2 4 1 4
		total **23**
Ethanol	"fatal interaction"	4

* more than one drug was noted in many cases

(n=78) of Glasgow-based drug addicts. This paper was of interest in that buprenorphine misuse was not associated with criminality in this group in contrast to heroin or other illicit drug use. The reason for this was thought to be the ready availability and cheap cost of buprenorphine in the marketplace, at the time.

Intravenous injection of buprenorphine was reported by 81% of patients (n=54) presenting to a drug treatment centre in New Zealand during 1990. When a buprenorphine-naloxone combination was launched in 1991, in the hope of reducing intravenous misuse, approximately half of the addicts (n=44) questioned over the next year stated that they continued to inject the combination product, even though it produced withdrawal symptoms in about 1/3 of the group (Robinson et al, 1993).

Intravenous injection of buprenorphine was also reported in Spain in heroin addicts (n=385) undergoing treatment – more than 60% reported use of buprenorphine at some time during their period of drug abuse and, of these, 70% used the intravenous route of administration (San et al, 1993). Further work by this group (Torrens et al, 1993) compared the psychopathological characteristics of buprenorphine abusers (n=22) with heroin abusers (n=45) in Spain and found no significant differences. They suggested that the reason for the abuse of buprenorphine was the availability of buprenorphine in the marketplace. The numbers are small in this study but the findings support those reported previously from Scotland.

A survey, carried out among 130 community pharmacists in South Western France in 1992/1993 into the abuse of prescription medicines, calculated that buprenorphine had the third highest addiction potential, coming after a dextroamphetamine combination and fenzolone, (a sympathomimetic agent) and higher than other opiates available on prescription (Baumevieille et al, 1997). The investigators based their calculation on the "abuse rate ratio" (derived from dividing the abuse rate of a medicine by that of a reference medicine without addictive potential – in this case frusemide). Buprenorphine was available only as an analgesic at the time and was subject to restriction of prescription and supply in line with the United Nations recommendations for drugs with addictive potential.

Most of the recently published information on abuse liability comes from France, where "high-dose" buprenorphine (i.e. higher doses than previously available for analgesia) was made available as a standard registered medication. This allowed it to be prescribed by any medical doctor, general practitioner (GP) or specialist, in public or private practice, both in in-patient and out-patient settings. Prescription is limited only as follows – a special prescription pad for controlled substances is needed and each prescription is valid for a maximum of 28 days' supply. (Auriacombe et al, 1999). In June 1996, 4 months after high dose buprenorphine was made available for the management of opioid addiction, a face-to-face survey was conducted at over 2,500 pharmacies throughout France to get information on the new drug treatment programme (Auriacombe et al, 1997). Results showed that pharmacists considered that buprenorphine was used in the correct fashion in 80% of cases, with intravenous injection of the crushed tablet being suspected in 10 – 15% of cases. More recent reports suggest that intravenous use of the crushed sublingual tablet may occur on an irregular basis in as many as 20 – 30% of subjects receiving buprenorphine maintenance treatment in France (Auriacombe et al, 1999).

Information on the level of abuse of buprenorphine has also come from several studies, undertaken in France in recent years to review the situation of opioid addiction. The SPESUB study was begun in May 1996 (Duburcq et al, 2000). This was a prospective epidemiological 2-year follow-up study, carried out among approximately 100 French GPs, involved in the management of drug abusers. Each GP was required to include the first 10 opioid drug addict patients to whom he/she prescribed high dose buprenorphine, with a maximum inclusion period of 3 months. The study reported that 14% of patients who remained in the treatment programme declared intravenous injection of high dosage buprenorphine in the previous month, although their intake of other drugs fell from baseline. All of these patients received several days'/ weeks' supply of buprenorphine at a time.

The OPPIDUM is an annual survey, which investigates drug dependent subjects attending specialized care centres in France. This survey is organised by the 6 national Centres for Evaluation and Information on Pharmaco-Dependence (CEIPs), under the responsibility of the Commission for Narcotics and Psychotropic Drugs/French Drug Agency. The CEIPs select the co-ordination centres and supervise the survey, which takes place over 4 weeks and collects socio-demographic data and drug consumption data for the previous week from attendees at the clinics. Barrau et al (2001) reported on the 1998 survey, which involved 46 substance abuse treatment centres and compared the buprenorphine treated group with those receiving methadone. It is important to note that in France, methadone treatment of opioid dependent subjects is subject to restriction of initial prescription from a limited number of specialised hospitals or specialised treatment units, with follow-up prescriptions allowed only from general practitioners who are in contact with these units (Moatti et al, 1998).

The OPPIDUM survey from 1998 involved 1,462 subjects with a 99% response rate. Methadone maintenance was the treatment used in 424 patients and buprenorphine was used in 616 patients. The remaining patients were receiving other forms of treatment and were not discussed in the Barrau report. It was noted that 99% of the methadone group consumed their dose orally, from a legitimate source and that 98% took their dose as prescribed on a daily basis. None reported intravenous/intranasal administration of methadone, although 15% reported use of at least one other intravenous drug in the previous week. (The intranasal route is used by some opioid dependent subjects to take illicit drugs). In contrast, intravenous/intranasal use of buprenorphine was reported by 16% and 4% of the buprenorphine group respectively, with 8% of their doses coming from an illicit source. Injection rates were even greater for subjects described as "outwith" the standard protocols (i.e. on buprenorphine maintenance treatment without any formal supervision). Daily use was reported in 94% of the group ($p = 0.001$ with respect to methadone). Further analysis of the buprenorphine group showed that those managed within a GP setting were more likely to abuse buprenorphine via the intravenous or intranasal routes. The investigators pointed out that the study did not represent the global situation, but they suggested that the behaviour of maintenance treatment subjects depends less on the nature of the maintenance drug than the nature of delivery and monitoring practices.

It is important to note that the OPPIDUM survey is subject to several biases, the most important one being selection bias, as the centres are not randomly chosen (personal communication, Dr Auriacombe). In addition, since the survey is undertaken in treatment centres and excludes general practice, the type of patient cannot be said to be representative of the French treatment population as a whole. However, it provides data on a large scale and the results are in keeping with the information received from the experts in both France and the UK (see Chapter 7, Review of buprenorphine use in Clinical Practice). It supports the need to ensure close monitoring of the patient and to limit take-away dosing until the patient is stabilised, both medically and socially.

A cross-sectional study, undertaken by Obadia and workers (2001) over a 3-day period in 1997, analysed the risk of illicit use of buprenorphine treatment. A questionnaire was offered to individuals at 39 sites where intravenous drug users had access to syringes, including pharmacies, needle exchange programmes and 3 syringe vending machines (which are located in several urban areas in France). Of 485 potential participants, completed questionnaires were returned for 343 (70.7%). A total of 112 respondents (32.7%) were on buprenorphine maintenance treatment and 79 of these reported intravenous injection of buprenorphine during the previous 6 months. Buprenorphine injection was also reported in the polydrug users who were not on maintenance programmes and therefore had procured buprenorphine through illicit means. Although the authors admit that the study had many limitations, the results support other studies in terms of the abuse potential of buprenorphine.

Buprenorphine is not authorised in the USA for the management of opioid dependence at the present time. In 1994, buprenorphine was granted Orphan Drug status in the USA for "the treatment of opiate addiction in opiate users", but such use is strictly confined to clinical trials (Henney, 2000). Results from many of the US trials are reported Chapter 5. All of the patients entered into these trials were closely monitored and had supervised administration of most if not all of their doses. Therefore, they would have had little opportunity to abuse their prescribed buprenorphine medication. Even those trials undertaken in primary care settings were strictly supervised (O'Connor et al, 1998). However, the abuse potential of buprenorphine has been recognised by the National Institute on Drug Abuse in the USA (NIDA 2000), which has funded much of the buprenorphine research both at national and international level. It is now working with its commercial partners to develop a buprenorphine/naloxone combination tablet (see Chapter 5, Review of Clinical Trials with buprenorphine). A new drug application is pending in the USA for the combination tablet (4:1 buprenorphine/naloxone, Raisch et al, 2002).

NIDA states that both buprenorphine (which is nearing final approval by the FDA – personal communication, NIDA) and the buprenorphine–naloxone combination are likely to be administered through "normal medical practice settings like physicians' offices" (NIDA 2000). Legislation was passed in 1999 (The Drug Addiction Treatment Act), which allowed for general practitioners in the USA to prescribe certain narcotics such as buprenorphine, for maintenance treatment of opioid-dependent patients (Raisch et al, 2002). The likelihood of a more liberal availability of buprenorphine in the USA has resulted in a Citizens' Petition being sent to the FDA seeking a restricted availability similar to that with methadone and LAAM (their use for outpatient treatment is restricted to treatment programmes that obtain a special licence and adhere to specific regulations on use – O'Connor et al, 1998). The final decision by the FDA on the method of supply and regulation of buprenorphine use is not yet available.

6.4 Overall summary and conclusions

The safety data available to date suggest that buprenorphine has a known and predictable toxicity profile, related to its opioid agonist pharmacology and its interactions with other medicines. Although causality has not been proven, there is a warning regarding possible hepatotoxicity associated with use and it is recommended that liver function tests are regularly performed in patients receiving buprenorphine. The biggest problem to date appears to be the risk of fatal interaction with benzodiazepines.

Buprenorphine has a known potential for abuse, because of its opioid effects. Studies from France suggest that abuse may occur in up to 30% of treatment subjects. It would appear from these studies that abuse is more likely in those subjects not closely supervised either by a physician or dispensing pharmacist.

Since harm reduction is a main aim of all substitution treatment programmes and reduction in the use of intravenous injections an important element of harm reduction, it is reasonable to conclude that buprenorphine usage should be subject to supervision by physician and/or dispensing pharmacist especially in the early phase of treatment (induction phase).

Chapter 7

Review of use in Clinical Practice

7.1 Use of buprenorphine within the European Union (EU)

The European Monitoring Centre for Drugs & Drug Addiction (EMCDDA) was set up by Council Regulation (EEC) no 302/93 and became fully operational in 1995. It is located in Lisbon and its mission is to provide the EU and member states with objective, reliable and comparable information at European level concerning drugs and drug addiction and their consequences. In a recent publication (Farrell et al, 2000) the EMCDDA reported that high-dose buprenorphine (in the form of Subutex®) was introduced into the substitution treatment programmes for opioid dependence of many EU member states in the late 1990s (including Denmark, Germany, Italy, Luxemburg, Austria, Finland and the UK). France was the first member state to authorise such usage (in 1996) and the EMCDDA estimated that buprenorphine treatment had been prescribed to as many as 60,000 opioid dependent subjects over a 5-year period in France (this figure has now risen to 70,000 – personal communication Dr. Auriacombe). The authorisation for Subutex® is pending in Ireland (personal communication, Irish Medicines Board).*

There have been several observational studies carried out in France since 1996 and these are outlined below (see section 7.3). There are no evaluation data from Denmark, Germany, Italy, Luxemburg or Finland as usage to date is too small. Several clinical trials were undertaken in Austria in the 1990s and these are reported elsewhere in this report (see Chapter 5). There are no data available regarding use in practice from Austria as there is no public funding available for surveillance programmes, but it is estimated that the average buprenorphine dosage used is 8-12mg/day (Fischer, 2000).

7.2 Use of buprenorphine in the UK

The UK authorised high dose buprenorphine (Subutex®) for the management of opioid dependence in 1998 but methadone continues to be the mainstay of substitution treatment (Farrell and Howes, 2000). A post-marketing surveillance study is currently being undertaken by the pharmaceutical company and interim results are reported elsewhere (see section 6.1). A qualitative study comparing buprenorphine with lofexidine for managed withdrawal in a community setting has also been undertaken and has shown that buprenorphine is more effective than lofexidine in terms of completion of withdrawal and alleviation of withdrawal symptoms (White et al, 2001).

Two treatment centres (general practice clinics) in London where buprenorphine has been used for the management of opioid dependence were contacted and a questionnaire on the use of buprenorphine was sent to the contact physician in each centre. This was discussed in detail with the respondent either on a face-to-face basis or by phone. The replies to the questionnaire were subsequently verified with each respondent, before inclusion in this report. The questionnaire is found in Appendix II and the results of the questionnaire are summarised in Table 7.1.

7.2.1 Reports from treatment centres

Treatment Centre (1) Report

Background note on centre

Dr. Gerada is a lead GP in the management of opioid dependency and the Chair of the Royal College of General Practitioners' Advisory group on drug abuse.

Her practice has direct management, at any one time of approximately 100 drug users. Furthermore, under the shared care services system, she oversees management of approximately 800 drug users, treated in other general practice clinics.

The clinic organises full assessment of each new patient including full physical examination and urinalysis. Patients are closely monitored by the physician in the induction phase (daily/alternate days) with daily dispensing of medication in the early weeks

* Authorisation of Subutex® occured in August 2002, after completion of the review.

of treatment. Administration of the dose is not supervised. The interval between clinic visits is increased as the patient becomes stabilised on the medication. In addition, the dispensing interval is also increased with time to a maximum of 1-2 weeks depending on the motivation and status of the patient.

Urinalysis is performed infrequently. The clinic aims to maintain good contact with and support for the patient, which helps with treatment retention.

