Report into the Feasibility of Trialling Hydromorphone as a Treatment for Heroin Dependence in the Australian Capital Territory

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Executive Summary

In 2003 the ACT Alcohol and Other Drug Task Force recommended

‘In line with the ACT Health Research Strategy, support researchers to seek funding for a clinical research trial of hydromorphone in the ACT and support the participation of the ACT in the trial’.

In July-August 2004, NCEPH was commissioned by the ACT Government to determine in essence how that recommendation could best be met.

We recommend that the ACT government commit $340,000 to undertake three Phase II clinical trials to fill significant gaps in knowledge about the use of hydromorphone in the treatment of heroin dependence. These studies will enhance understanding of the effective doses of hydromorphone and of the relationship between hydromorphone and methadone treatment. In addition, they will lay essential groundwork for more extensive Phase III trials examining the effectiveness and cost-effectiveness of hydromorphone as a treatment for heroin dependence. Phase III trials are not costed here. We expect that such funding could be sought through other sources, such as the National Health and Medical Research Council grants scheme. The background work undertaken through the Phase II trials proposed here is essential for such funding applications to be competitive.

The three Phase II clinical trials will examine:

1. the safety and feasibility of hydromorphone prescription in combination with oral methadone maintenance treatment
2. whether hydromorphone-supplementation or enhanced methadone treatment are effective and cost-effective in improving outcomes for the small, but significant, group of methadone maintenance clients, for whom existing treatment is not optimal.
3. if illicit heroin use can indeed be detected in clients receiving hydromorphone and methadone.

These will all be world-first investigations and will produce publishable results.

The ACT does not currently have structures in place that easily accommodate clinical trials of new treatment options for drug dependence, which increases the trial costs, as efficiencies through add-ons to existing services are generally not possible. Nevertheless successful trials have been undertaken in the ACT in the last 5 years examining buprenorphine and naltrexone, both of which have become standard treatment options. We recommend that the hydromorphone trial emulates the critical success factors from those trials. First is to undertake the trials in partnership with outside experienced clinician-researchers and to continue to build ACT capacity. Second is to provide resources for adequate preparation for the trials. These are both costed into the sum presented above.

Finally we recommend that the ACT develops an ongoing capacity to undertake clinical trials in the alcohol and other drugs area. This should be integrated with treatment service provision, along the lines of successful models in Victoria (Turning Point Alcohol and Drug Service Inc) and New South Wales (The Langton Centre). Such capacity is essential for more extensive Phase III clinical trials to be undertaken in the ACT.
Introduction

The treatment context for hydromorphone

For any medical condition, it is desirable to have a range of treatment options with different mechanisms of action. Clinical experience has shown that people differ in the treatments that work best for them and that even for the same person, different treatments may be more effective at different times. This experience also holds true for the treatment of heroin dependence. It is in this context that the feasibility of a new treatment option, hydromorphone, is explored. The key question is: does hydromorphone add value to the current range of treatment options? In particular, is it more effective than other options or, more likely, is it more effective for a particular patient group?

There are three broad contexts in which the ability of hydromorphone to improve treatment effectiveness could be tested:

1. Can it improve the effectiveness of a current treatment, in particular would hydromorphone improve the effectiveness of methadone maintenance treatment for the small, but significant, proportion of methadone clients for whom current methadone treatment is not fully successful?
2. Can it bring treatment drop-outs back into successful treatment?
3. Can it attract dependent heroin users who have never been in treatment into treatment more quickly and effectively?

These questions are all important, they all warrant examination and they all involve different trial designs and participants. We focus here on the first question.

The development of modern pharmaceuticals involves four clinical trial phases (see Appendix 1). The questions outlined in the previous paragraph are all ‘Phase III’ questions. Phase III extended clinical trials are undertaken with a reasonably large number of patients, once there is evidence that the drug has a potential benefit which outweighs possible hazards. That evidence is gathered in Phase II trials, which are the first trials of the drug in patients suffering from the disorder for which the drug is intended. These trials generally include establishing the therapeutic doses. Currently the clinical trials’ evidence about hydromorphone concerns its use in pain relief and there is almost no evidence pertaining to its potential use in the treatment of heroin dependence. We therefore recommend starting with a series of small Phase II trials to establish if the more extensive Phase III trials are warranted.

Appendix 2 outlines the current treatments available for heroin dependence and the rationale for trialling hydromorphone, as well as an outline of the pharmacology of hydromorphone compared with diamorphine (pharmaceutical heroin).

Background to this feasibility research

Essentially interest in trialling hydromorphone as a treatment for heroin dependence has stemmed from the success of using diamorphine to treat heroin dependence. An extensive feasibility study into an ACT diamorphine trial was undertaken between 1991 and 1995 (see Appendix 3), but a trial was blocked by the Prime Minister and Cabinet in August 1997 after gaining the support of the Ministerial Council on Drug Strategy. Nevertheless the ACT research informed successful Swiss and Dutch trials which showed that diamorphine is a cost-effective adjunct to current treatment options (Appendix 4 provides a brief summary of that evidence).

In 2002 Hall and others suggested that hydromorphone might be an effective alternative to diamorphine and could be trialled without the political approvals required to trial diamorphine. That suggestion was reflected in one of the recommendations of the ACT Alcohol and Other Drug Task Force which presented its report to the ACT Minister for Health in December 2003. Among its recommendations was

‘In line with the ACT Health Research Strategy, support researchers to seek funding for a clinical research trial of hydromorphone in the ACT and support the participation of the ACT in the trial’ (Alcohol and other Drug Taskforce 2003, p. 25).
On 21 November 2003, the ACT Minister for Health, Simon Corbell MLA, made a presentation to the Ministerial Council on Drug Strategy seeking the involvement of other jurisdictions in a hydromorphone trial, but none agreed to participate at that time. In August 2004 the ACT Government released its ACT alcohol, tobacco and other drug strategy 2004-2008. That document endorses the recommendation of the Task Force for an ACT hydromorphone trial. The rationale for this initiative, given in the Strategy, is that

‘the progression of a hydromorphone trial would expand the range of possible treatments available to opioid-dependent persons’ (page 40).

We were asked by ACT Health to investigate ‘the feasibility and costs associated with conducting a clinical trial of hydromorphone in the ACT’ and to produce a set of recommendations in a space of 5 weeks.

The approach used in the feasibility study

We were all involved in the feasibility research for an ACT diamorphine trial and one of us (Bammer) was also involved in the development of trials of buprenorphine, naltrexone and LAAM to treat heroin dependence in Victoria (New Pharmacotherapies Project), as well as being involved in the national comparison of these treatments (NEPOD: National Evaluation of Pharmacotherapies for Opioid Dependence). In addition, in 1999-2000, Bammer instigated successful ACT partnerships with Victoria and NSW to trial buprenorphine (Lintzeris et al. 2003) and naltrexone (Glasgow et al. 2001).

The feasibility research for an ACT diamorphine trial extensively investigated the potential risks and benefits associated with diamorphine prescribing (Appendix 3) and these are also relevant to a trial of hydromorphone. Subsequent research (Appendix 5) has shown that the potential risks associated with prescribing short-acting opioids can be effectively controlled. We did not therefore revisit those risks here, although in our consultations (Appendix 6) we did ascertain if there might be new risks.

There were two overarching major issues that were the focus of our efforts – how could a hydromorphone trial best be embedded in a clinical service in the ACT and what sort of trial was most appropriate?

We consulted with a range of clinicians and other service providers, as well as illicit drug user representatives and the police (see Appendix 6). In particular we sought advice from:

- Dr Nicholas Lintzeris who led the ACT buprenorphine trial and who is now at the National Addiction Centre in London researching short-acting opioids (specifically diamorphine) in the treatment of heroin dependence.
- Dr James Bell who was involved in the ACT naltrexone trials and who has run a very small trial of hydromorphone treatment at the Langton Centre in Sydney.
- Dr Benedikt Fischer and Professor Juergen Rehm from the Canadian Centre for Addiction and Mental Health, who are planning hydromorphone trials in that country.
- Associate Professor Nick Buckley, a clinical pharmacologist at The Australian National University Medical School and Director of the ACT Poisons Service, who has experience in drug development clinical trials.

We were also aware that New Zealand has a potential interest in partnering with the ACT in a hydromorphone trial and included some liaison with that jurisdiction.
Findings and Recommendations

Here we present an overview of our findings and recommendations. Details are provided in Appendices 7 and 8.

We recommend that the ACT undertake three Phase II clinical trials to examine:

1. the safety and feasibility of hydromorphone prescription in combination with oral methadone maintenance treatment
2. whether hydromorphone-supplementation or enhanced methadone treatment are effective and cost-effective in improving outcomes for the small, but significant, group of methadone maintenance clients, for whom existing treatment is not optimal. This would be a pilot study for a more extensive Phase III investigation
3. if illicit heroin use can indeed be detected in clients receiving hydromorphone and methadone.

As we outline below, an extensive preparatory phase will be required to undertake these trials. These three studies will involve 24 participants in two successive groups, with a follow-up monitoring period of three months.

**Trial 1**

Trial 1 is a one-month dose-ranging study involving eight participants, to assess the most effective doses of injectable hydromorphone in combination with oral methadone. Those eligible for participation will be current methadone clients who continue to use illicit heroin daily. The key research questions are:

- Can the addition of injectable hydromorphone to maintenance treatment for dependent heroin users be undertaken successfully on a small scale in the ACT context?
- Can dependent heroin users be safely stabilised on injectable hydromorphone plus oral methadone in such a manner that they do not experience either over-sedation or opioid withdrawal?
- What are the optimal hydromorphone dosage ranges for use in combination with oral methadone?

**Trial 2**

Trial 2 is a cross-over study involving 16 participants. This study is primarily a pilot study for a more extensive Phase III investigation and is essential for such a Phase III study to be considered for funding. This number of participants is also sufficient for a good indication of whether methadone treatment can be significantly improved; in other words, the study has merit in itself as well as providing the basis for a more extensive trial.

The participants will be divided into two equal groups; one will receive methadone treatment supplemented by daily hydromorphone for one month, while the other will receive an enhanced methadone treatment regime without hydromorphone. This will include review of methadone dose and extensive case management. Treatment regimes will be swapped for the second month. Those eligible for participation will be current methadone clients who continue to use illicit heroin daily. The key research questions are:

- Does methadone treatment supplemented by daily hydromorphone or enhanced methadone treatment reduce illicit heroin use among methadone clients?
- Is methadone treatment supplemented by daily hydromorphone more cost-effective than enhanced methadone treatment?
**Trial 3**

This trial is run in conjunction with Trials 1 and 2 and with the same participants and involves daily urinalysis and questionnaire completion on illicit heroin use to assess if hydromorphone can indeed be differentiated from illegal heroin use through metabolites in the urine. While this is theoretically possible (see Appendix 2) it has not been trialled in practice among regular opioid users. The key research question here is:

- Can concurrent illicit heroin use be detected in people receiving injectable hydromorphone?

Trial participants will have to have been on the ACT methadone program for a minimum of six months. Previous ACT research (see Appendix 7) suggests that around 13% of current methadone clients still use heroin daily and that most receive methadone doses ranging from 20-60 mg per day. We therefore expect about 87 methadone clients to be eligible for the proposed trials.

**Preparatory phase**

The ACT does not currently have structures in place that easily accommodate clinical trials of new treatment options for drug dependence, which increases the trial costs, as efficiencies through add-ons to existing services are generally not possible. As we outline in Appendix 8 there are a number of possibilities for clinical service provision, but there are no stand-out options. A primary task in establishing the trials we propose is to determine how the service will be provided and to resolve a number of service provision issues. It was not sensible or feasible for us to undertake this as part of this investigation. We recommend a six-month preparatory phase to be undertaken by the researchers and/or clinicians who will be involved in the trial.

We note that the service provision situation was similar in 1999, but that this did not prevent successful trials of buprenorphine and naltrexone from being undertaken. The scale of those trials was similar to the current hydromorphone proposals. In addition the ACT trials contributed to uptake of buprenorphine and naltrexone treatment in the ACT and both have now become standard and successful treatment options.

We recommend that the hydromorphone trials emulate the critical success factors from the buprenorphine and naltrexone trials. First is to undertake the trials in partnership with outside experienced clinician-researchers. Second is to provide resources for adequate preparation for the trials. These are both costed in the budget for this proposal.

Another noteworthy outcome from the buprenorphine and naltrexone trials was the positive reports from the clinical staff about being involved in those trials (Bammer et al. 2001). These trials began to build clinical trials capacity in the ACT and we recommend that this is continued through the hydromorphone trials. In particular, we recommend that the ACT develops an ongoing capacity to undertake clinical trials in the alcohol and other drugs area. This should be integrated with treatment service provision, along the lines of successful models in Victoria (Turning Point Alcohol and Drug Service Inc) and New South Wales (The Langton Centre). Such capacity is essential for more extensive Phase III clinical trials to be undertaken in the ACT.
## Budget

See Appendix 9 for more details about budget items.

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<td>Nursing staff</td>
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<td>Airfares, salary replacement and per diem for experienced clinician-researcher advisors</td>
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### Research costs, consumables, equipment, tests, etc

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<th>Item</th>
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</tr>
<tr>
<td>Hydromorphone and methadone</td>
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</table>

**Total**                                                   **$340 000**
References


List of appendices

1. An overview of clinical trial research
3. The ACT Diamorphine Feasibility Trial investigation
4. Overview of European experiences with diamorphine prescription
5. Potential risks associated with diamorphine prescribing
6. Consultations and acknowledgements
7. Trial design considerations
8. Options for clinical service provision
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Appendix 1. An overview of clinical trial research


Introduction

This appendix describes the processes which must be undertaken for hydromorphone to be trialled and registered to treat heroin dependence. It is currently registered in Australia only for the treatment of pain. To conduct a clinical trial with an unregistered therapeutic product or a product for an unregistered use, the trial must be notified to, or approved by, the Therapeutic Goods Administration.

If the trials are of interest to the pharmaceutical companies, they may be willing to support them. In the case of investigator driven research, the support is most often in the form of supplying the necessary pharmaceuticals free. The pharmaceutical company may also be interested in monitoring the trial for quality assurance and this also involves an investment of resources. To obtain such support from the pharmaceutical company, the protocol must be submitted to them for review. There may then be a process of negotiation where the protocol is modified, culminating, in general, in a signed contract between the company and the researchers to set out agreement on conduct of the trial, data management and dissemination of the results.

Where a pharmaceutical company supports a trial it is likely to act as the legal sponsor of the trial and provide the necessary legal liability coverage. Otherwise appropriate legal coverage must be provided through other means.

Registration of a pharmacotherapy for a new indication would generally, but not always, be undertaken by the pharmaceutical company. For the pharmacotherapies to become generally available, they may require subsidy through the Pharmaceutical Benefits Scheme.

Conducting a clinical trial

This section is based on the following documents from the Commonwealth Department of Health and Family Services:

- Clinical Trials of Drugs in Australia. Clinical Trial Notification (CTN) Scheme and the Clinical Trial Exemption (CTX) Scheme. DEB 1. May 1991(Therapeutic Goods Administration, 1991a)

Definition of clinical trial and phases of clinical trial research

The Australian Guidelines: Clinical Trials Exemption (CTX) Scheme for Drugs. DEB 5. September 1992 provides the following definitions (Appendix I):

**Clinical Investigational Use**

This involves the use of therapeutic goods in experiments in humans, where “experiment” is taken to mean either the use of a product included in the ARTG [Australian Register of Therapeutic Goods] for
purposes outside the details accepted for registration or listing, or the use of a drug product not in the ARTG.

