National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD):
Report of Results and Recommendations

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While these investigators all contributed to the Project, responsibility for any errors or omissions remains with the NDARC NEPOD Project staff. Subsequent peer reviewed publications based on the NEPOD data may vary slightly from this report due to the use of different sub-sets of data and different methods of analysis.
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1. EXECUTIVE SUMMARY

The NEPOD Project pooled data collected in 13 separate clinical trials of pharmacotherapies for opioid dependence conducted across Australia, resulting in a combined total of data on 1070 Heroin Users and 355 Methadone Patients. Investigators who conducted the independent trials contributed a standardised core data set for central analysis across a set of agreed outcomes.

This report provides the findings of these analyses. The treatment categories are methadone maintenance, buprenorphine maintenance, LAAM maintenance, naltrexone treatment, rapid opioid detoxification with anaesthesia or sedation, outpatient detoxification using buprenorphine, conventional inpatient detoxification and conventional outpatient detoxification. The data reported herein include short-term outcomes of detoxification. In addition, for naltrexone treatments and maintenance treatments, outcomes at three and six month follow-ups are reported relating to: retention of patients in treatment; heroin use; abstinence rates; criminal behaviour; incidence of serious adverse events. Costs and cost-effectiveness of detoxification and maintenance treatments are also reported.

It is important to note that many of the NEPOD analyses involved comparisons between treatments based on pooling of data collected in two or more separate trials. The trials were conducted under somewhat different conditions in different locations, and possibly with some differences in terms of patient selection criteria, and patients’ motivations when they entered their local trials. The main advantage of this approach is that pooling provided larger sample sizes than were available from individual trials. The main disadvantage is that some of the benefits of randomisation, in terms of ensuring that comparable groups of patients entered the various treatments, may have been lost. It is not considered this situation represents a significant problem in terms of the validity of NEPOD findings.

1.1 Overall impact of maintenance treatments and naltrexone treatments

The treatments examined in the NEPOD project were methadone maintenance, buprenorphine maintenance, levo-alpha-acetylmethadol (LAAM) maintenance, and naltrexone treatment. These pharmacotherapies produced substantial reductions in heroin use while patients remained in treatment.

- The 1070 Heroin Users in these trials reported substantial reductions in heroin use and criminal activity after entering treatment.
- Very good outcomes were achieved for Heroin Users while they remained in treatment. A key challenge is to improve patient retention in all pharmacotherapies, because a substantial proportion of patients dropped-out of treatment.
- The agonist maintenance treatments of LAAM, methadone and buprenorphine retained significantly more Heroin Users than naltrexone treatment.
- There were 355 Methadone Patients (who were already in methadone maintenance) who either remained in methadone maintenance or switched to buprenorphine, LAAM, or naltrexone. These Methadone Patients had relatively low levels of heroin use when they entered the trials.
- Methadone Patients who entered the alternative maintenance treatments (e.g., LAAM or buprenorphine) showed only a small increase in heroin-free days, as they had already
achieved treatment-related gains by virtue of being in methadone prior to entering the new trial pharmacotherapy. However, Methadone Patients who transferred to LAAM reported significantly more heroin-free days than Methadone Patients who remained on methadone, at both three and six months.

1.2 Short-term detoxification outcomes

- Rapid opioid detoxification under anaesthesia or sedation was a significantly more effective method for achieving short-term abstinence compared to conventional detoxification and detoxification using buprenorphine.
- Rapid detoxification under anaesthesia had no advantage over rapid detoxification with sedation. Both procedures were significantly more effective than conventional detoxification.
- Outpatient buprenorphine detoxification is less effective in achieving initial abstinence, but it links patients into ongoing treatment. Heroin Users who completed buprenorphine detoxification and entered post-detoxification treatment preferred buprenorphine maintenance or methadone maintenance over naltrexone treatment.
- Detoxification using buprenorphine was equally effective in specialist clinic and general practice (shared-care) settings.

1.3 Methadone, buprenorphine and LAAM maintenance treatment

The trials of methadone, buprenorphine and LAAM maintenance with 573 Heroin Users produced similar results for patients remaining in treatment, although LAAM was superior to methadone and buprenorphine in achieving additional heroin-free days and abstinence at six months when a conservative approach to data analysis was taken.

- Pooled across the three trials of methadone, buprenorphine and LAAM maintenance, approximately 60% of Heroin Users were retained in treatment at three months, and 44% at six months.
- LAAM and methadone maintenance retained significantly more Heroin Users than buprenorphine in the first six months of treatment.
- Heroin Users who remained in treatment substantially reduced their heroin use, with the number of heroin-free days increasing from 3 days in the month prior to treatment to 22 - 24 heroin-free days in the third month of treatment.
- Taking account of all Heroin Users who entered maintenance treatment with methadone, buprenorphine or LAAM (and assuming that patients who dropped out of treatment, or who were lost to follow-up, resumed their pre-treatment levels of heroin use), a large overall decline in heroin use was still observed. There was an increase of 9 -15 extra heroin-free days at the three month follow-up, and 6 -15 extra heroin-free days at six months.
- Complete abstinence from heroin use was achieved by over one quarter of Heroin Users who remained in treatment in the third and sixth month.
- Taking account of all Heroin Users who entered maintenance treatment with methadone, buprenorphine or LAAM (and assuming that patients who dropped out of treatment, or who were lost to follow-up, resumed their pre-treatment levels of heroin use), a significantly higher rate of abstinence was achieved with LAAM than either methadone or buprenorphine at three and six months.
1.4 Naltrexone treatment for already abstinent Heroin Users

Naltrexone treatment was provided to a group of 117 Heroin Users who were already detoxified and abstinent when they entered treatment (a self-selected patient group with relatively good prognosis).

- Naltrexone treatment retained 33% (38/117) of Heroin Users at the three month follow-up, and 5% at six months (1/20).
- Naltrexone treatment produced a large reduction in heroin use for patients who remained in treatment, with 8 heroin-free days in the month prior to detoxifying increasing to 27 heroin-free days for the 38 patients still in treatment at three months.
- Complete abstinence from heroin was achieved by 66% of Heroin Users who were still in treatment in the third month, and by the 1 patient known to be still in treatment at six months.
- Taking account of all previously detoxified Heroin Users who entered naltrexone treatment (and assuming that patients who dropped out of treatment resumed their pre-treatment levels of heroin use), a large decline in heroin use was still observed. There was an increase of nine heroin-free days in the third month of treatment, and this gain was maintained in the sixth month.

1.5 Naltrexone treatment after rapid detoxification

Naltrexone treatment after rapid detoxification from heroin was provided to 116 Heroin Users and 74 Methadone Patients.

- This treatment retained 19% (22/116) of Heroin Users in naltrexone treatment at the three month follow-up, and 7% (7/101) at six months.
- It produced a large reduction in heroin use for patients who remained in treatment, with only two heroin-free days in the month prior to commencing treatment, increasing to 26 heroin-free days in the third month of treatment, and 28 heroin-free days in the sixth month.
- Complete abstinence from heroin use in the previous month was achieved by 75% (15/20) of Heroin Users who were still in treatment and followed-up in the third month, and all 7 patients still in treatment in the sixth month.
- Taking account of all Heroin Users who entered rapid detoxification followed by naltrexone treatment (and assuming that patients who dropped out of treatment resumed their pre-treatment levels of heroin use), a large decline in heroin use was still observed. There was an increase of 8 heroin-free days in the third month of treatment, and this gain was maintained in the sixth month.

1.6 Naltrexone treatment after conventional inpatient detoxification

Naltrexone treatment after conventional inpatient detoxification (using clonidine and symptomatic medications) for Heroin Users had poor results.

- This treatment retained only 2% of Heroin Users (1 of 50) in treatment at the three month follow-up, and none at six months.
• Taking account of all Heroin Users who entered conventional inpatient detoxification followed by naltrexone treatment (including those who dropped out of treatment), complete abstinence from heroin use was achieved by 4% of the total sample in the third month of treatment, and 6% in the sixth month.

• Taking account of all Heroin Users who entered conventional inpatient detoxification followed by naltrexone treatment (including those who dropped out of treatment), there was an average increase of 3 heroin-free days in the third month of treatment, and 7 heroin-free days in the sixth month of treatment.

• This was a relatively poor result, which may have been influenced by the fact that the Heroin Users in the relevant trial had been randomly allocated to conventional inpatient detoxification rather than (their preferred) rapid detoxification under anaesthesia.

1.7 Criminal behaviour

• Self-reported criminal behaviour was more common among Heroin Users prior to entering trials than among Methadone Patients.

• Property crime was reported at baseline by a significantly greater proportion of Heroin Users (20%) than Methadone Patients (5%), as was drug dealing (23% vs. 8% respectively); fraud (8% vs. 2% respectively); and violence (3% vs. 1% respectively). Criminal behaviour among Heroin Users was halved at the three month follow-up.

• Heroin Users’ average monthly expenditure on heroin decreased from $2,611 at baseline to $572 at three-month follow-up, consistent with the decreases in heroin use.

1.8 Serious adverse events

Overall, serious adverse events (SAEs) were not common in the trials. However, several important observations were made.

• While patients were in treatment, most SAEs occurred in naltrexone treatment (56 SAEs per 100 patient-years), and fewest occurred in methadone maintenance and LAAM maintenance (10 SAEs per 100 patient-years).

• Naltrexone treatment was associated with a significantly higher (non-fatal and fatal) heroin overdose rate (11 heroin overdoses per 100 patient-years in treatment; and 35 overdoses per 100 patient-years if patients ceased naltrexone) compared with methadone, buprenorphine and LAAM (which had in total five heroin overdoses per 100 patient-years in and out of treatment).

• Naltrexone treatment was also associated with a trend towards a higher death rate (four deaths among 454 patients, a rate of nine deaths per 1000 patients) with two deaths for the methadone, buprenorphine and LAAM maintenance therapies combined (two deaths among 1067 patients, a rate of two per 1000). This difference was not statistically significant.

• SAE rates increased after patients left treatment.

1.9 Costs and cost-effectiveness

For detoxification short-outcome was defined as achieving abstinence for one week.

• Rapid detoxification under sedation was the most cost-effective method of detoxification at a cost of $3,317 per patient who achieved one week of abstinence.
- Conventional outpatient detoxification was found to be the least cost-effective detoxification procedure at a cost of $16,945 per abstinent patient. The very low rate of initial abstinence (2 of 50 patients) achieved for this procedure makes this finding unstable. A small increase in abstinence rates would significantly increase its cost-effectiveness. It is, by far, the least cost-effective withdrawal treatment in this study.

- Rapid detoxification under anaesthesia achieved high rates of abstinence in the first week. Its expense reduces its cost-effectiveness. Any efficiencies that could be achieved by streamlining this relatively new procedure would increase its cost-effectiveness.

For maintenance treatments:

- Overall, the daily costs of providing maintenance treatments were similar for methadone and LAAM, with naltrexone treatment being slightly more expensive. Buprenorphine maintenance was more expensive, but there may be potential for improving its cost-efficiency, that would make its cost similar to the other treatments.

- Methadone maintenance is the most cost-effective treatment currently available in Australia for the management of opioid dependence. Methadone maintenance also achieved one of the highest rates of retention among the four pharmacotherapies examined.

- LAAM is not registered for use in Australia, but it was more cost-effective than methadone maintenance due to its better retention and slightly better ability to suppress heroin use. Although this is a promising result, it is based on a small sample of patients, and the superiority of LAAM over methadone has not been observed in other studies. This result therefore needs to be interpreted cautiously.

- Buprenorphine ranks third overall in cost-effectiveness at both three and six months with retention rates of 50% and 38% respectively. Any reductions in the price of buprenorphine and increased efficiency in administering it (such as reductions in dosing time) may reduce its total cost and increase its cost-effectiveness.

- Naltrexone treatment appears to be the least cost-effective pharmacotherapy compared with methadone, LAAM and buprenorphine. The proportion of patients retained in treatment was much lower in naltrexone treatment than in the maintenance treatments. Only one in seven of all naltrexone patients completed three months of treatment, and 5% completed six months treatment.

- Across treatment modalities, treatment in the G.P. setting appears to be more cost-effective than the clinic setting at both three and six months. While every effort has been made to include all costs in the G.P. setting, there may be other costs such as outside counselling, support costs by the clinic and the Divisions of G.P.s which have not been captured. Although inclusion of these cost components may not change the results, it is also important to note that these GP trials were conducted in the context of support from specialist clinics.

All costs are in 1998/99 Australian dollars.
2. **RECOMMENDATIONS**

2.1 **Recommendations regarding clinical practice**

1. **Promote diversity of treatment options.** Noting that the new treatments evaluated by NEPOD resulted in a substantial reduction in heroin use, and that patients will require different forms of treatment at different stages of their drug-use career, there should be emphasis on providing a range of treatment options that includes methadone, buprenorphine and naltrexone to reduce opioid-related harm.

2. **Continue to support methadone maintenance treatment.** As methadone maintenance is the most cost-effective treatment currently available in Australia, it should continue to be supported as a treatment for opioid dependence. LAAM (which is not currently available in Australia) should be examined further as it was more cost-effective than methadone, a result that requires replication before it is accepted. It may be possible to increase the cost-efficiency of buprenorphine treatment by altering dosing practices to reduce staff costs. The cost of buprenorphine would also be reduced if a Commonwealth Government purchase price was negotiated that is lower than the current listed price.

3. **Improve retention in treatment.** As better outcomes are achieved by patients who remain in treatment, there should be increased emphasis on improving treatment retention, especially in naltrexone treatment, but also in methadone, buprenorphine and LAAM. This may involve a review of current policies and treatment practices to ensure availability of a variety of treatment options, and flexibility, accessibility and attractiveness of treatment services. It may be possible to improve retention and treatment outcomes by effectively addressing psychological comorbidity.

4. **Encourage general practitioner involvement in a shared-care model.** Treatment can be provided effectively, safely and cost-effectively in primary care (general practitioner) settings. No significant differences in outcomes (heroin-free days) were found between specialist clinic settings and GP treatment settings (which involved experienced GPs engaging in shared-care with specialist clinics). As the GP setting provides improved treatment access, an optimal mix of primary care, specialist clinics, and shared-care arrangements should be developed.

5. **Link detoxification to continuing treatment.** Detoxification does not ensure long-term abstinence from opioids, and should be regarded as a starting point for ongoing treatment, rather than as a complete treatment in its own right. It may be appropriate to reflect this concept in performance measures for detoxification services.

6. **Encourage the use of buprenorphine for outpatient detoxification.** Outpatient detoxification using buprenorphine is more cost-effective than conventional detoxification (inpatient or outpatient), less expensive than rapid detoxification procedures, and allows flexibility in post-detoxification linkage to either maintenance treatment (with methadone or buprenorphine) or naltrexone treatment.

7. **Make rapid detoxification under sedation available for Heroin Users seeking induction into naltrexone treatment.** There was no evidence that rapid detoxification under anaesthesia provides better outcomes than rapid detoxification under sedation. As the sedation procedure is less expensive, it should be made available following development
of approved clinical guidelines. It should be noted that naltrexone is not currently registered for use in rapid detoxification.

8. Disseminate the results of the NEPOD project. All jurisdictions should review their clinical guidelines, policy documents and systems of service delivery relating to opioid detoxification and maintenance treatment in the light of the NEPOD findings. An active, coordinated dissemination program should be implemented to maximise incorporation of the NEPOD findings into clinical practice throughout Australia, with the aim of increasing the effectiveness and cost-effectiveness of treatment services, and increasing the number of Heroin Users who participate in treatment. An outline of such a program is provided in Appendix 8.7.