Use of buprenorphine in practice
Buprenorphine is used both for managed withdrawal/detoxification and maintenance treatment. Withdrawal occurs rarely but buprenorphine has been found to be better than lofexidine, the alternative treatment used here. It is quicker than methadone taper, but if patients are being changed over from methadone, the methadone dose has to be reduced to 30mg/day and the dose carefully titrated to minimise the withdrawal symptoms, which nearly always occur. Dihydrocodeine may also be used for withdrawal and buprenorphine has been found to be as effective.

Buprenorphine is used primarily for maintenance treatment. Each patient's dose is individually titrated until he/she is stabilised on a daily dosage regimen. Alternate day/thrice weekly dosing is being considered for the future. A linear dose-response effect has been noted up to around 20mg. The majority of patients are stabilised on a dose of around 10mg/day.

There appears to be no absolute contra-indication to use in any group but patients with psychosocial problems do less well and methadone is the treatment of preference for this sub-group. Similarly patients on long-term heroin/methadone maintenance or those with a high opiate addiction may do less well.

Patients on medication for HIV, hepatitis C and depression have been treated with no ill effects to date. It is judged to be particularly suitable for highly motivated patients as it is not sedating and therefore they feel better much sooner than with methadone.

Clinical issues with usage
Side effects include insomnia, which can be debilitating and which may need pharmacological management, anxiety, agitation during the induction phase and a bad taste in the mouth from the tablet. Depression may occur during the maintenance but it may also be due to the underlying opioid dependency.

There are no figures on possible diversion from the clinic although studies from France suggest that diversion may occur in up to 30% of cases. Good interaction between the patient and the treatment is thought to reduce diversion and also injection of the dose (approximately 10% of cases may do this on an irregular basis). Buprenorphine is not used in a patient if there is a suspicion of possible abuse.

Buprenorphine is thought to be as efficacious as methadone, the current mainstay of treatment and safer for the patient. Other treatments such as naltrexone and slow-release morphine are used occasionally but buprenorphine would be considered to be more efficacious than these modalities.

Overall, it is currently considered for first line treatment of opioid dependence at this clinic, the only contra-indications being poor psychosocial circumstances or the possibility of abuse.

Treatment Centre (2) Report

Background note on Centre
Dr. Chris Ford is a general practitioner whose practice looks after approximately 100 drug users, of whom around 85 are on substitution therapy.

The team also includes a psychologist and a "drug worker" who work with the patients at practice level. Drug workers usually (but not always) have a paramedical background such as nursing.

Patients are managed in the clinic from the initial stage of treatment onwards. Each new patient is evaluated by the team and urinalysis (1 or 2 samples) is carried out before treatment begins. The patient is seen every few days by the team during the induction phase of treatment. The interval between visits is gradually lengthened, as the patient becomes

stabilised on substitution therapy. Urinalysis is performed frequently at the beginning and then randomly, about every 2-3 months, when the patient is stabilised on treatment. Urinalysis involves a general screen for all illicit drugs including cocaine, amphetamines and cannabis.

Patients receive their medication from a local pharmacy and consumption is not supervised. In the early stages of induction, a patient collects his/her dose on a daily basis (take-aways have to be given in areas where the pharmacies are not open at weekends). As treatment progresses, the patient may be allowed collect his/her medication every 2 days, with the interval gradually extending rarely to once weekly over time. A twice or thrice weekly collection is the commonest pattern for stable patients. More than a week's collection is never allowed except for holidays.

Use of buprenorphine in practice

Buprenorphine is used in the clinic for managed withdrawal/detoxification, although, in practice, this involves few patients. It is more efficacious than lofexidine, the other treatment used for this indication. It results in a much quicker and more effective withdrawal than methadone taper, which often takes several months, is rarely successful and is unpleasant. Patients need to be actively managed during the induction period of 3-4 days, because of the development of unpleasant symptoms, such as agitation, diarrhoea and sleep disturbance that may be quite severe. Patients need to have their dose carefully titrated to their needs and they need symptomatic support, otherwise there is a high attrition rate (especially noted for women patients).

Buprenorphine is used less commonly for maintenance treatment than methadone but is judged to be as effective as methadone in the appropriate person. Currently there would be a 20:1 ratio in terms of methadone to buprenorphine usage in the practice and only 2+ years' experience (in contrast to 15 years for methadone); therefore, experience is much less for buprenorphine. Patients' dosage is titrated until they are stabilised, within 3-4 days and then maintained on a daily dosage regimen. The average dosage used is 12mg/day. Doses greater than 20mg have rarely been used.

Buprenorphine has been suitable for all groups, although experience is small with certain groups. It has proved very useful in young people who are methadone naïve and are requesting a short detoxification. It has been used rarely in pregnant women but there is a lack of awareness of buprenorphine on the part of the other healthcare professionals dealing with pregnancy and this may interfere with the treatment regimen. Therefore methadone is still given in preference to pregnant women.

Drug interactions are not considered a contra-indication and in fact benzodiazepines have been co-prescribed on occasion especially in the induction phase of treatment, with no ill-effects.

Buprenorphine is particularly suitable for well-motivated patients who want to be not clouded by medication. People who are working have found it very helpful.

Clinical Issues with buprenorphine

Side effects, including agitation, sleep disturbance and anxiety, only seem to occur during the induction phase. There is a bad/bitter taste from the tablet, which may clear with time.

Diversion is not thought to be a problem but, because its use is fairly new, the extent of any diversion is unknown. No patients have been found to be injecting their dose.

Use of buprenorphine has increased the tools available for substitute medication and detoxification and has proven useful in primary care. Overall, it is thought to be a very useful addition and probably as good as methadone for maintenance, in certain individuals, and better than lofexidine for withdrawal. As more experience is gained a better insight into whether certain sup-groups are more suitable for buprenorphine treatment will be achieved.

7.3 Use of buprenorphine in France

In 1996, France introduced high-dose buprenorphine and methadone for use in the management of opioid dependency. Since then it is estimated that 10,000 patients have been treated with methadone and 70,000

with buprenorphine (personal communication – Dr Auriacombe). France was the first country in the world to allow use of high-dose buprenorphine for the treatment of opioid dependency through the primary care system. General practitioners are allowed to initiate treatment with buprenorphine in their practice and to manage these patients for the duration of their treatment (Auriacombe, 2000). In contrast, methadone is subject to greater restrictions (see section 6.3 Abuse Liability) and, in general, methadone-maintained patients are treated in specialist settings, only switching to general practice management when they are judged to have stabilised on treatment (usually several months after beginning of therapy).

Since its introduction in February 1996, there have been many outcome surveys undertaken in France to monitor the consequences of this programme. Early surveys showed unwillingness by GPs to become involved in the management of opioid dependent patients. Moatti and workers (1998) interviewed 1,186 GPs randomly chosen from across France in April 1996. Only 13% of those GPs interviewed were prepared to prescribe buprenorphine. Only 7% of those who had had little or no prior consultations with intravenous drug users said they would prescribe buprenorphine.

In May 1997, a survey of 200 GPs showed that 26% of them had prescribed buprenorphine but in the majority of cases, they had treated fewer than 5 patients. (Bouchez and Vignau, 1998). This survey also interviewed over 2,000 pharmacists of whom 52% had dispensed a substitution agent of some form in the previous months. Buprenorphine dispensing was supervised in 40% cases only and the survey reported poor communication between the pharmacist and prescribing doctor. Co-prescription with benzodiazepines was reported as "infrequent" although injection kits were bought at the same time as buprenorphine in 30% of cases suggesting intravenous abuse.

This survey was of particular interest because it collected data from 749 patients within the programme, using a questionnaire, distributed by GPs and pharmacists. Most of the respondents had attempted rapid detoxification an average of 3 times prior to the introduction of the maintenance programme. The mean dose of buprenorphine was reported to be 11mg/day, with 8% admitting to using the intravenous route. Over half of the group felt that they were "taking care of their health" by being in the programme and almost all of them (95%) reported improvements in psychosocial status. Although the method of collection of these data is open to criticism, the results were encouraging, especially with respect to the apparent improvement in the patient's wellbeing.

Vignau and workers (2001) undertook an in-depth review of the health insurance records for a semi-rural area of northern France, and identified cases where Subutex® had been used over the first two years of use (1996 – 8). The GP and pharmacist in each case were identified and asked to take part in an interview during which a detailed questionnaire was completed.

A total of 154 patient records were identified of which 142 (92%) were eligible for review. The survey noted that 27.5% of physicians and 51.8% of pharmacists in the area were involved in the treatment programme. During induction, 71% of Subutex® doses were supervised by the dispensing pharmacists (despite there being no legal requirement to do so and no additional payment for providing this service). This reduced to 23% supervised dispensing when the patients had stabilised on treatment. The mean dose prescribed was 6mg/day. This is now judged to be a sub-optimal dose, but probably reflected the lack of training for GPs at the time and the concerns of over prescribing high dose opiates. However, retention rates of 61% were noted at the end of the observation period (mean treatment follow-up of 61 weeks). These were associated with improvements in the patients' overall medical and psychosocial status, with the exception of improvement in depression. Urinalysis was not routinely performed (logistically difficult and expensive) and therefore it was not possible to give an objective evaluation of illicit opiate use with treatment.

The investigators concluded that the results were promising but highlighted the need for specific training (e.g. in terms of correct dosing and toxicological analysis) for GPs involved in the management of opioid dependency.

The SPESUB study was begun in May 1996 and was a prospective epidemiological 2-year follow-up study carried out among 100 French GPs, involved in the management of opioid dependency. Each GP enrolled the first 10 patients prescribed high dose buprenorphine (Duburcq et al, 2000; Fhima et al, 2001) in his/her practice. Standardised information on the patients such as social circumstances, illicit drug use and the doses of buprenorphine was collected at 1, 3, 6, 12 and 24 months. The main outcomes were treatment retention and follow up by the same GP at 2 years.

Of 919 patients enrolled in the study, 909 were eligible for evaluation at 2 years. Nearly 70% of the patients remained within a maintenance treatment programme – 508 (55.9%) were still under the care of the enrolling physician with 101 (11.1%) under the care of another healthcare professional. Among the patients followed by the same GP, the median dose was 8mg/day although the dose range widened over the 2 years. Declaration of heroin and other illicit drug intake was significantly reduced at 2 years with social conditions such as housing and employment significantly improved, although intravenous injection of buprenorphine was declared in 14% of patients. Evidence of reduced drug-related harm was noted in terms of reduction in the predicted numbers of seroconversions for hepatitis B, C and HIV.

This study highlighted the benefit of buprenorphine in terms of patient wellbeing and showed the importance of good interaction between the patient and physician/treatment team in order to retain the patient in treatment.

The OPPIDUM is an annual survey, undertaken in October each year, to investigate drug-dependence in France (for background details see section 6.3 Abuse Liability). Several different reports have been published on the OPPIDUM studies. Thirion and workers (2001) recently compared the results of the 1995 survey (which predates the introduction of the buprenorphine and methadone maintenance programmes) with those from 1997, one year after the programmes began. Approximately 1600 files were reviewed from the survey.

The results showed a marked drop off in the use of heroin (74% in 1995 versus 25% in 1997). In addition, the overall use of psychoactive substances, including benzodiazepines was significantly lower in 1997 compared with 1995. Patients maintained on methadone tended to be older and to consume more cocaine, cannabis and benzodiazepines than those on buprenorphine, while the latter group tended to abuse buprenorphine by intravenous injection. Sixteen percent of buprenorphine treated patients were also taking benzodiazepines (62% via medical prescription).

The problems associated with the OPPIDUM surveys, in terms of bias and lack of representativeness, have already been discussed (section 6.3). However, the results of this comparison have shown a significant reduction in heroin abuse as a result of the introduction of the maintenance programmes and support the use of both buprenorphine and methadone for the management of opioid dependence.

A recently published report has evaluated the profile of patients treated with buprenorphine, using computerised data on prescriptions extracted from the Social Security System for reimbursement of prescriptions (Thirion et al, 2002). This was a cross-sectional study, which analysed all buprenorphine prescriptions sent to the Social Security during a 4 month period (September – December 1999) for a specified (mainly urban) region in southeast France.

The group reviewed the buprenorphine demographics of the patients, the doses prescribed and the identity of the prescriber(s). In addition, co-prescription of benzodiazepines was reviewed.

Overall, 76.6% of all prescriptions had been coded and were available electronically, covering 86% of the region's population. These identified 2,078 patients who had received at least one prescription of buprenorphine. The mean number of prescriptions dispensed per person was 6 and the mean daily treatment was 11.5mg (in those patients with enough prescriptions to allow computation). Concomitant benzodiazepine consumption was noted in 43% of patients and on occasions the benzodiazepine and buprenorphine was on the same prescription form (exact details not given). Prescriptions came from GPs in 85% of the cases, with clinics accounting for 11% and

Table 7.1: Summary data on buprenorphine use in practice in the UK and France

Buprenorphine	London (1)	London (2)	Bordeaux (1)	Bordeaux (2)
Use in withdrawal	Yes	Yes	Rarely	No
Useful in withdrawal	Yes	Yes	–	–
Use in substitution/ maintenance treatment	Yes	Yes	Yes	Yes
Method of dosing	Titrated to individual	Titrated to individual	Titrated to individual	Titrated to individual
Average daily dose (stabilised)	10mg	12mg	13mg	10mg
Supervised administration	No	No	Yes	Yes
Use of thrice weekly dosing	No+	No	No++	No++
Upper level of dose-response effect	20mg	–	32mg	32mg
Use in pregnancy	Yes	Yes*	Yes**	Yes**
Use in HIV/Hep C/liver disease	Yes	Yes	Yes	Yes
Use with psychotropics	Yes	Yes	Yes	Yes
Use in longstanding addicts/ high opiate dependency	?	?	Yes	Yes
Risk of diversion	?	?	‹10 – 30%#	?
Risk of injection of dose	10%	?	10%	10%
Problem drug interactions	No	No	No	No
Problem side-effects	Insomnia	Bad taste in mouth	Bad taste in mouth	Constipation/ bad taste in mouth
Discontinuation due to side-effects	No	No	No	No
Useful in substitution treatment	Yes	Yes	Yes	Yes
Buprenorphine versus methadone	Same efficacy, safer, ? abuse	Probably as good in suitable patients	Same efficacy, safer, more abuse potential	Same efficacy, safer, more abuse potential

Legend for Table 7.1

London (1) Dr. Gerada, general practitioner.
London (2) Dr. Ford, general practitioner.
Bordeaux (1) Dr. Marc Auriacombe, consultant psychiatrist.
Bordeaux (2) Dr. Michel de Ducla, general practitioner.

