The Swiss Scientific Studies of Medically Prescribed Narcotics by W. Hall &
The effectiveness of other opioid replacement therapies: LAAM, heroin, buprenorphine and naltrexone by R.P. Mattick, D. Oliphant, J. Ward, W. Hall, & J. White

NDARC Technical Report No. 43
THE SWISS SCIENTIFIC STUDIES OF MEDICALLY
PRESCRIBED NARCOTICS

Wayne Hall
National Drug and Alcohol Research Centre
University of New South Wales

1997
Technical Report Number 43
ISBN No. 0 947229 71 X
Contents

The Swiss Scientific Studies of Medically Prescribed Narcotics by Wayne Hall

1. Introduction ............................................................................................................................. 1
   1.1 Basis for Opinion ............................................................................................................. 1
   1.2 Swiss Drug Policies ................................................................................................. 1
   1.3 The Political Context ................................................................................................. 2

2. Design of the Studies ................................................................................................................ 3
   2.1 Objectives .................................................................................................................... 3
   2.2 Subject selection ........................................................................................................ 3
   2.3 Trial Design ................................................................................................................ 4
   2.4 Type of Treatment offered .......................................................................................... 4
   2.5 Assessment of outcome .............................................................................................. 4

3. Provisional Findings .................................................................................................................. 5
   3.1 Attractiveness to population....................................................................................... 5
   3.2 Feasibility of Heroin Maintenance ............................................................................ 5
   3.3 Pharmaceutical issues ................................................................................................ 5
   3.4 Impact on trial participants ........................................................................................... 6
   3.5 Social impacts of the trial ........................................................................................... 6

4. Potential Significance of the Swiss Trials ................................................................................... 7

5. Implications for Future Research ............................................................................................... 7

6. Conclusions ............................................................................................................................. 9

References ........................................................................................................................................ 10
Contents

The effectiveness of other opioid replacement therapies: LAAM, heroin, buprenorphine and naltrexone by Richard P. Mattick, Dorothy Oliphant, Jeff Ward, Wayne Hall, and Jason White

Introduction ................................................................................................................................. 1
  Patient choice................................................................................................................... 1
  Disadvantages of methadone as a maintenance agent ................................................. 1
  Alternatives to methadone ....................................................................................... 2

LAAM ....................................................................................................................................... 2
  Pharmacokinetics and Pharmacodynamics ........................................................................ 3
  Treatment Effectiveness............................................................................................ 3
  Summary....................................................................................................................... 4

Heroin (Diacetylmorphine) Maintenance Therapy................................................................. 5
  Pharmacokinetics and Pharmacodynamics ........................................................................ 5
  Treatment Effectiveness............................................................................................ 6
  Summary....................................................................................................................... 7

Buprenorphine ............................................................................................................................. 8
  Pharmacokinetics and Pharmacodynamics ........................................................................ 8
  Treatment Effectiveness............................................................................................ 9
  Dosage and Alternate Day Dosing ............................................................................... 11
  Summary....................................................................................................................... 11

Narcotic Antagonists.................................................................................................................. 12
  Rationale.................................................................................................................... 12
  Naloxone..................................................................................................................... 12
  Naltrexone.................................................................................................................... 12
  Summary....................................................................................................................... 13

References................................................................................................................................. 14
1. Introduction

The "scientific studies of medically prescribed narcotics" in Switzerland (hereafter for brevity the Swiss trials) were set up to investigate the feasibility and effectiveness of prescribing injectable opioid drugs (including heroin, morphine and methadone) to severely opioid dependent and destitute patients under medical supervision. The aim of prescribing injectable opioids was to improve the health and psychosocial well-being of the dependent drug users who either had not responded to, or had not been reached by, existing forms of treatment (Swiss Strategy Against Illicit Drug Use, 1988).

A three-year program of studies was approved by the Swiss Council of Ministers in 1992. The first studies were set up in multiple sites throughout Switzerland in January 1994 to provide places for 700 patients (250 places for injectable heroin, 250 places for injectable morphine, and 200 places for injectable methadone). During the course of 1994 and 1995 the design was modified. The number of places on injectable heroin was increased to 800, of which 707 had been filled by April 1996 (as against 33 of 100 places for morphine and 35 of 100 places for intravenous methadone).

1.1 Basis for Opinion

The following opinion on the Swiss trials is based on a number of sources of information. These include: a critical reading of the study protocol and report of the interim results of the Swiss Trial (Dobler-Mikola et al, 1994; Uchtenhagen et al, 1994) which I received as a participant in Phase I of the WHO evaluation of the Swiss trials in 1995; a one day seminar in Geneva in May 1995 (which was organised by the Programme on Substance Abuse of the WHO) at which the interim results of the trials were presented and the trial design critically evaluated by persons expert in the evaluation of the effectiveness of drug treatment; and site visits over 11 days to the various trial sites which were undertaken as part of Phase II of the WHO Process Evaluation of the Swiss trials in May 1996. During the site visits I discussed the trial with study participants, key treatment personnel, researchers involved in evaluating its effectiveness, and senior Swiss health policy makers and politicians. I made the site visits as a member of a five person WHO team, discussions with whom have shaped my thinking. The Swiss trials were also discussed at the 30th Expert Committee on Drug Dependence which I attended in Geneva in October 1996.

1.2 Swiss Drug Policies

There are estimated to be 30,000 heroin and cocaine addicts in the Swiss population of approximately 7,000,000 (Swiss Federal Office of Public Health, 1995). This represents a prevalence of 430 per 100,000 compared with 333 per 100,000 in Australia (assuming that there are 60,000 dependent heroin users in Australia). Swiss addicts are similar to those in Australia, with a mean age of 30 years and a 10 year history of heroin and cocaine use, indicating the onset of the last major epidemic of illicit drug use in the mid 1980s. The major difference between dependent drug users in Switzerland and Australia is that Swiss drug users have much higher rates of cocaine use, especially in the major cities, such as, Zurich.
When the Swiss trials are seen within context they are a relatively minor part of the overall Swiss drug strategy (Rihs, 1994). Law enforcement is the largest area of drug policy expenditure in Switzerland with 500,000,000 SF pa being spent on "repression", i.e. law enforcement measures that aim to reduce the supply of illicit drugs (1 SF is approximately equal to A$1). This compares with the most recent estimate of the total spent in Australia on law enforcement for illicit drugs, namely, $450,600,000 (Collins and Lapsely, 1996).

The treatment of drug dependence is the next largest Swiss expenditure on drug policy. This amounts to 260,000,000 SF which covers the costs of maintaining 15,000 drug users in methadone maintenance treatment (MMT), 40% of which is provided by private practitioners and 60% by public programs. In addition, residential treatment is provided to around 1250 persons per year. The Swiss total dwarfs Collins and Lapsley's estimate of $42,700,000 spent on all health care for illicit drug users in Australia. According to the Swiss Federal Office of Public Health (SFOPH) 50% of their dependent heroin users are in contact with treatment services compared with the 30% of heroin users estimated to be in contact with MMT in Australia (Hall, 1995). Switzerland also spends 200,000,000 SF pa on harm reduction measures such as needle and syringe exchange programs, injection rooms and outreach services which are well developed in most Swiss cities. A further 35,000,000 SF pa is spent on prevention programs, such as drug education.

The Swiss government was prepared to consider the addition of heroin prescription to its drug strategy because of community concern about epidemic heroin and cocaine use in many Swiss cities in the mid to late 1980s. The "open drug scenes" that developed in Zurich and other cities apparently had a major influence on public attitudes according to Swiss officials and politicians. There was a high prevalence of HIV/AIDS among these drug users, with as many as 60% of those who initiated drug use before 1985 being HIV positive. Concern about the size of the heroin and cocaine dependent population, the public nature of open drug scenes, the severe social deterioration of many drug users who frequented these open drug scenes, and fears of an epidemic of AIDS among drug users, all made politicians and the public receptive to the advocacy of trials of heroin prescription as a "radical" solution to the drug problem.