2.2 Recommendations regarding further research

1. Investigate some current clinical issues.
   • The role and use of buprenorphine in pregnancy should be addressed given its categorisation of risk in pregnancy.
   • The use of buprenorphine in “medical maintenance” (dispensing to stable patients up to a week or more supply of buprenorphine to take-away) should be investigated to determine whether it can be effectively prescribed more liberally without increased rates of adverse events.
   • The relative efficacy and acceptability to patients of the combined buprenorphine/naloxone (Suboxone ®) tablet warrants investigation.
   • Optimal methods for transferring from buprenorphine to naltrexone treatment require further attention.
   • Research into methods of optimising retention in naltrexone treatment and achieving abstinence needs to be undertaken.
   • The finding that GPs were more cost-effective in the provision of pharmacotherapy treatment than clinics warrants further investigation. Additional research is required to validate this finding in light of: the small GP sample sizes used in the NEPOD analysis; the confinement of GP data to only two jurisdictions; and, the potential omission of some of the costs associated with GP support and the infrastructure underlying that support.
   • Given that LAAM was found to be a cost-effective maintenance treatment for opioid dependency, it is important that this finding be validated through additional research into LAAM as a treatment option in both clinic and GP-based settings. This research is particularly important if LAAM is to be registered and made available in Australia for the treatment of opioid dependency.
   • Maintenance treatment reduces criminal activity. Potential exists, using the NEPOD core data, to investigate the economic implications of changes in criminal activity as a consequence of pharmacotherapy treatment. Additional research in this area would provide a valuable contribution to the paucity of evidence that currently exists, especially if combined with objective data.

2. Monitor implementation of buprenorphine. During the implementation of widely available buprenorphine treatment, there should be monitoring of treatment uptake, retention and safety using existing government data collection systems.
3. **Support research infrastructure.** NEPOD has contributed to the establishment of a unique Australian research capacity. Australian treatment-outcome research in the drug and alcohol field should utilise similar methodology, including: (a) a core data set; (b) independent quality assurance; (c) centralised randomisation where appropriate; (d) health economics; and (e) an emphasis on high follow-up rates. Guidelines should be developed, based on the NEPOD health economics methodology, to facilitate costing of Australian drug and alcohol treatments in a consistent and comparable manner.
3. INTRODUCTION

Heroin dependence is one of the largest increasing causes of mortality in Australia (Mathers, Vos, & Stevenson, 1999). It has been estimated that there were 74,000 dependent Heroin Users in Australia in 1997, a number that has doubled in the past 15 years (Hall, Ross, Lynskey, Law, & Degenhardt, 2000), and has been accompanied by an increasing number of deaths from heroin overdose and other related causes. Furthermore, Heroin Users obtain most of their income illegally. Maher et al (1998) have estimated that the total cost of heroin related crime in Australia is between $535 million and $1.6 billion per annum (Maher, Dixon, Lynskey, & Hall, 1998).

In 1999, only an estimated 36% of dependent Heroin Users were in methadone maintenance treatment (Hall et al., 2000). In 1998, the Ministerial Council on Drug Strategy decided that a coordinated, national approach should be taken in investigating the nature and potential role of several “new” (in Australia) pharmacotherapies for opioid dependence. As a result, the Commonwealth Government commissioned a National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). This three-year project commenced in July 1998 and has been coordinated by the National Drug and Alcohol Research Centre (NDARC). NEPOD has involved collaboration by a large group of researchers and clinicians around Australia who have conducted studies on opioid pharmacotherapies. These studies have been undertaken in New South Wales, Victoria, South Australia, Queensland, the Australian Capital Territory, and Western Australia.

NEPOD includes 13 treatment outcome studies and other studies (see Appendix 8.2 and 8.4) that have evaluated a range of opioid detoxification and maintenance treatments involving methadone, naltrexone, buprenorphine, and LAAM, with associated psychosocial and medical interventions. This research program has involved total project funding of approximately $7 million. More than 250 clinical and research staff provided treatment, and collected the data that are presented in this report regarding 1,425 patients. This represents a very large investment in scientifically evaluating, and developing local familiarity with a range of current and prospective therapeutic options, and in establishing an accurate knowledge base for reviewing and improving treatment services for opioid dependence in Australia.

The basic goal of NEPOD has been to contribute to a national effort to develop and implement a range of effective, evidence-based, best practice treatment options for people who are opioid dependent by:

- Facilitating the adoption of a core data set of assessment measures to characterise research trial participants (patients) and their treatment outcomes;
- Providing research methodological support to the trials, including access to the NHMRC’s central randomisation service;
- Implementing an independent trial monitoring and quality assurance process, which verified patient existence, informed consent, conformity to trial inclusion and exclusion criteria, nature of treatment provision, and data collection;
- Facilitating communication and collaboration between the researchers who have conducted the trials;
• Analysing the core data set that has been collected in the participating trials prior to patients commencing the trial treatments, and at follow-up occasions up to six months, depending on the trial;

• Measuring the costs and cost-effectiveness of the trial treatments, with a view to informing governments about cost-effectiveness of pharmacotherapy treatment and potential funding implications of the pharmacotherapies;

• Collecting and interpreting international research literature, integrating it with the results of the Australian trials, and contributing to the development of nationally standardised clinical best-practice guidelines;

• Assisting to disseminate the trial results, clinical guidelines and accurate information about the pharmacotherapies to policy makers, treatment providers, opioid-dependent persons, and the community.
4. NEPOD METHODOLOGY

4.1 NEPOD core data set

An essential aspect of NEPOD was the use of a core data set that was defined to address research questions relating to the efficacy, safety and cost-effectiveness of the various trial treatments. Outcome data included in this report focuses on patients’ heroin use and criminal behaviour, and incidence of serious adverse events. A range of other data were collected and will be analysed later. It should be noted that a complete NEPOD core data set was not collected in every trial, primarily because these studies were planned and/or commenced prior to its formulation. Please refer to Appendix 8.3 for a complete listing of the NEPOD core data set.

Baseline and outcome data at one, three and six month follow-ups included herein are based on patients’ self-reports. Darke (1998) reviewed studies that have compared self-reported behaviours of drug users with data based on urine or hair sampling, criminal records and collateral interviews. Darke concluded that “self reports ... are sufficiently reliable and valid to provide descriptions of drug use and drug related problems”, a view that is supported by other reviews and individual studies (Digiusto, Seres, Bibby, & Batey, 1996; Kokkevi, Richardson, Palermou, & Leventakou, 1998; Maisto, McKay, & Connors, 1990).

Some of the trials included in NEPOD used urine or hair sampling to verify self-reported recent drug use at particular time points, however these data are not reported herein. Urine sampling can only reliably detect heroin use in the past two days (Digiusto et al., 1996), with the consequence that studies have found that self-reported heroin use is higher in some situations than results based on urinalysis (Darke, 1998; Digiusto et al., 1996; Maisto et al., 1990). As the main NEPOD results relate to the past 28 days at each follow-up, it was deemed neither feasible nor cost-effective to attempt to collect the number of urine samples or hair samples that would have been required to cover these periods of time in all trials.

4.2 Trial monitoring process

A systematic trial quality assurance process was implemented by NEPOD across the trials, supervised by an independent monitoring company (Panacea Research and Evaluation). The monitoring staff were employed by NEPOD and located at NDARC, but reported directly and confidentially to Panacea. In general, each study site was visited by NEPOD monitors at the beginning of recruitment, and on two or more subsequent occasions based on the recruitment progress and time frames of the individual trials.

Verification of the existence of patients, adherence to the trials’ inclusion and exclusion criteria, and completion of consent forms were examined for 100% of patients. Verification of random allocation to the correct treatment (in randomised trials) was checked for a sample of 10% of patients. At the first monitoring visit, research questionnaires were checked for inclusion of the NEPOD core data set. A minimum sample of 10% of trials’ core data was entered for cross-checking against the trial’s main data files at the end of each trial. Sites were asked to provide documentation of any serious adverse events at each monitoring visit.
Any queries raised through this process were reported back to the investigators in writing for resolution. A total of 811 queries were raised throughout the course of NEPOD, most of which were of a minor nature and were resolved.

4.3 NEPOD peer-review process

Another aspect of quality assurance related to the fact that the chief investigators of the trials included in NEPOD met as a group every few months with NEPOD staff throughout the three year project to discuss and resolve methodological issues, and the results of their trials. This process facilitated a shared understanding of issues and adoption of shared solutions to problems that arose, and ensured that results were peer-reviewed as they became available.

4.4 Randomisation within randomised trials

NEPOD resourced trials 3, 6, 7, 10, 11, 24 and 29 to utilise the National Health and Medical Research Council’s (NH&MRC) randomisation service. Trials 4, 9 and 12 had already adopted a local randomisation method. The NH&MRC service helped to ensure integrity of patient allocation to treatments by providing an independent audit trail which enabled checking of actual treatment allocation. This enhances the rigour of comparisons made between the treatment arms in individual trials and also in the NEPOD pooled data analyses.

4.5 Trial follow-up procedures

Heroin Users who enter treatment are notoriously difficult to follow up after they leave the treatment. The trials varied to some extent in terms of available resources for following up patients, and consequently varied in the contact rates that they achieved at the various follow-ups. The trials varied in the maximum length of time for which they attempted to follow-up patients (1, 3, or 6 months or longer), either because of resource constraints or because the trial’s research questions did not require extended follow-up. This report includes data collected at up to six-month follow-ups.

In some outcome analyses, missing follow-up data have been “imputed” by conservatively assuming that patients who were unable to be contacted for the relevant follow-up had returned to their pre-trial behaviour patterns. This was done only when some patients had missing data, not when a trial had not conducted follow-up at all at a particular time point.

4.6 Data entry procedures for the NEPOD trials

With the exception of the trials specified below, all NEPOD core data were entered into the NEPOD databases by Panacea trial monitors on site. Data entry was guided by manuals which were prepared for each trial which listed variable names, definitions and labels. These manuals also listed data entry conventions to be followed, covering, for example, the treatment of ranges, missing data, not applicable data, etc.

Core data for trials 4, 6, 7, 10, 11 and 12 were entered by trial staff using NEPOD data entry manuals to guide data entry and any required recoding. On completion of data entry for
these trials, a comparison of the data entered by the sites against the 10% sample of data that had been entered as part of the monitoring process was conducted. Any systematic problems were communicated to researchers and were resolved.

4.7 Coding and data analysis of short-term outcomes after detoxification

Initial abstinence outcomes were generally based on patients’ self-reports regarding heroin use or naltrexone use or, in some cases, on heroin-negative urine samples. In cases where a heroin-positive urine sample contradicted a patient’s self-reported abstinence, he/she was regarded as non-abstinent.

Patients were also regarded as non-abstinent in cases where short-term follow-up data were unavailable. These data were unavailable when patients had dropped out, or when a trial had not aimed to systematically collect short-term outcome data on all patients. Given these considerations, the short-term outcome analyses can be regarded as generally accurate, but possibly slightly conservative.

For most trials, the seven-day heroin abstinence period began on the first day on which abstinence was expected in each given treatment (e.g., the day of admission for inpatient treatments). The only exception was in the case of withdrawal from methadone using buprenorphine, in which the seven-day period began from the date on which the patient reached 0mg of buprenorphine. It may have been “easier” for inpatients to have achieved initial abstinence, given that they were monitored more closely and that they had less opportunity to obtain heroin than outpatients did.

In examining data regarding entry to post-detoxification treatment, it should be noted that different types of treatments were (appropriately) available following different types of detoxification. This situation may have introduced some bias into the comparisons that have been made. The rapid and conventional detoxification trials specifically aimed to induct patients onto naltrexone, but also allowed (re-) entry to methadone maintenance. The trial of methadone detoxification using buprenorphine and the conventional outpatient detoxification trial offered patients a choice of either naltrexone or methadone maintenance. The trials of buprenorphine detoxification for Heroin Users offered patients a choice of either naltrexone, methadone or buprenorphine maintenance.

Statistical significance of differences between types of detoxification was tested with chi-square tests corrected for continuity. These data provide a clear picture of what was achieved by the basic detoxification procedures separately from the longer-term effects of any subsequent maintenance treatment (which are presented later in this report). The main conclusions to be drawn from the analyses of short-term outcomes are outlined below.

4.8 Data analyses and statistical significance testing

Two sets of treatment outcome analyses were conducted. The first set of analyses focused on patients who were still in treatment and who were actually followed up at three or six months. In the second set of analyses (“imputed analyses”), all patients who entered the trials were included, with missing follow-up data relating to heroin use and criminal behaviour replaced by patients’ baseline values. This was a more conservative approach to data analysis,
which assumes that patients who had dropped out of treatment, or who were lost to follow-up, had returned to their pre-trial use.

Statistical significance testing was based on examining differences between treatments etc. which were pre-planned and specified in a Statistical Analysis Plan that was developed early in the project, independently of the trials’ results. Statistical significance of results was determined on the basis of decision-wise tests with an alpha level of 0.05.

Retention in treatment was defined in terms of retention in the first episode of a trial to which a patient was initially allocated until he or she left that treatment or was terminated from a trial. It should be noted that patients may have subsequently continued in some form of treatment outside of the trial and/or entered other treatments. Data collected from patients who withdrew their consent to participate in a trial were completely excluded from the database.

_Heroin-free days_ was defined as the number of days in the preceding 28 heroin was _not_ used. Information about heroin use in the past 28 days was collected by most of the trials using the drug use section of the ‘Opiate Treatment Index’ (OTI) (Darke, Ward, Hall, Heather, & Wodak, 1991).

‘Abstinence’ prior to treatment entry and at three and six-month follow-up was defined as _28 heroin-free days_ in the preceding month. The abstinence rate, therefore, is the percentage of patients who achieved this among a group of patients.

Information on criminal activity was collected using a modified version of the crime section of the OTI (Darke 1991 et al). Participants were asked to estimate how often they had committed the following four types of crime in the past month: _property crime_ (e.g., break and enter, robbery without violence, shoplifting, stealing a prescription pad, stealing a car, or receiving stolen goods), _drug dealing_ (i.e., selling any type of drug), _fraud_ (e.g., forging cheques, forging prescriptions, social security scams, or using someone else’s credit card), and _crimes involving violence_ (e.g., armed robbery, assault, violence in a robbery). In this report, the percentages of participants who reported committing each of the four types of crime have been provided.

Information on other drug use and expenditure was also collected using the OTI. For heroin and five other illicit drug classes, participants were asked to provide the average cost of a typical day’s use (or estimated cost if not purchased) in the past 28 days. In this report, monthly expenditure has been presented, derived by multiplying the cost of a typical day’s use by the number of days used for each drug class.

### 4.9 Quasi-experimental nature of NEPOD

Other than trials 1, 14, and 16, the trials that contributed data to NEPOD all randomly allocated patients to treatments (e.g., buprenorphine or methadone maintenance) which were provided in a balanced manner at one or more treatment sites. Such randomised studies allow direct outcome comparisons between treatments to be based on the assumption that the groups of patients who entered the (within-trial) treatments were similar in all important respects, and that any differences observed at follow-up are due to differences between the treatments themselves rather than being due to different “types” of patients who chose to enter the various treatments.
In contrast, many of the NEPOD analyses involved comparisons between treatments based on pooling of data collected in two or more separate trials. The trials were conducted under somewhat different conditions in different locations, and possibly with some differences in terms of patient selection criteria, and patients’ motivations when they entered their local trials. This approach has both advantages and disadvantages. The main advantage is that pooling provided larger sample sizes than were available from individual trials.