* in practice buprenorphine is used rarely as the other healthcare professionals involved in the care of pregnant women are still unfamiliar with it and therefore may interfere with the treatment protocol.

** because of the current legal situation in France buprenorphine is not started in a pregnant heroin addict presenting for treatment. However, a patient who becomes pregnant, while taking buprenorphine, is allowed to remain on the treatment.

\+ thrice weekly dosing may be introduced in the future.

++ patients have been offered thrice weekly dosing but have not accepted it.

\# ‹10% represents figures for this clinic. 30% diversion is seen in situations where supervised dispensing is not systematic.

specialist physicians 4%. A total of 21% of GPs in the region were involved in prescribing, but of these 61% had only one or 2 patients on treatment. These figures are consistent with other published reports and with the current involvement of GP's in the treatment programmes in France generally (personal communication, Dr. Auriacombe).

Of interest is the fact that 61% of patients received their prescriptions from one prescriber, 22% from 2, 11% from 3-5 and 1% from more than 5 prescribers. On the basis of the number of prescribers used, or a daily "consumption" of 20mg or more (computed from the files) the patients were divided into a "deviant group" a "regular follow-up group", or an "occasional consult group". There were significant differences between the regular follow-up and deviant groups in terms of concomitant use of benzodiazepines, which was much higher in the deviant group (71.4% versus 38.5%). It was not possible to identify the reasons for the higher daily dose of buprenorphine that the deviant group received – possibly due to either higher personal consumption, diversion or purchase for another person.

This study has limitations in that it was based on computerised data and therefore could not confirm the actual daily dose consumed by the patient (as opposed to dispensed to the patient). Furthermore it did not cover all of the prescriptions written during the period (76% coverage) and did not include all subjects within the region (estimated 85% coverage), which may result in selection bias. Finally some addicts may not be covered by social security and therefore would not be included in this survey. However, the results reaffirm the fact that only approximately 20% of GPs in France are involved in the buprenorphine treatment programme, the majority of whom treat only a few patients. In addition, it supports the findings from previous studies, that deviant patients are more likely to abuse their treatment medication and other medications, which may have safety implications.

Dr Auriacombe, from the University of Bordeaux, was contacted to seek information on experience of buprenorphine use in France. He is an expert in the management of substance abuse and runs a research-based substance abuse clinic in the university. He has extensive experience in the management of opioid dependent patients. Dr Auriacombe's centre was visited, in addition to a local general practice clinic, which manages opioid dependent patients, and a community pharmacy, which operates a system of supervised dispensing at community level. Information was gathered from the pharmacy and the treatment centres, using the questionnaire (Appendix II) as the basis for discussion. The replies to the questionnaire were subsequently verified with each respondent before inclusion in the report.

Each physician has extensive experience of use with buprenorphine. The information from each centre is included separately, together with a brief introduction to the clinic set-up. The findings are summarised in Table 7.1., which enables a comparison with the data collected from the UK treatment centres.

7.3.1 Reports from treatment centres

Treatment Centre (1) Report

This report relates to the general practice of Dr. Michel de Ducla, from the city of Bordeaux in France.

Background note on clinic

The opioid-dependent patients are seen by Dr. Michel de Ducla, GP, in his general surgery. Approximately 15-20% of his patients are drug addicts (n=60 at any one time).

Opioid dependent patients are referred by other doctors or patients or via self-referral. In France, GPs can prescribe only buprenorphine to such subjects (methadone initiation is restricted to specialist centres).

At first assessment, the patient has a full evaluation, including physical examination, and urinalysis. At the second visit the results of the urinalysis are available and the treatment plan is agreed with the patient (this is important) and then initiated.

A pharmacist, who has agreed to supply the medication is selected and it is arranged that the patient gets daily-supervised administration of the dose (unless the

pharmacy closes on Sunday when they must have take-aways). In the early stages of induction (usually the first 2 weeks) patients are seen regularly (several times a week) and the dose titrated according to the individual's needs. Close contact maintained between the pharmacist and the GP, which helps in the team approach to treatment.

Urinalysis is difficult in general practice, as it must be sent to a local laboratory for analysis. It is the practice to take a urine sample at every visit – this amounts to several samples per week in the early induction phase. Only one sample per week is sent for analysis. After some months the interval will be lengthened (as patient visits become less frequent). It is explained to the patient that this is part of the treatment protocol (i.e. a tool by which treatment is optimised) and therefore it is not viewed as a humiliation by the patient.

Supervised administration on a daily basis usually continues for a minimum of 3 months (usually longer) in the standard patient but this can be altered depending on the patient's motivation and need for support. During these 3 months, the patient is usually seen by the GP once a week, sometimes every 2 weeks. Afterwards, the patient can be seen once or twice a month, depending on how well he is from the psychological point of view.

This practice is part of a voluntary network of GPs in the area (RENAPSUD) who co-operate with each other by sharing expertise and information in order to facilitate the opioid-dependency treatment programme. The network currently receives no state funding.

Use of buprenorphine in practice

Buprenorphine is used for maintenance/substitution treatment only of opioid-dependent patients. It is not currently used for managed withdrawal. Because of the legal restrictions in France, methadone patients can be treated by GPs only when their management has been stabilised by a specialist centre and it is felt that they can now be managed in the community. No other drugs are used specifically for the management of opioid dependency.

In the maintenance setting buprenorphine dose is titrated to the patient's needs and administered on a daily basis. Alternate day/thrice weekly dosing has been offered to some patients but has not been acceptable to them. The average dose used is 10mg (range 6-12mg) although on occasions doses outside this range have been prescribed. A linear dose response has been noted up to 32mg in the one patient who was prescribed this dose.

Each dose is dispensed by a local pharmacy on a daily basis with supervised administration. This is continued until at least 3 months when the patient's condition has stabilised enough to get regular take-aways (up to a maximum of 7 days).

In terms of the patients who are suitable for buprenorphine, no groups are contra-indicated. To date, two patients attending the practice and who are taking buprenorphine, have become pregnant and have had a normal pregnancy and delivery, with no problems in the infant. Patients with psychosocial problems are more difficult to treat but that is due to their unstable life circumstances. Likewise, patients with high opiate requirements or long-standing dependence can be treated provided they are sufficiently motivated.

There have been no recorded problems with use of psychotropic agents, including benzodiazepines, which have to be co-prescribed on occasions.

Clinical issues with buprenorphine usage

Side effects noted in the early weeks of treatment include withdrawal symptoms (as early as 1-3 days of treatment) and the patient needs titration of dose and support in this phase. During the first month or so, patients may complain of constipation, urinary retention, impotence and excessive perspiration but these gradually clear spontaneously. The patients complain of a bad/bitter taste from the tablet, which often lasts indefinitely. None of these results in discontinuation of treatment.

The introduction of buprenorphine use into the general practice setting has not necessitated a change in the practice organisation. Opioid-dependent patients are rarely disruptive – in the initial phase they may be noisy or dishevelled but this rapidly disappears once treatment is underway. In fact it is considered beneficial for the opioid-

dependent patients to be treated in a general practice setting, as they are not stigmatised. Therefore, the visits of these individuals are spaced throughout the daily schedule, rather than having a specific clinic for opioid dependency. The non-opioid dependent patients have not objected to date and have not left the practice because of the attendance of opioid-dependent patients.

The abuse potential is a problem that is usually linked to poor supervision in the initial phases of treatment. It is estimated that approx 10% of the clinic's attendees would inject and those who do would do so on a regular basis.

Drug interactions are not a problem in clinical practice – the only possible problem that might occur is with a patient who abuses benzodiazepines in addition to taking buprenorphine, but this has not been a clinical issue so far.

The only factor, which is thought to be a contra-indication to the use of buprenorphine, is severe social deprivation or disturbance. It is felt that such patients cannot cope with the organisation necessary to enrol in the buprenorphine programme. Such patients would be referred for specialist clinic programmes.

The practice mainly deals with buprenorphine and has very small numbers of patients, who are stabilised on methadone. There is a big problem in terms of loss of stability with methadone when anti HIV or hepatitis C medication is introduced or changed, but this is not the case with buprenorphine stability. The main problem with buprenorphine is the issue of injection – there have been anecdotal reports of chemical hepatitis with injection of buprenorphine and injectors also run the risk of general adverse effects due to use of the intravenous route. It is important to note that buprenorphine injectors tend to do so safely (i.e. do not use dirty or shared needles) and therefore do not run the risk of contracting HIV or hepatitis B or C.

Overall, buprenorphine is judged to be a good and safe treatment for those opioid dependent patients who want to be treated discreetly in the community.

Treatment Centre (2) report

This report relates to the clinic of Dr. Auriacombe in the Department of Psychiatry, Victor Segalen University, Bordeaux II, France.

Background note on clinic

The clinic was established in the Department of Psychiatry in the University of Bordeaux. It is a research–oriented centre, which has been involved in the investigation and treatment of all types of substance abuse for approximately 20 years. It treats around 250 patients/year in its substitution treatment programme for opioid-dependent patients.

Patients are referred to the centre from healthcare professionals, via self-referral or referral from other patients in the programme. Patients are fully assessed to determine if they need treatment. For opioid dependent patients, the clinic recommends that they are treated with buprenorphine in the community (as a first option) by GPs. If possible the patient's own GP is used, otherwise a GP local/known to him/her is found and care is transferred to that general practice. The clinic would be available to give general advice on an ongoing basis if needed and if the patient is not doing well then he can always be referred back to the clinic at anytime (i.e. without going on the waiting list).

Whether the patient is treated in the clinic or referred to a GP for treatment, he/she is evaluated by the Addiction Severity Index and some other research tools. The clinic will monitor progress for research purposes as well as for therapeutic reasons.

The clinic manages the majority of patients by outpatient maintenance with either buprenorphine or methadone. The choice of medication would be buprenorphine in the first instance unless the patient has been previously treated with buprenorphine and has relapsed/not done well. It is also possible to initiate treatment as an inpatient, if this is judged to be necessary.

Before treatment starts, the doctor discusses the goals of treatment with the patient and evaluates the patient's perceptions/ expectations of treatment. The goal of the clinic is abstinence from problem opioid use – the timeframe is not discussed, although if

they ask, patients are told to expect treatment to last for several years. Patients are counselled (a psychiatric nurse is assigned to each case) and a medical social worker helps the patients in terms of social security (important for payment for treatment outside of clinic) and social circumstances (living conditions etc.).

A urine sample is taken at the first visit and the results are available for the next visit (when treatment is started).

Treatment is prescribed for daily use with daily-supervised administration, either at the clinic dispensary or a community pharmacy, in the early phase of treatment (any time up to 3 months or more).

In the early stages of treatment, take-aways are only given where local pharmacies are not available (e.g. on Sunday). They are introduced gradually once the patient is stabilised, with the maximum dispensing allowed being 7 days, except in exceptional circumstances (e.g. holidays/work commitments). The clinic has on-site dispensing which is open everyday for patients. Urine samples are taken each time the patient is seen in the early phases (daily/several times a week) but analysed only once a week – randomly chosen. As treatment progresses and the patient stabilises, visits to the doctor are less frequent (weekly and then fortnightly, then monthly) and a urine sample is taken on each occasion and analysed. Patients are told that collection of urine samples for analysis is part of the treatment programme and necessary to optimise treatment. Therefore, it is not seen as a sanction against the patient. It only becomes a tool used for sanction if a patient, who continually has positive urines, refuses to take a higher dose or to return to continue daily supervised dispensing.

Managed withdrawal/detoxification is used extremely rarely for patients by the clinic (e.g. rare case of recently addicted person of a few months and usually not intravenous abuse). There is a high relapse rate for patients in general with this treatment and therefore it would be reserved for those who have been on maintenance treatment for several years and who now wish to discontinue medication. Since buprenorphine has only been in general use since 1996, there are few patients on buprenorphine in this category. It is not the policy to switch methadone maintained patients to buprenorphine for withdrawal, therefore experience is limited. If the patient demands buprenorphine for withdrawal, methadone is reduced and the patient is warned that withdrawal symptoms for the first few days of buprenorphine are likely. It is not the policy of the clinic to initiate total discontinuation of maintenance therapy after a specific length of stable treatment.

Use of buprenorphine in practice

Buprenorphine is used primarily for substitution/maintenance treatment. It is not recommended for short-term "managed withdrawal" use and other methods are used in preference (e.g. electric therapy) but these are also used rarely in the clinic.