1.3 The Political Context

The Swiss trials have been conducted in a unique political context. The decision about whether to conduct the trials was necessarily a political one and continued debate about the trials has meant that the design and conduct of the trials has been strongly influenced by the political process.

The government decided what type of heroin prescription would be implemented. Heroin would only be prescribed to opioid-dependent persons who had a minimum history of two years of dependence and who had failed at previous drug treatment (including drug-free and methadone maintenance treatment). In order to minimise the risk of diversion heroin would only be administered under medical supervision at the clinic. The political process also determined the original number of participants in the trial and it imposed time constraints on the preparation and design of the studies, the period of recruitment for the trial, the completion of data collection and delivery of the final evaluation report.
The trials have been subject to a high degree of review and oversight to increase public confidence in the probity of the evaluation studies and the credibility of their results. The trials have been overseen by the following independent bodies: an advisory committee of eminent scientists with expertise relevant to the trial; ethical scrutiny of the trial design and protocol by an ethics committee of the Swiss Academy of Medical Sciences (as well as regional and local ethics committees); and an evaluation of the Swiss evaluation studies by an expert committee nominated by the WHO Programme on Substance Abuse.

Despite all these efforts there is still a debate about whether the Swiss trials should continue if the initial results of the trials are positive. There are, for example, competing referenda proposals that will be voted upon probably in early 1997. One proposal, from the Parents for a Drug-Free Youth, is to abolish all forms of drug substitution treatment and needle exchange programs and for the State to provide only abstinence-oriented drug treatment. The other proposal is to permit the distribution of any drug to any adult under medical supervision. There have also been criticisms of the trial from a public health perspective, namely, that the treatment of illicit drug dependence is receiving a disproportionate amount of public resources by comparison with other forms of treatment in general, and the treatment of other forms of drug dependence, such as, alcohol and tobacco, in particular.

2. Design of the Studies

2.1 Objectives

The main questions that the Swiss trials were designed to answer were:

will the prescription of injectable heroin attract into treatment dependent heroin users who have not been previously treated or who have been unsuccessfully treated?

will heroin prescription programs improve participants' health and social position, reduce their risk behaviour and increase their rates of abstinence from illicit drugs?

will the trials improve our understanding of the effects of opioids and their role in drug substitution treatment?

2.2 Subject selection

The criteria for subject selection were designed to select severely opioid dependent persons who had failed at previous treatment or whose health and social adjustment was severely impaired. To be eligible for inclusion, participants had to be: 20 years of age or older; to have had two years of daily heroin use, to have had either two previous treatment failures or to be unlikely to respond to available forms of treatment; to have major impairments of physical and psychological health, to have signs of social disintegration; to provide informed consent to participate in the trials; and to agree to abide by clinic rules.
2.3 Trial Design

The original design was a multisite comparison of 250 patients in each of the injectable heroin and morphine conditions with 200 patients receiving injectable methadone (700 in total). The aim was to compare retention in treatment and treatment outcomes (such as drug use, health and criminal involvement) in patients receiving each of these treatments with the outcomes among patients enrolled in oral methadone maintenance programs.

The original design was abandoned because it proved difficult to recruit and retain patients in the methadone and morphine conditions. Injectable morphine proved to be unacceptable to many subjects because of severe histamine reactions at the site of injections. Injectable methadone also adversely affected the participants’ veins. The numbers in these conditions were consequently too low to provide statistically powerful comparisons of the outcomes of these participants with those being prescribed injectable heroin.

The trial design was modified in the light of this experience. The numbers of subjects receiving injectable morphine and methadone were reduced to 100 each and the number of persons receiving injectable heroin was increased to 800. During the second phase of recruitment to the trials a cohort of 350 subjects entering methadone maintenance treatment will be recruited in the same studies sites to provide a comparison group. The subjects in injectable heroin and oral methadone maintenance will be compared with respect to: retention in treatment; rates of illicit opioid and other drug use; improvements in health, well-being and social adjustment; and reductions in criminality.

2.4 Type of Treatment offered

At all trial sites, heroin is only administered by injection under staff supervision. In a small number of sites, some participants are allowed takeaway heroin "reefers". In other respects heroin prescribing practices vary between sites. At some sites most participants were largely maintained on injectable heroin (with up to three injections a day of as much as a gram of heroin). Even so many of these patients received small doses of oral methadone, if required, to avert withdrawal. At other sites most participants were on substantial doses of oral methadone (30 mg), with one or two injections of heroin per day.

The trial sites also varied in their prescribing practices for benzodiazepines, a drug class widely used by the drug dependent population in Switzerland as in Australia. Some clinics prescribed maintenance doses of benzodiazepines; others did not. There was compulsory weekly psychotherapy in all programs as a requirement of the study. There was also a requirement for regular medical review of all trial participants. All participants made some contribution to the costs of their treatment by paying 10-15 SF per day.

2.5 Assessment of outcome

The outcome of heroin, morphine and methadone prescription will be assessed by comparing the medical, psychological and social status of trial participants on entry to the trial with their status at six monthly assessments made by independent interviewers. The outcomes on which they will be assessed
are self-reported: drug use, health status, health service utilisation, well-being, psychological symptoms, social functioning, and crime. In addition, there will be urinalysis data (collected two monthly while subjects are enrolled in treatment); laboratory tests of exposure to infectious diseases, body mass index as a measure of nutritional status; and police records of arrests and convictions for participants who have been recruited during phase 2 of the studies.

3. Provisional Findings

3.1. Attractiveness to population

The characteristics of the first 366 entrants have shown that dependent heroin users can be attracted into treatment. They had an average age of 30 years, two thirds were male, and they had a 10 year history of heroin and cocaine use. Only 16% were employed at the time of entry to the trial. All had received prior drug treatment, with a median of 6 treatment episodes (97% in detoxification and 58% in residential treatment). Almost all (95%) had been in MMT at some time, and 62% were in MMT at the time of entry to the trial. Criminal involvement was the norm, with 87% having been convicted of a criminal offence, 69% having been in gaol, and 64% of women were involved in prostitution. The trial succeeded in attracting the population for which it was designed but it is noteworthy that as at April 1996 only 707 of the 800 heroin places in the trial had been filled, and most study sites still had some vacant heroin places.

3.2. Feasibility of Heroin Maintenance

The trial results indicate that on-site heroin prescription is a feasible treatment option for some opioid dependent persons. They can be stabilised on doses of 500-600 mg of heroin per day, often in combination with oral methadone to minimise withdrawal. This can be done without leading to escalating doses of heroin. There have been no major problems with overdoses among trial participants, either on or off site, despite high rates of polydrug use. There have been no reported problems with neighbourhoods in which the clinics have been located. Diversion of heroin was not a major problem although some trial participants had been expelled from the study for attempting to divert heroin from the site, or for attempting to smuggle cocaine onto the site to mix with the heroin. There has been one reported theft of heroin cigarettes.

3.3. Pharmaceutical issues

The Swiss discovered that heroin was not a cheap drug to use for drug substitution treatment. They estimate that it cost 20 SF per gram to produce and administer it to a program participant. The major reasons for the cost are the difficulties in obtaining a dependable supply of pharmaceutical heroin; ensuring that it was of acceptable pharmaceutical quality; and securing the manufacture, distribution, and storage of the drug to minimise diversion between manufacture and administration in the clinic.

When the staffing costs for the clinic are added to the drug costs prescribing heroin proves to be a costly intervention. Although there are no final estimates of its cost, the guesstimate is that it cost 20,000 SF to provide each participant with heroin for a year. This is 2 to 3 times the cost of providing MMT in
Switzerland (Rihs, 1995, personal communication).