The main disadvantage is that some of the benefit of randomisation, in terms of ensuring that comparable groups of patients entered the various treatments, may have been lost. Although worth noting, we believe that this situation does not represent a significant problem in terms of the validity of NEPOD findings. It should also be noted that, pragmatically, there was no alternative, as the included trials were already planned, locally funded, in some cases already started, and in some cases actually completed.

### 4.10 Generalisability of NEPOD results

The fact that many of the NEPOD pooled results are drawn from multiple trials carried out in multiple sites should provide for more generalisability of the results to other treatment locations than would be the case with single-trial single-site results.

However, the reader should be aware that results from clinical trials may be biased in comparison with “real life” clinical activities in a number of ways. For example, all of the trials had explicit, detailed patient inclusion and exclusion criteria, and the patients who were included were people who gave informed consent to participate in a research process which involved providing a good deal of data, being followed up, etc. In addition, it is possible that trial patients were monitored more carefully during treatment than would be the case with patients who were not in a trial. These factors may have produced better outcomes than might be achieved in routine clinical practice. It should also be noted that results reported from GP settings generally involved experienced GPs in shared-care arrangements with specialist clinics.

Some trials involved patients being randomly allocated to either a “conventional” treatment or a “new” treatment (e.g., Trial 4: conventional inpatient detoxification vs. detoxification under anaesthesia). In such situations it is possible that patients who were allocated to the conventional treatment may have experienced some degree of resentment and demoralisation, if they had been hoping for the new treatment. This situation may have produced worse outcomes for conventional treatments in comparison with what could be achieved with patients who actively choose to enter such treatments in routine clinical practice. It is important to point out here that these issues potentially affect all clinical trials, not just those included in NEPOD.
5. RESULTS

The data from the NEPOD Trials are summarised separately for two distinct groups of patients: Heroin Users and Methadone Patients. In reading the results section, it is important to note that Heroin Users were new to treatment (or had not been in treatment for up to three months), whereas Methadone Patients were already in methadone treatment and were either seeking withdrawal from methadone (via detoxification) or were interested in entering a new maintenance treatment (i.e., LAAM or buprenorphine). The treatment categories are methadone maintenance, buprenorphine maintenance, LAAM maintenance, naltrexone treatment, rapid opioid detoxification with anaesthesia or sedation, outpatient detoxification using buprenorphine, conventional inpatient detoxification and conventional outpatient detoxification.

5.1 Characteristics of trial participants on entry to trials (baseline)

A total of 1,425 patients’ data made up the final NEPOD data set and were analysed. Of these 1,425 patients, 1,070 were current Heroin Users who had not received any treatment for a minimum of one month prior to entering a trial and 355 were Methadone Patients, currently participating in a methadone program. As shown in Table 1, the characteristics of trial participants were typical of opioid users either already in, or entering into, treatment. The majority were male, with an average age of 31 years (with the Heroin User group being three years younger, on average, than the Methadone Patients). The average age that participants first used heroin was 20 years, with a heroin “habit” first having developed at an average of 23 years of age. As well as being older than the Heroin Users, Methadone Patients were more likely to be employed, with approximately one third of Methadone Patients working full-time or part-time at entry into trials. Methadone Patients had started on a methadone program more times and had previously been in methadone treatment longer than Heroin Users, with a current average dose of 53mg methadone. No significant differences in age or sex were found between the groups of Heroin Users or Methadone Patients who entered various categories of treatment. A high level of psychological comorbidity was found among both Heroin Users and Methadone Patients.
Table 1: Characteristics of Heroin Users and Methadone Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heroin Users (n = 1,070)</th>
<th>Methadone Patients (n = 355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% male</td>
<td>66%</td>
<td>59% *a</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years (S.D.)</td>
<td>30 (8)</td>
<td>33 (7) **</td>
</tr>
<tr>
<td>Age first used heroin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years (S.D.)</td>
<td>20 (5) ** n=948b</td>
<td>20 (5) n=339</td>
</tr>
<tr>
<td>Age first heroin habit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years (S.D.)</td>
<td>23 (5) ** n=544</td>
<td>23 (5) n=335</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>54%</td>
<td>26%</td>
</tr>
<tr>
<td>Pensioner</td>
<td>9%</td>
<td>23%</td>
</tr>
<tr>
<td>Home duties, other</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>Student, part-time/casual work</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Full-time work</td>
<td>13%</td>
<td>21%</td>
</tr>
<tr>
<td>Highest level of education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to Year 10</td>
<td>42%</td>
<td>40%</td>
</tr>
<tr>
<td>Year 11-12</td>
<td>37%</td>
<td>34%</td>
</tr>
<tr>
<td>Tertiary</td>
<td>19%</td>
<td>23%</td>
</tr>
<tr>
<td>Present methadone dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean mg (S.D.)</td>
<td>n/a</td>
<td>53 (29)</td>
</tr>
<tr>
<td>Total previous months in methadone treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean months (S.D.)</td>
<td>10 (23) ** n=586</td>
<td>53 (57) ** n=330</td>
</tr>
<tr>
<td>No. times previously started methadone treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (1) n=1,053</td>
<td>2 (3) ** n=330</td>
<td></td>
</tr>
<tr>
<td>Depression T-scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68 (12) n=771</td>
<td>57 (11) ** n=107</td>
<td></td>
</tr>
</tbody>
</table>

Notes

* a = chi-squared test for percentages, t-test for independent samples, * = < 0.05, ** = < 0.005.

b = not all of the individual trials collected a complete NEPOD core data set. The number of cases upon which a statistic is based has been noted in these instances.
5.2 Short-term outcomes after detoxification treatments

5.2 Short-term outcomes of detoxification treatments

Rapid detoxification under general anaesthesia and sedation were equally effective. Rapid detoxification led to a higher rate of initial abstinence than was achieved with detoxification using buprenorphine, but a lower rate of entry to post-detoxification treatment for heroin users. Rapid detoxification was more effective than conventional inpatient detoxification. Detoxification using buprenorphine was equally effective in specialist clinic and general practice (shared-care) settings. Detoxification using buprenorphine and conventional outpatient detoxification were equivalent in terms of initial abstinence rates. However, detoxification using buprenorphine was more likely to be completed, and more likely to lead to entry to post-detoxification treatment. When Heroin Users were given a choice of naltrexone, methadone or buprenorphine treatment following detoxification using buprenorphine, only 5% chose naltrexone, whereas 60% chose buprenorphine or methadone.

Tables 2 and 3 present the short-term outcomes of detoxification, in terms of the numbers of Heroin Users and Methadone Patients who:

a. entered and completed each type of detoxification process,

b. completed detoxification and achieved (at least) a seven day period of initial abstinence from heroin use, and

c. entered some type of post-withdrawal pharmacotherapy maintenance treatment (naltrexone, methadone or buprenorphine).

5.2.1 Rapid inpatient detoxification under anaesthesia versus sedation

There was no significant difference in outcome between these two methods of induction onto naltrexone. Completion of withdrawal was equal for patients undergoing rapid detoxification under anaesthesia (RODA) and rapid detoxification under sedation (RODS), both for Heroin Users (average of 83%) \((X^2 = .04, \text{df} = 1, p = 0.84)\) and for Methadone Patients (average of 92%) \((X^2 = .00, \text{df} = 1, p = 1.00)\).

RODA and RODS also resulted in equivalent abstinence rates \((p > 0.05)\); 59% of Heroin Users and 72% of Methadone Patients remained abstinent for seven days. RODA and RODS led to equivalent rates of entry to post-detoxification treatment \((p > 0.05)\): 49% of Heroin Users, and 84% of Methadone Patients entered such further treatment. Because of the lack of differences, in the remainder of this section these two rapid detoxification procedures are referred to generically as “rapid detoxification”.

REPORT OF RESULTS AND RECOMMENDATIONS
## Table 2: Short term outcomes of detoxification for Heroin Users

<table>
<thead>
<tr>
<th>Type of patient and detoxification treatment</th>
<th>Percent achieving an initial seven days of abstinence(a)</th>
<th>Type of post-detoxification treatment entered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional inpatient detoxification (n = 50, 28%)</td>
<td>24%</td>
<td>Methadone or buprenorphine maintenance</td>
</tr>
<tr>
<td>Anaesthesia-based rapid detoxification (n = 76, 82%)</td>
<td>58%</td>
<td>n/a</td>
</tr>
<tr>
<td>Sedation-based rapid detoxification (n = 40, 85%)</td>
<td>60%</td>
<td>n/a</td>
</tr>
<tr>
<td>Anaesthesia &amp; sedation rapid detox. combined (n=116, 83%)</td>
<td>59%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

### Inpatient detoxification

<table>
<thead>
<tr>
<th>Type of patient and detoxification treatment</th>
<th>Percent achieving an initial seven days of abstinence(a)</th>
<th>Type of post-detoxification treatment entered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional outpatient (n = 56, 57%)</td>
<td>4%</td>
<td>Methadone or buprenorphine maintenance</td>
</tr>
<tr>
<td>Buprenorphine detoxification in specialist clinics (n = 107, 84%)</td>
<td>15%</td>
<td>23%</td>
</tr>
<tr>
<td>Buprenorphine detoxification in G.P. setting (n = 51, 77%)</td>
<td>6%</td>
<td>61%</td>
</tr>
<tr>
<td>All buprenorphine (n = 158, 82%)</td>
<td>12%</td>
<td>59%</td>
</tr>
</tbody>
</table>

### Outpatient detoxification

<table>
<thead>
<tr>
<th>Type of patient and detoxification treatment</th>
<th>Percent achieving an initial seven days of abstinence(a)</th>
<th>Type of post-detoxification treatment entered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional outpatient (n = 56, 57%)</td>
<td>4%</td>
<td>Methadone or buprenorphine maintenance</td>
</tr>
<tr>
<td>Buprenorphine detoxification in specialist clinics (n = 107, 84%)</td>
<td>15%</td>
<td>23%</td>
</tr>
<tr>
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<td>6%</td>
<td>61%</td>
</tr>
<tr>
<td>All buprenorphine (n = 158, 82%)</td>
<td>12%</td>
<td>59%</td>
</tr>
</tbody>
</table>

### Notes

- \(a\) = statistical significance of differences in percentage achieving initial 7 days of abstinence between treatments tested with chi-square tests corrected for continuity \((**p < 0.001; \ast p < 0.05): 2 \text{ vs } 3 \text{ NS; 1 vs 4**; 4 vs 8**; 6 vs 7 NS; 5 vs 8 NS.}\)
- n/a = this treatment was not available for this group.
- \(b\) = the figures in brackets provide the percentage of patients who entered methadone and buprenorphine, respectively.

### 5.2.2 Rapid detoxification versus outpatient detoxification using buprenorphine

*Heroin Users* completed these two procedures at similar rates (about 82%), but were more likely to achieve initial abstinence through rapid detoxification than through detoxification using buprenorphine (59% vs. 12% respectively, \(X^2 = 64.89, df = 1, p < 0.001\)). *Heroin Users* were less likely to enter post-detoxification treatment after rapid detoxification than after detoxification with buprenorphine (49% vs. 65%, respectively, \(X^2 = 6.45, df = 1, p < 0.05\)).
For Methadone Patients, rapid detoxification was associated with a higher rate of completion than was the case with detoxification using buprenorphine (92% vs. 66%, respectively), as well as higher rates of initial abstinence (72% vs. 46%, respectively), and entry to post-detoxification treatment (84% vs. 31%, respectively).

### Table 3: Short term outcomes of detoxification for Methadone Patients

<table>
<thead>
<tr>
<th>Type of patient and detoxification treatment</th>
<th>Percent achieving an initial seven days of abstinence</th>
<th>Type of post-detoxification treatment entered*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Number of patients, and % who completed treatment)</td>
<td></td>
<td>Methadone</td>
</tr>
<tr>
<td><strong>Inpatient detoxification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>¹Anaesthesia-based rapid detoxification (n = 42, 93%)</td>
<td>69%</td>
<td>10%</td>
</tr>
<tr>
<td>²Sedation-based rapid detoxification (n = 32, 91%)</td>
<td>75%</td>
<td>3%</td>
</tr>
<tr>
<td>³All rapid (anaesthesia + sedation) (n = 74, 92%)</td>
<td>72%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Outpatient detoxification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>⁴Buprenorphine (n = 55, 66%)</td>
<td>46%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Notes: *Not all treatments were available in each trial. Buprenorphine maintenance was not available for detoxified Methadone Patients.  
  a = statistical significance of differences in percentage achieving initial 7 days of abstinence between treatments tested with chi-square tests corrected for continuity (**p < 0.001; *p < 0.05): 1 vs 2 NS; 3 vs 4.*

### 5.2.3 Rapid detoxification versus conventional inpatient detoxification

More Heroin Users completed rapid detoxification than conventional inpatient detoxification (83% vs. 28% respectively, \(X^2 = 44.45, df = 1, p < 0.001\)), and rapid detoxification led to more initial abstinence (59% vs. 24% respectively, \(X^2 = 15.42, df = 1, p < 0.001\)), and entry to post-detoxification treatment (49% vs. 12% respectively, \(X^2 = 18.92, df = 1, p < 0.001\)).

### 5.2.4 Detoxification using buprenorphine at specialist clinics versus G.P. setting.

For Heroin Users, there were no significant differences between specialist clinic versus general practice settings in terms of either completion rates (average of 82%), initial abstinence (average of 12%), or entry to post-detoxification treatment (average of 65%).
5.2.5 Detoxification using buprenorphine versus conventional outpatient detoxification

*Heroin Users* were more likely to complete detoxification using buprenorphine than they were to complete conventional outpatient detoxification (82% vs. 57% respectively, $X^2 = 12.0, df = 1, p < 0.001$). They were also more likely to enter post-detoxification treatment after detoxification using buprenorphine than after conventional detoxification (65% vs. 27% respectively, $X^2 = 23.12, df = 1, p < 0.001$). However, the difference in initial abstinence rates between buprenorphine detoxification and conventional outpatient detoxification was not significant (12% vs. 4%, respectively).

5.2.6 Short-term outcomes in relation to types of patient and treatment setting

More *Methadone Patients* than *Heroin Users* completed detoxification and achieved initial abstinence, both with inpatient procedures (72% vs. 48% respectively, $p < 0.001$), and with outpatient procedures (46% vs. 10% respectively, $p < 0.001$). Inpatient detoxification was more effective than outpatient detoxification in terms of achieving initial abstinence, both for *Methadone Patients* (inpatient [rapid]: 72% vs. outpatient [buprenorphine]: 46%, $p < 0.01$), and for *Heroin Users* (inpatient: 48% vs. outpatient 10%, $p < .001$).

5.2.7 Discussion

It appears that better short-term outcomes (initial abstinence and entry into post-detoxification treatment) are achieved from newer methods of detoxification (rapid detoxification under anesthesia or sedation, and detoxification using buprenorphine), compared with existing conventional methods. However, the research, international literature and clinical experience shows that only a very small proportion of patients are able to maintain long-term abstinence or reductions in their heroin use without further treatment (Mattick & Hall, 1996). As such, detoxification is usually only the first step towards a reduction or elimination of heroin use (Mattick & Hall, 1996), and entry to post-detoxification treatment is arguably more clinically desirable than initial abstinence.

Detoxification using buprenorphine resulted in the largest proportion of *Heroin Users* continuing in post-detoxification treatment, even though rapid detoxification methods had superior rates of initial abstinence. Therefore, an important advantage of buprenorphine detoxification is the likelihood that it will engage *Heroin Users* in ongoing treatment.