**Clinical Trial (study)**

A clinical trial in the context of these guidelines means a systematic study of therapeutic goods (drugs or devices) conducted in humans in order to discover or verify the effects of and/or identify their adverse reactions to those products and/or identify study (sic) their absorption, distribution, metabolism and excretion in order to ascertain the efficacy and safety of the products.

**Clinical trial phases**

Clinical trials are generally classified according to the phase of development of the drug. While individual phases may not be clearly delineated and not all phases are relevant to some classes of drug the following definitions are broadly accepted.

**Phase 1. The first administration of the drug to man (sic).**

The drug is administered to a small number of volunteers, usually healthy, but sometimes patients, for the purpose of determining pharmacological activity, tolerance, absorption, distribution, metabolism, excretion.

These studies should be carried out in a laboratory appropriately equipped for the specialised monitoring and high degree of surveillance required.

Data from these studies should identify the preferred routes of administration for subsequent trials.

**Phase II: The first trials of the drug in patients suffering from the disorder for which the drug is intended.**

The purpose of these trials is to determine efficacy and safety in a small number of closely supervised patients. The trials are usually conducted by investigators regarded as specialists in the particular disorder and its treatment.

Several doses of the drug are often used to establish the therapeutic range and the maximum tolerated dose.

**Phase III: Extended clinical trials.**

These trials involve numerous patients and are undertaken by experienced clinical investigators when data from Phase II studies indicate that the drug has a potential benefit which outweighs possible hazards. The purpose of these trials is to ascertain whether the drug confers clinical benefit in the disease states for which effectiveness is to be claimed with an acceptable incidence of adverse effects. The trial design should preferably be randomised.

**Phase IV: Post-marketing studies.**

These trials involve the use of a drug with an approved indication, formulation and route of administration. They are designed to extend the information developed in pre-marketing trials.

**Sponsor, investigators and ethics committee**

There are generally three key groups in any clinical trial - the sponsor, the investigators and the ethics committee, although a clinical trial can be initiated and sponsored by an investigator without a separate pharmaceutical company sponsor.

For the purposes of conducting a clinical trial, the sponsor is interpreted as being the person, company, organisation, or institution responsible for the overall conduct of the trial. This definition is derived from the Therapeutic Goods Act where a sponsor is defined in terms relating to the importation, exportation, manufacture or supply of therapeutic goods. The sponsor of a clinical trial is usually a pharmaceutical company, but, as mentioned above, may also be an individual, for example, an investigator. The role of the sponsor includes providing the investigator and ethics committee with...
accurate, complete and current information as required; ensuring legislative requirements are met (such as notifications, permits, approvals); and overseeing the organisation and conduct of the trial. The sponsor should appoint a person responsible for quality assurance and that person should not otherwise be involved in the study. Where the sponsor and the investigator are different, contact between sponsor and investigator is usually through monitors appointed by the sponsor.

It is usual for a principal investigator to be nominated with overall responsibility for a study. The principal and other investigators should be appropriately qualified, have good knowledge of the investigational product and are responsible for the conduct of the study including selection of participants, informed consent, data management, reporting adverse events and care of participants, including appropriate treatment and follow-up after the study. These responsibilities are set out in Guidelines for Good Clinical Research Practice (GCRP) in Australia.

The ethics committee should ensure the protection of the rights and welfare of the research participants and should be guided by current versions of the Declaration of Helsinki (World Medical Association 2000) and the National Health and Medical Research Council’s National Statement on Ethical Conduct in Research Involving Humans (1999). Among other things, the ethics committee would be expected to carefully review and approve the trial protocol before a study could commence.

**CTX and CTN schemes**

Clinical investigation of a drug or use of a drug not registered under the Therapeutic Goods Act requires an exemption from the Act, which is obtained by making application under the clinical trials exemption (CTX) scheme or notification under the clinical trials notification (CTN) scheme.

Under the CTX scheme the Therapeutic Goods Administration (TGA) reviews a range of summary data on the pharmaceutical under investigation, including pharmaceutical chemistry, toxicology and safety data and proposed usage guidelines. The TGA will comment on the proposed usage guidelines and any trial protocol covered by the CTX application is unable to proceed until agreement is reached between the TGA and the sponsor on the usage guidelines. Under the CTX scheme, the TGA is not reviewing a trial protocol but usage guidelines for the clinical investigation of a pharmaceutical. The CTX route of clinical trial approval is generally used by sponsors for pharmaceuticals which have been little or poorly investigated in humans or for biotechnology products where the sponsor seeks feedback from the TGA on proposed manufacturing methods.

Under the CTN scheme, the TGA does not review data relating to the trial. However, notification of intention to conduct a clinical trial under CTN arrangements must be made prior to commencement of the study at each site.

Under both the CTX and CTN schemes approval of the trial by the institutional ethics committee is required.

**Registration and PBS Listing**

For pharmaceuticals to become available for patients after clinical trials, they must be registered or the existing registration must be varied to allow use in the treatment of heroin dependence. Some pharmaceuticals are subsidised by the Australian government through the Pharmaceutical Benefits Scheme (PBS). The Pharmaceutical Benefits Advisory Committee makes recommendations to the Federal Minister for Health about which drugs should be available as pharmaceutical benefits.
References


National Health and Medical Research Council 1999, National statement on ethical conduct in research involving humans, National Health and Medical Research Council, Canberra.


The treatment of opioid dependence

As illustrated in the Figure below, there are two broad approaches to treating heroin and other opioid dependence: substitution maintenance therapy leading eventually to withdrawal and relapse prevention, on the one hand, and withdrawal leading directly to relapse prevention, on the other.

Substitution pharmacotherapy or maintenance treatment involves substituting heroin with a legal opioid. Until recently methadone was the only such option, but buprenorphine is now also available. Hydromorphone is being tested for its suitability as an additional maintenance therapy.

Withdrawal (or detoxification) is not a full treatment itself, but rather a component of treatment, as it is rarely successful alone but requires additional strategies to prevent relapse to problematic opioid use. The process of withdrawal can be assisted by reducing doses of methadone or buprenorphine or by a range of pharmaceuticals that relieve withdrawal symptoms. Relapse prevention can be assisted by naltrexone and/or a range of psychological approaches.
Substitution maintenance therapy is highly effective and cost-effective in the treatment of opioid dependence. The treatment philosophy is built around considerable evidence showing that individuals maintained on a substitution drug are less likely to commit crime, including use of heroin and other illicit drugs, and are more likely to experience improved health and psychosocial functioning (Gowing et al. 2001). This has been recognised by the United Nations (World Health Organization, United Nations Office on Drugs and Crime & Joint United Nations Programme on HIV/AIDS 2004). The form of substitution maintenance therapy most commonly used, and for which the largest body of evidence exists, is methadone maintenance. When adequate doses of methadone are prescribed (60 mg or more per day) this therapy has relatively high retention rates. Its effectiveness is enhanced when combined with therapy addressing the social and psychological issues linked to dependence (Gowing et al. 2001).

Generally speaking, it is desirable that the drugs prescribed for substitution therapy are longer acting than those they replace, so as to lengthen the periods between administration of an opioid and delay the onset of withdrawal signs. The long-acting nature of methadone and buprenorphine reflect this. On the other hand, substitution maintenance therapy using short-acting opioids as an adjunct to, rather than a replacement for, methadone may also have a place.

Over recent years a number of studies have been conducted in Europe to ascertain the effectiveness of diamorphine (pharmaceutical heroin) substitution maintenance. They have demonstrated the feasibility of maintaining people on injectable diamorphine (usually in conjunction with oral methadone to prevent the development of withdrawal between injections) and the achievement of therapeutic goals such as reduced illicit heroin and other illegal drug use, reduced levels of criminal behaviour and improved physical and mental health (see Appendices 4 and 5 and Perneger et al. 1998; Rehm et al. 2001; Uchtenhagen et al. 1999; van den Brink et al. 2003).

In 2002 Hall and colleagues from the National Drug and Alcohol Research Centre recommended that a trial of hydromorphone substitution maintenance be conducted in Australia since, for political reasons, it is not possible at present to conduct a trial with diamorphine here. They argued that the pharmacological similarities of hydromorphone and diamorphine, along with the fact that hydromorphone is legally available here, make a hydromorphone trial an attractive proposition (Hall, Kimber & Mattick 2002). Others disagree, arguing that, even if such a trial were conducted, we would still need to conduct a diamorphine trial (Wodak, Ritter & Watson 2002). Some drug users have a different objection, expressing concern that a trial of hydromorphone is further evidence of what they see as the medicalisation of drug use and the concomitant interference by the authorities in people’s lives. They argue for the legalisation of opioids, rather than further research into their therapeutic potentials (Madden 2002).

**Hydromorphone**

Hydromorphone hydrochloride (hereafter hydromorphone) is a semi-synthetic opioid derived from morphine. Its proprietary name is Dilaudid and it is sold as tablets and in an injectable liquid form for the treatment of pain.

In Australia it is one of the Schedule 8 controlled drugs, that is, ‘substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence’. Doctors who have a special authority to do so may prescribe the drug. It is used almost exclusively for the control of extreme pain, especially among people tolerant to other opioids. In the ACT the drug is fairly commonly prescribed for analgesic purposes, including for the relief of pain among hospice residents.

Like, diamorphine, hydromorphone is a mu-opioid agonist, in other words it binds to particular types of opioid receptors, mimicking the actions of certain of the body’s natural chemicals. Hydromorphone does not have the histamine releasing (flushing) effects of morphine. Its analgesic potency is approximately eight times that of morphine and four times that of diamorphine. It has a shorter analgesic effect than morphine and withdrawal symptoms occur sooner and are of greater intensity than those of morphine (Faulding Pharmaceutical Co. 2003).
The half-life of the injectable form of the drug in people who are not opioid tolerant is reported to be 2.64 hours +/- 0.88 hours.

Hydromorphone is metabolized primarily in the liver. It is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites (Faulding Pharmaceutical Co. 2003).

This route of metabolism is different from that of diamorphine (and illicit heroin), making it possible to measure illicit heroin use:

Heroin is rapidly hydrolyzed to 6-monoacetylmorphine (6-MAM), which, in turn is hydrolyzed to morphine (Hardman, Limbird & Gilman 2001, p. 590).

Hydromorphone can be detected in urine for one to two days after administration, a shorter period than for morphine and diamorphine (three days) and methadone (three to four days) (Henry-Edwards et al. 2003).

Since heroin and hydromorphone can be readily differentiated in urine tests, a study of prescribed hydromorphone with urine testing for heroin can objectively determine the extent of concurrent illegal heroin use. This approach will be taken in the North American Opiate Medication Initiative (NAOMI) trial of prescribed diacetylmorphine which is soon to commence (Ontario Federation of Community Mental Health and Addiction Programs 2003).

In common with other narcotic analgesics, hydromorphone’s most serious side effects are dependence of the morphine type with a severe withdrawal syndrome, and respiration depression, which can be fatal. Other adverse reactions include circulatory depression, respiratory arrest, shock and cardiac arrest and a range of less serious, but nonetheless uncomfortable effects, including dizziness, lightheadedness, drowsiness, upset stomach, vomiting, constipation, stomach pain, rash and difficulty urinating (U.S. National Library of Medicine & National Institutes of Health 2004).

The manufacturers state that experience with administering hydromorphone by the intravenous route is limited and so injections should be given slowly, over at least two or three minutes. There is virtually no published research on the pharmacodynamics of the drug in opioid tolerant people who use it illegally. The administration of the opioid antagonist naloxone neutralises the most serious effects of hydromorphone and is used to treat overdoses, particularly when respiratory depression has occurred.

The effects of hydromorphone and diamorphine in the body are similar, whether assessed objectively or subjectively. The two opioids have similar time courses, peak effect times, onsets of action and dose response curves. Despite these similarities in objective tests, in clinical studies non-opioid-dependent volunteers are able to subjectively distinguish qualitatively between the effects of the two drugs, though the biological bases of this capacity are unknown (Bigelow et al. 2001; Brands et al. 2004). It appears that hydromorphone causes only a modest degree of psychomotor impairment among non-opioid-dependent study participants, and may not impair psychomotor functioning at all among people who are opioid dependent (Hill & Zacny 2000).

**Much is unknown about hydromorphone**

It needs to be emphasised that most of what is known about the pharmacology of hydromorphone, including its subjective effects, comes from clinical studies where the drug is used as a analgesic in people whose only use of opioids is those prescribed for analgesia. In other words, we have almost no empirical evidence about this drug in people with substantial levels of experience with illegal injectable opioids (such as heroin), nor among people who are physically dependent on illegal opioids. Furthermore, while a small number of clinical studies have been published comparing hydromorphone with diamorphine, we are not aware of any that provide direct evidence about the subjective and objective impacts of prescribing hydromorphone in people on methadone maintenance.
References


Appendix 3: The ACT Diamorphine Feasibility Trial investigation

We have reprinted a key overview paper here, namely Bammer, G.; Douglas, RM. 1996 'The ACT heroin trial proposal: an overview' Medical Journal of Australia, 164, 690-692.


The ACT heroin trial proposal: an overview

Gabriele Bammer and Robert M Douglas

Introduction

The proposal for a "heroin trial" in the Australian Capital Territory (ACT) builds on growing evidence that treatment is the most cost-effective approach to problems resulting from illicit drug use.1-4 A four-year feasibility study was undertaken after overwhelming encouragement from a national seminar of drug treatment and policy experts. It resulted in a proposal which addresses a key issue, is clinically workable, able to be rigorously evaluated and has minimal risks. The trial comprises two pilot studies and a full-scale clinical trial; evaluation is central and debate is welcomed.

Aims and outcome measures

The core of the proposed "heroin trial" is a clinical trial to compare a new treatment option against the current gold standard. In essence, it is a regular trial of a new treatment.

The question to be asked is: If maintenance treatment for opioid dependence is expanded, so that both injectable diacetylmorphine (heroin) and oral methadone are available, is this more effective than current maintenance treatment with oral methadone alone?

Measures of effectiveness are:

- Ability to attract dependent heroin users into treatment;
- Ability to prevent premature drop-out from treatment;
- Ability to improve health and well-being, including reducing drug use and criminal behaviour and improving social functioning; and
- Cost-effectiveness.

Pilot studies

The first step would be to conduct two six-month pilot studies in the ACT.

First pilot study: This would involve 40 participants who meet the following eligibility criteria:

- Either currently or formerly on the ACT methadone program; and
- Able to prove ACT residence since 1993.
Half would be drawn from volunteers currently receiving methadone treatment, who would prefer the expanded treatment option, and half from volunteers who have dropped out of methadone treatment. Equal numbers of men and women would be included from each of these groups. Participants would have a choice of treatments: injectable diacetylmorphine alone; injectable diacetylmorphine and oral methadone; and oral methadone alone. All could change treatments at will, within the limits of medical safety.