The pharmacists also discovered that there is little data on the pharmacodynamics, pharmacokinetics and metabolism of heroin and its metabolites. Heroin was proscribed for medical use in most countries in the early 1950s before the explosion of research into the pharmacodynamics and kinetics of opioid drugs. The Swiss found that smoking heroin impregnated cigarettes were an inferior way of delivering the drug and they have been investigating other non-injectable forms of heroin (including oral, slow release heroin) to prevent the vein problems caused by regular injection.

3.4. Impact on trial participants

Retention in treatment is a reasonable measure of the impact of MMT because the benefits of such treatment are clearest while people remain in treatment. In the Swiss trials, 82% of participants receiving a heroin prescription were still in treatment after 6 months (compared with 50% in Swiss MMT programs), and 73% were still in treatment after 12 months. Nearly half of the treatment drop outs (44%) returned to oral MMT, while 26% were expelled for non-compliance with program rules. A further 11% died, primarily from AIDS-related illnesses and accidents, with some overdoses occurring among those who had left treatment. Those who dropped out were most likely to be cocaine users and women involved in prostitution.

Trial participants reported that they used very little illicit heroin but 40% in the Zurich programs reported that they continued to use cocaine, although at a lower frequency than before treatment. Participants also reported that heroin prescription substantially reduced criminal activity to finance drug use, reduced their involvement in the drug scene, and substantially improved their health, well-being and social functioning. Corroboration of these self-report data are yet to come from urinalysis results, employment records, police records of criminal convictions, and weight and biochemical tests.

3.5. Social impacts of the trial

The impact of the trial on the broader community have not been formally evaluated. This has been a missed opportunity, given that community concerns about the impact of the trials were a major issue in Switzerland, and that the putative social benefits of heroin prescription were one of the reasons given for its implementation. Some Swiss politicians have claimed that the trials have been responsible for "solving" the heroin problem in Switzerland. This claim has been contested by law enforcement officials who point out problems in attributing reductions in heroin use and related problems to the heroin trials. The trials occurred, for example, well after the peak of the epidemic of heroin and cocaine use. By this time the number of new recruits to heroin use had probably declined, and there may have been a decline in the number of dependent drug users. There was also more active policing of the open drug scenes and a major expansion of MMT. In any case, the small size of trials (707 receiving heroin prescriptions vs 15,000 receiving oral MMT) makes it unlikely that they have had much impact on the prevalence of heroin use, or on the size of the black-market in illicit drugs.
4. Potential Significance of the Swiss Trials

The Swiss studies have demonstrated that it is feasible to maintain opioid dependent persons on injectable heroin for up to 2 years. Injectable heroin was attractive to the trial participants, it retained a substantial proportion in treatment, and there were no overdoses among trial participants or evidence of the diversion of prescribed heroin to the illicit drug market. The trials raise some doubts about the feasibility of injectible maintenance on morphine and methadone but this finding may well have been affected by the availability of heroin, preference for which dominated all else. This is suggested by the fact that the PROMI project in Fribourg (which was only allowed to provide injectable methadone) was able to attract and retain 29 heroin users.

According to clinic staff and patients the prescription of injectable heroin benefited the trial participants. These testimonials need to be substantiated by more rigorous and independent evaluation, and the magnitude and duration of the benefits need to be calibrated against the cost of providing treatment and possible adverse outcomes. The scientific evaluation of the trials will provide some answer to these questions.

The evaluation results reported to date rely upon self-reported drug use, health status, social functioning, and criminal activities collected by interviewers who are not involved in treatment. The credibility of these results will be increased if they are corroborated by other indicators of outcome such as: retention in treatment, physician assessments of health status, rates of infection with blood-borne viruses, premature mortality, and (for phase 2 patients) criminal records.

If the initial results withstand more critical analysis, it will be more difficult to decide how much of the improvement in patient status is attributable to the specific effects of heroin prescription. It will be impossible, for example, to say how much of the benefit is attributable to heroin prescription and how much is due to psychosocial interventions and the enthusiasm of the project staff and the trial participants that accompanies the introduction of a new therapeutic intervention for a chronic condition. The early results of methadone maintenance treatment, for example, were more optimistic than subsequent results in clinical practice (Ward et al, 1992).

In the Swiss trials the issue of causal attribution can only be addressed by quasi-experimental method. This involves a comparison of the outcomes of heroin prescription with those in oral MMT among persons recruited at the same time and places as new entrants to phase 2 of the Swiss trials. Since it is highly likely that the participants in the heroin prescription trials and MMT will not be equivalent in their baseline characteristics statistical adjustment will have to be used to deal with any differences between the groups at treatment entry.

5. Implications for Future Research

If the results of the Swiss trials are judged to be positive enough to justify their continuation a number of research questions will need to be addressed. Foremost among these is whether the good results in the trials persist when heroin prescription becomes a more routine form of treatment delivery. It is well-recognised that the results of clinical investigations often overestimate the benefits of treatment
under the exigencies of clinical practice, a fact acknowledged in distinguishing between studies of treatment efficacy and effectiveness. This is because treatment in clinical trials is delivered in an optimal way, with well-trained and enthusiastic staff, good clinical infrastructure, quality control over treatment delivery, and with the more difficult cases excluded from trials.

A second question is: what becomes of participants who are stably maintained on injectable heroin? There is often dramatic improvement in health status and social functioning on entry to treatment but what happens once a patient has been stabilised? Will they reduce their heroin doses in pursuit of abstinence? Will they be maintained long term on injectable heroin? Will they transfer to oral methadone?

A third set of questions are pharmacological. Are there new galenic forms of heroin, such as slow release heroin tablets, that could be used as an alternative to injectable heroin? Are there other short-acting opioids that could be used instead of heroin.

A fourth set of questions is raised by the high cost of heroin prescription. Can its costs be substantially reduced? Will it be cheaper to provide it within methadone maintenance programs? To what extent are its current high costs of delivery due to the fact that this is a well-resourced research study? What is the place of heroin prescribing in the Swiss drug treatment system? Who is most likely to benefit? Should current subject selection criteria be relaxed?

The critical question for observers in other countries, including Australia, is: how applicable is the Swiss experience with heroin prescription to other cultural settings? There are unique features of Swiss society that may be difficult to reproduce in other political systems. Switzerland has a Federal system and it is a very wealthy country that has a comprehensive health care system. It has a well developed drug treatment system that reaches as many as half of its drug dependent population. It has also had extensive experience with drug substitution treatment, and it has a well developed drug control system. It is also a small country with a well developed public transport system that makes it easy to provide treatment to large numbers of drug dependent persons. Even so heroin prescription in Switzerland is and is likely to remain a minority treatment option reserved for those who have failed at other types of drug treatment.

A sixth set of questions concerns the impact of heroin prescription on the natural history of heroin dependence. The Swiss trials provide an opportunity to follow-up a well-documented cohort of over 1000 opioid dependent persons (800 in heroin prescription and 350 in MMT). Since there are few long-term studies of drug dependent persons outside the USA it is commendable that the Swiss intend to follow this cohort over ten years to examine the impact of heroin prescribing on drug use career and rates of abstinence.

6. Conclusions

The Swiss trials suggest that it is feasible to prescribe heroin to severely dependent heroin users, under close medical supervision, with substantial benefit and without major adverse consequences for trial participants. On the available self-report data, the trial participants appear to benefit from heroin
prescription in that their use of illicit heroin is reduced, their health and social functioning improves, and their involvement in the drug scene and criminal activity declines. Confirmation of the promising initial self-reported benefits awaits the results of the more rigorous evaluation.

Unfortunately, the unique political context within which the trials were designed and approved meant that opportunities were lost for a more rigorous evaluation of the effectiveness of heroin prescription. The most unfortunate outcome was the lack of an adequate comparison group against which to compare the benefits of heroin prescription. There have also been missed opportunities to rigorously evaluate the social impact of heroin prescription, and to study the comparative cost effectiveness of heroin prescription and methadone maintenance. These opportunities should not be missed in any subsequent trials that are conducted.