A further clinical implication of this finding is that patients who entered post-detoxification treatments were more likely to choose a maintenance treatment (with a preference for buprenorphine over methadone) rather than naltrexone treatment. For example, when *Heroin Users* were given a choice of naltrexone, methadone or buprenorphine treatment following detoxification using buprenorphine, only 5% chose naltrexone, whereas 60% chose buprenorphine or methadone. Similarly, of the 27% of patients who entered a maintenance treatment following conventional outpatient detoxification, only 4% chose naltrexone compared with 23% who chose methadone. This preference could be caused partly by the fact that these patients could not easily enter naltrexone treatment; entry into naltrexone treatment requires abstinence for several days.

Another interpretation is that opioid-dependent people prefer an opioid maintenance treatment to abstinence-oriented treatment. As reviewed elsewhere (Mattick et al., 1997), a marked
preference for maintenance treatment with methadone, over naltrexone, has been noted in a number of large-scale North American studies of naltrexone wherein very few patients offered naltrexone actually commenced treatment (Lewis, Mayer, Hersch, & Black, 1978; National Research Committee on Clinical Evaluation of Narcotic Antagonists, 1978).

Another important finding from this research was that rapid detoxification under general anaesthesia and rapid detoxification under sedation did not differ in their ability to induct patients onto naltrexone and achieve one week of initial abstinence. This has been an issue in the past with some claiming that anaesthesia-based detoxification yields better results than can be achieved using sedation (Mattick et al., 1997). The equivalence of the two methods suggests that the use of sedation is preferred to the more expensive anaesthesia-based approach (see section 6) with the attendant risks of anaesthesia. One of the trial investigators felt that rapid detoxification under general anaesthesia was still a useful procedure for some patients.

5.3 Retention in treatment

Previous research has suggested that the effectiveness of opioid treatment programmes is related, at least in part, to the extent to which patients are able to be retained in treatment (Bell, Digiusto, & Byth, 1992a; Ward, Mattick, & Hall, 1998). Given this finding, three separate analyses were conducted using data from NEPOD trials: one compared rates of retention in methadone, buprenorphine and LAAM maintenance (Figure 1); a second compared rates of retention for naltrexone treatments aimed primarily at achieving abstinence (Figure 2); and a third compared methadone/buprenorphine/LAAM combined against naltrexone (Figure 3).

It is pointed out that these data refer to Heroin Users only in order to avoid artificially inflating retention rates by including existing Methadone Patients who were considered more likely to remain in treatment.

5.3.1 Retention in methadone, buprenorphine, and LAAM maintenance

Figure 1 shows rates of retention of Heroin Users in treatment using methadone, buprenorphine and LAAM. Figure 1 shows that methadone and LAAM maintenance treatments were both superior to buprenorphine in terms of their rates of retention in treatment in the first six months. This difference was statistically significant (p < 0.01 for both methadone and LAAM, compared to buprenorphine).
However, there was no significant difference between methadone and LAAM in rates of retention in treatment after six months. The retention rates for methadone and LAAM were 60% and 70%, respectively, at three months and 50% and 60%, respectively at six months.

5.3.2 Retention in naltrexone treatment

Figure 2 shows the rates of retention in treatment for conventional inpatient detoxification, naltrexone treatment only, and rapid detoxification. The rapid detoxification group includes anaesthesia and sedation, as their retention was not significantly different.

In interpreting Figure 2, it is important to note that the Heroin Users who entered the naltrexone treatment for already abstinent patients were a self-selected subgroup who had already successfully detoxified prior to entering the trial. It might reasonably be expected that they would be more motivated to remain in treatment than the other groups of Heroin Users (who had not yet detoxified when they entered the trials). The higher retention rate in the naltrexone-only trial, in comparison with the other two groups shown in Figure 2, was statistically significant (p < 0.01 for both naltrexone treatment after rapid detoxification and naltrexone treatment after conventional inpatient detoxification, compared to naltrexone treatment for already abstinent patients).

Notes  A total of 282 Heroin Users enrolled in treatment with methadone, 250 enrolled in buprenorphine maintenance, and 41 enrolled in LAAM maintenance.
The differences between the three groups were largely evident within the first week, with the retention curves being reasonably parallel thereafter. In part, this is due to these analyses being based on the intention-to-treat principle, and reflects the fact that some of the Heroin Users who were allocated to the conventional or rapid detoxification treatments either did not actually enter the treatment, or were not subsequently inducted onto naltrexone.

At three months, the retention rate in the naltrexone-only trial was 35%, compared with 18% for rapid detoxification under sedation or anaesthesia, and 2% for conventional inpatient detoxification. At six months, all three types of treatment had retained less than 10% of Heroin Users in naltrexone treatment.

Notes  A total of 116 Heroin Users enrolled in treatment with rapid detoxification; 50 enrolled in treatment with conventional inpatient detoxification; and 20 enrolled in treatment with naltrexone treatment for already abstinent patients. One trial of naltrexone treatment for already abstinent patients was omitted because its patients were offered naltrexone for three months only. Rapid detoxification includes the rapid detoxification procedure under either sedation or anaesthesia. Naltrexone treatment for already abstinent patients enrolled only Heroin Users who had successfully detoxified prior to enrolling in naltrexone treatment. Conventional inpatient detoxification is a detoxification procedure using medications including clonidine to relieve symptoms of withdrawal.
5.3.3 Retention in methadone/buprenorphine/LAAM compared with naltrexone

Figure 3 shows retention in treatment for all of the naltrexone treatments combined and for the agonist maintenance treatments (methadone, buprenorphine, and LAAM) combined. An inspection of Figure 3 shows that the agonist maintenance treatments combined were associated with a significantly higher retention rate than the naltrexone treatments combined. The retention rate at six months for the agonist maintenance treatments combined was 44%, compared with 4% for naltrexone treatments.

Figure 3: Retention of Heroin Users in naltrexone treatments and in maintenance treatments (using methadone, buprenorphine or LAAM)

Notes
A total of 573 Heroin Users enrolled in maintenance treatment with methadone, buprenorphine, or LAAM. A total of 186 Heroin Users enrolled in the combined naltrexone treatments. The combined naltrexone treatments comprised: naltrexone treatment after rapid detoxification under sedation or anaesthesia; naltrexone treatment for already abstinent patients who had successfully detoxified prior to enrolling in treatment; and conventional inpatient detoxification which is a detoxification procedure using medications including clonidine to relieve symptoms of withdrawal. One naltrexone trial was omitted because its patients were offered naltrexone for three months only.
5.3.4 Discussion

In terms of retaining Heroin Users in treatment, maintenance treatment (using methadone, buprenorphine or LAAM) were superior to naltrexone treatment (antagonist). Of the maintenance treatments, methadone and LAAM appear to be preferable to buprenorphine. The lower retention rate for buprenorphine may be due to several factors. As can be seen in Figure 1, a higher drop-out rate from buprenorphine occurred during the first two weeks of treatment, followed by a retention rate similar to methadone and LAAM. This suggests that the rate of successful induction onto buprenorphine was lower than that for methadone and LAAM. It could be the case that induction dosages of buprenorphine were too low (Fischer et al., 1999) and/or that buprenorphine absorption among newly inducted patients was not optimal given inexperience with sublingual tablets (Mendelson, Upton, Jones, & Jacob, 1995). Alternatively, it may be that patients do not like the partial agonist effect of buprenorphine. Finally, buprenorphine can cause a low level of withdrawal (as it displaces heroin from receptors).

Retention rates at six months of approximately 5% (naltrexone treatment) and 50% (maintenance treatment) point to a need for strategies aimed at globally improving treatment retention. Although drop-out continues steadily across the six month treatment period the most marked drop out for all four pharmacotherapies is evident within the first two weeks of treatment, suggesting that this period in particular is amenable to interventions aimed at improving retention. This might include a focus on more intensive contact with relevant clinicians to strengthen the therapeutic relationship, in addition to case management. More generally, enhanced availability and accessibility of ancillary services that might attract patients to stay in treatment for longer periods should also be considered. The international literature does suggest that ancillary services improve treatment outcomes (Ward et al., 1998).

The need to attend to co-morbid psychiatric states is often overlooked in these patients, and there are very high rates of treatable psychological disturbance (e.g., anxiety and depression) (see Appendix 8.5). Such treatment of psychological disturbance is associated with less ongoing illicit drug use (McLellan, Luborsky, Woody, O'Brien, & Druley, 1983). Finally, aftercare for those completing a treatment episode is also associated with better post-treatment outcomes (see literature review in Appendix 8.1).

In the case of naltrexone, sub-cutaneous slow release preparations, known as implants are currently receiving attention as a possible way of improving retention. Implants can provide effective blockade for up to 60 days compared with approximately 24 hours with a single 50mg oral naltrexone dose (Gooberman, Bradway, & Bartter, unpublished). It is important to note, however, that long-term retention would require that patients were sufficiently motivated to return for repeated re-implantation. Currently, there is no regulation on the manufacture of naltrexone implants and this device is not registered for use in Australia. The published data on naltrexone implants is limited and therefore conclusions on the relative efficacy and safety of the treatment cannot be made in the absence of well designed randomised controlled trials (see Appendix 8.1). Until such research is conducted, any claims of markedly enhanced efficacy from the use of implants or depot preparations of naltrexone are without evidence.
5.4 **Heroin-free days for those patients who remain in treatment**

5.4 Heroin-free days for patients who remain in treatment

Maintenance treatment (using methadone, buprenorphine or LAAM) produces a marked increase in heroin-free days for Heroin Users remaining in treatment at three months, an increase that is maintained at six months.

Naltrexone treatment also produces a marked increase in heroin-free days for Heroin Users remaining in naltrexone treatment at three months, but at six months the majority of these patients are no longer in this treatment.

Methadone Patients showed only a small increase in heroin-free days after entering a new pharmacotherapy (e.g., LAAM or buprenorphine), as they had already achieved treatment-related gains by virtue of being in methadone prior to entering the new trial pharmacotherapy. However, of the three maintenance treatments, LAAM resulted in the greatest number of heroin-free days for Methadone Patients. This result requires confirmation, as it is not consistent with the international research.

Table 4 outlines the number of heroin-free days in the month (defined as 28 days) prior to entering treatment, and at the three and six-month follow-up for Heroin Users and Methadone Patients still in treatment.

### 5.4.1 Methadone, buprenorphine and LAAM maintenance.

As can be seen in Table 4 Heroin Users had very few heroin-free days prior to entering methadone, buprenorphine, or LAAM maintenance, with approximately three days in the previous month. However, this increased substantially to an average of 23 heroin-free days at both the three-month and six month follow-up for Heroin Users who remained in any of these agonist treatments.

The baseline heroin use of Methadone Patients is remarkably similar to that of Heroin Users who remained in any agonist treatment at three and six months. For example, the Methadone Patients randomised to continue methadone maintenance reported 22 heroin-free days in the month prior to entering the trial, which is the same as the number of heroin-free days obtained by Heroin Users in methadone maintenance at the three and six month follow-up.

For Methadone Patients who remained in methadone treatment, the number of heroin-free days remained constant, with 24 days in the month prior to the three-month follow-up and 22 in the month prior to six-month follow-up. For those Methadone Patients who transferred to buprenorphine maintenance, their number of heroin-free days increased marginally to 24 days at three months and 26 days at six months.

Similarly, Methadone Patients who transferred to LAAM had an increase in heroin-free days from 24 days at baseline, to 27 days at three and six months. A significantly greater number of heroin-free days were reported by the Methadone Patients who randomised to LAAM compared with Methadone Patients who remained on methadone, at both three (27 vs. 24, F = 7.49, p < 0.05) and six months (27 vs 22, F = 9.45, p < 0.05). Thus, LAAM appeared to be a superior treatment for Methadone Patients.
5.4.2 Naltrexone treatment for already abstinent Heroin Users

These findings relate to Heroin Users who had already detoxified from heroin prior to entering a naltrexone treatment trial. The already abstinent Heroin Users are a select group with a better prognosis, as they had already successfully undertaken the opioid detoxification process. Any Heroin Users who were unable to detoxify could not enter these trials. As such, their data are presented separately from those who went through detoxification as part of the trial treatment prior to entering naltrexone treatment.

Those patients who remained in naltrexone treatment achieved 27 days heroin-free at three-months, and the one patient known to still be in naltrexone treatment at six months was completely abstinent. This result is significantly greater to that obtained by the agonist treatments at three months, but the large drop-out at six months from naltrexone treatment renders comparisons at that time invalid.

5.4.3 Naltrexone treatment after rapid detoxification

Heroin Users entering naltrexone treatment after rapid detoxification had used heroin nearly every day in the month prior to entering treatment. Patients who remained in treatment reported 26 and 28 heroin-free days respectively, in the month prior to the three and six month follow-ups. This increase in heroin-free days was significantly greater than was obtained by methadone treatment at three months (26 vs. 22, \( F = 4.72, p < 0.05 \)). No such difference, however, was detected at six months, when only seven patients remained in naltrexone treatment.

As might be expected, the Methadone Patients who entered naltrexone treatment after rapid detoxification had more heroin-free days than Heroin Users prior to naltrexone treatment (22 days). Their outcomes, however, at three and six months, were virtually identical to those of Heroin Patients, with 27 and 28 heroin-free days respectively. This increase in heroin-free days was significantly greater than was obtained by methadone treatment at three months (27 vs 24, \( F = 5.58, p < 0.05 \)). Similar to the Heroin Users, no such difference was detected for the Methadone Patients at six months, when only eight patients remained in naltrexone treatment.

5.4.4 Other forms of detoxification

While not presented in Table 4, Heroin Users undergoing outpatient buprenorphine detoxification used heroin nearly everyday in the month prior to entering treatment. Follow-up data was collected for some of these patients at one-month (Trial #6) and for the remainder at three months (Trial #29). At these time points, the number of heroin-free days had increased to 17 and 20 days respectively. These patients had the post detoxification options of buprenorphine or methadone maintenance or naltrexone treatment based on availability and patient preference. This situation is similar to what might happen in a normal clinical treatment setting where a range of alternatives is available after detoxification.

In the case of Methadone Patients undertaking outpatient buprenorphine detoxification, the number of heroin-free days decreased slightly after one-month post detoxification. That is, outcomes for stable Methadone Patients were slightly worsened by attempting withdrawal.
Table 4: Number of heroin-free days in the month before entering treatment, and at three months and at six months: patients remaining in treatment

<table>
<thead>
<tr>
<th></th>
<th>Heroin Users*</th>
<th>Methadone Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heroin-free days in past montha</td>
<td>Heroin-free days in past montha</td>
</tr>
<tr>
<td></td>
<td>Before treatment (No. patients enrolled in treatment)</td>
<td>At three months (No. patients remaining in treatment)</td>
</tr>
<tr>
<td>1 Methadone Maintenance</td>
<td>3 (n = 281)</td>
<td>22 (n = 159)</td>
</tr>
<tr>
<td>2 Buprenorphine Maintenance</td>
<td>3 (n = 250)</td>
<td>22 (n = 119)</td>
</tr>
<tr>
<td>3 LAAM Maintenance</td>
<td>2 (n = 41)</td>
<td>24 (n = 25)</td>
</tr>
<tr>
<td>4 Naltrexone treatment for already abstinent patients</td>
<td>8 (n = 117)</td>
<td>27 (n = 38)</td>
</tr>
<tr>
<td>5 Naltrexone treatment after rapid detoxification</td>
<td>2 (n = 116)</td>
<td>26 (n = 20)</td>
</tr>
<tr>
<td>6 Naltrexone treatment after conventional inpatient detoxification</td>
<td>0 (n = 50)</td>
<td>23# (n = 1)</td>
</tr>
</tbody>
</table>

Notes: * = Heroin Users had not been in a pharmacotherapy treatment for at least one month and up to three months at the time of entering the treatment, whereas Methadone Patients were already in methadone treatment at the start of the trial, and they consented to be randomised to enter a new treatment, or to remain in methadone maintenance.

a = statistical significance of differences in heroin-free days between treatments tested with ANCOVA with baseline heroin-free days as a co-variate (**p < 0.001; *p < 0.05): 3 month comparisons for Heroin Users = 1 vs 2 NS; 1 vs 3 NS; 2 vs 3 NS; 4 vs 5 NS; 1 vs 4*; 2 vs 4*; 3 vs 4*; 1 vs 5*; 2 vs 5*; 3 vs 5 NS. 6 month comparisons for Heroin Users = 1 vs 2 NS; 1 vs 3 NS; 2 vs 3 NS; 1 vs 5 NS. 3 month comparisons for Methadone Patients = 1 vs 2 NS; 1 vs 3*; 2 vs 3 NS; 1 vs 5*; 2 vs 5 NS; 3 vs 5 NS. 6 month comparisons for Methadone Patients = 1 vs 2 NS; 1 vs 3*; 2 vs 3 NS; 1 vs 5 NS.  

n = number of patients.