For maintenance treatment in the clinic, patients are titrated on a daily basis to achieve optimum level for stability (each individual is different).

It is important to note that induction begins when the patient has discontinued heroin for long enough to begin to experience withdrawal (time varies from patient to patient). The longer the interval between the last dose of heroin and first dose of buprenorphine, the less severe the withdrawal symptoms are likely to be.

Alternate day/thrice weekly dosing has been offered to patients, but does not appear to be acceptable to them and therefore is not used.

Each dose is dispensed by the clinic dispensary or community pharmacy and is supervised – the patient is given a tablet to put under his/her tongue and is asked to stay for approximately 10 minutes in the view of the dispensing pharmacist/clinic nurse to ensure absorption. If the patient requires more than one tablet, they may be given separately or together, depending on the patient and pharmacist choice. Separate administration of tablets (done to reduce or minimise diversion) extends the period of observation.

When the patient has stabilised and is seen less frequently by the team, then take-aways on a regular basis are possible at the patient's request (e.g. a patient who has negative urines

for opiates, for 3 consecutive months, as well as no other problematic substance use like alcohol or cocaine). Patients may also opt not to have take-aways. These are introduced gradually up to a maximum of 7 days unless a person's job requires a longer interval of 14 days. Unless the doctor specifically states it on the prescription, a pharmacist can only dispense 7 days supply at a time, even though the prescription is allowed for 28 days. It is important that the supervised dispensing is viewed as a support for the patient and not as a sanction/lack of trust of the patient.

The average dose of buprenorphine is currently 13mg/day. Approximately 80% of patients have doses between 8 and 16mg/day. The minimum dose currently prescribed is 0.2mg and the maximum dose is 32mg/day. A linear dose-response effect has been noted in doses up to 32mg for those individuals that require it (not often needed). The dose is titrated according to the level of positive urines, self-reports of craving and concomitant increase in tobacco or alcohol consumption (thought to be a sign of inadequate control).

In general, buprenorphine is suitable for all groups. However, it is not current policy to use buprenorphine in pregnant heroin users who present for treatment. Buprenorphine is not recommended for such use at present in the French product licence and there is much more experience of use with methadone. However, if a buprenorphine treated woman becomes pregnant her treatment is not changed. To date no adverse effects on the infant, have been noted in this group.

There is no problem with use of buprenorphine in patients with HIV, hepatitis C or liver disease. In fact, it is the view of the expert that these patients are more easily managed on buprenorphine than on methadone. Drug interactions with anti-HIV or anti-hepatitis C medication occur less frequently than with methadone and liver disease is easily monitored by blood tests. To date, no patient has required discontinuation of buprenorphine because of deteriorating liver function.

Neither is there a problem with use of buprenorphine in patients who are depressed or those requiring psychotropic medication.

The clinic's policy is to avoid use of benzodiazepines in this patient population but that is not always possible. There have been no problems with concomitant use of benzodiazepines and buprenorphine when this has been necessary.

Clinical issues with buprenorphine usage

The clinic is currently undertaking a formal review comparing use (in terms of safety) of buprenorphine and methadone since the treatments were introduced in the 1990s. In general buprenorphine treatment is associated, to varying degrees, with withdrawal symptoms at induction. Patients should be told of this and supported through this, otherwise they drop out of treatment. It is usually of short duration (a few days at most). If the dose used is too high at the beginning it causes gastrointestinal upset, which resolves with reduction of the dose. Patients complain of a bad taste from the tablet, which may be transient. None of the side effects would necessitate discontinuation of treatment. In this clinic both buprenorphine and methadone treatments are managed in the same way.

There is a problem with diversion of buprenorphine to the black market- it is hard to get exact figures but it may be as high as 30%. Supervised dispensing greatly reduces this, hence the need to continue supervised dispensing for many months until the patient is stabilised both socially and in terms of opioid abuse.

Some patients inject their prescribed buprenorphine (as many as 10%). Patients may inject their take-aways (e.g. the Sunday dose). The clinic, if it suspects this or if patients tell the team, maintain a long-term daily supervised dispensing for those patients. Once patients begin to inject their buprenorphine dose, it is unlikely that they will give up this practice and this may necessitate a change to methadone.

Drug interactions (either with concomitant legally prescribed medicines or with illicit drugs) are not a problem in clinical practice.

The only factor that contra-indicates the use of buprenorphine in practice is a heroin-dependent pregnant woman, presenting for the first time (as buprenorphine is not recommended for use during pregnancy in France).

The main problem in practice with buprenorphine is the risk of diversion and the risk of injection. It is important to note that self-injection is usually done in a safe fashion (i.e. it is not associated with risk of transmission of blood-borne viral disease through the use of shared needles).

In terms of comparison with other treatment modalities, buprenorphine is judged to be as effective as methadone, with fewer side effects, less interactions and less disruption of dose when medication for HIV/hepatitis C is introduced or changed. The clinic uses other medications such as clonidine, naltrexone and long-acting morphine patch so rarely that it is not possible to compare buprenorphine usage with them.

The overall conclusion is that buprenorphine is used in the clinic as first line treatment as it is as efficacious as methadone but safer and because buprenorphine is more available in France and therefore more accessible for patients.

7.3.2 Report on dispensing of buprenorphine and methadone in France

Substitution therapy in the community setting

Community pharmacists dispense buprenorphine/methadone for patients who attend GPs and also for some patients who attend specialist clinics but opt to receive substitution treatment at a community pharmacy in a more convenient location to their home or workplace or at a more convenient time. The patient may seek agreement from the pharmacy of his/her choice to dispense substitution treatment or alternatively the physician may select a pharmacy for the patient. Following selection, the physician telephones the pharmacist to confirm participation and to inform him/her of the treatment plan. The physician then specifies the pharmacy on the prescription. The physician will usually telephone the pharmacist in the event of alteration in dosage or administration schedule. Pharmacists are encouraged to telephone the physician if they observe any problems with administration e.g. absenteeism, attempts to avoid on-site consumption, intoxication etc. It is felt that collaboration between healthcare professionals involved in the substitution programme encourages a successful outcome of treatment.

Methadone supply constitutes a heavy administrative burden for community pharmacies. Storage must be in a locked safe. The pharmacist must order a supply for each individual patient to cover a specified period usually a week and never any longer then 14 days. Detailed records must be kept of each dispensing including patient's name, prescriber's name, doses dispensed and whether consumed on site in the pharmacy or dispensed as a take-away dose. Any methadone, which has not been dispensed during the specified period, must be returned to the wholesaler. All prescriptions for methadone and all records of receipt and supply must be kept for 10 years.

In contrast, buprenorphine dispensing requires much less administrative effort. Prescriptions must be kept for 10 years, but there are no other regulations governing documentation. Supplies are not ordered on an individual patient basis; rather the pharmacist may keep a stock for dispensing purposes. There are no regulations governing storage. Therefore buprenorphine constitutes much less of an administrative burden than methadone for community pharmacists which may serve as an incentive to take on patients. However, supervision of administration is more time consuming with buprenorphine. Patients remain in the pharmacy for five to ten minutes to allow time for the sublingual formulation to be absorbed. Patients are commonly prescribed more than one tablet, which may be administered individually (depending on the preference of the patient and/or pharmacist). In contrast oral administration of methadone liquid is faster, and consumption is easier to verify by either conversing with the patient or observing consumption of water after the methadone.

Pharmacists receive the same remuneration rate for prescription of methadone or buprenorphine as for all other medications and are not paid for time spent supervising administration. Despite lack of financial incentives, over 70% of French pharmacies have dispensed substitution treatment.

The patient must attend the physician at least once a month to receive a prescription but the pharmacist is obliged to dispense substitution treatment for a maximum of one week, unless specified by the physician in exceptional circumstances e.g. holidays/work commitments. This would only take place for patients well stabilised on treatment. In the case of the Bordeaux clinics, this means the presence of negative urines for opiates for at least 3 consecutive months, with no other problematic substance (e.g. alcohol or cocaine).

Substitution therapy in the specialist clinic setting

Methadone substitution therapy is usually initiated in the clinic setting. Initially, patients may have supervised daily doses dispensed on site at the clinic. Following stabilisation, patients may be transferred to GPs and community pharmacies. Some patients who commence buprenorphine in the clinic setting have supervised daily administration on site at the clinic. Others attend community pharmacies from the beginning for reasons of convenience of location or opening time. Patients who have proved difficult to stabilise in the community setting and hence have been referred to specialist clinics usually are dispensed substitution therapy on site.

The hospital pharmacy prepares individual doses for each patient in advance of clinic sessions. These doses are dispensed in plastic bottles and labelled with the patient's name, the dose of methadone and date to be administered. Dispensed doses are stored in a locked safe in the clinic. The hospital pharmacist must adhere to strict regulations with regard to methadone ordering and storage.

Buprenorphine is not dispensed on an individual patient basis in advance of the clinic session. Tablets are stored with other psychotropic medicines in the clinic and dispensed from stock as required during a clinic session. During clinic sessions, doses of methadone and buprenorphine are dispensed to individual patients by psychiatric nurse counsellors. Consumption is supervised in an office setting. Urine samples are provided in an adjacent lavatory at each clinic encounter but usually only analysed once weekly in a random fashion.

There is no central treatment list identifying all patients in treatment. However substitution therapy for the vast majority of patients is 100% reimbursed by Social Security insurance. Each patient has a unique 'smart card', which is scanned by the pharmacy at dispensing to facilitate reimbursement. The drug, dosage and prescription details are recorded in the patient's file on the Social Security database and therefore duplication of prescribing and dispensing may potentially be identified from this database. However, the system is currently not used routinely to identify patients who receive substitution treatment both at a specialist clinic and at a community pharmacy.

7.4 Use of buprenorphine outside of the EU

Buprenorphine is registered in Australia for use in the management of opioid dependence. Clinical trials have been undertaken at a number of sites across Australia and the results are expected to be published by early 2002 (Ali et al, 2001). National clinical guidelines were developed for the use of buprenorphine, based on extensive evaluation of the literature and discussions with experts from the USA and France (personal communication, Dr Lintzeris). The guidelines are very detailed and lay out the requirements for use of buprenorphine in practice. Prescription is limited to "medical practitioners who have recognised knowledge and skills in the assessment and treatment of opioid dependent people and knowledge of clinical guidelines" (Ali et al, 2001). Each jurisdiction is responsible for a system of authorising medical practitioners to prescribe buprenorphine to a particular patient (Lintzeris et al, 2001).

Supervised dispensing is recommended, especially in the induction phase of treatment. The policy of take-aways varies from jurisdiction to jurisdiction, but in general the guidelines state that uncontrolled access to take-aways leads to more diversion and increased adverse consequences and therefore they advise a cautious approach to their introduction.

In terms of dosing, it is recommended that patients who are stabilised on once daily dosing should be considered for alternate-day or thrice weekly dosing, although it is recognised that not all patients are suitable for less than daily dosing. The dosage to be used is calculated as follows:

3-day dose = 3 times the normal 24-hour dose if the 24-hour dose is < 12mg.

3-day dose = 32mg if the 24-hour dose is > 12mg.

The guidelines estimate that approximately 15% of patients are more comfortable and more effectively maintained on daily, rather than alternate-day or thrice weekly dosing regimens (Lintzeris et al, 2001).

Buprenorphine is not recommended for use in pregnant women, due to insufficient evidence of its safety, for either the developing foetus or breast-fed infant (Lintzeris et al, 2001).

The guidelines, which are extremely detailed were issued in March 2001. A randomised controlled trial comparing use of buprenorphine (according to the guidelines) versus methadone was undertaken in approximately 20 clinics/general practices and the results were comparable in each group (personal communication, Dr Lintzeris). The investigators believe that the results indicate that the guidelines are "clinician friendly" and that the use of buprenorphine, as recommended in them, is safe and effective.

Finally, the approval of buprenorphine for the management of opioid dependence in Australia has been welcomed because it has less regulatory control than methadone. This allows general practitioners to become more involved in its use, thereby expanding the treatment programme options and eventually reducing heroin-related deaths, blood borne viral infections and reducing crime and corruption, due to heroin abuse (Wodak and Hall, 2001).

In the USA, buprenorphine is still an unauthorised medicine, subject to strict regulation (Henney, 2000). Therefore, there are no data about use in clinical practice, other than results from clinical trials, already reported in Chapter 5, Clinical Trials.

7.5 Summary and conclusions

Buprenorphine is used for the management of opioid dependence in several countries throughout the world. It appears to be safe and as efficacious as methadone, the commonest comparator. Although the treatment regimens and practices vary from country to country, it appears that patients do best when the dose is titrated to their individual needs. Careful dispensing and supervision of individual doses reduces the risk of abuse, which is greater than that seen with methadone. Although problems with drug interactions (either with co-prescribed medications or illicit drugs) might be expected, based on an understanding of the pharmacology of buprenorphine, this has not been seen as a major clinical problem in practice. In fact, several experts report that drug interactions are less of a problem with buprenorphine, compared with methadone. There is little clinical experience with use in pregnant women to date. It is considered to be a useful medication for the management of opiate dependence by those clinical experts interviewed, who have used it in practice.