It is also unclear how transportable the Swiss experience with heroin prescription may be to other cultural contexts. The trials occurred because of widespread public concern about heroin use in Switzerland that was expressed through the Swiss political system in a way that permitted some Cantons to experiment with heroin prescription. These trials occurred within a wealthy society with a comprehensive health care system which had a well developed drug treatment system whose personnel had substantial experience with opioid substitution treatment.

Even so heroin prescription in Switzerland has been an addition to existing treatment approaches; it has not replaced other forms of drug substitution, such as MMT. Nor has it eliminated the need for drug-free treatment approaches for those who wish to become abstinent. Heroin prescription has also been an expensive treatment option for a minority of severely dependent opioid users. Its place in the Swiss drug treatment system for opioid dependence has been much like that of heart transplants in the Australian response to cardiovascular disease.

Given its limited role, the controversy about heroin prescription in Switzerland has arguably been out of all proportion to its importance as a treatment option. Debate about heroin prescription has threatened to dominate discussion of drug policy. Managing the trials and their evaluation has taken up a substantial part of the limited resources of the SFOPH. A similar outcome can be anticipated if a trial proceeds in Australia. An unintended consequence of the Swiss trials has been the public disparagement of MMT by some advocates of heroin prescription. The many opioid dependent persons who are successfully maintained on MMT are in danger of being forgotten, as is the fact that MMT continues to be the mainstay of the Swiss treatment response to opioid dependence.
References


The effectiveness of other opioid replacement therapies:
LAAM, heroin, buprenorphine and naltrexone

Richard P. Mattick$^1$, Dorothy Oliphant$^1$, Jeff Ward$^2$, Wayne Hall$^1$, and Jason White$^3$.

1. National Drug and Alcohol Research Centre
2. Australian National University
3. Adelaide University

1997

Technical Report Number 43
INTRODUCTION

Patient choice
The need to consider and develop alternative methods of management of opioid dependent patients is posited on the belief that there is an important element of patient choice which affects the decision to enter and stay in treatment, and hence the benefits achieved. The issue of patient compliance with treatment is well recognised in health care delivery generally. There is no doubt that patient choice in treatment of opioid dependence is an important factor. The experience in one US study was instructive in this regard (Bale et al., 1980). Bale and colleagues (1980) conducted a prospective observational study of treatment outcome among opiate addicted male veterans in which the intention was to randomly assign subjects to either a therapeutic community or to methadone maintenance and to compare their outcome with a detoxification-only control group. This plan had to be abandoned because treatment staff objected to patients being randomly assigned to treatment type. A compromise was reached in which subjects were required to enter the treatment program to which they had been assigned for one month following admission, after which they could change to the program of their choice. Very few of the patients remained in the programs to which they were originally assigned. Specifically, only 18% subjects who were assigned to therapeutic communities entered that modality and only 29% of those assigned to methadone maintenance engaged in that treatment.

We also need to be mindful of the work on heroin maintenance showing that patient choice or preference greatly affects retention (Hartnoll et al., 1980). In that study, at 12 months 74% of patients continued to receive a prescription while only 29% of methadone maintenance patients were still in treatment. Similar results are being obtained in the Swiss heroin trial (Hall, 1996). Given that retention is associated with other treatment benefits the better retention of the heroin maintenance group is important, however, it has to be balanced with the issue of treatment response. As will be discussed later, heroin maintenance is associated with less change in drug use that methadone maintenance, detracting from the benefits of heroin maintenance. Even so, it should remain clear that patients have views of the treatments which they are offered and these views affect their willingness to enter and stay in treatment. Only the balance of information concerning acceptability of each treatment and the effects achieved will allow a fully informed decision by policy makers and health care workers about the appropriate intervention for opioid dependence management.

It is also important to recognise that there are individual differences in both the pharmacokinetics and pharmacodynamics of any drug. The general properties of a drug reflect averages across the population, but typically within a population there is considerable variability in characteristics such as speed of onset of action, duration of action, peak effect, etc. There may also be idiosyncratic reactions which mean that a drug is unsuitable for use in a sub-group of the population. Currently, methadone is the only drug available for maintenance opioid replacement treatment for dependent users in Australia. In those individuals for whom the drug is unsuitable, the likely result is treatment dropout or poor compliance. The availability of alternative pharmacotherapies will allow a greater range of clients to be treated effectively.

Disadvantages of methadone as a maintenance agent
Oral methadone maintenance, like any pharmacotherapy, has some negative characteristics which have
led to an interest in alternative pharmacotherapies and methods of treatment delivery (Mattick & Hall, 1993). First, as methadone is a full opioid agonist, it has the potential to produce dependence. Even in those who are suitable for opioid replacement therapy, there have been concerns about maintaining patients on a full agonist for fear of prolonging or worsening their level of dependence on opiates. Second, in overdose, the level of respiratory depression or sedation of methadone can be fatal. Deaths have occurred in patients being stabilised on methadone and in non-tolerant individuals. Third, although methadone is a relatively long-acting opioid, the inconvenience of daily dosing and clinic visits may be unattractive to certain clients, and the restrictions imposed by the daily dosing schedule on clients’ opportunities to sustain employment may also limit its suitability. Fourth, the provision of takeaway doses has the attendant problem of diversion. Fifth, "street" myths and the stigma of methadone treatment create a barrier to entering treatment for those who might otherwise benefit from maintenance therapy (Rosenblum, Magura & Joseph, 1991), and some argue that the unattractiveness of methadone to many illicit opioid users is a barrier to entering treatment. Sixth, in some patients methadone fails to provide symptom relief over the full 24 hour dosing period, probably due to fast metabolism of the methadone causing trough serum levels, resulting in the occurrence of marked withdrawal symptoms (Holmstrøm, Angaard & Gunne, 1978). Finally, there is a desire among some users to be able to inject maintenance medications rather than ingest it orally. Thus, despite its success as a maintenance agent, methadone appears to have some negative characteristics as outlined above, and explored in more detail elsewhere (Mattick & Hall, 1993). These factors may restrict the ability of methadone to attract opioid users into treatment (although the experience is that the demand for treatment with methadone outstrips supply). As a result, interest in the development of alternatives to broaden the range of pharmacotherapies has been the focus of increasing research in recent years.

**Alternatives to methadone**

The most promising of these alternative opioid analgesics for management of opioid dependence in a maintenance regimen involve pharmacotherapies which treat clients with a pharmaceutical grade opioid which has a longer duration of action than methadone. These include the full agonist levo-alpha-acetylmethadol (LAAM) and the opioid partial agonist buprenorphine. Additionally, diacetylmorphine (heroin) has attracted interest as a possible maintenance agent and naltrexone, a full opioid receptor antagonist has been evaluated for the management of opioid dependence. Currently, only methadone is approved for treatment of opioid dependence. Other countries have approved buprenorphine (France) as well as naltrexone and LAAM (U.S.A.) for treatment of opioid dependence. It is likely that buprenorphine will be approved for treatment of opioid dependence in Australia within the next two years. The registration of LAAM and naltrexone may require special attention by the Australian Health Department regulatory body, if they are to become available in Australia in the near future. The fate of heroin maintenance will be determined based on research in process and political factors.

**LAAM**

LAAM (leva-alpha-acetylmethadol) is a synthetic opioid analgesic (related to methadone) of the morphine type which was extensively investigated in the 1970s as a pharmacological alternative to methadone. Its major advantage compared with methadone is that it has a longer half-life and patients can be dosed every 48 hours, rather than every 24 hours as required with methadone. In some cases
three day dosing has been achieved satisfactorily. Additionally, it is effective when ingested orally, like methadone.