# = the very low number of patients should be noted when interpreting this result.
Heroin Users entering naltrexone treatment after conventional inpatient detoxification had no heroin-free days at baseline. Only one patient remained in this treatment at three months, and there were none in naltrexone treatment at six months. The imputed data showed statistically significantly poorer results for naltrexone treatment after conventional inpatient detoxification compared with rapid detoxification (3 vs 10, F = 9.48, p < 0.05) at three months.

Heroin Users undertaking conventional outpatient detoxification had, on average, one heroin-free day in the month prior to commencing detoxification and in the month following detoxification this had increased to 13 days.

5.4.5 Discussion

The results herein indicate that methadone is an effective treatment in reducing heroin use while patients remain in treatment. Buprenorphine and LAAM also reduced heroin use substantially. The results are generally consistent with the international literature on these drugs, which has been comprehensively reviewed elsewhere (Mattick & Hall, 1993; Mattick, Oliphant, Hall, & Ward, 1998; Ward, Hall, & Mattick, 1999; Ward, Mattick, & Hall, 1992; Ward, Mattick, & Hall, 1994; Ward et al., 1998).

Naltrexone brought about very marked suppression of heroin use indicating that it is a useful medication in the treatment of opioid dependence, however, relatively few patients remain in naltrexone treatment. Again this result is consistent with the international literature (Mattick et al., 1997; Tucker & Ritter, 1997).

5.5 Change in heroin-free days

The data presented in Table 5 highlight the change in the number of heroin-free days from baseline assessment to three and six months. Two figures are presented for the follow-up data, the first for patients remaining in treatment and the second for the total sample of patients who entered the trial. For the total sample, a change score of zero heroin-free days has been imputed for patients who were not available for follow-up assessment. This is a conservative approach, but is a useful way to analyse the outcomes. The assumption of no change for patients who dropped out is reasonable given previous research about the natural history of opioid dependence following cessation of treatment, where prompt relapse is typical (Ward et al., 1998). This approach provides a worst-case scenario, with the data for patients who remain in treatment (Table 4) providing the best-case scenario.
Table 5: Increase in the number of heroin-free days at three months and six months, compared with the month prior to entering treatment: *Heroin Users*

<table>
<thead>
<tr>
<th></th>
<th>Increase in Heroin-free days at three month&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Increase in Heroin-free days at six month&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For patients remaining in treatment</td>
<td>For patients remaining in treatment</td>
</tr>
<tr>
<td></td>
<td>For the Total Sample** enrolled</td>
<td>For the Total Sample** enrolled</td>
</tr>
<tr>
<td><strong>1</strong> Methadone</td>
<td>19 (n = 158)</td>
<td>20 (n = 101)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>11 (n = 281)</td>
<td>8 (n = 281)</td>
</tr>
<tr>
<td><strong>2</strong> Buprenorphine</td>
<td>19 (n = 119)</td>
<td>18 (n = 77)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>9 (n = 250)</td>
<td>6 (n = 250)</td>
</tr>
<tr>
<td><strong>3</strong> LAAM</td>
<td>20 (n = 25)</td>
<td>23 (n = 23)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>15 (n = 41)</td>
<td>15 (n = 41)</td>
</tr>
<tr>
<td><strong>4</strong> Naltrexone</td>
<td>18 (n = 38)</td>
<td>6# (n = 1)</td>
</tr>
<tr>
<td>treatment for already</td>
<td></td>
<td>9 (n = 117)</td>
</tr>
<tr>
<td>abstinent patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5</strong> Naltrexone</td>
<td>24 (n = 20)</td>
<td>22# (n = 7)</td>
</tr>
<tr>
<td>treatment after rapid</td>
<td></td>
<td>7 (n = 101)</td>
</tr>
<tr>
<td>detoxification</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6</strong> Naltrexone</td>
<td>23# (n = 1)</td>
<td>No patients remained in treatment</td>
</tr>
<tr>
<td>treatment after</td>
<td></td>
<td>7 (n = 50)</td>
</tr>
<tr>
<td>conventional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inpatient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>detoxification</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: *Heroin Users* had not been in a pharmacotherapy treatment for at least one month and up to three months at the time of entering the treatment, whereas *Methadone Patients* were already in methadone treatment at the start of the trial, and they consented to be randomised to enter a new treatment, or to remain in methadone maintenance.

<sup>a</sup> Statistical significance of differences in heroin-free days between treatments tested with ANCOVA with baseline heroin-free days as a co-variate (**p < 0.001; *p < 0.05): 3 month comparisons for Total Sample = 1 vs 2 NS; 1 vs 3 NS; 2 vs 3*: 4 vs 5**; 4 vs 6**; 5 vs 6*; 1 vs 4 NS; 2 vs 4*(the heroin-free days comparison favouring naltrexone treatment); 3 vs 4 NS; 1 vs 5*; 2 vs 5 NS; 3 vs 5*; 1 vs 6**; 2 vs 6**; 3 vs 6**. 6 month comparisons for Total Sample = 1 vs 2 NS; 1 vs 3**; 2 vs 3**; 4 vs 5**; 4 vs 6**; 5 vs 6 NS; 1 vs 4*; 2 vs 4**; 3 vs 4 NS; 1 vs 5 NS; 2 vs 5 NS; 3 vs 5**; 1 vs 6 NS; 2 vs 6 NS; 3 vs 6**.

** = For the Total Sample some data were missing, and for those patients data were imputed, and results are based on a conservative assumption that patients who were not followed-up had the same heroin use pattern that they had in the baseline (pre-treatment) month.

<sup>n</sup> = number of patients.

# = The very low number of patients should be noted when interpreting this result.
5.5.1 Heroin Users entering methadone, buprenorphine and LAAM maintenance

As can be seen in Table 5 Heroin Users who remained in methadone, buprenorphine and LAAM maintenance treatment achieved on average an additional 20 heroin-free days in the third and sixth month of treatment. However, if the total sample of Heroin Users who entered these treatments is used for the calculation of heroin-free days, there was a smaller average overall increase of 12 days at three months and 10 days at six months.

Focusing on the outcomes for the total sample of Heroin Users, those who entered methadone maintenance gained an additional 11 heroin-free days after three months, this decreased to 8 days by six months. For buprenorphine maintenance, the number of heroin-free days for all patients entering treatment increased by 9 days at three months and then decreased to six days at six months, while those who entered LAAM maintenance had an additional 15 heroin-free days, which remained constant across six months.

For the total sample, there was a significantly greater number of heroin-free days for the Heroin Users who were randomly assigned to LAAM, compared with Heroin Users who received methadone or buprenorphine, at six months. LAAM again appeared to be a superior treatment. This result is not consistent with the international research on the relative effectiveness of LAAM compared with methadone (Ward et al., 1998), where equivalent results are typically reported for these drugs. One recent study did show slightly better suppression of heroin use with LAAM, above that achieved by methadone and buprenorphine (Johnson et al., 2000), but the better retention of LAAM-treated patients reported in section 5.3 of this report was not reported in that study.

5.5.2 Naltrexone treatment for already abstinent Heroin Users

As stated previously, it is important to note that these Heroin Users entering naltrexone treatment were already abstinent and had a better prognosis than the other groups of Heroin Users who had not been able to achieve initial abstinence. Specifically, they were a select group who had been able to successfully detoxify (often unassisted) and remain abstinent in order to enter naltrexone treatment.

As presented in Table 5, the number of additional heroin-free days for Heroin Users who remained in naltrexone treatment at three months is 18 days. By six months however, this has decreased to 6 days, with only one patient known to still be in treatment. If we look to the total sample of Heroin Users who entered naltrexone treatment there was a lesser gain of nine heroin-free days at three months, which was retained at six months.

For the total sample, there were significantly more heroin-free days for Heroin Users who entered naltrexone treatment compared with Heroin Users who entered methadone or buprenorphine maintenance, at six months. It is important to note, however, that those entering naltrexone treatment had a greater number of heroin-free days at baseline than the other treatment groups, and that missing data for the total sample analyses were imputed using baseline heroin use.
5.5.3 **Heroin Users in naltrexone treatment after rapid detoxification**

*Heroin Users* who entered naltrexone treatment after rapid detoxification and who remained in treatment (or were able to be followed up) reported 24 *heroin-free days* at three months and 22 *heroin-free days* in the sixth month, but only seven patients remained in treatment at six months.

However, when the total sample is considered a poorer overall outcome is apparent. Presuming that patients lost to follow-up (approximately 80% by three months) had returned to their baseline heroin use, the gain in *heroin-free days* decreases to approximately 8 days at three months and 7 days at six months.

In addition, even these *heroin-free days* cannot be simply attributed to naltrexone treatment, as some of the patients who were followed-up had entered other treatment. There was evidence from one trial, that 80% of patients had entered other forms of treatment at follow-up, predominantly methadone maintenance, by six months (Trial #4). This rate of entry into other treatments by those who left naltrexone treatment was not reported in some other trials and hence these data were not available for this report.

5.5.4 **Heroin Users entering other forms of detoxification**

Looking at the total sample of *Heroin Users* who underwent outpatient detoxification using buprenorphine, they experienced an increase of 12 *heroin-free days* at three months (or one month for Trial #6 patients) compared with the month prior to commencing treatment (see Appendix 8.6).

However, examining the total sample of patients who entered conventional inpatient detoxification followed by naltrexone treatment, there was a very limited increase of three *heroin-free days* at three months. Outcomes were slightly better for patients who entered conventional outpatient detoxification followed by a range of maintenance options, with an increase of nine *heroin-free days* at one month.

5.5.5 **Methadone Patients continuing on methadone, or on buprenorphine or LAAM**

*Methadone Patients* who continued on methadone or transferred to buprenorphine showed little change in *heroin-free days* at three and six month follow-up occasions with the majority of treatment gains already obtained (see Appendix 8.6). There was, however, a significant increase in *heroin-free days* for *Methadone Patients* who transferred to LAAM maintenance compared with *Methadone Patients* who remained in methadone maintenance treatment, at three and six months.

5.5.6 **Methadone Patients entering detoxification**

*Methadone Patients* who underwent naltrexone treatment after rapid detoxification reported an increase of four *heroin-free days* at three months, which was maintained at six months. When looking at the total sample, this becomes an increase of one *heroin-free day*.

It is noteworthy, however, that patients who entered outpatient buprenorphine detoxification were the only treatment group who experienced a reduction in *heroin-free days* at one month.
compared to baseline. On trial entry, these patients were very stable with an average of 27 heroin-free days at baseline. The patients were transferred from methadone to buprenorphine and then aimed to gradually reduce their buprenorphine dose. In doing so, some patients were destabilised and started to use heroin, and therefore a reduction of heroin-free days was seen at one-month follow up. Buprenorphine dose reductions for patients observed to destabilise were promptly ceased and they were returned to methadone maintenance.

5.5.7 Discussion

As noted in the previous section, the results herein indicate that methadone, buprenorphine and LAAM are effective treatment in reducing heroin use while patients remain in treatment. Very marked decreases in heroin use were reported by the patients who remained in treatment.

We have also taken a conservative approach and presented data for patients who have left treatment, either by using their follow-up data or by imputing data using their baseline drug use (and assuming no change in heroin use). This conservative approach gives the “worst case” scenario for the entire sample.

Naltrexone treatments brought about very marked suppression of heroin use indicating that it is a useful medication in the treatment of opioid dependence, however, relatively few patients remain in naltrexone treatment. Again this result is consistent with the international literature where high drop-out rates are frequently reported, but where naltrexone can be effective if patients remain in treatment (Mattick et al., 1997; Tucker & Ritter, 1997). Although naltrexone treatments did result in heroin-free days at three and at six-month follow-ups, even these heroin-free days cannot be simply attributed to naltrexone treatment, as some of the patients who were followed-up had entered other treatment. There is evidence from one trial, wherein 80% of patients had entered other forms of treatment, predominantly methadone maintenance, by six months (Trial #4). This rate of entry into other treatments by those who left naltrexone treatment was not reported in some other trials, and hence these data were not available for this report.

5.6 Abstinence rates

5.6 Abstinence rates

Rates of abstinence increased markedly while Heroin Users were in treatment.

The few Heroin Users (4%) who remained in naltrexone treatment at six months achieved 100% abstinence at six months, but the vast majority (96%) ceased naltrexone treatment.

LAAM appears to produce higher rates of abstinence than methadone or buprenorphine. The advantage of LAAM over methadone and buprenorphine has not been reported in the international literature on these drugs; typically equivalent effects are reported for methadone and LAAM. The result requires further replication.
Tables 6 and 7 provide data on the rates of abstinence (i.e., no use of heroin in the prior month) from heroin in the month prior to treatment entry, and at the three and six-month follow-up for *Heroin Users* and *Methadone Patients* respectively. As described in Section 5.5, two figures are presented for the follow-up data, the first for patients remaining in treatment and the second for the total sample of patients who entered the trial. For the total sample analyses, patients who were not available for follow-up assessment were assigned their baseline abstinence status.

### 5.6.1 Methadone, buprenorphine and LAAM maintenance

As would be expected, Table 6 shows a very low rate of abstinence (0-1%) from heroin use in the previous month amongst *Heroin Users* at baseline. If one assumes that patients who were not followed up were not abstinent, the heroin abstinence rates at three months were 15%, 15% and 32% for methadone, buprenorphine and LAAM, respectively. Abstinence rates had decreased slightly at six months, with 10%, 11%, and 29% for methadone, buprenorphine and LAAM, respectively. LAAM appears to be performing better than methadone and buprenorphine. The difference between LAAM and methadone was tested and found to be significant at three and six months for the *total sample*. As noted earlier, the advantage of LAAM over methadone and buprenorphine has not been reported in the international literature on these drugs; typically equivalent effects are reported for methadone and LAAM (Ward et al., 1998) and more recently for LAAM and buprenorphine (Johnson et al., 2000). Thus, while the results for LAAM in these trials appear promising, caution is advised when inferring an advantage for LAAM. The results reported herein for LAAM require replication.

*Methadone Patients* who were already in methadone treatment (see Table 7), and who were then randomised to remain in methadone treatment or enter buprenorphine or LAAM maintenance reported 31% to 43% abstinence rates at baseline. These results clearly show that stabilised methadone patients were (not surprisingly) using less heroin at baseline than *Heroin Users*. Furthermore, patients who were initially in methadone maintenance and continued in methadone or buprenorphine maintenance essentially maintained their heroin abstinence rates at three and six months. LAAM performed significantly better than methadone (43% vs 40% at baseline increasing to 63% vs. 46% at three months, \(X^2 = 4.93, \text{df} = 1, p < 0.05\), and 67% vs. 44% at six months, \(X^2 = 5.86, \text{df} = 1, p < 0.05\)) for the *total sample*.