To warrant moving to the second pilot study, the first would have to show that:

- A stable maintenance dose of injectable diacetylmorphine or injectable diacetylmorphine plus oral methadone could be found for more than half the participants;
- Participants could safely and easily move between the three treatment options; and
- There was improvement in at least half of the outcome measures for health and well-being.

The first pilot study would also allow investigation of the pharmacokinetics and psychopharmacology of diacetylmorphine, especially effects on driving skills.

Stability is a key issue for the first pilot study. Stabilised consumption within a defined therapeutic range was identified as a criterion for effective maintenance treatment by a meeting of experts on drug substitution organised by the World Health Organization in May 1995. Participants in the proposed trial would be able to attend the clinic to inject heroin up to three times a day. Current Swiss experience is that this works very well; those who cannot be stabilised on heroin under these conditions are prescribed a low dose of methadone as well.

**Second pilot study**: This would be a small randomised controlled trial with 250 participants and the same eligibility criteria as the first pilot study. In contrast to the first pilot study, half the participants would be allocated to the choice of treatment options and half to oral methadone alone.

The **second pilot study would**:

- Further investigate the questions addressed in the first pilot study;
- Begin to examine attraction into, and retention in, treatment; and
- Assess if randomisation is practicable for this group.

A full-scale randomised controlled trial is the standard and most rigorous way to test a new treatment option. However, before launching such a full-scale trial, it is necessary to test whether it is practicable for dependent drug users. If not, there will be hard decisions about the value of less convincing forms of assessment. Alternatively, if drop-outs from the randomised pilot study are relatively few, then the sample size would be sufficient for statistically meaningful comparisons on outcome measures.

**Full-scale clinical trial**

This would involve:

- 1000 participants in three cities; and
- Volunteers drawn evenly from three groups: dependent heroin users who have never been in treatment; those who have dropped out of treatment; and those currently in methadone treatment.

The trial would run for two years. In the first year it would be a randomised controlled trial, but in the second all participants would be given choice of treatment.

At the end of the trial there could be evidence-based assessment of the role of diacetylmorphine in maintenance treatment, the subgroups in which this treatment is most likely to be useful, and other indications and contraindications. This would allow a more balanced perspective on medical prescription of this drug.
Development of the proposal

The proposal resulted from a four-year feasibility study that concluded that the benefits of testing this new treatment option outweighed the risks. While all currently available options (such as methadone maintenance, detoxification, residential rehabilitation and counselling) are beneficial for some dependent users, none appear satisfactory for a further significant proportion. Additional options are needed. Diacetylmorphine is not the only potential new treatment; others include buprenorphine, levomethadyl acetate (LAAM), naltrexone and injectable methadone. However, the feasibility study focused on diacetylmorphine because it is the most controversial, among the least carefully studied and the preferred option for many dependent heroin users.

Some of the controversy arises from uncertainties about whether prescribing diacetylmorphine can have positive outcomes, whether it can be cost-effective and whether stability is achievable on this short-acting opioid. These questions can be resolved only through empirical research and are the focus of the trial.

Moral arguments about the value of maintenance treatment, about providing treatment for self-inflicted problems and about making a currently illicit substance available under carefully controlled conditions are not resolvable but are open to ethical debate (some issues are covered by Ostini et al.6).

Finally, controversy arises because a trial has risks. These include that dependent heroin users may move to the ACT; a trial may lead to more permissive attitudes to illicit drug use; the trial drugs may cause road accidents or be diverted onto the black market; participants may congregate at the trial site; women in the trial may give birth to diacetylmorphine-affected babies; and a trial might further institutionalise or marginalise dependent heroin users.

Much of the feasibility research involved working with critics of a trial, firstly to identify these risks and then to develop ways to minimise them. In summary, these include using well-defined eligibility criteria, not providing take-away doses of heroin, strictly supervising injection at the clinic, carefully monitoring participants before they leave and setting the trial within the current context of law enforcement and preventive activities. Potential risks would also be carefully monitored.

The feasibility research was conducted in collaboration with the Australian Institute of Criminology. Well over 100 people have been involved -- as collaborators, assistants and advisers -- and many hundreds have provided feedback through workshops, seminars and discussions. Opinions have also been elicited from around 5000 members of the general community through ACT and national surveys.

A wide range of options was initially explored. The development of a proposal that was clinically workable, able to be rigorously evaluated and minimised risks was an iterative process -- any one change to the protocol could have multiple ramifications. The process involved integrating both the findings of many disciplines (anthropology, clinical science and health care, criminology, demography, economics, epidemiology, law, pharmacology, philosophy, political science, policy analysis, psychology, sociology and statistics) and the insights of the key interest groups (people who are or have been dependent on heroin, police, people involved in providing treatment and other services to illicit drug users, the general community and policy makers).

Heroin has long been prescribed for dependent users in the United Kingdom and, while there is evidence that this can be a useful option, it is contested. The same is true of historical evidence from the United States. No evaluation to date has been as rigorous as would now be required before introducing a new treatment. Other countries, most notably Switzerland and the Netherlands, are either undertaking, or about to undertake, “heroin trials”. Much will be learnt from them, but many questions will remain unanswered and these are the focus of the ACT proposal.

The future

The future of the trial is now in the hands of the policy makers. The immediate stimulus for the feasibility research came from the deliberations of an ACT Legislative Assembly Select Committee on HIV, Illegal Drugs and Prostitution in early 1991. The final report and recommendations from the feasibility study were presented to the ACT Chief Minister, Ms Kate Carnell, in June 1995; she has
maintained that a trial will not proceed without support from other States and financing from outside the ACT.

In the meantime, we welcome public and private critiques and debate on the proposal. If a trial does eventuate it must be as well conceived as possible. Opportunities for clinical trials are rare and justified only when there is a real research question, with doubt about the outcome. In addition, trials are expensive. We estimate the cost of the two pilot studies alone at $2.3 million. A trial cannot be paid for from funding currently allocated to drug treatment or research; there are too many other urgent priorities. New money will have to be allocated --ultimately, this is the real test of political will.

Of necessity this overview must be brief. A more detailed proposal can be found in the 1995 report on feasibility of the heroin trial.9 The results of the feasibility research are presented in four reports, thirteen working papers and, to date, 16 peer-reviewed papers, which are available from the authors (for a selection see references 10-14). A detailed response to the critique by Dr Matt Gaughwin is also available from the authors.

References

Appendix 4: Overview of European experiences with diamorphine prescription

We have reprinted a key overview paper here, namely Bammer, G. 1999 ‘Provision of diamorphine (heroin) by prescription for drug dependency: issues and recommendations.’ CNS Drugs, 11 (4), 253-262.

A brief summary of Dutch trials is attached after the paper.

Provision of Diamorphine (Heroin) by Prescription for Drug Dependency

Issues and Recommendations

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Abstract

Existing evidence for the efficacy of diamorphine treatment of heroin dependence is presented, focusing first on “gold standard” randomised controlled trials and then on other forms of evidence. The evidence strongly suggests that diamorphine treatment may be of some value and that further trials are warranted. Nevertheless, there are a range of risks associated with diamorphine trials and these are also discussed. It is recommended that: (i) extensive trialling of the efficacy, safety and cost-effectiveness of diamorphine should be undertaken; (ii) trials should be conducted to the highest scientific standards, but the standards should be realistic; (iii) the risks associated with diamorphine prescribing must be taken seriously and included in trial planning and evaluation; (iv) competing moral positions about diamorphine prescribing should be spelled out and debated; and (v) diamorphine prescription should be viewed as only one of a number of treatment options and should be investigated as part of a pluralist approach to the treatment of heroin dependence.

1. Overview of Treatment for Heroin Dependence

1.1 Brief History of Diamorphine Treatment

There is growing international interest in investigating the prescription of diamorphine (pharmaceutical heroin) as a treatment for heroin dependence. Diamorphine prescription has always been an option in the UK (for overviews see Strang and Gossop,[11] Strang[2] and Stimson[3]) and there was intense interest in the ‘British System’, especially in the US in the 1960s and 1970s. A proposal for a trial in New York City was narrowly thwarted by political opponents in the early 1970s. Instead, the position of oral methadone maintenance treatment was strengthened and this also became the dominant treatment in the UK, where diamorphine prescription now represents only 1 to 2% of prescriptions for the treatment of heroin dependence.[9]

With the advent of HIV/AIDS the unresolved debate about diamorphine prescription resurfaced. More recently, it has been given added stimulus by the encouraging results of a 3-year Swiss cohort study and by the initiation of clinical trials in The Netherlands. Discussions about conducting trials are also being held in a number of other countries.

1.2 Current Treatment Options

The challenge is for those involved in the treatment of heroin dependence to embrace a pluralist approach. As in the treatment of other medical conditions, practitioners should have several options,
so that if one does not suit a particular individual, others are there to be tried.

Essentially there are currently 2 major treatment pathways for heroin dependence (Fig. 1). One begins with withdrawal (detoxification) from heroin, followed by treatment to prevent relapse, which may include residential rehabilitation, outpatient psychosocial assistance and/or self-help groups. The introduction of oral methadone maintenance 30 years ago essentially turned this treatment model on its head. It showed that stabilisation through prescription of an agonist can effectively allow dependent users to be reintegrated into society.\(^{[10]}\) Psychosocial assistance at this stage can be beneficial in allowing the person to deal with factors which led to the dependence or problems arising because of it. Withdrawal from the agonist happens after reintegration.

Oral methadone maintenance has become the most widely used modality internationally and has dramatically reduced the cost of treatment. With growing evidence that treatment is the most cost-effective way of responding to drug dependence, expanding treatment availability and increasing the proportion of dependent heroin users in treatment are high priorities.

A number of pharmacotherapies — buprenorphine, levacetymethadol (LAAM), naltrexone and slow-release oral morphine — have been available for several years, but enthusiasm for them has been patchy and international interest in trialling and marketing has only recently been revived.

Although the focus of the remainder of this commentary is on diamorphine, an effective consideration of its role must take into account this broader context. In particular, research on diamorphine should focus on the treatment niche, if any, that it can best fill and both effectiveness and cost-effectiveness should be considered. The starting point for both the Swiss and Dutch trials has been that the niche for diamorphine is for people who have not found existing treatments to be satisfactory. The Swiss cohort study concentrated on people who had withdrawn from treatment,\(^{[14]}\) whereas the Dutch trials focus on those in methadone treatment who are not doing well.\(^{[15]}\) The Australian feasibility study also considered another potential, and more controversial, niche, namely as an option to bring new people into treatment.\(^{[16,17]}\)

This review focuses on the scientific arguments rather than political debate about heroin prescription.

2. How Should Diamorphine Maintenance be Assessed?

If diamorphine was a new pharmaceutical that a drug company was seeking to develop and market, considerable evidence would still need to be gathered before its value could be properly assessed. It is standard for the development of new pharmaceuticals to follow a 4-phase procedure with regard to trialling in humans.\(^{[18,19]}\) Because diamorphine was developed before this procedure became standard,
the information available about it is patchy. Phase I trials seek to establish pharmacological activity, tolerance, absorption, metabolism and excretion, and there are gaps in knowledge here. Most interesting is a country-based discrepancy in doses used. The average daily dose of diamorphine prescribed in Britain is around 200mg, whereas in Switzerland it is around 500mg. There should be a comparison of clients in both countries on total dose of prescribed opioid (i.e. diamorphine plus methadone plus morphine etc.), additional use of illegal opioids and perhaps also patterns of administration. The pattern is regulated in Switzerland through the requirement to attend a clinic for each administration of diamorphine, but this is not the case in Britain where daily or weekly pick-up of diamorphine from a pharmacy allows considerable freedom concerning when the drug is administered.

Phase II and III trials seek to establish safety and efficacy, first with small numbers and then with large-scale randomised controlled trials. Phase IV studies involve the use of a drug with approved indication, formulation and route of administration and are often conducted after the drug has been marketed when there is access to broader-based populations. Phase III randomised controlled trials are generally considered to provide the most rigorous evidence for efficacy; hence, the following examination of existing knowledge about diamorphine prescription starts with what we know from these trials and then considers other forms of evidence.

Although it is useful to deal with diamorphine in the same way as any other new treatment, there are also other considerations. One is that there are also significant risks associated with treating a problem with the drug that causes the problem. These have been studied in detail and are also outlined in section 5. Another is that trials of diamorphine occur in a highly politicised context. This can lead to pressures to set unrealistically high standards for the assessment of diamorphine, in terms of expected outcomes and/or safeguards, and these can cause excessive costs or set the trial up to fail. While randomised controlled trials are the accepted "gold standard", their limitations in terms of real world applicability must also be recognised. Thus phase IV trials must also be considered, and the Swiss cohort study went a considerable way towards addressing real world issues.

3. Randomised Controlled Trials of Diamorphine

To date there have been only 2 randomised controlled trials which have assessed the efficacy of diamorphine. The first, conducted in the 1970s, compared oral methadone, the new treatment at the time, with injectable diamorphine, then the standard treatment. The context of this trial means that the results, which in any case were equivocal, have only limited applicability now. Most importantly, the current view is that the place of diamorphine is not as a replacement for methadone and other maintenance treatments, but as an adjunct to them.

A more recent randomised controlled trial was conducted as part of the Swiss cohort studies. In Geneva, 25 long term dependent users were randomly allocated to receive diamorphine prescription (with at least occasionally also receiving an oral opioid) and 21 were put on a 6-month waiting list for diamorphine, during which time they received conventional treatment with most (n = 19) receiving methadone maintenance. Compared with the control group, those in the diamorphine group showed significant reductions in illegal heroin use, income from drug dealing, criminal charges for drug use and possession, property theft and other offences, and amount of money spent on drugs. The group receiving diamorphine also showed improved mental health and social functioning. There were no differences between the groups on a number of other health and social variables, although the diamorphine group often showed improvements compared with pretreatment assessment. At the end of the 6-month waiting time, only 38% of those on the waiting list opted for diamorphine prescription. Most of those who did not want to transfer were doing well on methadone maintenance.

The Dutch trials, which commenced in July 1998, will focus on those in oral methadone treatment who are not being well stabilised by that treatment.
One-third will be randomly assigned to continue in methadone treatment alone (although they will have the option of being prescribed diamorphine after 12 months if it is shown to be successful), while the rest can be prescribed diamorphine along with oral methadone. The unique features of this trial are that diamorphine prescription will be time limited, with one-third of participants receiving it for 6 months and another third for 12 months. In addition, diamorphine will be made available in both injectable and inhalable forms (in 2 separate trials). In The Netherlands heroin is commonly administered by inhalation (‘chasing the dragon’) and this is also becoming more popular in other countries.

4. Other Studies of Diamorphine

4.1 The Swiss Cohort Study

The promising results obtained in the Swiss cohort study conducted between 1994 and 1996 underpin and justify the push for further research.\(^{14,25,26}\) In that study, 800 treatment slots were allocated for diamorphine treatment for ‘socially disintegrated’ dependent heroin users who had previously failed to respond to other treatment. There were significant improvements in mental and physical health and in social functioning, and reductions in drug use and other criminal behaviour. For example, illicit heroin use was dramatically reduced from almost all participants reporting daily use before the trial to only 26% reporting occasional or daily use after 18 months. There were also marked reductions in cocaine use, with 15% reporting no cocaine use before the trials, increasing to 41% after 18 months.