A number of rationales have been put forward to support the use of LAAM in the treatment of opioid dependence. First, its use was to provide better suppression of withdrawal symptoms in patients who reported such symptoms before the end of the usual 24 hour dosing period on methadone. A second rationale for the use of LAAM rather than methadone was to reduce the need for "take-away" or "take-home" doses of methadone, overcoming problems of diversion and deaths associated with ingestion of the drug by non-tolerant individuals. A third rationale for the use of LAAM is its potential to offer a more cost-effective intervention than methadone. A fourth rationale was that the less frequent clinic attendance also brings the additional benefit of reduced congregation at dosing sites because of less frequent clinic visits (Prendergast et al., 1995).

**Pharmacokinetics and Pharmacodynamics**

Administration of LAAM produces typical mu-opioid agonist activity. LAAM is characterised by a relatively long duration of action. The activity of LAAM appears to be due to two metabolites: nor-LAAM and di-nor-LAAM. While the two metabolites are pharmacologically active, it appears that the parent drug has no or little opioid activity. The half life of LAAM is 2.6 days, of nor-LAAM 2 days, and 4 days for di-nor-LAAM (Kreek, 1996a). As a result of these properties, LAAM tends to have a relatively slow onset of action (relying on conversion to metabolites) and a long duration of action. While such a long duration of action is potentially valuable in the management of opioid dependence, Kreek (1996) has noted the potential problems of toxic levels of LAAM's active metabolites to build-up during the stabilisation phase of maintenance dosing with this medication. Because of these problems, Kreek (1996) cautions against daily dosing with LAAM, suggesting that 48 hours is the minimum period between doses. However, as induction onto LAAM is affected by a delay in opioid activity as LAAM forms the long-acting active metabolites, administration of other medications to deal with transient withdrawal symptoms for the initial 96 hours of dosing may be warranted (Tennant, Rawson, Pumphrey & Seecof, 1986). Once stabilised, alternate day dosing is feasible.

**Treatment Effectiveness**

Jaffe et al. (Jaffe et al., 1972) compared LAAM and methadone with a wait-list control group. Over a 15-week study period, they found no statistical difference in outcome between the methadone and LAAM groups on employment status, drug use, and clinic and therapy group attendance. However, both the LAAM and methadone groups did better in terms of employment than the wait-list group, with the former improving while the employment status of the wait-list group deteriorated.

Others have also found positive results for LAAM. Ling et al. (Ling, Charuvastra, Kaim & Klett, 1976) reported on a 40 week double blind randomised controlled trial to compare the safety and efficacy of LAAM (80 mg thrice weekly with placebo on non-dose days) with that of high-dose (100 mg) and low-dose methadone (50 mg) administered daily. The study was conducted at 12 sites with 430 subjects. Both LAAM and high-dose methadone were found to be more effective treatments than low-dose methadone. The authors concluded that LAAM is as safe and efficacious as high dose methadone.
In a second controlled trial from this group, Ling (Ling, Klett & Gillis, 1980) examined the feasibility of maintaining patients on methadone from Monday through to Thursday and then with a single dose of LAAM on Friday until the following Monday. Unfortunately, there was a high drop-out rate in both groups, with 65% of the LAAM subjects and 48% of the methadone subjects leaving the study. The majority of LAAM drop-outs were due to “medication not holding” (48%). The authors concluded that this approach does not have wide general clinical application, but felt it may be useful for particular subjects, because some people found the regimen satisfactory.

Freedman and Czertko (Freedman & Czertko, 1981) compared the relative clinical efficacy of low-dose daily methadone (mean = 26 mg) with a thrice weekly low-dose LAAM regimen (mean = 24 mg) in a group of employed male heroin addicts. They found that the LAAM subjects used illicit drugs less and had better retention in treatment than the daily methadone subjects. As the LAAM subjects had previously been maintained on methadone, they were asked to complete a drug performance questionnaire to examine their satisfaction with both regimens. Patients preferred LAAM to methadone on nine out of 15 items, which included questions about frequency of dosing, health status and the extent to which each of the drugs reduced craving for heroin. The authors concluded that LAAM was acceptable to patients as a form of opioid maintenance and is particularly indicated for employed patients.

Savage and his colleagues (Savage, Karp, Curran, Hanlon & McCabe, 1976) used a double-blind cross-over design to compare the relative safety and effectiveness of LAAM and methadone. A sample of 99 males who had been stabilised on methadone were randomly assigned to one of two groups. One group received methadone for three months and were then switched to LAAM. The other group received LAAM for the first three months and then transferred to methadone. Their results showed that significantly more participants in the LAAM group dropped out of treatment during the first three months, but there was no difference in outcome between the two groups in the second three month period. Side-effects of the medication were given as the main reason for withdrawing from the study, and this was just as likely for patients on methadone as for patients on LAAM. In addition, there was no association between the type of drug and particular side-effects, and no significant difference between the two drug groups in terms of illicit drug use or absenteeism from the clinic. The authors concluded that for those who remained in treatment, LAAM was at least as effective as methadone and that both were safe treatment procedures. One study examined a reported side-effect that is troublesome for some patients on LAAM maintenance therapy. That is, the experience of stimulation in the 24 hours following administration of LAAM and then sedation in the following 24 hours. Investigation (Crowley et al., 1979) found that there were differences in activity levels consistent with the patients' self-report. This characteristic may be one disadvantage of LAAM treatment.

There has been relatively little study of LAAM since the early 1980s. Clinical experience with the medication has been reported on (Tennant et al., 1986). Tennant et al. (1986) provide an overview of clinical experience with LAAM with almost 1000 patients for periods of up to 36 months. Doses of 20mg to 140mg per dosage were used. There was no evidence of long-term toxicological effects. They suggest that the medication is safe, and efficacious for the majority of patients treated.

Summary
LAAM has been shown to be an effective maintenance agent in a number of randomised clinical trials. It has advantages over methadone as a maintenance drug: its longer half-life allows alternate or three day dosing; it provides greater flexibility for the patient; and there is less opportunity for illicit diversion. It should be considered as a contender in a range of pharmacological approaches to opioid dependence. The evidence to date suggests that the necessary research and application procedures for the registration of LAAM for clinical use in Australia would provide a useful additional alternative to methadone.

**HEROIN (DIACETYLMORPHINE) MAINTENANCE THERAPY**

Heroin (diacetylmorphine) is a opioid analgesic which has been not been extensively investigated as a pharmacological alternative for the management of opioid dependence. Its major disadvantage is that it has a shorter half-life than methadone and patients need more frequent dosing. Its use as a therapeutic medication is also affected by its illicit status.

Proponents of heroin maintenance argue that the HIV epidemic requires all approaches to management of illicit drug use to be expanded. Specifically, often arguing for the controlled availability of illicit drugs, they point out that: the prohibition of heroin has failed to eradicate the availability of illicit heroin; the unregulated illicit heroin market continues with no control over quality, purity, price, dose, mode of administration or the associated hazards of use; heroin maintenance will attract and retain heroin users who are not interested in entering methadone maintenance treatment; and heroin maintenance is a legitimate intermediate goal in treatment, and can be used in the short-term to attract those initially disinterested in methadone to attend treatment settings, thereafter allowing gradual transfer to long-acting opioids for maintenance.

A number of arguments against heroin maintenance therapy have been made. First, the short duration of action of heroin requires frequent administration at a clinic is expensive and inconvenient for all concerned, and focuses users in a particular geographic area. The alternative to the short-half life problem is to give the patient sufficient supplies to self-administer the drug elsewhere, but this solution risks inappropriate self-administration or significant diversion of the drug to others (Dole & Nyswander, 1965). Moreover, the continued injection practices may result in continued exposure to risk of infection with HIV and other viruses. It has been argued that patients cannot be adequately "stabilised" on short-acting opioids (e.g., morphine, heroin, hydromorphone, codeine, oxycodone, and meperidine) (Fink, 1972), early attempts at maintenance with short-acting agents reportedly finding that despite frequent injections, the patients' condition fluctuated between somnolence and agitation throughout each day, with tolerance increasing over consecutive days to the point where patients were almost continuously agitated even when receiving huge doses of morphine (Dole, 1972; Dole, 1988).