### 5.6.2 Naltrexone treatment for already abstinent *Heroin Users*

*Heroin Users* who had already detoxified prior to entering a trial showed an abstinence rate at three months of 27%, assuming that those not followed-up were not abstinent. This remained constant at six months, at 28%. This rate was significantly higher than was achieved by methadone and buprenorphine maintenance, but not significantly higher than LAAM.

### 5.6.3 Naltrexone treatment after rapid detoxification

At three months, 19% of the *total sample* of *Heroin Users* who entered naltrexone treatment after rapid detoxification were abstinent and this rate remained largely unchanged at 6 months (16%). This outcome was not significantly different to the results obtained by methadone, buprenorphine and LAAM maintenance, but was significantly lower than the result among patients who had already successfully detoxified before entering a naltrexone treatment trial.
### 5.6.4 Naltrexone treatment after conventional inpatient detoxification

Two of the 50 patients offered naltrexone treatment after conventional detoxification reported abstinence from heroin three months later, a rate of 4% if we assume that those lost to follow-up were not abstinent. At six months, 6% were abstinent.

#### Table 6: Rates of abstinence in the month before entering treatment, and at three months and six months: Heroin Users

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Three months</th>
<th>Six months&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Patients remaining in treatment</th>
<th>Total Sample**</th>
<th>Patients remaining in treatment</th>
<th>Total Sample**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>remaining</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1</strong> Methadone</td>
<td>1% (2/282)</td>
<td>26% (41/159)</td>
<td>15% (43/282)</td>
<td></td>
<td></td>
<td>24% (24/102)</td>
<td>10% (28/282)</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2</strong> Buprenorphine</td>
<td>1% (2/250)</td>
<td>28% (33/119)</td>
<td>15% (38/250)</td>
<td></td>
<td></td>
<td>30% (23/77)</td>
<td>11% (28/250)</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3</strong> LAAM</td>
<td>0% (0/41)</td>
<td>44% (11/25)</td>
<td>32% (13/41)</td>
<td></td>
<td></td>
<td>44% (10/23)</td>
<td>29% (12/41)</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4</strong> Naltrexone</td>
<td>0% (0/117)</td>
<td>66% (25/38)</td>
<td>27% (32/117)</td>
<td></td>
<td></td>
<td>100%# (1/1)</td>
<td>28% (33/117)</td>
</tr>
<tr>
<td>treatment for already abstinent patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5</strong> Naltrexone</td>
<td>0% (0/116)</td>
<td>75% (15/20)</td>
<td>19% (22/116)</td>
<td></td>
<td></td>
<td>100%# (7/7)</td>
<td>16% (16/101)</td>
</tr>
<tr>
<td>treatment after rapid detoxification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6</strong> Naltrexone</td>
<td>0% (0/50)</td>
<td>0%# (0/1)</td>
<td>4% (2/50)</td>
<td></td>
<td></td>
<td>No patients remained in treatment</td>
<td>6% (3/50)</td>
</tr>
<tr>
<td>treatment after conventional inpatient detoxification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes**  
*Heroin Users* had not been in a pharmacotherapy treatment for at least one month and up to three months at the time of entering the treatment, whereas *Methadone Patients* were already in methadone treatment at the start of the trial, and they consented to be randomised to enter a new treatment, or to remain in methadone maintenance.

<sup>a</sup> = statistical significance of differences in rates of abstinence at six months between treatments tested with chi-square tests corrected for continuity (**p < 0.001; *p < 0.05): 6 month comparisons for patients remaining in treatment = 1 vs 2 NS; 2 vs 3 NS; 1 vs 3 NS. 6 month comparisons for Total Sample = 1 vs 2 NS; 2 vs 3*; 1 vs 3*; 4 vs 5*; 5 vs 6 NS; 4 vs 6*; 1 vs 4**; 2 vs 4**; 3 vs 4 NS; 1 vs 5 NS; 2 vs 5 NS; 3 vs 5 NS; 1 vs 6 NS; 2 vs 6 NS; 3 vs 6*.

** = for the Total Sample some data were missing, and for those patients data were imputed, and the results are based on a conservative assumption that patients who were not followed-up had the same heroin use pattern that they had in the baseline (pre-treatment) month.

n = number of patients.

# = the very low number of patients should be noted when interpreting this result.
5.6.5 Discussion

The rates of abstinence at entry to any of the treatments were (predictably) very low. Even the Heroin Users entering naltrexone treatment for initially abstinent patients, had used some heroin in the month prior to treatment. At follow-up, the rates of abstinence had increased, consistent with the reduction in heroin-free days. The rates of abstinence in methadone and buprenorphine were similar for both sets of analyses: for patients remaining in treatment and for the Total Sample. LAAM seemed to produce higher rates of abstinence, but again this result is not generally reported in the literature.

Rates of complete abstinence from heroin at three and six months were lower than might be desired. Abstinence could be increased by increasing doses especially for methadone and possibly for the other maintenance treatments (Ward et al., 1998). Additionally, attention to other psychosocial problems which patients have is likely to increase abstinence rates. This issue has been discussed earlier. Better engagement in treatment with clinicians to increase the therapeutic relationship, plus case management, and enhanced ancillary services that might attract patients to stay in treatment for longer periods should be considered. The international literature suggests that ancillary services improve outcomes (Ward et al., 1998).

Table 7: Rates of abstinence in the month before entering treatment, and at three months and six months: Methadone Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline Patients</th>
<th>Three months Patients</th>
<th>Six months Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total Sample**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Remaining in treatment</td>
<td>Remaining in treatment</td>
<td></td>
</tr>
<tr>
<td>1 Methadone Maintenance</td>
<td>40% (46/114)</td>
<td>46% (39/85)</td>
<td>46% (52/114)</td>
</tr>
<tr>
<td>2 Buprenorphine Maintenance</td>
<td>31% (9/29)</td>
<td>44% (8/18)</td>
<td>31% (9/29)</td>
</tr>
<tr>
<td>3 LAAM Maintenance</td>
<td>43% (35/82)</td>
<td>64% (39/61)</td>
<td>63% (52/83)</td>
</tr>
<tr>
<td>4 Naltrexone treatment</td>
<td>32% (23/73)</td>
<td>84% (16/19)</td>
<td>47% (35/74)</td>
</tr>
<tr>
<td>for already abstinent</td>
<td></td>
<td></td>
<td>100%# (8/8)</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td></td>
<td>36% (15/42)</td>
</tr>
</tbody>
</table>

Notes: Methadone Patients were already in methadone treatment at the start of the trial, and they consented to be randomised to enter a new treatment, or to remain in methadone maintenance.

a = statistical significance of differences in rates of abstinence at six months between treatments tested with chi-square tests corrected for continuity (**p < 0.001; *p < 0.05): 6 month comparisons for patients remaining in treatment = 1 vs 2 NS; 2 vs 3 NS; 1 vs 3*. 6 month comparisons for Total Sample = 1 vs 2 NS; 2 vs 3*; 1 vs 3*; 1 vs 4 NS; 2 vs 4 NS; 3 vs 4*.

** = For the Total Sample some data were missing, and for those patients data were imputed, and the results are based on a conservative assumption that patients who were not followed-up had the same heroin use pattern that they had in the baseline (pre-treatment) month.

n = number of patients.

# = The very low number of patients should be noted when interpreting this result.
In addition, aftercare for those who leave treatment is an important intervention as it is associated with better outcomes (see Appendix 8.1). The need to attend to comorbid psychiatric states is typically overlooked in these patients, and there are very high rates of treatable psychological disturbance (e.g., anxiety and depression) (see Appendix 8.5). Treatment of comorbid anxiety and depression enhances outcomes in terms of illicit drug use (McLellan et al., 1983).

5.7 Other drug use outcomes

5.7.1 Expenditure on Illicit Drugs

As shown in Table 8, the average monthly expenditure on heroin at baseline was much higher for Heroin Users ($2,611), compared with Methadone Patients ($435), a difference that persisted at the three month follow-up ($572 vs. $280 respectively). This decrease in expenditure on heroin is consistent with the self-reported decrease in heroin use days reported by the Heroin Users. As would be expected, and similar to the self-report data on the number of days used heroin in the previous month, the reduction in expenditure on heroin was much larger for Heroin Users ($2,039) than for Methadone Patients ($155).

Table 8: Monthly expenditure on illicit drugs ($)

<table>
<thead>
<tr>
<th></th>
<th>Heroin Users</th>
<th>Methadone Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>(n=471)</td>
<td>(n=399)</td>
</tr>
<tr>
<td>Heroin</td>
<td>$2,611</td>
<td>$572</td>
</tr>
<tr>
<td>Other illicit drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other opiates</td>
<td>$8</td>
<td>$1</td>
</tr>
<tr>
<td>Cannabis</td>
<td>$97</td>
<td>$93</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>$6</td>
<td>$16</td>
</tr>
<tr>
<td>Cocaine</td>
<td>$15</td>
<td>$8</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>$3</td>
<td>$6</td>
</tr>
<tr>
<td>Total</td>
<td>$129</td>
<td>$124</td>
</tr>
<tr>
<td>Total average cost per month</td>
<td>$2,740</td>
<td>$696</td>
</tr>
</tbody>
</table>

Notes  Data from some trials could not be included in this analysis.
Total expenditure on illicit drugs other than heroin was similar for Heroin Users and Methadone Patients (although slightly higher for Methadone Patients) at both baseline and follow-up. Expenditure on other illicit drugs was generally low in comparison with expenditure on heroin.

It was noteworthy that, after entering treatment, Heroin Users did not substantially increase either their total expenditure on illicit drugs or their expenditure on any particular type of illicit drug, suggesting an absence of any “substitution effect.”

5.7.2 Discussion

Although specific data related to use of drugs other than heroin are yet to be analysed, the finding in this section that Heroin Users reduce their expenditure on heroin after entry to treatment with no concomitant increase in expenditure on other illicit drugs suggests that there was no change in other drug use.

5.8 Self reported criminal behaviour

5.8.1 Heroin Users

Table 9 shows that at baseline, Heroin Users reported involvement in property crime (20%), drug dealing (23%), fraud (8%) and violent crime (3%) in the previous month. In contrast, for patients who were in treatment at three / six months, reductions were apparent for property crime (10% and 7% respectively), drug dealing (13% and 14% respectively), fraud (5% and 7% respectively) and violent crime (2% at both time periods).

5.8.2 Methadone Patients

The same analyses were conducted for Methadone Patients. As can be seen in Table 9, the corresponding rates of self-reported property crime, drug dealing, fraud and violent crime were all substantially lower than for Heroin Users. Given that these patients were already in methadone treatment at the start of the trials, these lower rates of crime are expected.
It is also evident from Table 9 that the reductions in all crime categories from baseline to three and six months were smaller for Methadone Patients than for Heroin Users. This finding most likely reflects the relatively lower levels of crime reported at baseline for Methadone Patients, such that substantial changes over further time in treatment were not expected.

### 5.8.3 Discussion

As might be anticipated, property crime and drug dealing were the most common forms of criminal activity at entry into treatment for Heroin Users, reflecting their status as a major source of income (Weatherburn & Lind, 1999). Consistent with previous studies, however, a considerable reduction in criminal behaviour among Heroin Users was associated with being in treatment (Bell et al., 1997; Marsch, 1998).

That a proportion of Heroin Users and Methadone Patients continued to report committing crime at both three and six months is also consistent with the published literature. Many people become involved in crime prior to their heroin dependence and then increase their criminal behaviour further after becoming dependent (Weatherburn & Lind, 1999), such that involvement in treatment is more likely to reduce their criminal activity to pre-dependence levels rather than eradicating it entirely.

The relationship between crime and illicit drug use is complex. The extent to which crime will be reduced during treatment appears to be influenced by a number of factors, including individuals’ levels of co-existing social dysfunction and illicit drug use, their age of first exposure to the criminal justice system, the quality of treatment provided, their length of retention in treatment, and the extent to which patients are required to pay for their treatment.

---

### Table 9: Self-reported criminal behaviour

<table>
<thead>
<tr>
<th>Category of criminal behaviour</th>
<th>Baseline % (n = 583)</th>
<th>Three months % (n = 583)</th>
<th>Six months % (n = 312)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heroin Users</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Property crimea</td>
<td>20%</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>Drug dealing crimeb</td>
<td>23%</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Fraudc</td>
<td>8%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Violent crime</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Methadone Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Property crime</td>
<td>5%</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Drug dealing crime</td>
<td>8%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Fraud</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Violent crime</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Notes**

- a = includes break and enter, receiving stolen goods, car theft, shoplifting, robbery & prescription pad theft,
- b = includes selling heroin, cannabis, cocaine, amphetamines, hallucinogens, barbiturates, tranquilisers & other drugs
- c = includes forging cheques, credit card fraud, forging prescriptions & social security fraud,
- d = includes violence in a robbery, armed robbery, assault & rape.

It is also evident from Table 9 that the reductions in all crime categories from baseline to three and six months were smaller for Methadone Patients than for Heroin Users. This finding most likely reflects the relatively lower levels of crime reported at baseline for Methadone Patients, such that substantial changes over further time in treatment were not expected.
5.9 Treatment safety – Serious adverse events (SAEs)

Serious adverse events are usually monitored in trials of pharmacotherapies. The Therapeutic Goods Administration (TGA) defines serious adverse events (SAEs) as those events that result in death or significant disability, are life-threatening, require inpatient hospitalisation or prolonging of an existing hospital stay, or are a congenital anomaly, birth defect or malignancy. The trial investigators reported SAEs to the NEPOD Project on the basis of this definition.

This section provides information about SAEs that occurred within the follow-up observation periods of the trials (ranging from one to six months). These results are presented in terms of the rates of four categories of SAEs per 100 patient-years for the patients who entered each pharmacotherapy. The contents of each category are explained in the table footnotes. SAEs were grouped in this manner to provide increased stability of estimates.

Table 10 shows SAE rates while patients were retained in their initial trial treatments, based on a total of 61 SAEs which occurred during those periods (24,243 days in naltrexone treatment, and a total of 97,814 days in methadone, buprenorphine, and LAAM treatments). The overall rate of serious adverse events during treatment was low. Across all treatments, SAEs occurred at a rate of 20 per 100 patient-years, meaning that patients would be expected to experience one such SAE every five years while in treatment. When considered separately for each pharmacotherapy, the total SAE rates per hundred patient-years were 10 for both methadone and LAAM, 20 for buprenorphine, and 56 for naltrexone.
Table 11 shows the rates after patients had left their initial trial treatments, based on a total of 68 SAEs which occurred during those periods of time (24,243 days after exit from naltrexone, and a total of 12,112 days after exit from methadone, buprenorphine, and LAAM). It should be noted that some patients entered other treatments after leaving their initial trial treatments. These data therefore should not be regarded as purely representing patients who were not in treatment at all. Across all treatment groups, SAEs occurred at a rate 68 per 100 patient-years, meaning that patients who leave treatment would be thereafter expected to experience one SAE about every 1.5 years.

When considered separately for patients who left each pharmacotherapy, the total SAE rates per hundred patient-years were 18 for patients who had left buprenorphine treatment, 68 for naltrexone, 101 for methadone, and 155 for LAAM.