Chapter 8

Pharmacoeconomics

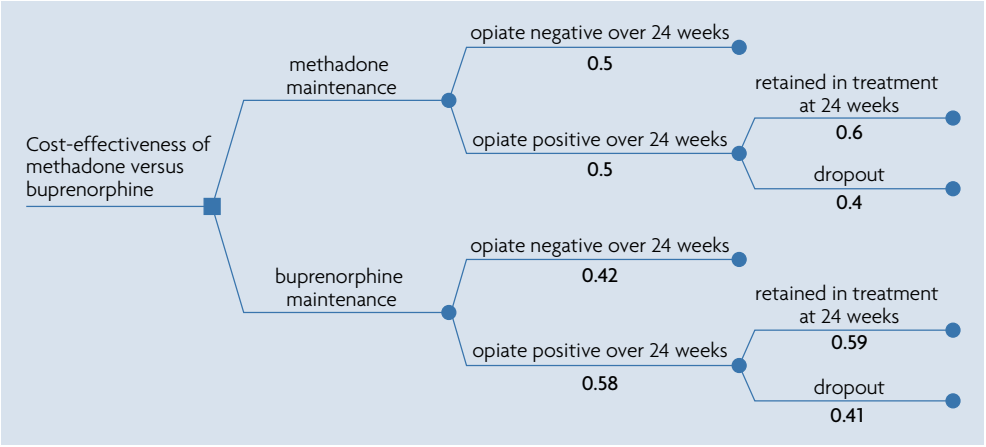
8.1 Pharmacoeconomic analysis of the impact of introducing buprenorphine as an alternative to methadone for maintenance therapy of opiate addiction in Ireland

There are two features that characterise pharmacoeconomic analysis. Firstly, it determines both the input (costs) and output (consequences) resulting from drug intervention. Second, economic analysis concerns itself with choices as resource scarcity necessitates that choices must be made. As a result, pharmacoeconomic evaluation is frequently a comparative analysis of alternative courses of action (in this case methadone versus buprenorphine therapy) in terms of their costs and consequences. Although buprenorphine is not yet licensed in the United States, a recent pharmacoeconomic analysis of the cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the US suggested that buprenorphine is cost-effective at a price of $5 per dose. At $15 per dose it is cost-effective if adoption leads to an overall expansion in the numbers engaged in maintenance treatment (Barnett et al, 2001). However, a pharmacoeconomic evaluation carried out in one setting is frequently not generalisable to another very different healthcare setting characterised by different models of care, resource utilisation and unit costs. Therefore, with reference to the Irish context as there is no study comparing methadone with buprenorphine therapy, an economic model was constructed, which incorporates health outcome data from the literature and cost data from the Irish healthcare setting. A decision tree analysis format was adopted where probabilities and payoff values were assigned to each option. All options presented for methadone were duplicated for buprenorphine but the probability of occurrence differs (depending on the meta analysis). By rolling back the decision tree it is possible to demonstrate whether adopting buprenorphine as an alternative treatment strategy to methadone is a cost-effective option in the Irish healthcare system

A decision tree was constructed outlining the likely treatment plan with each therapy (Figure 3). Methadone is currently the treatment of choice for management of opiate addiction in Ireland and the treatment plan for methadone is based on protocols used locally. Incorporating buprenorphine into current models for delivery of care formed the basis for this analysis. Clinical efficacy data was taken from a meta-analysis of clinical trial data, which is included in this report and adapted for local expert opinion on retention rates. A time horizon of 24 weeks was chosen for the pharmacoeconomic evaluation as patients included in studies in the meta analysis were followed up for 16 – 24 weeks. Cost estimates were derived from data supplied by the ERHA and GMS. Medication costs were taken from published sources with modification for currency exchange and for estimated bulk discounts. All assumptions used in the models are stated explicitly.

The results are presented in terms of cost per opiate negative patient and cost per patient retained in treatment at 24 weeks. Analyses of two of the models of care delivery i.e. Health Board dispensing clinic and community GP/community pharmacy are presented separately. Sensitivity analysis was carried out to determine the impact of assuming that the therapies are equi-effective in terms of proportion of patients who are opiate negative and proportion of patients retained in treatment. The impact of alternative dosing schedules i.e. daily versus thrice weekly buprenorphine was also evaluated. In addition, the impact of different doses of methadone in the community setting was investigated.

Figure 3: A decision tree used to determine the cost-effectiveness of methadone and buprenorphine in the specialist clinic setting using base case parameters.



Models of delivery of care

Following consultation with local experts, the treatment plan for each of three models of delivering care was outlined. In December 2000, 67.6% of patients on the Central Methadone Treatment List attended specialist clinics while 32.4% of patients attend GPs (Building on Experience – Ireland's National Drug's Strategy 2001 – 2008). The three models described include:

1. Health Board dispensing clinic
2. Health Board scripting clinic, dispensed by community pharmacist
3. Review in GP surgery, dispensed by community pharmacist

1. Health Board dispensing clinic treatment plan

Two opiate positive urines are required prior to initiation on the programme. In general, admission to a programme is constrained by waiting lists and limits on the number of individuals for whom the clinic can provide treatment. Patients are usually initiated on 20mg of methadone on Day 1. Following medical review on a daily basis, the dose is increased by 10mg per day until the appropriate dose for the individual has been attained. Thereafter, the doctor usually sees the client at least once a week.

The patient attends daily for supervised administration of methadone for the first 28 days of the programme. Random urinalysis is carried out twice weekly. If the urine remains opiate negative at 28 days, the patient is allowed one take-away dose. If the patient's urine remains opiate negative after a further 28 days the patient receives an extra take-away. As long as the patient's urine is opiate negative, this pattern continues until eventually the patient is in receipt of 6 take-away doses per week. At this point, frequency of urinalysis is reduced to once weekly. Patients who remain opiate negative on once weekly attendance may be transferred to community GPs for continuity of care.

Consecutive opiate positive urines at any time during the programme will result in withdrawal of take-away privileges and return to daily-supervised doses.

2. Health Board scripting clinic, dispensed by community pharmacist

The programme followed is very similar to that of the dispensing clinic except that patients are reviewed on average twice weekly. At programme initiation, doses can only be increased following medical review and therefore are increased at twice weekly intervals. Patients receive a prescription, which is dispensed by their community pharmacy twice weekly. The community pharmacist supervises administration of the dose for the day that the prescription is dispensed and dispenses take-away doses for the other days. It usually takes 6 months (6 x 28 days) of opiate negative urines before a patient is required to attend only once weekly.

3. GP review in GP surgery, dispensed by community pharmacist

Patients who have been stabilised on once weekly attendance at the Health Board clinics may be transferred to community GPs for continuity of care. These patients are seen once weekly by the GP, provide a urine sample for analysis and are provided with a prescription for a week's supply of methadone to be dispensed at their local community pharmacy. The community pharmacist supervises administration of the dose for the day that the prescription is dispensed and provides take-away doses for the other days.

In some cases, usually in areas where Health Board clinics have not been established, some level 2 GPs may initiate patients on methadone maintenance therapy. In general, the programme as outlined for the scripting clinic is followed with patients attending on average twice weekly and receiving prescriptions to be dispensed by the community pharmacist. Initially doses are supervised on a daily basis for 28 days. Urinalysis is carried out twice weekly. If the urine remains opiate negative at 28 days, the patient is allowed one take-away dose. If the patient's urine remains opiate negative after a further 28 days the patient receives an extra take-away. As long as the patient's urine is opiate negative, this pattern continues until eventually the patient is in receipt of 6 take-away doses per week. At this point frequency of attendance at the GP surgery and urinalysis is reduced to once weekly.

Decision analytical models were constructed to represent the first and third modalities of care delivery as outlined above. Data to populate these trees may be categorised as clinical efficacy data, which is common to both models and economic data, which is specific to each model of care. The analysis was carried out from the perspective of the healthcare provider. Average cost-effectiveness ratios were calculated for alternative treatment options.

8.2 Decision analytical model for Health Board dispensing clinic treatment plan

The following base case parameter estimates were used to populate the decision tree model shown in Figure 3.

Assumptions and Reference Sources for clinical efficacy base case parameter estimates (Table 8.1):

1. The probability of opiate negative urine for each substitution treatment over 24 weeks is based on the mean proportion of opiate negative urines noted for each drug in the meta-analysis of clinical trials comparing the two drugs (Chapter 4). It has been assumed that the proportion of opiate negative urines approximates the probability of opiate negative urine over the 24 week treatment period.

2. The probability of opiate positive urine = 1 – probability of opiate negative urine.

Table 8.1: Clinical efficacy base case parameter estimates

Methadone:	Value	Source
Probability of opiate negative urine at 24 weeks:	0.50	1
Probability of opiate positive urine at 24 weeks:	0.50	2
Probability of dropout from treatment at 24 weeks:	0.20	3
Probability of patient with opiate positive urine and retained in treatment at 24 weeks:	0.30	5
Buprenorphine:	**Value**	**Source**
Probability of opiate negative urine at 24 weeks:	0.42	1
Probability of opiate positive urine at 24 weeks:	0.58	2
Probability of dropout from treatment at 24 weeks:	0.24	4
Probability of patient with opiate positive urine and retained in treatment at 24 weeks:	0.34	5

3. The probability of dropout from methadone treatment at 24 weeks is based on expert opinion of the Irish clinical experience.

4. The probability of dropout from buprenorphine treatment at 24 weeks = probability of dropout in methadone treatment X hazard ratio of dropping out for buprenorphine compared to methadone taken from the meta-analysis of clinical trials comparing the two drugs (Table 5.4b).

5. Probability of patient with opiate positive urine and retained in treatment at 24 weeks = 1 – probability of opiate negative urine – probability of dropout from treatment.

Assumptions and Reference Sources for economic base case parameter estimates for management in an ERHA dispensing clinic (Table 8.2):

1. Assume daily methadone dose of 80mg. A review of prescriptions for 60 patients attending one clinic in the South Western Area Health Board during January 2001 revealed a median dose of 80mg. The price used was an estimation of the ERHA contract price at 33% of the standard price taken from MIMS (September 2001) to approximate likely bulk discounts.

2. Assume a daily buprenorphine dose of 12mg, which was the median dose, noted in the final meta-analysis of clinical trial data and is within the average dose range used at the Bordeaux site. The price used was the UK price in sterling (BNF 42, September 2001) converted to euro.

3. Attendance daily for 4 weeks, then 6 days per week for 4 weeks, then 5 days per week for 4 weeks, then 4 days per week for 4 weeks, then 3 days per week for 4 weeks, then twice per week for the last 4 weeks. Cost per clinic visit was derived from a top-down budget estimation of the overall cost per patient per month attending a single clinic in the ERHA, which provides treatment to 43 patients. This estimation included the cost of medication, staff (medical, pharmacy, nursing, social work, administration, outreach, security etc.), urinalysis, overheads etc. The drug acquisition cost of 1 month's methadone at 80 mg daily was subtracted from the above estimate to give a cost per patient per month excluding methadone. An attempt to calculate the average number of clinic visits per patient per month was made as follows: it was assumed that 50% of patients attended daily, 10% attended once

Table 8.2: Economic base case parameter estimates for management in an ERHA dispensing clinic

Methadone:	Cost	Source
Cost of 24 weeks therapy at 80mg per day	€113.68	1
Cost of 24 weeks of clinic visits if opiate negative	€17,234.64	3
Cost of 24 weeks of clinic visits if opiate positive	€26,809.44	4
Total cost of 24 week programme if opiate negative	€17,348.32	
Total cost of 24 week programme if opiate positive	€26,923.12	
Total cost of drop out	€13,461.56	5
Buprenorphine:	**Cost**	**Source**
Cost of 24 weeks therapy at 12mg per day	€1,301.50	2
Cost of 24 weeks of clinic visits if opiate negative	€17,234.64	3
Cost of 24 weeks of clinic visits if opiate positive	€26,809.44	4
Total cost of 24 week programme if opiate negative	€18,536.14	
Total cost of 24 week programme if opiate positive	€28,110.94	
Total cost of drop out	€14,055.47	5

weekly and the remaining 40% attended four times weekly resulting in an average of 22.6 visits per patient per month. The cost per patient per month excluding methadone was divided by the average number of clinic visits per patient per month to give an average cost per clinic visit.

4. Attendance daily for 24 weeks. Cost per clinic visit was calculated as in 3.

5. Total cost of drop out assumed to be half the cost of patient with opiate positive urines attending daily.

Sensitivity analysis

In the base case scenario it is assumed that buprenorphine is administered on a daily basis. The average dose of methadone for patients attending the ERHA clinic is assumed to be 80mg. Efficacy in terms of negative urinalysis and retention in treatment is based on the meta-analysis of randomised clinical trial data with some adaptation for the local setting.

In the sensitivity analysis the impact of administering buprenorphine three times a week is explored. In this case it is assumed that the patient attends daily for the first seven days to facilitate dose titration and thereafter attends thrice weekly (Johnson et al 2001). If opiate free the patient attends three times weekly from week 2 to week 20 and then twice weekly from week 21 to week 24.

Although the meta-analysis suggests that buprenorphine may be less effective than methadone in terms of proportion of negative urines, this is not thought to be clinically relevant as the clinical practitioners consulted in Chapter 7 consider buprenorphine to be at least as effective as methadone. Therefore, the impact of assuming that methadone and buprenorphine are equally effective was also determined.