**Pharmacokinetics and Pharmacodynamics**

Heroin produces typical mu-opioid effects. However, these may not be due to the action of heroin itself. Heroin is rapidly metabolised in the body to 6-O-acetylmorphine and then more slowly to morphine. It has been suggested that the action of heroin is due principally to these two metabolites.
One important characteristic of heroin is the rapid onset of action. This can be accounted for by the relative ability of heroin and 6-O-acetylmorphine to pass through the blood-brain barrier compared to morphine. The picture is further complicated by the existence of active metabolites of morphine, including morphine-3-glucuronide and morphine-6-glucuronide. Heroin is effective after administration by a number of routes, including oral and intravenous administration. Following oral administration, the effect of the drug is likely to be due almost solely to the actions of morphine and its metabolites. Compared to morphine, heroin typically has a more rapid onset of action and somewhat shorter duration of action, although for some parameters the differences are relatively small. Typical duration of action is 4-5 hours.

Treatment Effectiveness

The literature on the effects of maintenance prescribing of heroin is markedly different from that available on methadone, buprenorphine and LAAM, being largely dominated by personal views and opinions for and against the approach, views which appear to have more to do with ideological stance, and unfortunately little to do with empirical data. However, some information is available.

On the claim that drug misusers cannot be adequately be stabilised on heroin, there appeared to be only limited evidence to support the view (Volavka, Zaks, Roubicek & Fink, 1970), in the references cited by those who made the claim (Dole, 1972; Dole, 1988; Fink, 1972), or in other literature. Double blind randomised research has shown that patients can be adequately stabilised on heroin (Ghodse, Creighton & Bhat, 1990).

There is only one randomised controlled clinical trial of maintenance on injectable heroin compared against oral methadone maintenance treatment (Hartnoll et al., 1980), conducted in the U.K. Hartnoll and colleagues studied 96 heroin dependent subjects who were offered one or other treatment and followed for one year, and it was found that the majority of those prescribed injectable heroin continued to inject heroin regularly (daily) and to supplement their maintenance prescription from other sources. Those who received oral methadone, were more likely to be abstinent. Those in methadone maintenance treatment who continued to inject were (not surprisingly) more reliant on illegal sources of drugs. The significant differences tended to favour oral methadone maintenance, in that, methadone maintenance patients had a significantly lower daily opioid consumption level, injected less frequently, and spent less of their time with other users. However, the drop-out rates differed markedly, with a 26% drop-out rate in the heroin maintenance group and a 71% drop-out rate in the methadone maintenance group. Thus, it appeared that oral methadone forced patients to either become abstinent or to continue illicit involvement. Heroin maintenance patients maintained the status quo. There were no differences in terms of physical health, criminal activity or employment between the two groups. However, in considering these data, it is important to note that the methadone maintained group dropout rate was much higher than normally expected in such programs, raising the question of the quality of the program provided in the Hartnoll study.

Hartnoll and colleagues (Hartnoll et al., 1980) note that the mixed results "do not indicate a clear overall superiority of either approach. Both treatments have advantages in some areas, but at the expense of disadvantages in other areas. The approach favoured depends on the priorities assigned to the various outcomes" (p.882). They make the point that the approach taken must reflect the relative "clinical,
ethical and political judgements”. In a HIV-aware world, the reduced frequency of injecting might be the prime goal, or having more heroin dependent patients in treatment may be preferred so that risk reduction procedures can be put in place.

Others (Marks, 1991) are more optimistic concerning the value of heroin prescribing. Marks presents results from the Widnes Clinic suggestive of lowered criminal activity, injecting, needle sharing and HIV rates associated with prescribing of heroin. He provides data comparing Merseyside to the rest of England and Scotland. The results are interesting, but do not equate to a controlled trial, and there are numerous rival hypotheses which could explain the difference in apparent rates.

Most recently, the Swiss have been investigating the value of heroin prescribing in a multi-site trial. The trial was to study the effects of injectable heroin and injectable morphine at one site in a randomised controlled trial, and at other sites in quasi-experimental studies compare those interventions and against usual oral methadone treatment. The research is to be completed and it will be at that time that the relative benefits and disadvantages of heroin maintenance will be more clearly documented. However, preliminary information (Hall, 1996) suggests that the cost of the delivery of heroin in a clinic-based system is at least double that of the cost of methadone maintenance in Switzerland. The trial has some preliminary data suggesting relatively good retention in the heroin maintenance arm of the study, but the final analysis will be required for firm conclusions.

Not surprisingly, given the lack of empirical data, there appears to be more energy put into debating the issues surrounding heroin maintenance therapy (Bammer, 1992; Bammer, 1993; Bammer, McDonald, Jarrett, Solomon & Sibthorpe, 1994; Fink, 1972; Marks, 1991; Marks, 1990; Parry, 1992; Stimmel, 1975; Stimson & Oppenheimer, 1982; Strang, Ruben, Farrell & Gossop, 1994) than into further careful evaluation of the relative efficacy of heroin maintenance, who it is suitable for, whether it can function to attract and retain users who would not otherwise enter treatment, whether it would serve as a bridge to oral long-acting opioid replacement therapy, and whether it can be administered in a fashion that is economic and cost-beneficial to the users and community. Strang and colleagues (Strang et al., 1994) concluded a recent consideration of the area by noting the lack of research and by stating that "no reliable conclusions can be reached about such prescribing, and the issue is open to hijack by those who wish to reinforce their pre-selected position" within the debate (p.203). The research currently being carried out in Europe may, however, shed further light on the value of heroin maintenance (Karel, 1993; Rihs, 1994).

**Summary**

Proponents of heroin maintenance argue that the HIV epidemic, the failure of prohibition, the lack of control over heroin quality, the potential of heroin maintenance to attract and retain heroin users in treatment, make heroin maintenance a legitimate approach. Arguments against heroin maintenance include: the short half-life of heroin requires frequent administration being costly and/or risking diversion, and the difficulty of stabilising patients adequately. Heroin maintenance treatment is not well researched. There is little evidence that patients cannot be adequately stabilised on heroin, and some research which shows that they can. The one randomised controlled clinical trial completed to date provided mixed advantages and disadvantages for heroin maintenance compared to methadone maintenance. Methadone was associated with poorer retention in treatment, but also produced lower levels of daily
opioid use, less injecting and less time spent with other drug users. However, this single trial is too little as a basis for confident conclusions about the relative impact of heroin maintenance.

**BUPRENORPHINE**

Buprenorphine is a mixed opioid agonist-antagonist. It has been used extensively in many countries for the management of acute pain, and is as effective an analgesic as morphine with a longer duration of action and greater safety in overdose (Lewis, 1985). Pharmacologically, buprenorphine invokes morphine-like subjective effects and produces cross-tolerance to other opioids. The mixed opioid-action/blocking-action appears to make buprenorphine safer in overdose and possibly less likely to be diverted than pure opioids. It may also provide a potentially easier withdrawal phase and the unusual receptor kinetics (see below) which cause a long duration of action allows for alternate day dosing. Buprenorphine has been the subject of recent research, and applications for approval for use of the drug in the U.S.A. (Swan, 1993) and in European countries are in train. It is registered for the treatment of opioid dependence in France.

A major consideration in the development of a viable treatment product for opioid dependence has been the perceived need to avoid injectable formulations. Since buprenorphine has poor oral bio-availability due to intestinal metabolism, most of the subsequent clinical pharmacology and clinical studies have administered buprenorphine beneath the tongue, via the sublingual route in an ethanol solution. For a time, this offered the most convenient formulation for the range of doses used in the various studies. The successful development of the sublingual analgesic tablet has also proved it to be an acceptable route of administration, albeit with lower bioavailability than the ethanol formulation (Mendelson, Upton, Jones & Jacob, 1995).