---

**Table 10: Rates of serious adverse events per 100 patient-years while in treatment**

<table>
<thead>
<tr>
<th>Type of serious adverse event(^a)</th>
<th>Methadone (n=420)</th>
<th>Buprenorphine (n=492)</th>
<th>LAAM (n=124)</th>
<th>Naltrexone (n=380)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patient-days in treatment</td>
<td>48,565</td>
<td>34,756</td>
<td>14,493</td>
<td>16,409</td>
</tr>
<tr>
<td>Heroin overdose</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Other overdose</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric/ mood/suicide</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>All other SAE’s</td>
<td>8</td>
<td>13</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Total SAEs(^b)</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>56</td>
</tr>
</tbody>
</table>

**Notes**

\(^a\) A Heroin overdose SAE included all fatal and non-fatal, as well as intentional and accidental, overdose episodes where heroin was the main, though not necessarily the only, drug involved. Other overdose involved other opioids or other drugs. Psychiatric/mood/suicide-related SAEs included severe mood swings, presence of psychiatric symptoms, as well as both suicide attempts and significant suicidal ideation. All other SAEs include: accidents and injuries, including motor vehicle accidents, falls requiring hospital treatment, injuries resulting from physical violence; anticipated sequelae, including events commonly associated with these treatments which are therefore predictable and treatable (e.g. encephalopathy); general medical, including a wide range of medical events such as cardiac abnormalities, seizures, pneumonia, severe vomiting; pregnancy-related, including miscarriages, ectopic pregnancies, terminations; admission for detoxification, including detoxification episodes reported as severe, persistent or requiring longer than expected hospitalisation. An additional 22 admission for detoxification SAEs were reported for naltrexone, but are not included here as it was not clear if they occurred during or after treatment.

\(^b\) Total numbers are accurate, but may not equal the sum of individual values due to rounding.
The overall rate of serious adverse events during treatment was low. The rates were 10–20 per hundred patient-years in methadone, buprenorphine and LAAM treatment, and a higher rate of 56 per hundred patient-years in naltrexone treatment. Across all treatments, SAEs occurred at a rate of 20 per 100 patient-years, meaning that patients would be expected to experience one such SAE every five years of treatment. The rate of SAEs after patients left treatment was higher, at 68 per 100 patient-years, meaning that patients leaving treatment would be expected to experience one SAE about every 1.5 years.

The rates per hundred patient-years of (both fatal or non-fatal) heroin overdose among patients who entered naltrexone were 11 while in treatment, and 35 after leaving treatment. There were two heroin-related overdose deaths among all patients who entered naltrexone treatment. An odds ratio of 14.1 (95% confidence interval: 6.9 to 28.5) confirms that patients who entered naltrexone treatment were significantly (approximately 14 times) more likely to experience a heroin-related overdose than patients who entered methadone, buprenorphine, or LAAM treatment.

Table 11: Rates of serious adverse events per 100 patient-years of observation after patients had left their initial trial treatment

<table>
<thead>
<tr>
<th>Type of serious adverse eventa</th>
<th>Methadone (n=420)</th>
<th>Buprenorphine (n=492)</th>
<th>LAAM (n=124)</th>
<th>Naltrexone (n=380)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patient-days of observation</td>
<td>3,627</td>
<td>6,135</td>
<td>2,350</td>
<td>24,243</td>
</tr>
<tr>
<td>Heroin overdose</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Other overdose</td>
<td>0</td>
<td>0</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric/mood/suicide</td>
<td>20</td>
<td>0</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>All other SAE’s</td>
<td>81</td>
<td>18</td>
<td>109</td>
<td>24</td>
</tr>
<tr>
<td>Total SAEs b</td>
<td>101</td>
<td>18</td>
<td>155</td>
<td>68</td>
</tr>
</tbody>
</table>

Notes
a = A Heroin overdose SAE included all fatal and non-fatal, as well as intentional and accidental, overdose episodes where heroin was the main, though not necessarily the only, drug involved. Other overdose involved other opioids or other drugs. Psychiatric/mood/suicide-related SAEs included severe mood swings, presence of psychiatric symptoms, as well as both suicide attempts and significant suicidal ideation. All other SAEs include: accidents and injuries, including motor vehicle accidents, falls requiring hospital treatment, injuries resulting from physical violence; anticipated sequelae, including events commonly associated with these treatments which are therefore predictable and treatable (e.g., encephalopathy); general medical, including a wide range of medical events such as cardiac abnormalities, seizures, pneumonia, severe vomiting; pregnancy-related, including miscarriages, ectopic pregnancies, terminations; admission for detoxification, including detoxification episodes reported as severe, persistent or requiring longer than expected hospitalisation. An additional 22 admission for detoxification SAEs were reported for naltrexone, but are not included here as it was not clear if they occurred during or after treatment. b = some patients may have entered other treatments after leaving their initial trial treatments. c = total numbers are accurate, but may not equal the sum of individual values due to rounding.

5.9.1 Discussion

The overall rate of serious adverse events during treatment was low. The rates were 10–20 per hundred patient-years in methadone, buprenorphine and LAAM treatment, and a higher rate of 56 per hundred patient-years in naltrexone treatment. Across all treatments, SAEs occurred at a rate of 20 per 100 patient-years, meaning that patients would be expected to experience one such SAE every five years of treatment. The rate of SAEs after patients left treatment was higher, at 68 per 100 patient-years, meaning that patients leaving treatment would be expected to experience one SAE about every 1.5 years.

The rates per hundred patient-years of (both fatal or non-fatal) heroin overdose among patients who entered naltrexone were 11 while in treatment, and 35 after leaving treatment. There were two heroin-related overdose deaths among all patients who entered naltrexone treatment. An odds ratio of 14.1 (95% confidence interval: 6.9 to 28.5) confirms that patients who entered naltrexone treatment were significantly (approximately 14 times) more likely to experience a heroin-related overdose than patients who entered methadone, buprenorphine, or LAAM treatment.
Entry to naltrexone treatment was associated with a higher rate of death from all causes than was the case for methadone, buprenorphine and LAAM treatments combined. Nine fatalities occurred in total: two due to heroin overdose (naltrexone); one due to an overdose on drugs other than heroin (naltrexone); three due to suicide (naltrexone); one due to a motor vehicle accident (LAAM); one due to a brain tumour (methadone); and one of unknown causes (buprenorphine).

It is important to note when considering the data presented in this section that serious adverse events occur for a wide range of reasons in this population of patients, both in and out of treatment. A large proportion of the SAEs were probably not caused by the pharmacotherapies themselves in most cases. In particular, overdoses that occurred among patients who entered naltrexone treatment occurred partly because of the reduced tolerance to opioids that is a feature of any (opioid agonist) abstinence-oriented form of treatment. Taking naltrexone regularly (generally daily) provides protection against overdose.

These results point to the need for clinicians to alert both patients and their families about the potential risk of heroin overdose if naltrexone is not taken regularly (generally daily) and after naltrexone treatment is ceased, as tolerance for opioids will be low at such times. See Appendix 8.1.6 for a detailed discussion of the issue of serious adverse events.
6. HEALTH ECONOMIC METHODS AND ANALYSIS

6.1 Health economic overview

This section reports on the economic evaluation conducted as part of the NEPOD evaluation. Included is a discussion of the methods used to transform the data on resource use collected by NEPOD staff, collaborators and their research staff into the costs and consequences required for an economic evaluation. The section is structured so as to provide the reader with:

- an overview of the health economic methodology;
- cost estimates for each method of detoxification and for the different pharmacotherapies; and,
- the cost-effectiveness ratios for each intervention.

An overview of the methodology used in evaluating the various pharmacotherapy trials in NEPOD is included in this section. This is followed by a set of tables that present the results combining the same types of treatments across the various trials. First, the results for the detoxification portion of the trials are presented, this is followed by costs of providing the various pharmacotherapies and finally the overall cost-effectiveness results are presented. The data were generated to evaluate each trial separately, however, as the goal of this project was to compare the various pharmacotherapies, only the combined results are presented here.

As well as the costs and cost-effectiveness, data are provided on the number of patients randomised to each treatment, retention rates, and outcomes achieved. The data presented in this section may be supplemented with other data reported in previous sections of this report, particularly interesting are the integration of criminal activity (and changes in) and utilisation of other health service pertaining to individual treatments – an issue that is not formally addressed herein, but of significant social, economic and political interest.

6.2 Heath economic methodology

As part of the NEPOD project an economic evaluation was undertaken to compare a range of interventions being evaluated in the NEPOD trials. In order to combine the results from individual trials of different durations, of different commencement times, and conducted using a variety of treatment modalities across a range of different institutional settings, a standardised health economic methodology was developed. To undertake the health economic evaluation, uniform data collection instruments were developed and implemented in addition to the NEPOD core data outlined in Appendix 8.3. Resource use, costs and outcomes for the individual trials were assessed according to their trial procedures with the standardised methodology enabling the results from various trials to be combined.

Standard methods of economic evaluation were employed but for transparency a brief overview of the health economic methods are provided below.

- In conducting an economic evaluation it is necessary to identify the perspective from which the analysis is viewed. The broadest perspective, the societal perspective, considers
all identifiable costs and consequences arising from an intervention. A narrower perspective would be that of a single treatment provider. The perspective chosen for this evaluation is the viewpoint of the health sector and includes the costs and consequences arising from the provision of detoxification and pharmacotherapy treatment. By adopting such a perspective, the analysis does not incorporate costs (or savings) to individuals, non-treatment related health sector expenditures or broader social considerations such as the costs (or cost savings) related to crime.

• The research question identified for the purpose of this economic evaluation was to assess the relative cost-effectiveness of various methods of detoxification and pharmacotherapies for the treatment of opioid dependency. Although a wide range of approaches to economic evaluation exist, such as cost-minimisation, cost-utility and cost-benefit analysis, for this study cost-effectiveness analysis (CEA) was considered the appropriate method. CEA measures resource use in dollar terms and presents results in terms of a cost per additional unit of outcome achieved. This allows comparisons of the efficiency of different interventions designed to produce a similar outcome.

• In order to facilitate the combining of data from the various studies a base year of 1998/99 was chosen. Interventions across studies ranged in duration from one to twelve months, but for the purpose of the economic evaluation, resource use was determined for the duration of the treatment for detoxification, and for six-months for maintenance therapies with the exception of one trial which had a duration of only three months. Thus, resource use was tracked for the time a patient continued on the treatment they were randomised to, up to a maximum of six months.

• The health economic methodology was used to determine resource use at both the level of the patient and the facility. At the patient level a “bottom-up” approach was implemented. This involved identifying the time involved in, and arising from, staff-patient contacts; diagnostic procedures undertaken; and medication provided. A “top-down” approach was taken at the facility level. Facility level costs include many of the costs often referred to as overheads, such as the infrastructure required to maintain and operate the facility or unit of interest, but also includes the support staff and unit managers. Facility costs also includes supplies, consumables, capital, equipment, general administration and other overhead expenses.

• The combining of patient and facility costs provided an estimate of the total cost of treating a patient.

• Given the diversity of trial settings, from specialist clinics to tertiary hospitals, consistent methods of identifying and apportioning facility costs were required to ensure comparability of cost estimates across various treatment sites. Such consistency facilitates the combining of data from detoxification and maintenance therapies across states and service providers.

• Two measures of effectiveness, change in heroin-free days and abstinence, have been used in the NEPOD economic evaluation. See section 4.8 for a discussion of these measures. A decision was made to exclude the methadone patients (i.e., those attempting to withdraw from methadone) from the economic analysis as these measures of effectiveness may not be an appropriate outcome for this treatment.

• Costs and effectiveness are compared and expressed as a cost-effectiveness ratio for Heroin Users receiving treatment. This ratio provides an indication of cost per successful treatment outcome and in general, the treatment with the lowest ratio is considered the most cost-effective.
6.3 Health economic results: detoxification

6.3.1 Combining data from the detoxification treatments: overview

The following section provides results from the pooling of data from trials that use similar methods of detoxification. These results have been condensed into two tables. Table 12 provides data on the cost of a detoxification procedure while Table 13 presents the cost of achieving abstinence for a seven day period following the commencement of detoxification. In both tables, information is presented on the type of detoxification treatment, the number of patients randomised and the percentage of patients that initiated treatment.

6.3.2 Detoxification treatment: cost per episode

• The estimate of detoxification cost per episode in Table 12 is the total detoxification costs from Table 13 divided by the number of patients that initiated treatment.

• From the treatments presented in Table 12, detoxification using buprenorphine in an outpatient setting is the least expensive treatment at $489 per episode compared to $2,689 per episode for rapid detoxification under anaesthesia for Heroin Users.

6.3.3 Detoxification treatments: cost of achieving abstinence

• Table 13 presents the cost of achieving one additional person’s abstinence from heroin for the initial week post-detoxification. Cost per abstinicnt patient is calculated by dividing total detoxification costs by the number of patients abstinent from heroin for the initial week post-detoxification.

• Rapid detoxification under sedation is the most cost-effective treatment at a cost of $3,317 per-abstinent patient. The next most cost-effective treatment is buprenorphine in an outpatient setting at a cost of $4,065 per abstinent patient. Detoxification through a conventional outpatient setting is the least cost-effective treatment at $16,945 per abstinent patient.

• It is interesting to observe from the results in Tables 12 and 13 that the cheapest treatment per-episode does not equate to the most cost-effective. As an example, buprenorphine detoxification is the cheapest treatment per episode but achieves a low rate of abstinence (12%), ranks second in terms of cost-effectiveness. Detoxification through a conventional outpatient setting, and is the least cost-effective method.
### Table 12: Detoxification treatments: cost per episode

<table>
<thead>
<tr>
<th>Detoxification treatment (number of patients and % initiating treatment)</th>
<th>Detoxification cost per episode&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine outpatient for Heroin Users&lt;sup&gt;a&lt;/sup&gt; (N=158, 100%)</td>
<td>$489</td>
</tr>
<tr>
<td>Conventional outpatient for Heroin Users (N=56, 100%)</td>
<td>$605</td>
</tr>
<tr>
<td>Conventional inpatient for Heroin Users (N=50, 68%)</td>
<td>$1,398</td>
</tr>
<tr>
<td>Rapid detoxification under sedation for Heroin Users (N=25, 96%)</td>
<td>$1,990</td>
</tr>
<tr>
<td>Rapid detoxification under anaesthesia for Heroin Users&lt;sup&gt;b&lt;/sup&gt; (N=76, 93%)</td>
<td>$2,689</td>
</tr>
</tbody>
</table>

Notes  
<sup>a</sup> = pooling of two buprenorphine outpatient detoxification trials,  
<sup>b</sup> = pooling of two rapid detoxification under anaesthesia trials,  
<sup>c</sup> = a multiple comparison of mean costs, with a Bonforoni adjustment, indicated that the only cost comparison that was not statistically significantly different at the 5% level was that between buprenorphine and conventional outpatient treatments.

### Table 13: Detoxification treatments: costs and outcomes

<table>
<thead>
<tr>
<th>Treatment group (number of patients and % initiating treatment)</th>
<th>Total detoxification costs</th>
<th>N (%) Abstinent achieving heroin for initial week</th>
<th>Cost of achieving initial week of abstinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid detoxification under sedation</td>
<td>$49,754</td>
<td>15 (60%)</td>
<td>$3,317</td>
</tr>
<tr>
<td>Buprenorphine outpatient&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$77,233</td>
<td>19 (12%)</td>
<td>$4,065</td>
</tr>
<tr>
<td>Rapid detoxification under anaesthesia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$204,384</td>
<td>44 (58%)</td>
<td>$4,645</td>
</tr>
<tr>
<td>Conventional inpatient</td>
<td>$69,893</td>
<td>12 (24%)</td>
<td>$5,824</td>
</tr>
<tr>
<td>Conventional outpatient</td>
<td>$33,890</td>
<td>2 (4%)</td>
<td>$16,945</td>
</tr>
</tbody>
</table>

Notes  
<sup>a</sup> = pooling of two buprenorphine outpatient detoxification trials,  
<sup>b</sup> = pooling of two rapid detoxification under anaesthesia trials.
6.3.4 Detoxification treatments: main findings and caveats

- For Heroin Users, rapid detoxification under sedation was found to be the most cost-effective treatment method of obtaining seven days of initial abstinence at a cost of $3,317 per patient. Although conventional outpatient detoxification was found to be the least cost-effective treatment at a cost of $16,945 per abstinent patient, a small improvement in rates of abstinence would likely impact positively on the cost-effectiveness.