8.3 Results from decision analytical model for Health Board dispensing clinic treatment plan

Table 8.3: The cost of treating opiate addiction in an ERHA dispensing clinic using either methadone or buprenorphine

Base case analysis	Methadone	Buprenorphine
Average cost per opiate negative patient at 24 weeks	€38,886.81	€49,190.44
Average cost per patient retained in treatment at 24 weeks	€24,304.26	€27,328.02
Sensitivity analysis	**Methadone**	**Buprenorphine**
(1) Administering buprenorphine thrice weekly:		
Average cost per opiate negative patient at 24 weeks	€38,886.81	€26,714.96
Average cost per patient retained in treatment at 24 weeks	€24,304.26	€14,841.65
(2) Assuming that methadone and buprenorphine are equi-effective:		
Average cost per opiate negative patient at 24 weeks	€38,886.81	€41,024.88
Average cost per patient retained in treatment at 24 weeks	€24,304.26	€25,640.55

8.4 Decision analytical model for community based treatment plan

Assumptions and Reference sources for economic base case parameter estimates for management by a community GP and dispensing by a community pharmacist (Table 8.4):

1. Assume daily methadone dose of 30mg based on expert opinion for the Irish clinical experience. The price used was taken from MIMS (September 2001).

2. Assume a daily buprenorphine dose of 12mg, which was the median dose, noted in the meta-analysis of clinical trial data and is within the average dose range used at the Bordeaux site. The price used was the UK price in sterling (BNF 42, September 2001) converted to Euro.

3. Attendance at GP surgery twice weekly for 24 weeks. Cost per GP visit derived from the schedule for GP fees (2001 GMS Report for the year ended 31st December 2000) @ €105.83 per month and added to cost of urinalysis i.e. urinalysis using "Surestep" kit twice weekly and by contract laboratory on average once a month. Cost of urinalysis was provided by ERHA.

4. Dispensing cost for 24 weeks if opiate negative: assume supervised dosing at community pharmacy daily for 4 weeks, then 6 days per week for 4 weeks, then 5 days per week for 4 weeks, then 4 days per week for 4 weeks, then 3 days per week for 4 weeks, then twice per week for the last 4 weeks. Cost of dispensing was taken from the current schedule for community pharmacist fees.

5. Dispensing cost for 24 weeks if opiate positive: assume supervised dosing daily for 24 weeks. Cost of dispensing was taken from 2000 GMS schedule for community pharmacist fees (2001 GMS Report for the year ended 31st December 2000).

6. Total cost of drop out assumed to be half the cost of patient with opiate positive urines attending daily.

Table 8.4: Economic base case parameter estimates for management by a community GP and dispensing by a community pharmacist

Methadone:	Cost	Source
Cost of 24 weeks therapy at 30mg per day	€128.02	2
Cost of 24 weeks of GP visits plus urinalysis whether opiate negative or positive	€1,192.01	4
Dispensing cost for 24 weeks if opiate negative	€915.79	5
Dispensing cost for 24 weeks if opiate positive	€1,331.91	6
Total cost of 24 week programme if opiate negative	€2,235.81	
Total cost of 24 week programme if opiate positive	€2,651.93	
Total cost of drop out	€1,325.97	7
Buprenorphine:	**Cost**	**Source**
Cost of 24 weeks therapy at 12mg per day	€1,301.50	3
Cost of 24 weeks of GP visits plus urinalysis whether opiate negative or positive	€1,192.01	4
Dispensing cost for 24 weeks if opiate negative	€915.79	5
Dispensing cost for 24 weeks if opiate positive	€1,331.91	6
Total cost of 24 week programme if opiate negative	€3,409.29	
Total cost of 24 week programme if opiate positive	€3,825.41	
Total cost of drop out	€1,912.71	7

Sensitivity analysis

In the base case scenario it is assumed that buprenorphine is administered on a daily basis. The average dose of methadone for patients attending a community GP is assumed to be 30mg. Efficacy in terms of negative urinalysis and retention in treatment is based on the meta-analysis of randomised clinical trial data with some adaptation for the local setting.

In the sensitivity analysis the impact of administering buprenorphine three times a week is explored. In this case it is assumed that administration is daily for the first seven days to facilitate dose titration and thereafter thrice weekly. If opiate negative, the patient attends for supervised dispensing three times weekly from week 2 to week 20 and then twice weekly from week 21 to week 24.

The impact of assuming that methadone and buprenorphine are equally effective was also determined. In addition the effect of increasing the methadone dose to 80 mg is examined to facilitate a direct comparison with cost of providing care in the ERHA clinic setting.

8.5 Results of decision analytical model for community based treatment plan

8.6 Discussion and conclusions

This analysis suggests that it is seven to twelve times more cost-effective to treat opiate addiction in the community setting than in the specialist clinic over a 24 week period. However, this analysis assumes that efficacy determined from clinical trials carried out in specialist clinics is maintained in the community setting. In addition, expenditure on community care includes fees paid to GPs and community pharmacies only, whereas the cost of the specialist clinic service includes the cost of nursing staff, social workers, outreach workers, administration and security staff as well as clinic overheads.

With respect to the base case scenario in the ERHA clinic, it is seen that methadone is more cost-effective than daily buprenorphine at a cost of €38,886.81 per opiate negative patient and €24,304.26 per patient retained in treatment compared to €49,190.44 and €27,328.02 respectively. This difference is in part due to the slightly lower efficacy of buprenorphine in the meta-analysis but mostly attributable to the eleven-fold increase in drug acquisition cost for buprenorphine i.e. (€1301.50 for 24 weeks of buprenorphine 12mg daily compared to €113.68 for 24 weeks of methadone 80mg daily). Several generic preparations of methadone are available which

Table 8.5: The cost of treating opiate addiction in the community setting using either methadone or buprenorphine.

Base case analysis:	Methadone	Buprenorphine
Average cost per opiate negative patient at 24 weeks	€3,307.76	€7,425.41
Average cost per patient retained in treatment at 24 weeks	€2,067.35	€4,125.23
Sensitivity analysis:	**Methadone**	**Buprenorphine**
(1) Administering buprenorphine thrice weekly:		
Average cost per opiate negative patient at 24 weeks	€3,307.76	€6,281.36
Average cost per patient retained in treatment at 24 weeks	€2,067.35	€3,489.64
(2) Assuming that methadone and buprenorphine are equi-effective:		
Average cost per opiate negative patient at 24 weeks	€3,307.76	€6,335.81
Average cost per patient retained in treatment at 24 weeks	€2,067.35	€3,959.88
(3) Increasing the methadone dose to 80mg daily		
Average cost per opiate negative patient at 24 weeks	€3,691.80	€7,425.41
Average cost per patient retained in treatment at 24 weeks	€2,307.38	€4,125.23

facilitates the negotiation of bulk discounts by the clinic. If buprenorphine is licensed in Ireland for management of opiate addiction, it will be protected by patent from generic competition for several years.

The difference in cost-effectiveness between options is even more exaggerated in the community setting where methadone costs €3,307.76 per opiate negative patient and €2,067.35 per patient retained in treatment compared to €7,425.41 and €4,125.23 respectively for buprenorphine. This greater difference may be explained by the fact that drug acquisition accounts for a much greater proportion of total cost in the community setting than in the specialist clinic (7.7% for methadone and 41.7% for buprenorphine in the community compared to 0.6% and 6.3% respectively in the ERHA clinic).

The patterns observed in the base case scenario changed little in the sensitivity analysis when we investigated the impact of considering both treatment options to be equally effective (cost-minimisation analysis). This was not unexpected as the difference in proportion retained in treatment in the meta-analysis was not statistically significant and the difference in proportion of opiate positive urines noted in the meta-analysis although statistically significant was small and not considered to be clinically relevant. This analysis therefore highlights the impact of high drug acquisition cost associated with buprenorphine.

We also investigated the impact of prescribing buprenorphine three times weekly rather than daily in both models of care delivery. In the specialist clinic setting, buprenorphine became more cost-effective than daily methadone when administered three times weekly, due to the saving in expensive clinic visits. Thrice weekly administration of buprenorphine remained less cost-effective than daily methadone in the community setting as there is no impact on cost of GP care which is reimbursed on a capitation, rather than fee for service basis, and saving on community dispensing fees is of a small order of magnitude i.e. €246.91 per 24 weeks per opiate negative patient. In addition, any savings on community dispensing fees may be negated should community pharmacists seek higher remuneration for supervised dispensing of buprenorphine in recognition of the longer supervision period required.

It is seen from this analysis that prescribing of buprenorphine in the community setting is up to twelve times more cost-effective than use of this agent in the specialist clinic, but remains twice as expensive as use of methadone maintenance in the community over a 24 week time horizon. However, this analysis has been carried out from the healthcare provider perspective i.e. direct medical costs only and savings on care for complications of illicit intravenous drug use including HIV and Hepatitis C have not been included. When consideration is taken of the fact that buprenorphine is potentially a safer option, and easier to use than methadone, and if the broader societal perspective is adopted i.e. benefits of expanding the treated cohort are included, such as savings on criminal justice costs and on lost productivity, then buprenorphine may well constitute a cost-effective option for the management of opiate addiction in this country, especially in the community setting. Utilising a thrice-weekly administration regimen for buprenorphine would greatly enhance its cost-effectiveness in the specialist setting. A reduction in the number of clinic visits would potentially allow a greater number of individuals to be treated in a clinic but this advantage may be limited by the increase in time required to supervise administration of buprenorphine compared to methadone.

The results from the pharmacoeconomic evaluation of the use of buprenorphine in the management of opiate dependence syndrome, show that use of buprenorphine appears to be less cost-effective than the current methadone system. It may prove to be a cost-effective treatment option in selected Irish settings, but further studies are needed to identify these settings.

Chapter 9

Summary and Conclusions

Illicit opiate use became a public health problem in Ireland in the early 1980s. Methadone maintenance has been available since the 1990s and is the mainstay of treatment in Ireland. A review was undertaken on the effectiveness of buprenorphine as a form of treatment for opiate addiction. A systematic review of all available data, retrieved from the literature, was undertaken. In addition, experts who have experience in the use of buprenorphine, were interviewed to evaluate the practical issues associated with the use of buprenorphine. Economic data were reviewed to estimate the costs of such usage in the Irish setting.

The results of the review may be summarised as follows:

1. Buprenorphine has been evaluated for use in managed opioid withdrawal (detoxification) and has been seen to be at least as effective as the currently used treatment modalities (clonidine and lofexidine). It was not possible to identify the most appropriate treatment regimen (either in terms of dosage or treatment duration) because of the heterogeneity of the studies reviewed.

2. Buprenorphine appeared to be at least as effective as methadone, when used in the maintenance/substitution treatment of opiate dependence (in terms of treatment retention and positive urinalysis). It was not possible to identify the most appropriate treatment regimen but it was noted that in general, doses of greater than 8mg/day were needed.

3. It is not possible to make definitive statements about its use in specific subgroups but it appears that responders are more likely to have higher baseline levels of psychosocial functioning.

4. Less than daily dosing (e.g. thrice weekly) has been shown to be as effective (in terms of treatment retention and positive urinalysis) as daily dosing, using comparable total weekly doses, although this may not be suitable for all subjects.

5. Buprenorphine is most effective when the dosage is titrated to the individual needs and the patients are closely monitored in the early induction phase with symptomatic treatment and dosage adjustments to manage withdrawal symptoms.

6. Buprenorphine is not recommended for use in pregnancy in several countries at present. However, it has been used in pregnancy (approximately 100 cases recorded in the literature to date) with no ill effect on either the mother or infant.

7. It is capable of being abused, because of its ability to induce opioid effects. Therefore, its administration would need to be supervised in the same way as the current Irish methadone protocol system. The commercially available tablet can be crushed and injected. Supervised dispensing will mean keeping the patient for up to 10 minutes to ensure full absorption has occurred from the sublingual site. Swallowing the tablet results in absorption from the gut with extensive first pass metabolism and inactivation.

8. Because of its partial agonist properties it is less likely than methadone to cause withdrawal symptoms after abrupt discontinuation. This makes it useful for subjects who wish to (1) undergo detoxification or (2) withdraw from a methadone maintenance programme and become opiate-free.

9. Its partial agonist properties may cause problems when trying to change a methadone-maintained individual to buprenorphine therapy as opioid withdrawal symptoms may occur. Therefore, methadone levels will need to be reduced to approximately 30mg/day prior to the changeover with close monitoring and management of the patient in the early phases of buprenorphine treatment.

10. Although the known kinetic profile of buprenorphine would suggest that there might be a potential for interaction when the drug is co-prescribed with a variety of medications, (including certain anti-HIV medications), this has not been seen to be a problem in clinical practice in any of the treatment clinics evaluated in either the UK or France. Fatal interactions between buprenorphine and benzodiazepines and/or other psychotropic agents have been reported. However, such interactions do not appear to be a problem in clinical practice when these are co-prescribed at therapeutic doses.

11. The presence of liver disease may alter the kinetics of buprenorphine and warrants particular supervision of the patient. In addition it is recommended that liver function is assessed regularly while taking buprenorphine, because of the possibility of hepatoxicity. However, patients with liver disease have been treated with buprenorphine in clinical practice, with no deterioration in liver function due to treatment.

12. The results from a pharmacoeconomic evaluation of the use of buprenorphine in the management of opiate dependence syndrome, showed that buprenorphine appeared to be less cost-effective than the current methadone system. It may prove to be a cost-effective treatment option in selected Irish settings, but further studies are needed to identify these settings.

In conclusion, this systematic review suggests that buprenorphine may be viewed as an effective treatment option in the management of opiate dependence syndrome, with an acceptable safety profile.