**Pharmacokinetics and Pharmacodynamics**

Buprenorphine is classified as a mixed agonist-antagonist or as a partial i-type opioid agonist (Lewis, 1985). It has partial agonist activity at mu and antagonist activity at kappa opioid receptors and may also be an agonist at delta receptors. Consistent with the mu partial agonist activity, the opioid effects of this drug appear to plateau as dose the increases. However, there is also some evidence suggesting that increasing doses beyond the plateau can produce decreased opioid effects. Thus, the dose response curve may resemble a classical bell shaped or inverted U-type dose response curve (Kreek, 1996b). It appears to be very safe relative to other opioids, such that overdose has not occurred in doses many times the therapeutic dose (Banks, 1979).

The half-life of buprenorphine in humans by the intravenous route is relatively short, at 3 - 5 hours, although it is pointed out that the relatively short half-life is unrelated to the relatively long duration of the drug. Specifically, the drug appears to have the property of binding very tightly to receptor sites causing a very slow release from opioid receptors, and this property produces the kinetics which are important in bringing about the long duration of action (Lewis, 1985). This strong binding has been shown in studies of the effects of pure opioid antagonists which indicate that it is quite difficult to antagonise the effects of buprenorphine once it has bound to opioid receptors (Kreek, 1996b; Lehmann, U. & Wirtz, 1988). However, the respiratory depression associated with buprenorphine is quite mild, relative to
other pure opioid agonists. This property suggests that it has the potential to markedly reduce the incidence of opioid death in patients and others (Walsh, Preston, Sitzer, Cone & Bigelow, 1994).

The tightness of binding of buprenorphine onto opioid receptor sites has been one explanation put forward for the very low level of withdrawal symptoms associated with the abrupt cessation of chronic dosing with buprenorphine compared with other opioids such as morphine (Lewis, 1985). Others have suggested that the mixed agonist-antagonist effects of buprenorphine may reduce the extent of significant physical dependence and this may be the mechanism whereby the less severe withdrawal symptoms occur (Jasinski, Pevnick & Griffith, 1978).

**Treatment Effectiveness**

As with methadone, the number of randomised controlled trials which compare buprenorphine with a relevant comparison treatment are few. Fortunately, the recent interest (both scientific and financial) provoked by government and community recognition of the necessity for alternative pharmacological interventions for opioid dependence has proved a boon for such research, as evidenced by the number of recent randomised controlled clinical trials which have been published.

The majority of clinical studies have been conducted in the USA, and have used opioid dependent subjects, many of whom were unemployed and were using a range of drugs in addition to opioids, especially cocaine, but also benzodiazepines, amphetamines, etc. Based on the clinical pharmacology and initial clinical studies, a sublingual buprenorphine dose of 8mg/day in an ethanol solution was identified as potentially offering the best maintenance dose and was used in most of the comparative studies. In nearly all of these studies, which range in duration from 3 weeks to one year, methadone was used as the reference therapy.

Bickel and colleagues (Bickel et al., 1988) were the first to conduct a randomised, double-blind trial which compared buprenorphine with methadone. Forty-five opioid dependent male subjects were randomised to receive either 2mg/day of buprenorphine or 30mg/day of methadone for the first three weeks of the study. Following this stabilisation, doses were reduced over a 4 week period, after which placebo was administered for the final 6 weeks. No differences were observed between buprenorphine and methadone with respect retention in treatment, symptom report or reduction of illicit opioid use. However, the study demonstrated that 2mg of sublingual buprenorphine in ethanol solution was less effective than 30mg of oral methadone in its ability to attenuate the physiological and subjective effects of a 6mg hydromorphone challenge.

In a longer randomised double-blind trial, Johnson and his colleagues recruited 162 volunteers seeking treatment for their opioid dependence (Johnson, Jaffe & Fudala, 1992). All subjects received both an oral (methadone or placebo) and a sublingual (buprenorphine or placebo) dose on each day of treatment ("double-dummy"). Three treatment groups were used: 8mg per day sublingual buprenorphine in ethanol solution (n=53), 20mg/d oral methadone (n=55) and 60mg/d oral methadone (n=54). The study was conducted over 180 days, which included 120 days of induction and maintenance, and 60 days of dose reduction and placebo dosing.

The authors concluded that buprenorphine 8mg/day was at least as effective as methadone 60mg/day
and both were superior to methadone 20mg/day in reducing illicit opioid use and maintaining patients in treatment. The results were indicative of buprenorphine being as effective as methadone at the fixed doses given.

Kosten and his colleagues compared sublingual buprenorphine (2mg or 6mg/day) with methadone maintenance (35mg or 65mg/day) in a 24-week double-blind, double-dummy, randomised clinical trial (Kosten, Schottenfeld, Ziedonis & Falcioni, 1993). The 125 subjects received fixed doses of both an oral syrup and sublingual ethanol solution (active and placebo). Comparison of the two buprenorphine groups revealed that there was less illicit opioid abuse in the 6mg group than in the 2mg group, as demonstrated by fewer opioid positive urines and self-reported illicit opioid use. Continued opioid withdrawal symptoms were also associated with the 2mg group. Treatment retention was better in the methadone groups (20 weeks) compared to the buprenorphine groups (16 weeks), and opioid-free urines were higher for methadone than for buprenorphine (51% vs 27%), as was abstinence for at least 3 weeks (65% vs 27%). The authors concluded that both buprenorphine doses were clearly less effective than methadone, and that comparison studies of buprenorphine and methadone need to utilise doses of buprenorphine which are higher. Again, the suggestion of a dose response relationship is clear, and others have been critical of the low doses used (Newman, 1994). It is unfortunate that most researchers have used fixed dose rather than flexible dose regimens, as there is a lack of information about the relative dose equivalence of buprenorphine and methadone.

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

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

Johnson and colleagues were the first to use a placebo controlled design in their buprenorphine research, in which buprenorphine treatment is compared with a placebo control condition, rather than with methadone (as in previous studies) (Johnson et al., 1995a). This was a 2 week (14 day) double-blind study, which was part of a 20 week study. Participants were randomly assigned to one of 3
treatment conditions in a 2:2:1 ratio: placebo (n=60), sublingual buprenorphine 2mg (n=60), or buprenorphine 8mg (n=30). On days 6-13 patients could request to change to another dose condition, which would be randomly chosen from the two to which they had not been originally assigned. Outcome measures included the percentage of patients on initial dose, percentage of opioid positive urines, and dose adequacy, as measured by patients' responses to a visual analogue scale incorporating such questions as "How well has this dose of medicine been holding you?".

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

Ling and colleagues (Ling, Wesson, Charuvastra & Klett, 1996) recently reported on a trial comparing 30mg methadone, 80mg methadone and 8mg buprenorphine in ethanol solution with 225 opioid dependent individuals. The results showed that 80mg methadone was superior to both 30mg methadone and to 8mg buprenorphine in retaining patients in treatment, reducing illicit opioid use, and decreasing craving for opioids. The 30mg methadone and 8mg buprenorphine were largely equivalent to each other in their effects on these variables. Ling and colleagues noted the 8mg of buprenorphine in ethanol solution was not an optimal dosage, and that higher doses would probably provide a better outcome. They also noted the discrepancy between their results and those of earlier research (Johnson et al., 1992), and pointed out the need for research to address the dose levels of buprenorphine which are effective, rather than pre-determine doses. Such research is in train in the USA and Australia.

**Dosage and Alternate Day Dosing**

Dose induction has been studied (Johnson, Cone, Henningfield & Fudala, 1989) with 19 subjects given sublingual buprenorphine in ascending daily doses of 2, 4, and 8mg, then maintained on 8mg for 15 days. Results from the first 4 days showed subjects reported significantly elevated ratings of "good effects" and "overall well-being" and decreased ratings of "overall sickness", and correctly identified buprenorphine as an opioid (not an opioid antagonist). It was concluded that buprenorphine was acceptable to heroin dependent users, and that rapid dose induction causes minimal withdrawal symptoms.