After 18 months there were also marked improvements in health, including bodyweight gain, virtual disappearance of injection-related skin problems and improvement in overall rating of both physical and psychiatric health. Psychiatric checklists showed clear reductions in depression, anxiety, aggressive behaviour and overall affective disorders.

Among the most pronounced changes were those in criminal behaviour. For example, at the beginning of the trials 31% reported no income from illicit or semi-licit sources; after 18 months this rose to 90%. There were 4 separate studies of criminal behaviour, all of which verified the marked reductions in all kinds of criminal behaviour. Self-reported results were confirmed by separate studies using police records and official crime statistics (see also Killias and Uchtenhagen\(^{27}\)).

4.2 UK Case-Control Study

As part of an overall evaluation of 3 services in the same provincial region, 27 people receiving prescriptions for injectable or smokable diamorphine were compared with 37 people receiving oral methadone. The 2 groups were matched for age, sex, length of time using opioids and length of time on their current prescription programme.\(^{28}\) Those receiving diamorphine were first interviewed after an average of 11.4 (± 4.9) months on their current prescription and those on methadone at 9.2 (± 17.2) months on their prescription. Both groups were interviewed again 6 months later. Overall, the group receiving diamorphine was more likely to stay in treatment and to attend appointments with their community drug worker, used less illicit diamorphine, spent less money on all forms of illicit drugs, was less likely to share injecting equipment, had better psychological health and was less likely to be involved in criminal activity. There were no significant differences between the groups in use of other illicit drugs or benzodiazepines, in measures of physical health and in unemployment rates. The diamorphine group was more likely to use cocaine and less likely to have achieving abstinence as a personal goal.

4.3 UK Observational Cohort Study

58 long term dependent opioid users who had continued to inject illicit opioids while receiving oral methadone (>80 mg/day) were allowed to choose treatment with either injectable diamorphine or injectable methadone. They were followed up for another year. Two-thirds (\(n = 37\)) chose injectable diamorphine (with 71% also receiving oral methadone to prevent withdrawal during the night) and the rest chose injectable methadone. The results for
the 2 groups combined showed that there were significant reductions in illicit drug use, HIV risk behaviour scores and criminal behaviour and significant improvements in physical and mental health and in social functioning.\cite{28}

4.4 Long Term Follow-up Study in the UK

In 1969, a long term follow-up study was started of a randomly selected sample of one-third of the people who were prescribed diamorphine at 13 of 15 London clinics; this numbered 128 patients.\cite{30,31} It is worth reiterating that at that time diamorphine was the standard treatment for heroin dependence. 10 years later, around 38% had ceased to use heroin and other opioids and this was not replaced by alcohol or other drug dependence. Most of this group were leading ‘ordinary lives’. Another 38% were still attending the clinics, with half still receiving prescriptions for diamorphine. A further 15% had died, and while all of that group were using drugs at the time of death there is no information about the number still receiving prescriptions. The status of the remainder was uncertain.

5. Risks Associated with Diamorphine Trials

As part of an Australian feasibility study,\cite{16,32} discussions were held with interest groups holding a range of views about a trial of diamorphine prescription and this resulted in extensive documentation of risks, as well as strategies for both minimising and evaluating them.

It is difficult to estimate the likely magnitude of these potential risks. Although they will vary according to trial context, evidence from the many years of experience of prescribing in the UK and from recent trials suggests that many of the risks can be managed.

To some extent the concerns about diamorphine prescription reflect moral positions. One such position insists on the primacy of abstinence as the outcome of any trial (and of treatment generally). Thus some would argue that any reduction (real or perceived) in the likelihood that trial participants will cease both legal and illegal heroin use is a risk, while others would downplay the importance of abstinence in favour of other positive outcomes such as improved health and social reintegration and reduced criminal activity. A related ethical argument, which also influences positions on risks, is the issue of acts and omissions. Some argue for a more deontological approach where a harm resulting from an intervention is a major problem, even if similar or even greater harms might otherwise have happened. Others argue for a more utilitarian approach which judges the harms caused by the intervention in light of those which would have happened had there been no intervention (for more detail see O'Leary et al.\cite{33}).

A compilation of risks posited by different groups follows, along with a brief explanation and/or discussion of how each risk could be approached.

A trial may lead to more permissive attitudes towards illicit drug use. Prescription of diamorphine and permissiveness towards illegal drug use are not inextricably linked. Any trials should be careful not to engender a sense of permissiveness towards illegal drug use, should be monitored to determine if permissiveness is occurring and should have countervailing strategies ready. Diamorphine prescription, which has been a long-standing option in the UK, has existed within an overall policy of prohibition, with no evidence of permissiveness towards illegal drug use. Permissiveness towards illegal drug use also seems to have been successfully avoided in the Swiss trials, where there was also concurrent research aimed at strengthening prevention activities.\cite{34} It is also worth mentioning here that a trial would not breach the 1961 United Nations Single Convention on Narcotic Drugs or subsequent conventions.\cite{35}

Dependent users from around the country and/or from neighbouring countries may move to the trial city(ies). Divorcing diamorphine prescription from permissiveness should also reduce the likelihood of a ‘honeypot effect’ and this risk can be further minimised by enforcement of strict residency criteria, by limiting the number of trial places and by close co-operation with police.\cite{36} Again, strategies...
should be in place to monitor and, if necessary, combat, such an effect.

Diamorphine prescription may reduce motivation to completely cease all heroin use and may institutionalise and further marginalise trial participants. This is an area which requires further research. The UK follow-up of people prescribed diamorphine indicates that some may receive long-term prescriptions.\[31\] The Swiss trials have shown that around 7% of participants move to drug-free treatments within 18 months.\[33\] While this might seem like a low figure, there are no comparative data which allow it to be put in perspective. It is commonly asserted that around 5% of dependent heroin users become drug-free each year, although this is now an old, and somewhat dubious, figure. What the Swiss research does show is that diamorphine prescription does not necessarily reduce the motivation to become abstinent, but this needs further investigation. The Dutch trials, which will limit the duration of diamorphine prescription to either 6 or 12 months, may also shed more light on this issue.\[15\]

There is also concern that diamorphine prescription provides an easy option which may allow those in treatment to avoid confronting both the causes and consequences of dependence, a step which is believed to be necessary to achieve abstinence. Simply making pharmaceutical diamorphine available could undermine willingness to attempt other treatments. This also needs further research. The Swiss trials showed no evident impact on either oral methadone programmes or on drug-free residential treatment, with the number of treatment slots increasing for both of these options. Although the Swiss cohort study showed that diamorphine treatment was considerably more attractive than treatment with either injectable morphine or injectable methadone, the study by Morebien and colleagues\[20\] showed that injectable heroin is not always the drug of choice, with one-third preferring injectable methadone. Similarly, the study by Perme et al.\[24\] showed that people who found other treatments satisfactory were unlikely to transfer to injectable diamorphine treatment.

Trialling diamorphine may have opportunity costs; in particular, it may be trialled at the expense of other treatments. There are 2 issues here. One is that diamorphine might be trialled at the expense of other new treatments, and the other is that some would argue that the money spent on diamorphine treatment would be better spent improving existing treatments. It is difficult to assess if diamorphine would be trialled at the expense of other treatments, and this could vary from country to country. In Australia, discussions about diamorphine treatment raised the profile of buprenorphine, levacetylmethadol, naltrexone and slow-release oral morphine as new treatment options, and governments originally agreed to support the whole range of trials of new treatments. Although federal government support for trialling diamorphine was withdrawn, trials of other new pharmacotherapies are continuing.

The argument that existing treatments should be improved rather than new ones trialled is also difficult to assess. This issue is particularly relevant if the niche for diamorphine treatment is considered to be those who have not done well in existing treatments. Some would argue that there are other adjuncts to existing treatments that would serve this group and that would be cheaper, less controversial and easier to implement than diamorphine treatment. This may well be so, but it is generally easier to obtain funding and political support for new initiatives than for improvements to existing treatments, especially if those treatments have been available for 30 or more years, as is the case for both methadone and residential rehabilitation programmes. The real choice may therefore be between trialling or not trialling the new treatment, as the alternative of spending money on improving existing treatments may simply not be viable.

Diamorphine treatment may be unaffordable in the long term. Because of the need to closely supervise diamorphine administration to prevent diversion, this is likely to be an expensive treatment. For diamorphine to be introduced as an available treatment option there would therefore need to be clear evidence of cost-effectiveness over other treatments for certain well-defined subgroups of users.
Results from the Swiss trials, which targeted people with substantial health and social problems associated with heroin use and who had found other treatments to be unsuccessful, indicate significant net savings (SF45 per person per day) associated with crime and healthcare.\(^1\) This treatment could therefore more than pay for itself. However, with governments worried about spiralling health costs, savings which benefit other government departments (such as law enforcement) may offer little attraction.

Once trials have been started it may be difficult to 'turn the clock back' to once again completely ban diamorphine prescription. A number of arguments are intertwined in this concern. One is that it could be argued that if the results of a trial show that the benefits outweigh the risks, diamorphine should be made available as a standard treatment option (to carefully chosen patients and with suitable restrictions). However, there is unlikely to be unanimity on the overall outcome, with different groups weighting the positives and negatives differently. Those who oppose diamorphine prescription on moral grounds would be unlikely to accept any of the benefits as being of overriding importance; even if they might have an academic interest in the results of a trial, they would not support it because of the risk that there would be majority support for a position that the benefits outweighed the risks and consequently that diamorphine should become a standard treatment option. A related concern is that some would worry that the safeguards set in place during a trial would not be maintained in the long term and that this might lead to unregulated prescription or even unregulated availability. If this had major negative social consequences, there might be an argument for again completely prohibiting the use of diamorphine, but this might be difficult to implement. This could also be the case if research showed that the long term effects of diamorphine prescribing were problematic, even if short term outcomes were positive.

Trials may make law enforcement more difficult by blurring the differentiation between lawful and unlawful heroin use or by allowing justification of crimes committed under the influence of diamorphine prescription. These concerns were raised by Australian police during consultations about the feasibility of a trial of diamorphine prescription; they point to a need for laws about diamorphine prescription to be clear, but also for evaluation of their effects on law enforcement.

Trial diamorphine may be diverted onto the illegal market. In the UK in the 1960s, there was considerable diversion of prescribed diamorphine, which was partly combated by tighter regulations on the prescribing doctors. Diversion is potentially facilitated in the UK because, like other pharmaceuticals, diamorphine is dispensed through pharmacies on a take-home basis. With only a small amount of diamorphine being prescribed nowadays, diversion is less of an issue. Nevertheless, one of the major contributions of the Swiss research has been to show that supervised administration at clinics with limited opening hours is workable and that there has been no diversion of trial drugs from the clinics.\(^2\) The clinics have also been shown to be socially and politically feasible, with no substantial reported problems with neighbours and with more than 70\% of voters supporting continuation of the trials in a referendum in 1997. Thus it is possible to put in place successful strategies against diversion, but they increase the costs associated with prescribing diamorphine.

A trial may encourage non-dependent users to become dependent in order to qualify for a place on a trial. As part of the Australian feasibility research, a survey of non-dependent current heroin users found that around 1 in 6 said they would increase their use if it was necessary to get on a trial.\(^3\) This highlights the need for strict eligibility criteria which include a substantial period of dependent use.

Road safety may be compromised by trial participants driving under the influence of diamorphine. This is an area that needs further research. While existing evidence suggests that opioids do not greatly affect driving skills,\(^4\) driving skills are likely to be affected when people are in a state either of withdrawal or intoxication. Thus the ability of diamorphine prescription to effectively stabilise par-
participants becomes crucial. In both the Swiss and Dutch trials, participants are required to surrender their drivers’ licences. While this may be reasonable in a trial, it is unlikely to be workable if diamorphine becomes available as a treatment option.

A trial may increase ‘public nuisance’ through participants congregating outside clinics or by leading to tension between those who have been and have not been successful in obtaining a trial place. As with most other risks, there must be strategies in place to minimise these risks, ways of monitoring them and, if necessary, counteracting them.

There may be problems for babies born to women on a trial. This is a difficult issue. It is generally accepted that the babies of heroin-dependent women are at greatest risk when their mothers are using illegal heroin, mainly because of fluctuating blood concentrations, other drugs that may be used to alleviate withdrawal symptoms and lack of ante- and post-natal care. Stabilising heroin-dependent pregnant women on methadone is an accepted way of minimising these risks and the limited existing research evidence suggests that this does not have major adverse consequences for their children (e.g. see Finnegan and Randall[130]). There is no evidence about stabilisation on diamorphine and it might be most feasible to transfer all pregnant women to methadone.

Overall, these risks must be taken seriously and be included in trial planning and evaluation. There should be predetermined criteria for halting a trial. Effects on participants and on social outcomes should be considered in evaluating the overall success of a trial and whether or not diamorphine should become a standard treatment option.

6. Recommendations

1. Extensive trialling of the efficacy, safety and cost-effectiveness of diamorphine should be undertaken. This will assist in resolving decades-old debate about the value of diamorphine prescription. Existing evidence suggests that diamorphine has some value and this warrants rigorous evaluation through a number of complementary trials, which address unresolved questions about diamorphine prescription.

2. Trials should be conducted to the highest scientific standards, but the standards should be realistic. There is little disagreement that trials of diamorphine prescription should be conducted to the highest standards, including rigorous trial design, and careful monitoring of clinical procedures and potential risks. However, the standards must also be realistic in terms of procedures commonly used in trials of new treatments, limitations associated with conducting trials with dependent heroin users and available budgets. Trials should not be set up to fail by the imposition of unrealistic standards.

3. The risks associated with diamorphine prescribing must be taken seriously and included in trial planning and evaluation. Strategies to deal with potential risks should be included in trial planning, and effects on participants and on social outcomes should be considered in evaluating the overall success of a trial. The costs of minimising risks should also be included in trial cost-effectiveness calculations and in assessing whether or not diamorphine should become a standard treatment option.

4. Competing moral positions about diamorphine prescribing should be spelt out and debated. Some of the debate about diamorphine prescription rests on competing moral positions. Although many of the issues underlying the debate about diamorphine prescription are amenable to resolution through trials, moral debate cannot be resolved by science.

5. Diamorphine prescription should be viewed as only one of a number of treatment options and should be investigated as part of a pluralist approach to the treatment of heroin dependence. There is renewed interest in other pharmacotherapies to assist maintenance (levacetamethadone, buprenorphine and slow-release oral morphine, as well as diamorphine), withdrawal (buprenorphine and naloxone) and relapse prevention (naloxone). These are in addition to methadone, which is now widely used for both maintenance and withdrawal, and to various forms of psychosocial assistance which aid relapse prevention. Ideally, those involved in the treatment of heroin dependence should be familiar
with the range of options and government policy should allow the full range of options which have been shown to be effective to be available. This may involve spending more money on treatment.

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A comprehensive report on the Dutch heroin trials has recently been published. The authors’ abstract follows:

**Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials**

OBJECTIVE: To determine whether supervised medical prescription of heroin can successfully treat addicts who do not sufficiently benefit from methadone maintenance treatment.

DESIGN: Two open label randomised controlled trials.