Appendix 1

Details of the Analytical Methodology Used in the Meta-Analysis

Statistical Appendix for "A Meta-analysis Comparing Buprenorphine to Methadone for Treatment of Opiate Dependence"

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The meta-analysis examined the two measures that were used in all five studies. Every study conducted a periodic urinalysis for opiates and reported the length of time that each subject remained in treatment. In order to apply the same analytical methods to all data, we obtained the original urinalysis and retention data on the subjects in each of the individual studies.

Urinalysis data

Each subject had an outcome, which was the number of events (positive urinalyses) divided by the number of possible events (number of urinalyses). The urinalysis data of each subject was characterized by a number between zero and one. The mean of these values was determined for each group, and the difference in group means was found for each study. The meta-analysis estimated the average size of this difference. This was the mean difference between buprenorphine and methadone treatment groups while participants were still in treatment.

We used two different methods of handling missing urinalyses. The first method treated missing tests as positive, thereby creating a complete data set. This assumes that a subject who missed providing a specimen had been using illicit opiates. Since we considered only the period while the subject was retained in treatment, the assumption was not applied to tests missed because subjects had dropped out or had been terminated from the study. The second method ignored missing values. This approach is valid if the missing status of the specimen provides no information – if subjects who had used illicit opiates were just as likely to fail to provide a urine specimen as those who had abstained.

The difference (D_i) in outcomes between the treatment groups was simply the difference between the mean percent positive of subjects in the buprenorphine and methadone treatment groups.

We found the variance for these estimates for each study (V_i) using the standard deviation of the buprenorphine (SD_b) and methadone treatment (SD_m) groups, and the number of subjects in each group (n_b and n_m respectively):

$$Vi = \left(\frac{(n_b - 1)\, SD_b^2 + (n_m - 1)\, SD_m^2 +}{n_b + n_m - 2} \right) \left(\frac{1}{n_b} + \frac{1}{n_m} \right)$$

Retention data

The other outcome measured was the length of time the subject was retained in treatment. Since patients were followed only until the last day of each study, this outcome was censored by the length of follow-up. We analysed data from each study with a Cox proportional hazards model. The regression used the number of days the subject was retained as the dependent variable, and a single independent variable, an indicator which took a value of 1 if the subject was in the buprenorphine treatment group. To provide a clear interpretation of the effect, we expressed the hazard parameter as the relative risk of discontinuing buprenorphine treatment compared to methadone.

We used the coefficient from the Cox proportional hazards regressions as the study level difference (D_i) in outcomes between the treatment groups. The variance from each study (V_i) was the square of the standard error of the Cox regression parameter.

Meta-analysis method.

We determined the weighted mean different in treatment effect by using reciprocal of the variance was used to weight each study. The weighted mean over all M studies was thus found as:

$$\overline{D} = \frac{\sum_{1}^{M} \frac{D_i}{V_i}}{\sum_{1}^{M} \frac{1}{V_i}}$$

The variance of this estimate was:

$$\overline{V} = \frac{1}{\sum_{1}^{M} \frac{1}{V_i}}$$

The 95% confidence interval around the mean difference was found as:

$$\overline{D} \pm 1.96\sqrt{\overline{V}}$$

We also tested the validity of the statistical assumptions needed to pool data for meta-analysis. This is a test of the homogeneity of the effect. The null hypothesis of this test is that the effect size is the same in all of the studies, that is, the studies are similar enough to be pooled. The Q statistic for the homogeneity of effects is:

$$Q = \sum_{1}^{M} W_i (D_i - \overline{D})^2$$

This statistic is chi-square distributed with M-1 degrees of freedom. If the test was significant, then we reject the hypothesis of homogeneity, and conclude that the data from the different studies cannot be pooled. If this test was not significant (if we failed to reject the hypothesis of homogeneity), then we reported the weighted mean of the difference between the buprenorphine and methadone treatment groups.

Appendix II

Background Data on Clinic Protocol

Please give a brief description of the clinic set-up in terms of doctor/pharmacist input and whether patients have dispensing and supervised administration of substitution drug at clinic or local pharmacy level (irrespective of drug type)

How often are patients seen (assuming a daily dosage regimen for all medications) (tick for yes as appropriate)

Daily ☐

Alternate days ☐

Weekly ☐

›Weekly ☐

Do patients get each dose on a daily basis (either at clinic or local pharmacy)?

Yes/No (please delete as appropriate)

If no, do they get majority of doses under daily supervision with "take-aways" according to their compliance?

Yes/No (please delete tick as appropriate)

If no, how are their supplies of medication controlled? (please specify)

_____

_____

_____

_____

How often are urines taken for analysis in induction phase? (tick for yes as appropriate)

Daily ☐

2-3 per week ☐

Weekly ☐

›Weekly ☐

How often are urines taken for analysis in maintenance phase? (tick for yes as appropriate)

Daily ☐

2-3 per week ☐

Weekly ☐

›Weekly ☐

Use of buprenorphine for the Pharmacological Management of Opiate Dependence – Questionnaire on Practical Aspects of Usage

Use of buprenorphine

1. **Do you use buprenorphine for the management of opiate dependence?**

Yes/No (please delete as appropriate)

2. **If yes to 1, do you use it for** (tick for yes as appropriate)

   a) treatment of withdrawal ☐

   b) maintenance treatment/ substitution treatment ☐

3. **Do you use other therapies for the management of opiate dependence?** (tick as appropriate)

   a) Methadone Yes ☐ No ☐

   b) Lofexidine Yes ☐ No ☐

   c) Naltrexone Yes ☐ No ☐

   d) Naloxone Yes ☐ No ☐

   e) Diamorphine Yes ☐ No ☐

   f) Other opiate substance (please specify)

   _____

   _____

   g) Other drug (please specify)

   _____

   _____

4. **If buprenorphine is used for treatment of withdrawal, what dosage regimen is used?** (please specify)

   _____

   _____

   _____

   _____

   _____

   _____

5. **How does buprenorphine compare with other drug regimens in the treatment of withdrawal?** (tick for yes as appropriate and assume optimal dosage of buprenorphine)

   a) Equal to comparator regimen(s) (please specify) ☐

   _____

   b) More efficacious ☐

   c) Less efficacious ☐

   d) Less side effects ☐

   e) Less withdrawal symptoms ☐

   f) Other comment (please specify) ☐

   _____

   _____

6. **In the maintenance treatment setting how is buprenorphine prescribed?** (tick for yes as appropriate)

   a) Fixed daily dose ☐

   b) Daily dose according to a standard regimen ☐

   c) Daily dose titrated to the individual ☐

   d) Alternate day/thrice weekly dosing ☐

   e) Other regimens (please specify) ☐

   _____

   _____

7. **In the maintenance treatment setting, how is buprenorphine administered?** (tick one or more options as appropriate)

   a) Each dose dispensed individually by pharmacist in the clinic who supervises administration to ensure complete absorption* ☐

   b) Each dose dispensed individually by pharmacist in the clinic who doesn't check absorption ☐

c) Doses dispensed by pharmacist in the clinic but allowed to take dose(s) home for one/more days (take-aways) ☐

d) Dispensed by local pharmacy on a daily treatment basis with supervision of administered dose to ensure absorption* ☐

e) Dispensed by local pharmacy on a daily treatment basis without supervision of administered dose ☐

f) Dispensed by local pharmacy – several days' supply allowed (please specify) ☐

_____

_____

_____

g) Other forms of dispensing/ administration (please specify) ☐

_____

_____

_____

h) Other comments on any aspect of dispensing practice ☐

_____

_____

_____

_____

_____

_____

_____

_____

_____

*how is absorption verified?

8. **What is the average dose required for substitution therapy?** (tick as appropriate)

a) 1 – 8mg/day ☐

b) 8 – 12mg/day ☐

c) 12 – 16mg/day ☐

d) 16 – 32mg/day ☐

e) Weekly dosage (in case of alternate day/thrice weekly administration) ☐

f) Other regimens (please specify) ☐

_____

_____

_____

Do you notice a linear dose-response for buprenorphine?

Yes/No (please delete as appropriate)

Any additional comments on this issue

_____

_____

_____

_____

_____

_____

9. **Is buprenorphine suitable for the following patient groups?** (tick for yes as appropriate)

   a) Males ☐
   b) Females ☐
   c) Pregnant females ☐
   d) Patients on anti-HIV medication ☐
   e) Pregnant females on anti-HIV medication ☐
   f) Patients with liver disease ☐
   g) Patients currently on methadone maintenance ☐
   h) Patients with high opiate requirements ☐
   i) Patients with longstanding dependence ☐
   j) Patients with active/history of depression ☐
   k) Patients with psychosocial problems ☐
   l) Patients requiring treatment with psychotropics (please specify drugs) ☐

   _____
   _____
   _____

   Any other group (please specify)

   _____
   _____
   _____

10. **If buprenorphine is not suitable for specific groups in question 9, please state the reasons**

    _____
    _____
    _____
    _____

11. **In your opinion, does buprenorphine have an advantage over other treatment modalities in any of the subgroups outlined in question 9?**

    Yes/No (please delete as appropriate)

    Please give reasons for your answer

    _____
    _____
    _____
    _____
    _____
    _____

Practical/Clinical issues with buprenorphine usage

12. **What are the common side effects encountered with buprenorphine:**

    a) in the treatment of withdrawal? (Used/not used- delete as appropriate)

    _____
    _____
    _____

    b) used as maintenance treatment? (Used/not used – delete as appropriate)

    _____
    _____
    _____

    Are the side-effects transient/present for duration of treatment? (delete as appropriate)

    Would the occurrence of side-effects result in the discontinuation of use of buprenorphine Yes/No? (delete as appropriate)

    If yes, state circumstances

    _____
    _____
    _____

13. **Does the use of buprenorphine necessitate a change in the way opiate dependent patients are managed at clinic level, with respect to other treatment modalities (in terms of prescribing/dispensing/ supervised administration/other)?**

Yes/No (delete as appropriate)

Please give reasons for your answer

_____

_____

_____

14. **Is the abuse potential of buprenorphine a problem in practice?**

Yes/No (delete as appropriate)

Please give reasons for your answer

_____

_____

_____

In your opinion do many subjects inject the tablet formulation prescribed as maintenance/withdrawal therapy

Yes/No (delete as appropriate)

If yes please give estimate of occurrence

a) <10% ☐

b) 10 – 20% ☐

c) 21 – 30% ☐

d) 31 – 40% ☐

e) 41 – 50% ☐

f) 51 – 60% ☐

g) 61 – 70% ☐

h) >70% ☐

Would injection occur on a regular/irregular basis in these cases? (delete as appropriate)

15. **In general, is the issue of buprenorphine-drug interactions (either with co-prescribed drugs/illicit drugs) a problem in clinical practice?** (see also next question)

Yes/No (delete as appropriate)

If yes, would you describe the problem as major/moderate/minor? (delete as appropriate)

Please give reasons for your answer

_____

_____

_____

_____

_____

_____

16. **If yes to 15, which drugs are most problematic? (please number 1 – 7 with 1 being the most problematic)**

a) Benzodiazepines ☐
(please record specific drug(s) if difference between the class)

_____

_____

b) SSRIs/SRIs ☐
(please record specific drug(s) if difference between the class)

_____

_____

c) Other anti-depressants ☐
(please specify)

_____

_____

d) Neuroleptics (please specify) ☐

_____

_____

e) Other opiates (please specify) ☐

_____

_____

f) Alcohol (please specify details of amount, if appropriate) ☐

_____

_____

g) Other drugs (please specify) ☐

_____

_____

17. **Are there factors which contra-indicate the use of buprenorphine in clinical practice (medical/practical/other – e.g. risk of illicit usage of buprenorphine)?**

Yes/No (delete as appropriate)

Please outline these reasons

_____

_____

_____

_____

18. **Are there any other particular problems with use of buprenorphine in practice (i.e. not seen with the other medications used)?**

Yes/No (delete as appropriate)

Please give reasons for your answer

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_____

_____

19. **How do you rate buprenorphine in comparison to other treatment modalities (assume optimal dosage of buprenorphine)?**

Methadone:

a) Treatment not used in clinic ☐

b) Equal to methadone ☐

c) Better than methadone ☐

d) Less efficacious than methadone ☐

e) Less side effects ☐

f) More side effects ☐

g) Less abuse potential ☐

h) More abuse potential ☐

i) Better than methadone for some subgroups (please specify) ☐

_____

_____

_____

Lofexidine:

a) Treatment not used in the clinic ☐

b) Equal to lofexidine ☐

c) Better than lofexidine ☐

d) Less efficacious than lofexidine ☐

e) Less side effects ☐

f) More side effects ☐

g) Less abuse potential ☐

h) More abuse potential ☐

i) Better than lofexidine for some subgroups (please specify) ☐

_____

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Naltrexone:

a) Treatment not used in the clinic ☐

b) Equal to naltrexone ☐

c) Better than naltrexone ☐

d) Less efficacious than naltrexone ☐

e) Less side effects ☐

f) More side effects ☐

g) Less abuse potential ☐

h) More abuse potential ☐

i) Better than naltrexone for some subgroups (please specify) ☐

Diamorphine:

a) Treatment not used in the clinic ☐

b) Equal to diamorphine ☐

c) Better than diamorphine ☐

d) Less efficacious than diamorphine ☐

e) Less side effects ☐

f) More side effects ☐

g) Better than diamorphine for some subgroups (please specify) ☐

Other opiates/other treatment modalities (please specify)

a) Equal ☐

b) Better ☐

c) less efficacious ☐

d) less side effects ☐

e) more side effects ☐

f) Better than ..... for some subgroups (please specify groups and reasons) ☐

20. **Overall, what is your impression of the usefulness of buprenorphine in the management of opiate dependence?**

Any additional comments you may wish to make may be included here.