Doses of buprenorphine between 2mg and 16mg have been assessed, and 32mg doses have been evaluated in some trials. Currently, the maximum safe dose which has been tested for buprenorphine appears to be 32mg per day. There may be a ceiling on the effects of buprenorphine at doses beyond 32mg per day in terms of its ability to produce further opioid effects. Because of this ceiling effect, the benefit of higher doses may not be increased efficacy through increasing agonist effects, but rather increased duration of action. Given the potential for longer duration of dosing, alternate day dosing with buprenorphine has been examined and found acceptable to many patients. The feasibility of dosing on alternate days has been investigated and confirmed in a number of studies (Amass, Bickel, Higgins & Badger, 1994; Fudala, Jaffe, Dax & Johnson, 1990; Johnson et al., 1995b; Resnick, Pycha & Galanter, 1994). The conclusion from these studies is that alternate day dosing could be effective in and
acceptable to a substantial number of opioid-dependent patients.

Summary
Generally, studies have shown buprenorphine to be as effective as methadone as a maintenance agent in reducing illicit opioid use, retaining clients in treatment, and in reducing withdrawal symptoms. Studies have also shown that buprenorphine: is acceptable to heroin addicts; has few side effects; binds well to opioid receptors; appears to induce a low level of physical dependence; diminishes self-administration of heroin; has subjective effects which are opioid-agonist-like; blocks or greatly attenuates the self-reported drug effects of concurrently administered opioids; induces a relatively mild withdrawal syndrome; is safe at high doses; and has a long duration of action which may allow for less than daily dosing. There are a number of limitations associated with buprenorphine: the sublingual route of administration may prove cumbersome and inconvenient; the medication is water soluble and highly concentrated so can be absorbed sublingually, and because of this it is relatively easy to inject; a ceiling effect may limit its applicability to certain individuals, especially the more severely dependent. Nevertheless, it is likely to find a place as an alternative maintenance pharmacotherapy in the treatment of opioid dependence.

NARCOTIC ANTAGONISTS

Rationale
Opioid antagonists such as naloxone and naltrexone have been considered as maintenance drugs for treatment of the opioid dependence. These opioid antagonists are typically used to reverse the effects of opioid agonists in cases of overdose. They competitively displace opioids from 1-opioid receptor sites. The rationale for their use as a maintenance treatment was that an individual being maintained on an opiate antagonist will not experience any opioid agonist effects after use of heroin. It was proposed that this lack of effect from injecting opioids in the presence of pre-treatment with an antagonist might result in a decline in injecting drug use.

Naloxone
Naloxone was thought suitable as an opiate replacement therapy as it does not produce dependence and does not have serious side-effects (Kurland, McCabe & Hanlon, 1975). However, it has the disadvantages that oral doses as high as 2-3 gm were necessary to provide 24-hour blockade, making it costly to use. The alternative of parenteral route of administration by injection was not thought appropriate for obvious reasons.

Trials of naloxone maintenance were carried out by Kurland and his colleagues (Kurland & Hanlon, 1974; Kurland et al., 1975) with a group of parolees who were required to attend a clinic, to provide daily urines, and to receive weekly psychotherapy sessions after they had been discharged from U.S. correctional institutions. Pilot studies established that a oral regimen of naloxone was feasible and that there were no serious side-effects or toxicity associated with long-term administration. Subsequent controlled trials were carried out to assess the effectiveness or otherwise of naloxone maintenance.

In the first controlled trial, 119 parolees were randomly assigned to one of three groups: a no-treatment
control condition in which no medication was prescribed; a group which received naloxone; and a group which received a placebo in place of naloxone (Kurland & Hanlon, 1974). All participants had to provide regular urine samples and attend a weekly psychotherapy group. Outcome was measured by opioid use and retention in treatment over the nine months of the study. The results failed to show any difference between the placebo and naloxone on retention in treatment or opioid use.

**Naltrexone**

Naltrexone is a long-acting (up to 72 hours, depending on the dose) opioid antagonist with many advantages as a maintenance drug. It can be administered orally, it blocks the euphoric and other effects of opioids, and it has no major side-effects. Despite these advantages, many of the programs using naltrexone report substantial drop-out rates early in the program, in some cases, even before the first dose of naltrexone is given. Indeed, one major disadvantage of naltrexone in this patient group is the need for the patient to be opioid free at the commencement of treatment. Administration of opioid antagonists such as naltrexone to someone who is opioid dependent will result in the precipitation of a withdrawal syndrome which can be very aversive. This contrasts with the relative ease of transfer from heroin to opioid agonist therapy such as methadone or LAAM.

There have been a number of controlled trials comparing naltrexone with methadone or placebo. Compared with methadone maintenance, naltrexone treatment retained fewer patients over a 12-week study period, although there were no differences between the two regimens in terms of extent of illicit drug use (Osborn, Grey & Reznikoff, 1986). When compared with a placebo, there was a trend towards naltrexone patients having less illicit drug use and better retention, however the data remained equivocal because of a high drop-out rate in both groups (National-Research-Committee-on-Clinical-Evaluation-of-Narcotic-Antagonists, 1978).

In another study, 117 patients who had completed a trial of LAAM were given the opportunity to transfer to naltrexone (Judson & Goldstein, 1984). Forty patients entered treatment and 77 did not. At the follow-up, more patients who had received naltrexone were opioid-free compared with those who did not receive naltrexone. The authors make the point that the two groups were not comparable in motivation at the outset. More recently, Israeli researchers (Shufman et al., 1994) have reported on a double-blind which demonstrated that naltrexone had a superior impact on heroin use compared with placebo. However, possibly because of the small sample size the differences between naltrexone and placebo were non-significant. Spanish research had also failed to detect significant differences in favour of naltrexone above placebo (San, Pomarol, Peri, Olle & Cami, 1991).

Although retention in naltrexone maintenance has proved difficult for even short periods of time with illicit drug using populations, it has been found to be quite successful with highly motivated individuals who wish to cease opioid use. Thomas and her colleagues first described success with naltrexone maintenance in a small sample of opiate dependent medical professionals (Thomas et al., 1976). In a subsequent study, 114 opiate-dependent businessmen and 15 opiate-dependent physicians were treated with naltrexone as part of a structured aftercare program following clonidine detoxification (Washton, Pottash & Gold, 1984). More than 80% of the patients completed at least six months of treatment and remained drug-free 12-18 months later.
It is clear that naltrexone has a potential role as a maintenance medication with these selected and highly motivated patients, but the target population is small. It may prove with time that it also has a role in the final stage of a sequence wherein patients begin on full opioid agonist therapy, progress to partial agonist treatment and then eventually to full antagonist treatment. This method may facilitate the transition to an opioid-free state which is very difficult for patients who have been maintained on methadone.

**Summary**

Naloxone is a doubtful alternative to methadone as a replacement therapy in view of its high cost and the lack of evidence of its effectiveness. Naltrexone treatment has more potential as a useful treatment option and this has been demonstrated with selected patients. It has mild side-effects and can be used on flexible dosage regimens ranging from daily to thrice weekly, depending on patients’ needs. Medical practitioners, business executives, parolees and other groups who are highly motivated to remain drug free in environments where their drug of choice is freely available have responded well to naltrexone maintenance.

**References**


Clinical Pharmacology and Therapeutics, 46, 335-343.


Swan, N. (1993). Two NIDA-tested heroin treatment medications move toward FDA approval. *NIDA Notes, 8*(1), 4-5.


pharmacology of buprenorphine: Ceiling effects at high doses. *Clinical Pharmacology and Therapeutics*, 55, 569-580.