SETTING: Methadone maintenance programmes in six cities in the Netherlands.

PARTICIPANTS: 549 heroin addicts. Interventions Inhalable heroin (n = 375) or injectable heroin (n = 174) prescribed over 12 months. Heroin (maximum 1000 mg per day) plus methadone (maximum 150 mg per day) compared with methadone alone (maximum 150 mg per day). Psychosocial treatment was offered throughout.

MAIN OUTCOME MEASURES: Dichotomous, multidomain response index, including validated indicators of physical health, mental status, and social functioning.

RESULTS: Adherence was excellent with 12 month outcome data available for 94% of the randomised participants. With intention to treat analysis, 12 month treatment with heroin plus methadone was significantly more effective than treatment with methadone alone in the trial of inhalable heroin (response rate 49.7% v 26.9%; difference 22.8%, 95% confidence interval 11.0% to 34.6%) and in the trial of injectable heroin (55.5% v 31.2%; difference 24.3%, 9.6% to 39.0%). Discontinuation of the coprescribed heroin resulted in a rapid deterioration in 82% (94/115) of those who responded to the coprescribed heroin. The incidence of serious adverse events was similar across treatment conditions.

CONCLUSIONS: Supervised coprescription of heroin is feasible, more effective, and probably as safe as methadone alone in reducing the many physical, mental, and social problems of treatment resistant heroin addicts.

(This article has been corrected. See BMJ. 2003 September 27; 327 (7417): 724)

Appendix 5: Potential risks associated with diamorphine prescribing

We have reprinted a key overview paper here, namely Bammer, G.; Brink, W. van den.; Gschwend, P.; Hendriks, V.; Rehm, J. 2003 ‘What can the Swiss and Dutch trials tell us about the potential risks associated with heroin prescribing?’ Drug and Alcohol Review 22, 363-371.

HARM REDUCTION DIGEST 22

What can the Swiss and Dutch trials tell us about the potential risks associated with heroin prescribing?

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Following on from last edition’s Harm Reduction Digest on drug consumption facilities this Digest investigates what can be learnt from the Swiss and Dutch trials of heroin prescribing about the unintended consequences of this controversial intervention to reduce heroin related harm. The authors of the paper bring considerable experience in the implementation and evaluation of such schemes in Europe and their consideration in Australia. The paper systematically addresses concerns about heroin prescribing and suggests further research to respond to some unanswered questions.

SIMON LENTON
Editor, Harm Reduction Digest

Introduction

Making heroin available on prescription as an additional form of treatment for dependent heroin users has a history of being a contested policy. A small amount of prescribing occurred in the United States in the early 1960s, but was outlawed after a 1970 Supreme Court interpretation of the Harrison Act (1914) found “addiction maintenance” to be unlawful [1]. Heroin addiction was not a major public issue again until the 1960s, when the foundations for the current epidemics of illicit drug use were laid. At that time the United Kingdom was noteworthy for continuing to allow medical practitioners to prescribe heroin to dependent users, although their ability to do so was considerably circumscribed in 1968 [2]. The establishment of special drug clinics and the introduction of oral and injectable methadone were combined with clinicians adopting a “more active and confrontational style” [3, p. 113] leading to the overshadowing of heroin prescription as a major form of treatment by the 1970s. Scientific evaluation of the effectiveness of heroin prescription was limited, so that both proponents and opponents of heroin prescription have selectively used the British experience to support their cause.

Interest in heroin prescribing was revived in the 1990s. Three of the key countries in this resurgence were Switzerland, the Netherlands and Australia. The
context in Switzerland was a dramatic increase in heroin and other illicit drug use in the late 1980s and early 1990s, with associated spread of HIV/AIDS and other infectious diseases [4] and a large increase in open drug scenes [5]. There were no such immediate pressing concerns in either the Netherlands or Australia. Instead, both these countries have a history of innovation in drug treatment and policy. For example, in the Netherlands, small-scale experiments had been conducted with injectable morphine, injectable methadone and oral dextroromorphide [6]. Visible drug use was a long-standing issue in the Netherlands, but insignificant in Australia until the late 1990s. Both countries introduced measures to combat HIV/AIDS early, so that infection levels remained relatively low [7,8]. Another significant feature in the Netherlands was the importance of inhalation (“chasing the dragon”) as a route of heroin self-administration, with it becoming the dominant technique for most (75–90%) heroin addicts in the late 1990s [9].

The social and policy contexts for considering and, for the Swiss and Dutch, trialling heroin prescription therefore differed from country to country. In all three countries, consideration of heroin prescribing occurred in the context of a comprehensive treatment system. In both Switzerland and the Netherlands the primary concern was for severely dependent heroin users for whom methadone maintenance was not providing adequate treatment [10–12]. Both countries undertook trials focusing on that group. The Swiss trials started in 1994 and the Dutch trials in 1998. In the Australian feasibility study, heroin prescribing was also considered as an option for attracting new people into treatment, as well as providing an additional option for those already in treatment [13]. After initial government approval, the Australian trial was blocked in 1997 by the Prime Minister and cabinet, who stated particular concerns about a trial “sending the wrong message” [14].

A final significant background factor for the introduction of heroin prescription trials was the specific treatment context. In no country was heroin prescription seen to be a stand-alone treatment, as it was in the early 1900s in the United States or in the 1960–1970s in the United Kingdom. In the Swiss trials, injectable heroin was provided in the context of substantial mandatory psychosocial and medical treatment, with oral methadone or slow-release heroin available as needed to provide additional stabilisation. In this context heroin prescription is more accurately described as “heroin-assisted treatment”. In the Dutch context, injectable or inhalable heroin was provided as an adjunct to oral methadone maintenance, with standard psychosocial treatment also available and is more accurately described as “co-prescribed heroin”. For convenience, the shorthand “heroin prescription” will continue to be used in this paper, except when a specific trial is being referred to.

Although no trial has yet been undertaken in Australia, the feasibility research was unique in its detailed consideration of the potential risks associated with heroin prescribing and of how these risks might be minimized and evaluated [14,15]. Because of the lack of solid empirical evidence, this assessment largely rested on expert opinion—sought primarily from police, providers of treatment and other services, users and ex-users and particularly from opponents of heroin prescribing. The Swiss and Dutch trials begin to provide an empirical base for reassessing those risks and that is the primary purpose of this paper. The potential risks identified in the Australian feasibility research were that heroin prescription:

- simply would not achieve positive outcomes;
- was unworkable if it was to occur through a clinic-based system which required user attendance for each administration;
- could lead to more permissive attitudes towards illicit drug use;
- could attract dependent users from around the country and/or from neighbouring countries, in a “honeytrap effect”;
- could reduce motivation to completely cease all heroin use and could institutionalize and further marginalize trial participants;
- could undermine other treatments by encouraging people to drop out in order to qualify for heroin. Further, it could have opportunity costs through being funded at the expense of other treatments and it could be unaffordable in the long term;
- could make law enforcement more difficult by blurring the differentiation between lawful and unlawful heroin use or by allowing justification of crimes committed under the influence of heroin prescription;
- could be diverted onto the illegal market;
- could compromise road safety by recipients driving under the influence of heroin;
- could increase “public nuisance” through participants congregating outside clinics or by leading to violence between those who were and were not successful in obtaining a treatment place; and
- could cause problems for babies born to women recipients.

Heroin prescription simply would not achieve positive outcomes

Some critics of heroin prescribing argued that trials should not take place because they could not imagine
any chance of positive outcomes. If the outcomes can be confidently predicted, scientific trials are not only unnecessary but also unethical. On the other hand, the British and US experience indicated that positive effects were possible, so that there were real questions to investigate. Approval for the Swiss study was obtained from the Swiss Academy of Medical Sciences' super-regional ethics committee. The Dutch trials were approved by the Central Committee on Medical Ethics, and were conducted according to International Conference on Harmonisation/European Union Guidelines for Good Clinical Practice (ICH/GCP).

The trials produced a range of positive outcomes, summarized below. Full descriptions are reported elsewhere [10,16–18].

The Swiss cohort study of injectable heroin-assisted treatment involved 2160 admissions, corresponding to 1969 participants who were seen between January 1994 and December 2000 at 21 centres in 19 cities. In brief, the Swiss results showed that:

- There were marked improvements in both physical and mental health for those who stayed in treatment for 18 months or longer.
- Consumption of illicit substances, especially illegal heroin, decreased. There was also a significant reduction in cocaine consumption [19,20].
- With the exception of employment, for which there was no significant change, there were improvements in a range of indicators of social integration. Reduction in criminality was especially marked and the estimated monetary benefits associated with this reduction were greater than the treatment costs [21,22].
- Most of the positive results described above were still evident in a 6-year follow-up study, regardless of the treatment status of participants [23,24].

The positive results from the Swiss studies meant that further investigation of other research questions was warranted. One key issue was to examine the effectiveness of heroin prescription when standard rather than intensive psychosocial support was provided. Another was to compare treatment which included heroin prescription with the best currently available treatment, namely methadone, with participants assigned randomly to one or other treatment. These issues were addressed in the Netherlands, where an open-label randomized controlled multi-centre study was conducted in six cities from 1998 to 2002. There were separate trials examining the effectiveness of injectable heroin (n= 174) and inhalable heroin (n= 375). The experimental condition consisted of 6 or 12 months' treatment with oral methadone plus co-prescribed heroin and these participants were compared with methadone-only controls. Heroin prescription was discontinued for at least 2 months at the end of the experimental treatment period. In summary:

- Twelve months of co-prescribed heroin plus methadone treatment was significantly more effective than methadone-only treatment for both the injectable and inhalable trial. Predetermined criteria had to be met for the response to be counted as effective, which in essence meant that there were considerable improvements in the area of physical and/or mental health and/or a substantial decrease in illegal activities, without any deterioration in other areas, such as increased cocaine use [18].
- Discontinuation of the co-prescribed heroin after 12 months resulted in a rapid deterioration in 82% of the participants who had responded to the treatment [18].
- In both trials, the incidence of serious adverse events was similar for the experimental and control conditions [18].

The risk that heroin prescription would not achieve positive outcomes, meaning that trials were not warranted, has therefore been shown to be without foundation.

Harm reduction through clinics, which required user attendance for each administration, was unworkable.

Although the context of heroin prescribing in the United Kingdom in the 1960–1970s was different from that pertaining to the more recent trials, an important lesson from the British experience was that lack of monitoring and enforcement could lead to over-prescribing by “the gullible, and the generous” [2, p. 9]. Further, over-prescribing by only a handful of doctors, under the normal arrangements for pharmaceuticals, where drugs were dispensed at a pharmacy and consumption was not monitored, could lead to significant diversion to other users [2].

As a consequence, there was general agreement that the best way for controlling prescription, dispensing and consumption was for all to be carefully monitored in a clinic-based system. Many argued that while this seemed ideal, it was unlikely to be workable. In particular, they claimed that a 24-hour service would have to be provided, otherwise users would not be maintained in treatment. It was also argued widely that (a) users would require ever-escalating doses of heroin and (b) providing only heroin would not be adequate to obtain positive effects, as most used a wide variety of illicit drugs.
A generally overlooked contribution of the Swiss trials is the development of a workable clinic-based system, which did not require 24-hour opening and which had high retention rates. The Swiss clinics generally opened for a few hours three times per day (morning, midday, late afternoon/early evening). Retention in treatment was relatively high, particularly as this was a group who had dropped out of treatment previously. A total of 86% (SE 0.8%) stayed for at least 3 months, 70% (SE 1%) stayed for at least a year, 50% (SE 1%) stayed for at least 2.5 years and 34% (SE 1%) stayed 5 years or longer.

Similarly, the Dutch clinics opened for 2- or 3-hour blocks at 8:30 a.m., 1 p.m. and 6 p.m. Retention rates in the Dutch trials were similar to those found in Switzerland with 72% of those receiving injectable heroin and 68% of those receiving inhalable heroin completing 12 months of treatment.

Both the Swiss and the Dutch trials showed that the doses prescribed could be stabilized successfully. In the Swiss trials, the average dose of injectable heroin was 474 mg (SD = 206 mg; median: 460 mg; 25th percentile: 340 mg, 75th percentile: 600 mg) [25]. As methadone was prescribed on an as-needs basis, this varied from participant to participant. Of average, participants received methadone on 50% of trial days; the average dose was 53 mg (SD = 44 mg; median: 40 mg, 25th percentile: 30 mg, 75th percentile: 75 mg). In the Dutch trials, where heroin was co-prescribed with methadone, the average daily heroin doses among treatment completers were 549 mg (SD = 193 mg) in the injecting trial and 547 mg (SD = 174 mg) in the inhaling trial. This was supplemented with average doses of 60 mg (SD = 17 mg) and 57 mg (SD = 18 mg) of oral methadone in the experimental groups of the respective trials and 71 mg (SD = 24 mg) and 67 mg (SD = 23 mg) in the control groups.

Finally, both trials showed that significant benefits could be obtained even though only one of the illicit drugs being used regularly was provided on prescription. For example, more than 90% of the participants in the Dutch trials had used (crack) cocaine on a regular basis in the years prior to the start of the trials. Among responders in the co-prescribed heroin condition, the average number of cocaine using days in the previous month decreased from 17 at baseline to 12 days after 12 months (injecting trial), and from 15 to 10 days (inhaling trial) [18]. Cocaine use was less prevalent in Switzerland, but reductions were still seen. In the first cohort, 32% consumed cocaine at baseline, and use was at least 10% lower at every follow-up, including the 6-year follow-up [20].

The evidence shows that a workable and successful clinic-based system can be developed. Affordability is discussed below.

**Heroin prescription could lead to more permissive attitudes towards illicit drug use**

Prescription of heroin and permissiveness towards illegal drug use are not linked inextricably. Indeed, permissiveness results from complex interacting factors, over which a trial can exert relatively little influence. Nevertheless, the way a trial is presented and discussed could potentially impact on community perceptions about permissiveness. This issue was addressed specifically in the Dutch trials where both the Health Council of the Netherlands and the Central Committee on the Treatment of Heroin Addicts (CCBH), which was responsible for the trials, communicated clearly from the start that there was a sharp distinction between the medical concept of “prescription”—where a medical doctor attempts to cure or alleviate the patient’s symptoms by means of medical treatment and on medical indication—and “free distribution” or any other form of legalization—where substances are provided without medical indication [26,27]. During the development and execution of the trials, messages in the media, which reflected the societal debate in the Netherlands, indicated that heroin prescription was generally perceived within the context of treatment specifically meant for methadone patients with serious health and social problems, and not as a legalization issue.

Similarly for the Swiss trials, the results of two referenda suggested that the general public made a clear distinction between medical treatment and legalization. In 1998 74% of the Swiss population voted against an initiative to legalize use of and to allow restricted access to currently illegal drugs. In 1999, 54% of voters supported the continuation of heroin-assisted treatment [10]. There had been even greater majority support for treatment in referenda held in various cantons before trials were started [28]. Another indirect indication is the use of and attitudes towards cannabis, the most commonly used illicit drug, among adolescents. In Switzerland, these have been parallel with major European and North American trends [29], and there is no indication that these attitudes were influenced by heroin-assisted treatment. Because the Dutch trials have been conducted more recently, comparable data are not yet available.