End of Questionnaire
Thank You!

Appendix III

Individual Summaries of Randomised Controlled Comparative Trials Reviewed

1988	Bickel et al (Am Pharm & Ther)	First RCT comparing BPN & Meth (db)
Nos/gp	22/23	BPN/Meth (45 in total)
Doses	BPN	2mg/day x 3 weeks & then gradually reduced x 4 weeks and then placebo x 6 weeks
	Meth	30mg/day x 3 weeks & then gradually reduced x 4 weeks and then placebo x 6 weeks
Trial Duration	Total study period 13 weeks	
Outcomes Measured	• Retention in treatment • Illicit opioid use • Symptom score (withdrawal symptoms)	
Results	No difference between outcomes measured	
	But BPN 2mg less able to attenuate effects of opioid challenge (hyromorphine 6mg administered 1/M)	

Note: Patients had access to supportive counselling but attendance was not measured as an outcome

BPN = buprenorphine
METH = methadone
db = double blind
dd = double dummy
RCT = randomised control trial

1992	Johnson et al (JAMA)	RCT comparing BPN & Meth (1)+(2) for short-term management of opioid dependence (db)
Nos/gp	53(BPN) 55/54 Meth (1+2)	(162 in total)
Doses	BPN	2/4/8mg on days 1,2,3 & then 8mg daily up to day 120 (17 weeks) followed by gradual reduction over 49 days (7 weeks) & then 11 days of placebo
	Meth (1)	20/30/25/20mg on days 1, 2-5, 6-9, 10 & then 20 mg daily up to day 120 followed by gradual reduction over 49 days & then 11 days of placebo
	Meth (2)	20/30/40/50/60mg on days 1,2,3,4,5 & then 60mg daily up to day 120 followed by gradual reduction over 49 days & then 11 days of placebo
Trial Duration	180 days	(120 days induction/maintenance & 60 days detoxification)
Outcomes Measured	• Retention time on Study • Illicit opioid use (thrice weekly urine samples) • Daily self-reported questionnaires on withdrawal symptoms	
Results	BPN & Meth 60 were significantly better than meth 20mg in the endpoints (neg urine samples & retention in study) BPN equivalent to Meth 60 No difference in ADRs between groups	

Note: Counselling was offered but not required but percentages attending did not differ between groups

1993	Kosten et al (J Nerv Ment Dis)	RCT comparing 2 doses of BPN with 2 doses of meth in the management of opioid dependence (db)
Nos/gp	BPN 28/28 Meth 34/35	(125/140) in total
Doses	BPN (1)	2mg/day for 24 weeks
	BPN (2)	2mg/day increasing gradually to 6mg/day for a total of 24 weeks
	Meth (1)	35mg/day for 24 weeks
	Meth (2)	35mg/day increasing gradually to 65mg/day for a total of 24 weeks
Duration of Trial	Total Study period 24 weeks	
Outcomes Measured	• Treatment retention • Illicit drug use (urinalysis weekly & self-reported drug use) • Self-assessment of opioid withdrawal symptoms	
Result	Methadone at 2 doses was significantly better than BPN at 2 doses for retention time & opiate-free urines No difference in effect between 2 Meth groups or between 2 BPN groups	

Note: Non-pharmacologic intervention (group therapy) was part of the study but no mention made of how the various groups attended the sessions

1994	Strain et al (Am J Psy)	RCT comparing BPN with meth over 26 weeks (db/dd) – flexible dosing
Nos/gp	84/80 (BPN/Meth)	164 in total
Doses	BPN	2/4/6/8mg on days 1,2,3,4 & then 8mg daily up to week 16. Possible to have increases/decreases during this time (increments of 2mg up to max of 16mg) Dose tapered by 10% each week thereafter until at placebo at 26 weeks
	Meth	20/30/40/50mg on days 1,2,3,4 & then 50mg daily up to week 16. Possible to have increases/decreases during this time (increments of 10mg up to max of 90mg) Dose tapered by 10% each week thereafter until at placebo at 26 weeks
Trial duration	26 weeks	
Outcomes Measured	• Retention in treatment • Compliance (clinic attendance & counselling contacts) • Urinalysis thrice weekly	
Result	No significant difference in outcomes	Note: Mean doses used 8.9mg BPN 54mg Meth

Note: Weekly detailed Counselling (one-to-one and group therapy) provided. Attendance was assessed as part of outcome / endpoint – no difference between groups

1994	Strain et al (Psychopharmacology)	RCT comparing efficacy of BPN with meth for decreasing cocaine use in patients with combined opioid & cocaine use (db/dd)
Nos/gp	24/27 BPN/Meth	51 in total
Doses	BPN	2/4/6/8mg on days 1,2,3,4 & then 8mg daily up to 3 weeks Dose increments (2mg) allowed to a max of 4 until week 16 & then dose tapered by 10% weekly until week 26 when it was zero (placebo)
	Meth	20/30/40/50mg on days 1,2,3,4, and then 50mg daily up to 3 weeks. Dose increments (10mg) allowed to a max of 4 until week 16 and then dose tapered by 10% weekly until week 26 when it was zero (placebo)
Trial Duration	26 weeks	
Outcomes Measured	• Treatment retention (up to week 16) • Compliance (attendance for treatment & counselling) • Urinalysis thrice weekly	
Result	No difference between treatments in endpoint outcomes. No selectivity with regard to attenuation of cocaine abuse	

Note: Counselling given on one-to-one basis as well as group therapy. Important part of treatment – one of endpoints measured

1995	Johnson et al (Drug & Alcohol Dependence)	RCT comparing buprenorphine to placebo for treatment of opioid dependence (db)
Nos/gp	60/30/60 BPN 2/BPN 8/Placebo	(150 in total)
Doses	BPN	2mg/daily on days 1-6 after which a dose change (to either of the other 2 groups) was allowed. This dose was continued until day 14.
	BPN	2/4/8mg on days 1-3 & then 8mg until day 6 when a dose change (as above) was allowed. This dose was continued until day 14
	Placebo	0mg medication on days 1-6 after which a dose change as above was allowed and this dose was continued until day 14.
Trial Duration	14 days	
Outcomes Measured	• Primary – Numbers remaining with original dosing schedule • Secondary – Urinalysis (3 samples) • Self reports of withdrawal	
Result	BPN–treated patients scored better than placebo patients, in terms of retention in treatment, % of +ve urinalysis. Males showed greater decrease in +ve urines No significant difference in response between 2 doses of BPN was noted.	

Note

1) Counselling (one-to-one) was part of protocol

2) This was done to satisfy FDA guidelines on evaluations of new drugs (need for placebo – controlled studies if feasible)

3) This was part of a subsequent (larger) study undertaken in this research unit

1996	Ling et al (Arch Gen Psy)	RCT comparing fixed dose BPN with 2 doses of methadone over a long-term period (db)
Nos/gp	75/75/75	(225 in total)
Doses*	BPN	2/4/8mg on days 1,2,3 & then 8mg for 52 weeks
	Meth (1)	30mg daily for 52 weeks
	Meth (2)	30 mg on day 1 increasing by 5mg daily up to 80mg which was maintained for a total of 52 weeks
	*Although a fixed-dosing study there was a facility to monitor the adequacy of the dose in order to identify potential problems. Such patients were redirected to other protocols without breaking the study code	
Duration of Study	52 weeks	
Outcomes Measured	• Retention Rates • Urinalysis (thrice weekly) • Self reports of craving • Self reports of withdrawal symptoms	
Results	Meth 80mg was significantly better than the other 2 groups at 26 and 52 weeks. No real difference between BPN and Meth 30mg	

Note: Counselling provided but not obliged to attend. No difference between groups here

1997	Schottenfeld et al (Arch Gen Psy)	RCT comparing 2 doses of BPN with 2 doses of Meth. over a 24 week period (db)
Nos/gp	28/29/30/29	(total 116/ 132 randomised)
Doses	BPN (1)	1mg daily for 1 week, 2mg daily for 1 week, 4mg daily thereafter for the duration of study
	BPN (2)	4mg daily for 1 week, 8mg daily for 1 week, 12mg daily thereafter for the duration of the study
	Meth (1)	20mg daily for the duration of the study
	Meth (2)	35mg daily for 1 week, 50mg daily for 1 week, 65mg daily thereafter for the duration of the study
Duration of study	24 weeks	
Outcomes Measured	• Urinalysis (2-3 times weekly) • Concurrent cocaine use • Self reports of illicit drug & opioid withdrawal symptoms • Retention in treatment	
Results	BPN 12mg & Meth 65mg significantly superior to lower doses +ve urinalysis: 58% BPN 2; 45% Meth 2 77% BPN 1; 72% Meth 1 No superior beneficial effect for either with regard to cocaine use	Note: Non significant trend for increased illicit drug use in BPN 12mg compared with Meth 65mg. Significance unknown.

Note:
Counselling provided and subjects had to attend one hour per week for group therapy (could be discharged from study for not attending)

1998	Eder et al (Eur Addict Res)	Randomised control trial comparing variable doses of BPN & Meth
Nos/gp	16/18 BPN/Meth	34 in total
Doses	BPN	Free dosing schedule used (max dose 8mg/day)
	Meth	Free dosing schedule used (no upper unit)
Duration of study	24 weeks	
Outcomes Measured	• Retention Rates • Urinalysis (weekly)	
Results	Less +ve urinalysis in BPN group but better retention in Meth group (differences not significant)	

Note: Psychosocial counselling not compared in the study

1998	Uehlinger et al (Eur Addict Res)	RCT comparing variable doses of BPN & Meth (db)
Nos/gp	29/29 BPN/Meth	58
Doses	BPN	4 – 16mg daily (variable dosing allowed)
	Meth	30 – 120mg daily
Duration of study	6 weeks	
Outcomes Measured	• Retention Rates • Urinalysis (weekly) • Self reports of craving/withdrawal	
Results	No differences in Urinalysis results. Retention rate lower with BPN but not significant.	

Note: Psychosocial counselling not compared in the study

1999	Fischer et al (Addiction)	RCT comparing flexible doses of BPN with flexible doses of methadone in an open setting for 24 weeks
Nos/gp	29/31	(total of 60)
Doses	BPN	2mg on day one, with a dose titration of up to max of 8mg daily for the duration of the study
	Meth	20mg on day one with a dose titration of up to max of 80mg daily for the duration of the study
Trial duration	24 weeks	
Outcomes Measured	• Urinalysis (twice weekly x 3 and then weekly) • Retention rates	
Results	Methadone group showed significantly greater retention rates but the BPN "completers" showed significantly lower illicit drug use compared with meth "completers"	

Note:

- First time BPN tablets used in a clinical trial.
- Psychosocial counselling available but not compared in study
- Open study
- Patient got "take-aways" and did not have to attend the clinic daily

2000	Johnson et al (NEJM)	RCT comparing BPN (flexible dose) LAAM (flexible dose) with meth low and high doses over a 17 week period (db)
Nos/gp		55 per group
Doses	BPN	Thrice weekly dosing (intricate schedule) consisting of dose induction (weeks 1 & 2) maintenance (weeks 3-17) disposition (18-28) average dose 16-32mg Mon and Weds and 24-48mg on Friday
	LAAM	Thrice weekly dosing with above schedule to give 75-115mg Mon and Weds and 105-161mg on Friday
	Meth	Low dose – 20mg daily for study Higher dose – titrated in above schedule to give 60-100mg daily
Outcomes Measured	• Retention times • Urinalysis for illicit drug use • Self reports of illicit use/ withdrawal symptoms	
Result	BPN, LAAM and high dose Meth significantly better than meth 20mg for all the study variables	

Note:

- Concomitant psychosocial counselling not mentioned
- Subjects were allowed "take aways" after week 3 (attended clinic thrice weekly only)
- LAAM has been removed from the market in the EU but is still available in the US

2000	Pani et al (Drug & Alcohol Depend)	RCT comparing fixed dose of BPN with fixed dose of Meth (db)
Nos/group	38/34 BPN/Meth	72 in total
Doses	BPN	2mg/day increasing every second day by 2mg to reach 8mg/day by day 7. Maintained on 8mg/day for study
	Meth	20mg/day increasing every second day by 10mg to reach 60mg/day on day 9. Maintained on 60mg/day for study
Duration of Study	26 weeks	
Outcomes Measured	• Retention in study • Urinalysis self reports of cravings and illicit drug use	
Result	No significant difference between groups in terms of urinalysis, retention in treatment or self reports.	

Note: Weekly 20-minute individual counselling session provided (not obligatory)

2001	Petitjean et al (Drug & Alcohol Depend)	RCT comparing flexible doses of BPN & Meth (db)
Nos/group	27/31 BPN/Meth	58 in total
Doses	BPN	4mg/day X 3 and then flexible dosing up to a maximum of 16mg/day
	Meth	30mg/day X 3 and then flexible dosing up to a maximum of 60mg/day
Duration of Study	6 weeks	
Outcomes Measured	• Urinalysis (weekly) • Retention in treatment • Self reports of craving	
Results	Significantly better retention rates for Meth. Thought to be due to inadequate BPN induction dose. Other outcomes similar	

Note: Obligatory 1-hour weekly individual counselling session provided

Appendix IV

Details on the Working Party Members

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