Both trials indicate that it is possible, in practice, to separate heroin prescription from general attitudes of permissiveness. However, neither the Swiss nor the Dutch undertook general population surveys on changes in attitudes towards illicit drug use during the trials, which could have provided additional information. Trends among Swiss high school students show more negative attitudes towards heroin. The issue of permissiveness is likely to continue to be important, so that governments and those involved in drug
treatment will need ongoing watchfulness about the messages being transmitted.

Dependent users from around the country and/or from neighbouring countries could move to the cities where heroin prescription is available.

A major concern of police was the so-called "honeypot effect", particularly if prescribing was poorly monitored and regulated. Certainly in the 1980s a small number of Canadian and US citizens had migrated to or visited the United Kingdom to receive prescription heroin [2]. To a large extent this risk can be controlled by careful attention to residency criteria, which was the case in both the Swiss and Dutch trials. In the Swiss trials, the Federal Office of Public Health required that those receiving heroin-assisted treatment had to be domiciled in the country for at least 1 year before being prescribed. Similarly, thecantons and communities had additional requirements with respect to their own population. Eligibility in the Dutch trials required participants to have been living in the Netherlands for at least 2 years and to be registered as residents in the city where the treatment centre was situated for a minimum period of 3 years [27,30].

There was no formal evaluation of a honeypot effect, but there was no indication in either country that one occurred. Indirect supporting evidence from Switzerland was that the proportion of foreigners in heroin-assisted treatment (13%) [31] was less than the corresponding proportion in the general population (17% in 1990 and 20% in 2000) [32]. It would seem, therefore, that the risk of a honeypot effect can be controlled.

Heroin prescription could reduce motivation to completely cease all heroin use and could institutionalize and further marginalize trial participants.

The concern here was that heroin prescription could provide an easy option, preventing those receiving such treatment from ever stopping heroin use. A further worry was that clinic attendance up to three times daily would make it impossible for participants to lead a normal life and would make them more dependent on the clinic and other helping institutions. Concerns about motivation and institutionalization were key in changing UK prescribing policy in the 1970s [3].

In the Swiss trials, more than 60% of those who left heroin-assisted treatment transferred to other forms of treatment, with 22% (n = 224) transferring to abstinence-based treatments. Those who stayed in heroin-assisted treatment for at least 1 year before leaving had a significantly higher chance of transferring to abstinence-oriented treatments compared to those leaving earlier [16]. Given that these participants had failed previously in the treatment system, the results are even more noteworthy.

Comparable data from the Dutch trials have not yet been analysed and a Dutch substudy of motivation to reduce or stop heroin and other substance use will also provide valuable information. It is also noteworthy that 16% of the participants who benefited from the heroin treatment ("responders") continued to do well in terms of health, social functioning and reduced criminal activities when heroin co-prescription was terminated as planned after 12 months. The Dutch trials focused on those otherwise unlikely to become abstinent, by restricting trial eligibility to those who had been heroin dependent for at least 5 years and excluding anyone who had been voluntarily abstinent for 2 or more months in the preceding year.

Measures of social functioning in the core trial evaluation of both the Swiss and Dutch trials showed that heroin prescription led to social integration rather than institutionalization and further marginalization, through increased contacts outside the drug scene, improved living conditions and reductions in illegal activities. It is also noteworthy that participants tended to visit the clinic less often than they were eligible to. Rather than three visits per day, Swiss trial participants tended to visit 2.6 times per day [25] and Dutch participants 2.1 times per day [18].

Again these potential risks have not been realized. Instead of leading to institutionalization or further marginalization in populations that are already marginalized, as in the Swiss and Dutch trials, heroin prescription improves social integration. In addition, results from both trials indicate that heroin prescription does not preclude eventual cessation of heroin use. It is worth noting that the achievement of abstinence is a poorly studied area and that no available treatment produces long-term abstinence in a large proportion of users. It is not currently possible to compare heroin prescription with other treatments in relation to abstinence.

Prescribing heroin could undermine other treatments by encouraging people to drop out in order to qualify for heroin. It could have opportunity costs, in particular it may be funded at the expense of other treatments and it may be unaffordable in the long term.

Restricting heroin prescription to those who have been unsuccessful in other treatments could make users more likely to drop out of other modalities. Some critics and treatment providers also worried that heroin might be trialled at the expense of other new treatments or thought that the money spent on heroin treatment would be better spent improving existing treatments. Finally there was a concern that heroin prescription would simply be too expensive.
The issue of dropout from other treatments to qualify for heroin prescription was not investigated in either the Swiss or the Dutch trials. The issue was obviated to some extent in the Dutch trials, as participants were eligible only if they were registered in a methadone programme in the preceding year and if they had been in regular contact with the methadone programme in the preceding 6 months [27,30].

None of the trials evaluated specifically the impact on other treatments. However, in Switzerland heroin-assisted treatment was introduced in circumstances of an overall expansion of the treatment system. Abstinence-oriented treatment and methadone maintenance treatment expanded to a proportionally larger degree than heroin-assisted treatment from 1994 onwards. At the same time, the estimated number of people dependent on opioids was stable, so that the proportion of dependent users in treatment increased. Further, there is evidence to suggest that the implementation of heroin-assisted treatment sharpened awareness regarding treatment standards and quality, with positive spin-offs for other forms of treatment, particularly remedying deficiencies in the methadone treatment system [33,34].

In the Netherlands, the costs of co-prescribed heroin treatment were found to be strongly dependent upon the type of treatment implementation. The total costs of treatment, embodied in the special treatment centres established for the scientific trials, were estimated to amount to €15 000 per patient per treatment year for a unit with a capacity of 75 participants and up to €27 000 for a 25-patient unit [18].

A cost–benefit analysis of the Swiss studies showed a considerable reduction in costs for medical care and, in particular, law enforcement; the benefits per day amounted to twice the daily treatment costs [21,22]. Outcomes of cost-effectiveness and cost-benefit analyses for the Dutch trials are not yet available.

The effect on treatment dropout of restricting heroin prescription to those for whom other treatments have been unsuccessful warrants further investigation. Although the factors influencing the effect of heroin prescription on national drug treatment policy are complex and outside the control of those providing heroin treatment, the Swiss experience shows that introducing heroin prescription can occur in, and even help stimulate, a context of overall improvement in the treatment system. Finally, heroin prescription is expensive. The results from the Swiss trials suggest that the benefits of heroin prescription considerably outweigh the costs, but further cost-benefit and cost-effectiveness analysis is needed. This includes assessment of the cost-effectiveness of other forms of treatments for the same patient group.

Heroin prescription could make law enforcement more difficult by blurring the differentiation between lawful and unlawful heroin use or by allowing justification of crimes committed under the influence of heroin prescription.

These concerns were raised by police. While these issues were not part of the specific evaluation of either the Swiss or Dutch trials, there were no indications in either country that such blurring or justification occurred. In both countries heroin prescription led to marked reductions in criminal behaviour, as measured by both self-report and police records [18,35]. This overwhelmed any other potential effects on law enforcement.

Prescription heroin could be diverted onto the illegal market

As outlined earlier, one of the attractions of prescribing heroin in a clinic-based system is that it potentially makes diversion easier to control. The three possible sources of diversion are participants, staff and outsiders through break-ins or robbery.

A number of measures were taken to prevent diversion in both the Swiss and Dutch trials. Only a limited number of participants were allowed into the injecting (and in the case of the Dutch trials, inhalation) rooms at any one time and they were observed carefully. This number varied from centre to centre, but in the Dutch trials was 5–6 participants. In addition, there were tight accounting and security procedures for the heroin from manufacture to dispensing. In the Dutch trials the clinics employed security guards to monitor those entering the clinics. In Switzerland, no diversion of injectable heroin was reported in more than 7 years of heroin-assisted treatment. In both the Swiss and Dutch trials the penalty for attempted diversion by participants could be exclusion from heroin treatment. In the Dutch trial no aberrations were found in the accounting process. In addition, a total of 50 attempts by participants to take small amounts (in all cases smaller than the participant’s daily dose) of prescription heroin out of the unit were intercepted. These attempts should be seen in context, namely that approximately 140,000 heroin doses were dispensed to more than 300 participants over a period of 3 years.

It can be concluded that effective procedures to prevent heroin diversion can be enacted.

Road safety may be compromised by prescription recipients driving under the influence of heroin

There is little conclusive evidence about the effects of opioids on driving skills, although a review by Cheek [36] suggested they were slight, especially when compared with alcohol and benzodiazepines. Never-
theless, this was an issue of concern from both law enforcement and public health viewpoints.

In the Swiss trials participants were required to relinquish their drivers' licences, which were held by the treatment centre for the duration of the treatment. If participants did not comply, the driver's licence could be revoked by Swiss law. While this does not necessarily prevent participants from driving without a licence, no deaths were reported and there were few accidents noted in the monitoring system on adverse events, which was initiated in September 1997. In particular, from 1997–2002, there were three reports of accidents with motorized vehicles, all with motorbikes, and none with cars. There may have been an increase in bicycle accidents, but there are no clear comparison data.

In the Netherlands, a controlled clinical side-study investigated the bioavailability and pharmacodynamic effects of inhaled heroin [37]. A 50-mg dose (one-fifth of the average treatment dose) produced a decline in reaction times, as reported to that of 0.7% of alcohol [38]. The decline was identifiable 25 minutes following the start of heroin inhalation, reached its maximum after 25–60 minutes, and then returned to normal in the following hours. This strongly suggests that heroin prescription is likely to affect driving skills.

On the basis of these results, firm advice on traffic precautions was given to participants in the main trial. As in the Swiss trials, serious adverse events were monitored and only one of possible relevance occurred during the 12-month experimental study period, where a patient was found wandering in traffic in a confused state.

Further research is needed to assess the impact of heroin on driving and other motor and perceptual skills, as there may be a significant risk here for heroin prescription. It is possible that this risk could be effectively managed by individual titration of heroin doses, but this needs further investigation. The risk may also be able to be minimized where effective public transport systems are available, although such systems do not exist in all countries.

**Heroin prescription could increase "public nuisance" through participants congregating outside clinics or by leading to violence between those who were and were not successful in obtaining a treatment place**

These risks were not specifically assessed in the Swiss trials, but there was no evidence to suggest any significant public nuisance. If there had been, it is unlikely that the referendum to continue heroin-assisted treatment would have been successful [10]. The likelihood of violence between those who were and those who were not successful in receiving a treatment place was minimal, as treatment places were generally not limited.

In the Netherlands, adverse events in the area of public order and controllability were monitored. There were a total of 191 events within the treatment units, mainly of verbal aggression towards the treatment-staff. There were 28 events outside the clinics where the individuals involved were not identified; of these 20 were complaints from residents living in the neighbourhood of treatment centres. None of these events was classified as severe.

Unfortunately, there seems to be little comparative information about public nuisance associated with other forms of drug treatment and with non-drug treatment facilities. Nevertheless, it seems that public nuisance associated with heroin prescription is low and manageable.

**There could be problems for babies born to women receiving heroin prescription**

Little is known about the effects of heroin on fetal or subsequent development. For babies born to women who use heroin illegally examination of the effects is confounded by the lifestyle of their mothers, which may include other drug use, inadequate nutrition, widely fluctuating blood levels of heroin, other health problems and poor pre- and post-natal care.

There were 12 pregnancies in the Swiss heroin-assisted treatment trials between 1994 and 1996 [39]. Four of the women were transferred to institutional treatment with oral methadone, one gave up heroin treatment 4 months before the birth of the baby and the rest were continued on heroin treatment. The women were generally in poor health. All had hepatitis B, all but one had hepatitis C, two were HIV positive and the majority had mental health problems (depression, eating disorders and personality disorders). There were eight live births, three terminations and one spontaneous abortion during heroin withdrawal in the third month of pregnancy. The abortion may be explained by opioid-induced contractions of the uterus [40]. There were no other complications during the course of pregnancy or at birth. The children had no malformations. All children were underweight and in the smallest 10th percentile of birth weights. There were no reports of sudden infant death syndrome (SIDS). These results are similar to those for women receiving methadone maintenance treatment [34].

In the Dutch trials, pregnancy or breastfeeding were among the exclusion criteria at study entry. Women trial participants were tested for pregnancy every month, with the intention of referring any who tested positive to a general practitioner or gynaecologist for
further prenatal care. No such referrals were necessary.

Further research on the effects of heroin on fetal and subsequent development is warranted, but again there are no indications of substantial risk.

Conclusions

Overall, the results of the Swiss and Dutch trials suggest that fears about potential risks of heroin prescription were largely unfounded and that many potential risks can be minimised through prudent measures. However, a less cautious attitude could see an increase in negative effects and we recommend ongoing attentiveness to possible risks.

Certainly risks cannot be eliminated entirely, and there are two different positions which influence approaches to possible problems [41]. Some argue for a voluntarist approach, which judges the harms caused by an intervention in light of harms that would have occurred had there been no intervention. Using such an approach, the problems associated with heroin prescription are less than when heroin is used illegally. Others argue for a deontological approach where any harm resulting from an intervention is problematic, even if similar or greater harms might otherwise have happened. Even using this approach, the problems associated with heroin prescribing would seem to be minor.

Research trials of heroin prescribing provide opportunities to learn more about this drug and we recommend further investigations of effects on skills relevant to driving and on fetal development, in particular. Ongoing and new trials also provide opportunities to shed light on other potential risks, such as long-term effects on abstinence, the cost-effectiveness of different approaches to clinic-based prescribing and comparisons with other treatment options.

The Swiss government has decided to continue heroin-assisted substitution treatment for dependent heroin users refractory to other treatments. In 2001, about 1200 participants were in this form of treatment, compared to around 18,000 in methadone substitution treatment [42], less than 1000 in buprenorphine substitution treatment and about 1700 in abstinence-based treatment [43].

At the beginning of 2002, the CCBH recommended that the Dutch government introduce medical co-prescription of heroin, under stringent conditions, to chronic treatment-resistant methadone patients as a last-resort pharmacotherapy. However, political instability, leading to two general elections, has prejudiced consideration of this recommendation. Currently, political support is limited to continuing the existing treatment capacity in the six established heroin treatment centres.

References


Appendix 6: Consultations and acknowledgements

We consulted individuals and staff from agencies as listed below. We thank them all for their very valuable input into this report.

*The staff of the following agencies*
Alcohol and Drug Program, Community Health, ACT Health
Australian Injecting and Illicit Drug Users’ League
Canberra Alliance for Harm Minimisation and Advocacy staff and clients
The Opiate Project Nurses, ACT Division of General Practice

*Individuals*
Professor Paul Arbon, University of Canberra and The Canberra Hospital
Two ACT General Practitioners
Dr James Bell, The Langton Centre, Sydney
Professor Frank Bowden, ANU Medical School and The Canberra Hospital
Professor Nick Buckley, ANU Medical School and The Canberra Hospital
Ms Colleen Duff, Secretary, Australian Nurses Federation, ACT Branch
Ms Andrea Coss, Australian Federal Police
Dr Benedikt Fischer, Centre for Addiction and Mental Health, Ontario, Canada
Dr Anne Gardner, University of Canberra and The Canberra Hospital
Professor Nick Glasgow, Australian Primary Health Care Research Institute
Dr Geetha Isaac-Toua, NCEPH, ANU
Dr Nick Lintzeris, National Addiction Centre, London
Ms Colette McGrath, RN, The Medically Supervised Injecting Centre, Sydney
Ms Nikki Main, former clinical trials research assistant, NCEPH, ANU
Dr Juergen Rehm, Centre for Addiction and Mental Health, Ontario, Canada

We also acknowledge with thanks the support of the staff of the National Resource Centre, Alcohol and other Drugs Council of Australia, and the contribution to report preparation made by our NCEPH colleagues, Ms Ros Hales and Ms Olivia Harkin.
Appendix 7: Trial design considerations

A core finding of the feasibility research is that the ACT does not currently have structures in place that easily accommodate clinical trials of new treatment options for drug dependence. Nevertheless, successful trials have been undertaken in the last five years examining buprenorphine and naltrexone, both of which have become standard treatment options. We recommend that the hydromorphone trial emulates the critical success factors from those trials. The first is to undertake the trials in partnership with outside experienced clinician-researchers and to continue to build ACT clinical research capacity in the field of drug dependence. The second is to provide resources for adequate preparation for the trials.

Based upon our consultations with a range of stakeholders, including drug user representatives and health research colleagues who are also experienced in this field of study, we identified a number of options for an ACT hydromorphone trial. In considering their feasibility and appropriateness we assessed each option taking into account the current state of knowledge about the use of hydromorphone, the characteristics of the potential participants, clinical service delivery issues, trial evaluation issues, ethical issues and likely financial costs. The options identified are as follows:

**Option 1:** A preparatory phase followed by three small Phase II clinical studies to assess the safety and feasibility of hydromorphone prescription in combination with oral methadone maintenance treatment, whether hydromorphone-supplementation or enhanced methadone treatment are effective and cost-effective in improving outcomes for the small but significant group of methadone maintenance clients for whom existing treatment is not optimal, and if illicit heroin use can indeed be detected in people receiving hydromorphone and methadone.

**Option 2:** A full Phase III randomised controlled clinical trial comparing, among people who are opioid dependent, oral methadone maintenance treatment with an expanded service that includes injectable hydromorphone in addition to methadone.

Consideration was also given to studies assessing the feasibility of providing, among people who are opioid dependent, injectable hydromorphone alone as maintenance therapy, and studies which would assess the results of administering a single daily dose of hydromorphone in people who are opioid dependent. These approaches were rejected as less appropriate owing to the current gaps in knowledge about hydromorphone maintenance.

*We have concluded that Option 1 (above) is the most appropriate place to start for the following reasons:*

- Insufficient is known about injectable hydromorphone and nothing about it as an opioid substitution therapy, meaning that it is premature to proceed directly to a full randomised controlled trial of the drug.

- Although some people urged us to recommend a trial of maintaining people on hydromorphone alone, we rejected this since oral methadone maintenance works well for a significant proportion of opioid users and is widely accepted by them. Accordingly, an approach which reflects that used in the heroin trials is better, namely one in which participants are offered injectable hydromorphone to supplement (rather than replace) their oral methadone, with the capacity to switch between various doses of both drugs (subject to safety considerations) as participants and their supervising doctors feel the need to do so. We anticipate that many participants would like to inject hydromorphone during clinic opening hours and to use methadone to prevent the onset of withdrawal, for example overnight.

- At this stage, insufficient is known about hydromorphone as a maintenance therapy to offer participants who are opioid dependent just a single daily dose of hydromorphone without any other opioid medication.
• The new knowledge gained from the small studies identified as Option 1 would form the basis for decision-making on a larger controlled trial comparing treatment incorporating hydromorphone to other treatment regimes.

It is recommended, then, that the trial be a cautious examination of the use of prescribed injectable hydromorphone in people who are opioid dependent, assessing concerns such as the following:

• the practical feasibility of recruiting trial research and participant care staff and undertaking service delivery including managing participant throughput
• can people be safely stabilised on a hydromorphone/methadone combination, if so at what levels and frequency of dosing
• impacts on psychomotor performance
• what inclusion/exclusion criteria work best
• the likely demand for hydromorphone as an adjunct to methadone maintenance treatment
• the service’s capacity to attract and retain people in treatment
• participants’ subjective assessments of the characteristics of hydromorphone/methadone combinations, and how they compare to illicit heroin
• what types of participants seem to be most attracted to and retained in treatment incorporating hydromorphone
• what outcome measures work well with this population,
• any differences in outcomes and cost effectiveness from methadone treatment supplemented by hydromorphone compared with an enhanced treatment regime
• cost-effectiveness of the different treatment options, and
• the financial costs of the service.

The overall goal should be to move towards a position where we can systematically ascertain if the current oral methadone maintenance programs can be usefully supplemented by making hydromorphone available as well. Before we can conduct research to address this question directly, however, we need to gain more knowledge than we have now about the safety and practical feasibility of providing injectable hydromorphone as a component of maintenance therapy.

A staged approach

The study will be in two stages over a nine-month period. It will entail a preparatory phase followed by three small Phase II clinical trials.

The preparatory stage will last six months. During this time the trial premises will be identified, acquired and equipped; the ACT Epidemiological Studies (Confidentiality) Regulations will be amended to cover the study; policies and research protocols determined; details of the trial evaluation settled; applications made to Human Research Ethics Committees; and staff will be recruited and trained.

We anticipate that a number of challenges will have to be overcome in this phase. Finding suitable senior research staff is always difficult in the small Canberra research community. Both a research team leader and a senior medical practitioner responsible for prescribing and participant well-being will need to be identified and recruited. (One person could potentially fill both roles.) The local and nation-wide shortage of nursing staff will also present recruitment challenges. Furthermore, not having a dedicated alcohol and other drugs clinical research facility in Canberra means that facilities designed for other purposes will need to be identified and, possibly, modified to meet the needs of the trial.
Three small Phase II clinical trials will be conducted over nine months.¹ On the basis of previous experience with trial drop-out, we expect to recruit around 50 participants, of whom 24 will complete the relevant research program.

- **The first trial** will focus on dose-ranging. Eight people currently receiving methadone maintenance treatment and concurrently using street heroin daily or almost daily will be offered a daily dose of hydromorphone to supplement their prescribed methadone. The researchers will develop knowledge on how to administer injectable hydromorphone alone and in combination with oral methadone, assessing safety considerations and side-effects. The hydromorphone doses will be gradually increased with the aim of identifying levels that are both safe and prevent the development of uncomfortable withdrawal signs.

The starting point for this trial will be what is already known about the use of hydromorphone for analgesic purposes, especially among people with well-developed tolerance to opioid analgesics. The new knowledge will be about the use of hydromorphone as a component of opioid substitution therapy, rather than as an analgesic.

The research questions for this trial will be:

- Can the addition of injectable hydromorphone to maintenance treatment for dependent heroin users be undertaken successfully on a small scale in the Canberra context?
- Can dependent heroin users be safely stabilised on injectable hydromorphone plus oral methadone in such a manner that they do not experience either over-sedation or opioid withdrawal?
- What are the optimal hydromorphone dosage ranges for use in combination with oral methadone?

- **The second trial** will use a prospective cross-over design. This has been defined as:

  a method of comparing two or more treatments or interventions in which the subjects or patients, upon completion of the course of one treatment, are switched to another. In the case of two treatments, A and B, half the subjects are randomly allocated to receive these in the order A, B and half to receive them in the order B, A (Last 1988, p. 32).

Eight trial participants will be allocated to receive standard methadone maintenance treatment supplemented by hydromorphone and another eight will receive a methadone maintenance regime that is enhanced by providing additional case management support, as well as review of their methadone dose (but they will not receive hydromorphone). After four weeks those in each arm will switch to the other arm. In this design, each participant is her or his own control. Further, individual results are also compared to pre-trial measures. At the conclusion of the trial, participants will be assisted to return to the standard treatment regimes appropriate to their needs.

The trial outcomes will be assessed using a number of biomedical tests and interviews using the Opioid Treatment Index (Darke et al. 1991), assessing participants’ physical and mental health, criminal behaviour and recent drug use. Their subjective perceptions of hydromorphone will also be assessed, and the clinical service delivery processes will be studied.

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¹ As discussed in Appendix 1, a Phase II trial may be defined as follows:

‘The first trials of the drug in patients suffering from the disorder for which the drug is intended. The purpose of these trials is to determine efficacy and safety in a small number of closely supervised patients. The trials are usually conducted by investigators regarded as specialists in the particular disorder and its treatment. Several doses of the drug are often used to establish the therapeutic range and the maximum tolerated dose.’
The research questions for this trial will be:

- Does methadone treatment supplemented by daily hydromorphone or enhanced methadone treatment reduce illicit heroin use among methadone patients?
- Is methadone treatment supplemented by daily hydromorphone more cost-effective than enhanced methadone treatments?

The third trial will assess whether or not it is feasible (in practical and financial terms) to identify concurrent heroin use among trial participants, using urinalysis. This will take place concurrently with the first two trials.
- Can concurrent illicit heroin use be detected in people receiving injectable hydromorphone?

A follow-up period of three months to monitor trial participants will be needed. The main purpose of this stage is to identify and assist with any problems participants have in reverting to the post-trial treatment regimes, and the nature of their transition to the use of other drugs including prescribed maintenance therapies, and illegal opioid use.

Trial participants

Inclusion criteria

It is recommended that the trial participants are people receiving methadone maintenance treatment who are not doing well in treatment, as indicated by daily or near-daily use of heroin as well as prescribed methadone. They will be recruited from the Canberra methadone maintenance program, including clients of ACT Health’s public clinic and of private medical practitioners. Preference will be given to people whose methadone doses are still relatively low, i.e. 20 to 60 mg per day. Trial participants will have to have been on the ACT methadone program for a minimum of six months to be eligible to enrol in the trial.

Since part of the underlying rationale for prescribing injectable hydromorphone is that it will cause a reduction in their use of illegal heroin, participants should also be current heroin users as well as registered methadone clients. Their concurrent use of heroin will be assessed initially by reports from trial applicants themselves and their methadone prescribers. Research evidence indicates that most people who stay on methadone for an extended period (particularly over six months) benefit greatly from the treatment (Ward, Hall & Mattick 1998). Some methadone program clients, however, do not do well on the program and continue to use heroin. The study will assess the degree to which it is possible to substitute, in this group, prescribed hydromorphone for street heroin.

Yet to be published ACT research data, kindly provided by Dr Geetha Isaac-Toua, assists in estimating the potential number of trial participants when these criteria are applied. In a study of 60 methadone clients, Isaac-Toua found that 8 (13 per cent) reported using heroin daily or almost daily. All had been in methadone treatment for over six months and 7/8 received daily doses of methadone in the 20-60 mg range. Since the ACT methadone program currently has approximately 650 clients, we estimate that some 87 clients would meet the eligibility criterion of concurrent heroin use, a large enough pool of potential trial participants for the trial to be viable.

Where couples are current methadone and/or heroin users, the couple could apply to be admitted to the trial together to avoid having one member receiving prescribed hydromorphone but not the other.
Exclusion criteria
Detailed inclusion/exclusion criteria for participation in the trial will need to be established. Useful
guidance is provided in a publication of the UK National Health Service’s National Treatment Agency
(2003, pp. 22-23). The following exclusion criteria are suggested as a starting point:

- unwillingness or inability to comply with the trial protocols, including providing informed
  consent
- age less than 18 years
- inability to safely self-administer the injectable hydromorphone owing to inadequate venous
  access in relatively low-risk sites
- concurrent dependence on or regular problematic use of alcohol, benzodiazepines, stimulants or
  sedatives
- disabling psychiatric symptoms
- active medical treatment (except for hepatitis C where participants have normal livers)
- pregnancy
- breastfeeding.

Termination criteria
A participant would be terminated from the trial if one or more of the following criteria were met:

- the participant had an adverse response to hydromorphone
- the participant becomes pregnant
- administrative discharge for non-compliance with trial protocols
- voluntary discharge.

The trial as a whole would be terminated if several participants experienced severe adverse responses to
hydromorphone.

Ethical issues
The study will need ethical coverage from the Human Research Ethics Committees of ACT Health (in
whose facilities the trial will be conducted) and the research institution responsible for trial evaluation.
The dominant ethical issues will be:

1) ensuring, as far as possible, the safety of trial participants and staff; and
2) ensuring that trial participants provide fully informed consent to participation.

Related issues include the fairness of the recruitment process, the confidentiality of documentation,
creation of the expectation of a ‘miracle cure’ and resulting disappointment among current heroin users,
and meeting the treatment and other needs of participants once the trial ends. It would be desirable if the
Legislative Assembly amended the regulations to the ACT Epidemiological Studies (Confidentiality)
Act to provide legal protection to trial participants and researchers.

Legal and policing issues
The civil and criminal liability issues associated with this type of trial, in the Australian context, were
canvassed in our feasibility research for the Australian diamorphine trial (Bronitt 1995; Cica 1995). No
serious impediments to conducting the hydromorphone trial exist in these domains.
An issue that touches on public safety/policing considerations is the fact that opioids, such as hydromorphone and methadone, depress the functioning of the central nervous system with the result that psychomotor functioning may be impaired. This can, in turn, mean an elevated risk of road crashes or injury from using machinery after people consume these drugs. The liability issues in this area were systematically canvassed in the papers cited above. Appendix 2 cites research evidence indicating that psychomotor impairment from hydromorphone is minimal among people who are opioid tolerant.

The security of stocks of hydromorphone will need to be ensured. It is classified as a Schedule 8 drug, and medical and nursing personnel are familiar with the safe storage regulations that apply to this class of controlled drug. Protocols will need to be in place to ensure that the drugs are not diverted.

A potential exists for illicit drug dealing in or close to the clinic dispensing hydromorphone. The issues here are the same as for existing methadone outlets; a protocol for preventing and responding to such incidents will be needed.

The designers of the various diamorphine trials were conscious of the possible ‘honey-pot effect’ of prescribed diamorphine: the potential for drug users and/or dealers to be attracted from elsewhere to the city where the drug was prescribed. The likelihood of this occurring is far less in the case of hydromorphone than diamorphine but nonetheless needs to be taken into consideration in deciding upon the trial inclusion criteria. To address this, we have recommended, above, that trial participants would need to have been clients of the ACT methadone program for six months prior to the trial.

Appendix 5 deals with these issues in more detail.

**Trial outcomes and subsequent action**

Two main outcomes of these studies can be identified. The first is the creation of new knowledge about hydromorphone as a maintenance therapy in people who are opioid tolerant. This will be a substantial contribution at the local, national and global levels owing to the widespread interest among opioid users, clinicians, researchers and people responsible for treatment resource allocation in learning more about hydromorphone and its potential roles role in increasing the range of treatment options available, and attracting new drug users into treatment.

Secondly, they would provide a firm basis for moving to a Phase III clinical trial that would systematically ascertain if the current oral methadone maintenance programs can be usefully supplemented by making hydromorphone available as well. A pilot study, entailing randomisation, with perhaps 40 participants and funded by the ACT Government, would be a useful intermediate stage between the Phase II studies recommended above and a full-scale Phase III randomised clinical trial. Undertaking such a pilot study would strengthen a case for NHMRC funding which could be in the vicinity of $1 million for a three-year study. This cost could be substantially reduced if structures for a clinical trials capacity were established in the ACT.

As noted above, the ACT does not have the drug dependence clinical research infrastructure needed for such a trial. Accordingly, we recommend that the ACT plan for a clinical trials capacity in the alcohol and other drugs area that is integrated with treatment service provision, along the lines of successful models in Victoria (Turning Point Alcohol and Drug Service Inc) and New South Wales (The Langton Centre).

**References**

Bronitt, S 1995, *Criminal liability issues associated with a ‘heroin trial’*, Feasibility Research into the Controlled Availability of Opioids Stage 2; working paper no.13, National Centre for Epidemiology and Population Health, The Australian National University and the Australian Institute of Criminology, Canberra.

Cica, N 1995, *Civil liability issues associated with a ‘heroin trial’*, Feasibility Research into the Controlled Availability of Opioids Stage 2; working paper no.11, National Centre for Epidemiology and Population Health, The Australian National University and the Australian Institute of Criminology, Canberra.


Appendix 8: Options for clinical service provision

Venue

We explored several possibilities for a venue for the trials. Those listed below are all feasible but require further investigation, once the go-ahead for a trial has been received.

The Alcohol and Drug Program, The Canberra Hospital

In the first instance we were interested to see if it would be feasible to run a trial through the Alcohol and Drug Methadone Program situated in Building 7 in the grounds of The Canberra Hospital. Alcohol and Drug Program personnel we consulted believed that the current service did not have the capacity to run a hydromorphone trial since staff at all levels were already over-committed.

Users we spoke to had several concerns about this possibility. They believed that it would be necessary to run a trial separately from the methadone clinic since there might be problems with people being dispensed methadone and people being dispensed hydromorphone in the clinic at the same time. All users spoke of the need for a more central location (than the Alcohol and Drug Program at Woden), especially if it was necessary for participants to attend the clinic more than once a day, in particular those who had transport problems.

Despite these reservations and current capacity issues, we note that the Alcohol and Drug Program was the venue for the successful buprenorphine and naltrexone trials.

Other venues at The Canberra Hospital

We also explored the possibility of other venues at The Canberra Hospital. It was pointed out to us that there are already some out-patient drug trials running, and that there is a clinical trials unit at the hospital. It may also be possible to run a trial through an out-patient department, which already has clients who are injecting drug users.

Moore Street Health Building

Some respondents mentioned the Moore Street Health building as a possible venue since it is close to the bus Interchange and also has reasonable parking. One user was concerned about Civic because of the police cameras situated in the area.

Other Community Health Services

Other respondents thought one of the Community Health Service buildings might be suitable. They amplified this by noting the advantages of this option; such as gateway services for participants, many Community Health Services being close to transport services and the economic advantage of utilising existing buildings.

General Practitioner location

We briefly investigated the possibility of running a small trial through a General Practice. One way to do this would be to have a large number of practitioners each with a very small number of clients; another would be to have one practice willing to run a clinic.
Issues and challenges

Clinical staff

Prescribers

Prescribers would be responsible for a range of issues, including:

- developing a detailed trial protocol;
- assessing clients;
- prescribing hydromorphone and other drugs;
- making decisions about hydromorphone doses for clients who had missed one or more doses;
- referring participants on to other services;
- conducting frequent client reviews;
- in case of emergencies (such as hospitalisation of a trial participant), a prescriber would need to be on call 24 hours a day. Even with a small trial, more than one prescriber would, therefore, be required.

The possibilities for prescribers are listed below.

- Alcohol and Drug Program medical staff.
  Given the current shortage of staff in the Alcohol and Drug Program it may not be feasible for prescribers from that service to be involved.

- Medical school.
  It is likely that a suitable prescriber could be found from within the ANU Medical School. Assoc Prof Nick Buckley has expressed an interest.

- Prescriber/s from one of the general practices.
  We have consulted two general practitioner prescribers, one of whom may be interested in being a prescriber for a trial. Further investigation is required.

The ACT prescribers would most probably benefit from expert advice from opioid clinical trial prescribers, particularly those who have been instrumental in previous ACT trial research: Dr Nick Lintzeris (the National Addiction Centre in London) and Dr James Bell (the Langton Centre, Sydney).

Nurses

Nurses would be required to have a range of skills and undertake a range of tasks, including:

- have recent resuscitation training;
- be able to properly assess clients who are in danger of overdosing and, where necessary, be able to judge the appropriate time at which to administer Narcan;
- be experienced in assessing intoxication (particularly opioid, alcohol and benzodiazepine intoxication);
- be experienced in issues related to injecting drug use;
- be skilled in the relevant clinical competencies required for the trial (such as venipuncture [obtaining blood specimens], taking ECGs, etc);
- be fully conversant with safe injecting techniques and have the ability to appropriately educate clients who do not practice safe injecting techniques (see below);
- be aware of issues related to Occupational Health and Safety (in particular, proper disposal of used injecting equipment);
• have an attitude appropriate for working with people who inject drugs;
• be skilled in case management (for the enhanced methadone treatment arm of the second trial)
• be authorised by law to observe people injecting a schedule 8 drug.

The possibilities for nursing staff are:

• Nurses currently employed in the Alcohol and Drug Program
  Given the previous positive experiences of nurses involved in the previous ACT trials, it is possible that some nurses currently employed in the Alcohol and Drug Program might wish to be involved in the research. The current nursing capacity in the Alcohol and Drug Program would not, however, allow for an increased workload.

• Hospital nurses
  If a trial was to run from within the hospital, it may be possible to recruit nurses from the hospital in a nurse/researcher role.

• Community nurses
  It is possible that there are some Community nurses who would want to be employed for the duration of the trials.

Identifying and recruiting participants

The trials will be for people on prescribed methadone and who by self-identification, and verification by their prescriber, are also injecting heroin on a daily basis. Recruitment will be through the Alcohol and Drug Program and private prescribers.

Payment

It is not usual for people trialling new pharmacotherapies to pay pharmaceutical or other service costs related to the trial. We would also recommend this for the hydromorphone trials.

Opening times

Most people we interviewed suggested an early morning and a late afternoon/evening session.

We recommend two opening sessions. The first, a morning session from 7.30 to 10.30 am and the second, a late afternoon session from 3pm to 5pm.

**First session**

During the first session participants will be given their hydromorphone, the self-administration will be observed by nurses, and participants will be observed by a nurse for at least half an hour after injecting. During this period, assessments (such as blood pressure measurements, ECGs and oxygen levels) will be undertaken by clinical staff. Blood and urine specimens may also be obtained. Dispensing will cease half an hour before the second session ends to allow time for observing clients post-injection.

**Second session**

In the second session, clients will be given their usual dose of methadone and other general nursing services will be provided.

Time participants would need to spend in the clinic

As a basis for estimating the period of time participants would need to spend in the clinic we looked at the time clients spend in the Medically Supervised Injecting Centre in Sydney. The average time clients
spent at the Medically Supervised Injecting Centre during its trial was 28 minutes: two minutes (or less) in reception, 12 minutes in the injecting room and 14 minutes in the after care area.²

Some participants will be able to inject their hydromorphone quite quickly but if there are difficulties in finding a vein this period of time may be quite extensive.

Participants will need to spend at least half an hour in the clinic post-injection to ensure their safety when the hydromorphone dose peaks.

Overall then, the period of time participants will spend in the clinic will range from a little over 30 minutes to perhaps as long as an hour. If client observation to ensure safety has not been completed by clinic closing time, the best option may be to admit them to the Accident and Emergency department for observation. This will need to be more fully explored in the trial preparatory phase.

Injecting technique

Several people we spoke with mentioned the need for nurses to ensure that participants are practising safe injecting techniques and, if they are not, to educate them to do so.

Potential adverse consequences.

**Overdoses**

The most serious potential adverse consequence of injecting opioids is an overdose, particularly if clients have recently consumed other drugs (in particular, other opioids, alcohol or benzodiazepines).

As part of the pre-trial screening, participants will be advised that they should not take other drugs that may potentiate the effect of hydromorphone, particularly before they receive their dose. They will also be advised they will not be allowed to bring in, or administer, other drugs in the clinic.

Introduction to hydromorphone must be carefully staged with experienced medical personnel incrementally prescribing safe doses.

As reported above, nurses dispensing hydromorphone must be skilled in assessing clients for signs of intoxication and have the appropriate skills to assess if clients have brought any drugs in with them. Nurses with experience in drug and alcohol work are already skilled in these assessments.

Participants will be observed during their time in the clinic to ensure they do not take other drugs with, or after, their hydromorphone.

As already indicated, clients will be required to spend at least half an hour in the clinic post-injection.

If the trials were to be conducted within the Alcohol and Drug Program or hospital setting, resuscitation equipment is already available but if the trial were to take place in a Community Health Setting or General Practice, resuscitation equipment would need to be provided as part of the trial.

In whichever venue the trial takes place there would need to be processes in place to allow nurses to administer Narcan to people who do not respond to initial resuscitation (oxygen provided by an Ambubag).

In case further resuscitation measures are required, as part of the pre-trial planning the ambulance service (as well as Accident and Emergency departments) should be informed of the forthcoming trial.

**Arterial bleeds**

An arterial bleed might occur following accidental injection into an artery. Nurses must be trained to deal with this potential adverse consequence.

**Vomiting**
One of the people we consulted believed that the potential for vomiting (which commonly occurs after opioid administration) might be accentuated when participants were experiencing the effects of a new opioid. Antiemetics will be available to deal with this eventuality.

**Safety and security**

**Security guard**
If the trial were to be run in a Community Health Centre or General Practice, a security guard would probably be required.

**Duress alarms**
All staff involved with clients should carry a Duress alarm.

**Storage of drugs**
If the trial were to be run through the Alcohol and Drug program there is already a secure system for storage of Schedule 8 drugs. If the trial were to be run in a Community Health Centre, General Practice, or in The Canberra Hospital, there would need to be proper storage for trial drugs.

If the trial were to be run through the Alcohol and Drug Program or the Canberra Hospital, there would be fewer concerns around security issues.

**Driving and employment**
Potential participants will be informed that they should not drive when they leave the clinic.

Occupations of potential participants will be ascertained. Those working in industries that involve them, for example driving, operating heavy machinery, or climbing will not be eligible for trial participation.
Appendix 9: Budget details

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Researcher/Clinician six months full time for trial preparation</td>
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<tr>
<td>Researcher nine months full time</td>
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</tr>
<tr>
<td>Senior trial doctor</td>
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<tr>
<td>Nursing staff</td>
<td>$104,000</td>
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<tr>
<td>Airfares, salary replacement and per diem for experienced clinician-researcher advisors</td>
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**Research costs, consumables, equipment, tests, etc**

<table>
<thead>
<tr>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research costs</td>
</tr>
<tr>
<td>Urinalyses, blood tests and disposables</td>
</tr>
<tr>
<td>Hydromorphone and methadone</td>
</tr>
<tr>
<td>Furniture and equipment, including ECG and PO2 monitors</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

This budget is based on the trials being conducted in a hospital setting. If the trials were conducted in a community clinic or private setting, we estimate that an additional $20,000 would be required to cover resuscitation equipment and various security measures.

We were unable to determine exactly where the trials would be conducted, so could not ascertain if refurbishment would be required or budget for it.

We anticipate that the clinical staff will be employed by the ACT government and the researchers by a University, so that additional insurance would not be necessary.

**Personnel**

*Researcher/ Clinician six months full time for trial preparation*

This person will be employed for six months prior to commencement of the trial to address the issues outlined in Appendix 8. This costing is based on ANU Research Fellow Level B and includes on-costs.

*Researcher nine months full time*

The researcher will be employed for nine months: the three months of the trial, three months for follow up of participants and three months for data analysis and report writing. This costing is based on ANU Research Fellow Level B and includes on-costs.

*Senior trial doctor*

A senior trial doctor will need to be employed part-time for the three months of the trial, as well as a two-week training period. It is not expected that a doctor would be in the clinic during all of the opening sessions, but a senior physician involved with the trial would be required to be on call in case of medical emergencies for its duration. The costing is based on Career Medical Officer Level 3.

*Nursing staff*

Three nursing staff will be required for a morning shift of three and a half hours (hydromorphone dosing) and an afternoon shift of two and a half hours (methadone dosing). Costing is based on one RN
Level 3 and one RN Level 4 being employed Monday to Friday at a full time rate, one RN Level 2
being employed Monday to Friday for clinic sessions and three Level 2 RNs being employed Saturday
and Sunday for clinic sessions. The costing includes estimates for on-costs, weekend penalty rates and
on-call rates for the senior nursing staff.

Our advice from the Australian Nursing Federation, ACT Branch is that the Registered Nurse (RN)
levels should be as a minimum at RN Level 2, at RN Level 3 and RN Level 4, depending on the role
and responsibility in either research or clinical practice. Three RNs would need to be employed in the
Clinic 6 hours a day 7 days a week for the three months of the trial and all nurses involved in the trial
would need two weeks training prior to commencement of the trial at full time rates.

**Airfares, salary replacement and per diem for experienced clinician-researcher advisors**

We have budgeted for Dr Nick Lintzeris and Dr James Bell to each spend two weeks, early in the first
trial, in Canberra. Economy class airfares are budgeted from London and Sydney, respectively. Salary
replacement and per diem are budgeted at $700 per day.

**Research costs consumables, equipment, tests, etc**

**Research costs**

The research costs cover standard University overheads, including IT and administrative support,
library access, printing, transport, stationery, phone call, faxes etc.

**Urine analyses, blood tests and disposables**

Urine specimens will be collected on a daily basis from trial participants for drug, particularly heroin,
screening. We have budgeted $20 for each urine test at a total cost of $14,000.

Liver function tests will be performed via analysis of blood specimens prior to the trial. Women
participants in the trial will have blood tests for pregnancy prior to them being allowed onto the trial
and monthly whilst they are on the trial. We have budgeted $5,000 for all blood tests.

Disposables are for the cost of injecting equipment, rubber gloves etc., estimated at $2,000.

**Hydromorphone and methadone**

The bulk of the costing for trial drugs is for hydromorphone, which is currently available in 500 mg
ampoules costing $80 each. When full trial protocols have been developed, we recommend that an
approach be made to the pharmaceutical company (Abbott Australasia Pty Ltd) to determine if they
would be prepared to provide trial drugs free or at reduced cost. The company has indicated willingness
to receive such an approach. This is an important task for the preparatory phase of the trials.

Other drug costs are for methadone, Narcan and antiemetics.

**Furniture and equipment, including ECG and PO2 monitors**

We have included a small budget for tables and chairs.

There is now some concern about opioid maintenance effects on the heart, especially the QT interval.
During the trial, the effects of hydromorphone on the heart will be measured by ECGs, as well as by
blood pressure and pulse rate.

The issue of measuring blood oxygen levels (PO2) is important because recent overseas research has
demonstrated major reductions in oxygen levels in patients on intravenous heroin but this has been less
so with intravenous methadone. The PO2 machine will allow a non-invasive measurements of
participants’ blood oxygen levels to assess any effect of hydromorphone.

A breathalyser will be required in case there is an indication that clients are alcohol-affected when they
present for assessment prior to hydromorphone administration.