- Rapid detoxification treatments were found to be the most effective treatments in terms of abstinence from heroin at seven-days post-detoxification. Given that these procedures are relatively new to the Australian environment, it is envisaged that potential efficiencies may be gained through the streamlining of the procedure and identification of cost reduction strategies.

6.4 Health economic results: maintenance therapies

<table>
<thead>
<tr>
<th>Source of medication costs and daily costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of medication costs:</td>
</tr>
<tr>
<td>Methadone is costed using the price paid by the Commonwealth Government per litre ($33.26 per 5000 mg).</td>
</tr>
<tr>
<td>Buprenorphine was not listed on the PBS at the time of this study. Therefore buprenorphine is costed using the MIMS-listed price ($10.50 for seven 2mg tablets and $30.10 for seven 8mg tablets).</td>
</tr>
<tr>
<td>LAAM is not registered in Australia. LAAM is costed using the British National Formulary price, converted to Australian dollars using purchasing price parity (AUD$375.71 per 5000mg).</td>
</tr>
<tr>
<td>The variations in medication prices needs to be kept in mind when considering the cost analyses and the cost-effectiveness estimates reported later.</td>
</tr>
<tr>
<td>Daily cost of maintence treatment for the various pharmacotherapies for Heroin Users over six months are:</td>
</tr>
<tr>
<td>Methadone maintenance – $ 9.63 per day</td>
</tr>
<tr>
<td>LAAM – $10.58 per day</td>
</tr>
<tr>
<td>Naltrexone treatment – $12.10 per day</td>
</tr>
<tr>
<td>Buprenorphine maintenance – $15.93 per day</td>
</tr>
</tbody>
</table>

The differences in the daily costs of treatments are relatively small between methadone, LAAM and naltrexone, which suggest an opportunity to provide a choice of treatment to heroin users. Buprenorphine appears to be more expensive but these costs may be reduced over time.
6.4.1 Combining data on maintenance treatments: overview

- The following section provides results from the pooling of data from trials which provided the same maintenance treatment. Again these results have been condensed into two tables. Table 14 provides data on the daily cost of treatment for three months while Table 15 outlines the cost for six months. In both tables, information is presented that identifies the pharmacotherapy, the treatment modality (i.e., clinic, GP setting or overall) and the number of patients randomised.

- The daily cost of pharmacotherapy treatment is calculated by dividing the total costs of treatment with the total number of days in treatment. The cost of treatment includes medication expenses, staff costs associated with the provision of treatment, any medical visits and counselling. The number of days a patient is in treatment reflects patient length of stay in the treatment of randomisation.

6.4 Buprenorphine maintenance: potential cost-savings

If buprenorphine is introduced in Australia, efficiencies in clinical practice, the safety of buprenorphine, and the PBS negotiated price, are likely to provide cost-savings:

In the trials reported herein, patients were inducted onto buprenorphine in the same way as is used for methadone (gradual doses and slow increases with frequent monitoring). With buprenorphine, a safer, quicker and less costly induction and stabilisation phase can be achieved than is possible with methadone (or LAAM). Clinicians will not need to examine the patient as frequently for signs of buprenorphine toxicity during the first week of dosing.

Dosing times with buprenorphine can be significantly reduced by changing methods of checking on tablet dissolution and by introducing thrice weekly dosing rather than alternate-day dosing. This could significantly reduce dosing-staff costs and provide significant savings to patients in terms of reduced travel. However, the assumption that neither of these will affect effectiveness of treatment should be investigated.

The price of buprenorphine, used to calculate cost and cost-effectiveness herein, is higher than the price that it is likely to be paid by the government (the perspective in this study). The PBS-negotiated price might introduce significant cost-savings.
6.4.2 Pooling of data from maintenance treatments: daily cost of treatment

- Results presented in Table 14 indicate that the provision of LAAM overall is the least expensive maintenance treatment for Heroin Users with an average daily cost of $11.77 over three months.

- From the data in Table 15 methadone and LAAM are again the cheapest maintenance therapies for both Heroin Users over six months. The only variation from three months is the ranking of pharmacotherapies for Heroin Users with methadone having a lower daily cost than LAAM, $9.63 and $10.58 respectively.

- Buprenorphine and naltrexone are the most expensive treatments over three and six months. The dramatic fall in the daily cost of naltrexone for six months for Heroin Users may be attributable in part to the fact that one NTX trial was only three-months in duration, and this was an expensive trial.

- The daily cost of maintenance treatment was consistently cheaper in the GP setting compared to the clinic setting. For example, Table 15 indicates that the cost per day on average for buprenorphine in the GP setting for Heroin Users was $13.79 compared to $16.33 in the clinic setting. As a consequence of this finding, the average daily costs of maintenance therapy overall will be influenced by the number of patients receiving treatment in the GP or clinic setting.

- The results presented in Tables 14 and 15 support the conclusion that the longer a patient remains in treatment, the lower the average daily cost of that treatment. Average daily costs over six months of treatment are consistently lower than the daily costs over three months of treatment. As an example, the daily cost of LAAM for Heroin Users was $11.77 and $10.58 over three and six months respectively. This reflects both the resource intensity at the initiation of treatment and the length of time a patient stays in treatment.

6.4.3 Maintenance therapy: main findings and caveats

- Treatment by methadone or LAAM achieves the lowest average daily cost over both three and six months. Buprenorphine and naltrexone were the most expensive treatments on a daily basis over both three and six months.

- A number of factors impact on these findings.
  1. Dosing time: methadone and LAAM are syrup-based medications while buprenorphine and naltrexone are provided in tablet form. Hence the time (and subsequent cost) required to dose methadone and LAAM are lower than that required for buprenorphine and naltrexone.
  2. Cost efficiencies: methadone as a well established form of treatment enjoys a number of advantages in administration and implementation when compared to the relatively new pharmacotherapies. It may be anticipated that such cost-efficiencies contribute to the lower overall costs of methadone maintenance in current practice.
  3. Setting: given that the daily cost of maintenance therapy was found to be cheaper in the GP setting, the low daily cost of LAAM is driven primarily by the relative weighting of patients receiving treatment in the GP setting. For example, of the 44 Heroin Users receiving LAAM, 73% of these patients receive medication in the GP setting.
### Table 14: Average cost of maintenance therapy at 3 months

<table>
<thead>
<tr>
<th>Maintenance therapy (number of patients)</th>
<th>Daily cost of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEROIN USERS</strong></td>
<td></td>
</tr>
<tr>
<td>LAAM maintenance overall (N=44)</td>
<td>$ 11.77</td>
</tr>
<tr>
<td>LAAM - GP setting (N=32)</td>
<td>$ 9.92</td>
</tr>
<tr>
<td>LAAM - specialist clinic (N=12)</td>
<td>$ 17.40</td>
</tr>
<tr>
<td>Methadone maintenance overall (N=287)</td>
<td>$ 14.00</td>
</tr>
<tr>
<td>Methadone - GP setting (N=61)</td>
<td>$ 8.94</td>
</tr>
<tr>
<td>Methadone - specialist clinic (N=226)</td>
<td>$ 15.53</td>
</tr>
<tr>
<td>Buprenorphine maintenance overall (N=250)</td>
<td>$ 20.23</td>
</tr>
<tr>
<td>Buprenorphine - GP setting (N=37)</td>
<td>$ 7.23</td>
</tr>
<tr>
<td>Buprenorphine - specialist clinic (N=213)</td>
<td>$ 20.80</td>
</tr>
<tr>
<td>Naltrexone treatment overall (N=268)</td>
<td>$ 21.19</td>
</tr>
<tr>
<td>NTX post rapid detoxification under sedation (N=25)</td>
<td>$ 11.97</td>
</tr>
<tr>
<td>NTX post rapid detoxification under anaesthesia (N=76)</td>
<td>$ 12.74</td>
</tr>
<tr>
<td>NTX (50mg) (N=20)</td>
<td>$ 14.37</td>
</tr>
<tr>
<td>NTX post conventional inpatient (N=50)</td>
<td>$ 19.05</td>
</tr>
<tr>
<td>NTX program + counselling (N=97)</td>
<td>$ 27.23</td>
</tr>
</tbody>
</table>

### Table 15: Daily cost of maintenance therapy at 6 months

<table>
<thead>
<tr>
<th>Maintenance therapy (number of patients)</th>
<th>Daily cost of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEROIN USERS</strong></td>
<td></td>
</tr>
<tr>
<td>Methadone maintenance overall (N=287)</td>
<td>$ 9.63</td>
</tr>
<tr>
<td>Methadone - GP setting (N=61)</td>
<td>$ 6.72</td>
</tr>
<tr>
<td>Methadone - specialist clinic (N=226)</td>
<td>$ 10.58</td>
</tr>
<tr>
<td>LAAM maintenance overall (N=44)</td>
<td>$ 10.58</td>
</tr>
<tr>
<td>LAAM - GP setting (N=32, 63%)</td>
<td>$ 9.09</td>
</tr>
<tr>
<td>LAAM - specialist clinic (N=12)</td>
<td>$ 14.93</td>
</tr>
<tr>
<td>Naltrexone treatment overall (N=171, 6%)</td>
<td>$ 12.10</td>
</tr>
<tr>
<td>NTX post rapid detoxification under anaesthesia (N=76)</td>
<td>$ 11.46</td>
</tr>
<tr>
<td>NTX (50mg) (N=20)</td>
<td>$ 11.82</td>
</tr>
<tr>
<td>NTX post rapid detoxification under sedation (N=25)</td>
<td>$ 11.97</td>
</tr>
<tr>
<td>NTX post conventional inpatient (N=50)</td>
<td>$ 17.38</td>
</tr>
<tr>
<td>Buprenorphine maintenance overall (N=250)</td>
<td>$ 15.93</td>
</tr>
<tr>
<td>Buprenorphine - GP setting (N=37)</td>
<td>$ 13.79</td>
</tr>
<tr>
<td>Buprenorphine - specialist clinic (N=213)</td>
<td>$ 16.33</td>
</tr>
</tbody>
</table>
6.5 Cost-effectiveness results

6.5 Cost-effectiveness results

Overall cost-effectiveness results indicate that:

Generally, agonist maintenance therapies using methadone, LAAM and buprenorphine are more cost-effective and achieve higher rates of completion than antagonist treatments.

Specifically, methadone and LAAM appear to be the more cost-effective pharmacotherapies with results for methadone maintenance being more stable and reliable than for LAAM maintenance.

Across treatment modalities, treatment in the GP setting is more cost-effective than treatment in a clinical setting. Care is needed in the interpretation of this finding, given the variations inherent between GP and clinical settings, and in particular the level of support provided in these trials to the GP by the clinics.

6.5.1 Cost-effectiveness results: overview

This section presents cost-effectiveness results at three and six months. Trials with similar detoxification procedures and pharmacotherapies are combined to provide an overall assessment of cost-effectiveness and an examination of cost-effectiveness by treatment modality (i.e., by GP or clinic setting). Table 16 considers cost-effectiveness at three months while Table 17 provides data pertaining to cost-effectiveness at six months.

In both tables, information is presented that identifies the type of pharmacotherapy, treatment modality (i.e., overall, in the GP or clinical setting), the number of patients randomised and the percentage of patients that are retained (i.e., completed) in treatment.

The total costs presented in these tables represent the total costs incurred for all patients while in treatment and include assessment costs, detoxification costs (if relevant) and costs associated with pharmacotherapy treatment. The cost effectiveness ratio was estimated by dividing the total difference in the number of heroin-free days achieved in either the 3rd or 6th month from the baseline month, to provide an estimate of the cost-per-additional heroin-free day for each pharmacotherapy or treatment modality.

6.5.2 Cost-effectiveness results: three and six months

- From the results presented in the tables, LAAM overall appears to be the most cost-effective pharmacotherapy. However, some caution should be exercised in the interpretation of these results due to the relatively small sample size for LAAM overall (N=44).

- Methadone is clearly the next most cost-effective pharmacotherapy and given the largest sample size of any pharmacotherapy, this finding is likely to be more stable. Approximately 62% of patients randomised to methadone overall completed three months of treatment with 50% completing six months. This completion rate is second only to LAAM overall that achieved 75% completion rates at three months and 61% at six months.
### Table 16: Cost-effectiveness results at 3 months

<table>
<thead>
<tr>
<th>Treatment (number of patients and % completing treatment)</th>
<th>Total costs 3 months</th>
<th>Additional heroin-free days</th>
<th>Cost per additional heroin-free day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAAM overall (N=44, 75%)</td>
<td>$42,732</td>
<td>655</td>
<td>$65.20</td>
</tr>
<tr>
<td>LAAM – GP setting (N=32, 75%)</td>
<td>$25,518</td>
<td>392</td>
<td>$65.11</td>
</tr>
<tr>
<td>LAAM – specialist clinic (N=12, 75%)</td>
<td>$17,213</td>
<td>263</td>
<td>$65.35</td>
</tr>
<tr>
<td>Methadone overall (N=287, 62%)</td>
<td>$329,232</td>
<td>3294</td>
<td>$99.95</td>
</tr>
<tr>
<td>Methadone – GP setting (N=61, 72%)</td>
<td>$40,179</td>
<td>611</td>
<td>$65.75</td>
</tr>
<tr>
<td>Methadone – specialist clinic (N=226, 59%)</td>
<td>$289,052</td>
<td>2683</td>
<td>$107.74</td>
</tr>
<tr>
<td>Buprenorphine overall (N=250, 50%)</td>
<td>$344,387</td>
<td>2364</td>
<td>$145.67</td>
</tr>
<tr>
<td>Buprenorphine – GP setting (N=37, 57%)</td>
<td>$39,470</td>
<td>430</td>
<td>$91.90</td>
</tr>
<tr>
<td>Buprenorphine – specialist clinic (N=213, 49%)</td>
<td>$304,917</td>
<td>1935</td>
<td>$157.60</td>
</tr>
<tr>
<td>Naltrexone overall (N=151, 14%)</td>
<td>$363,948</td>
<td>989</td>
<td>$368.14</td>
</tr>
<tr>
<td>NTX post rapid detoxification under anaesthesia (N=76, 20%)</td>
<td>$228,974</td>
<td>699</td>
<td>$327.52</td>
</tr>
<tr>
<td>NTX post rapid detoxification under sedation (N=25, 20%)</td>
<td>$58,130</td>
<td>162</td>
<td>$359.94</td>
</tr>
<tr>
<td>NTX post conventional inpatient (N=50, 2%)</td>
<td>$76,845</td>
<td>128</td>
<td>$600.35</td>
</tr>
</tbody>
</table>

### Table 17: Cost-effectiveness results at 6 months

<table>
<thead>
<tr>
<th>Treatment (number of patients and % completing treatment)</th>
<th>Total costs 6 months</th>
<th>Additional heroin-free days</th>
<th>Cost per additional heroin-free day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAAM overall (N=44, 61%)</td>
<td>$65,146</td>
<td>661</td>
<td>$98.52</td>
</tr>
<tr>
<td>LAAM – GP setting (N=32, 63%)</td>
<td>$40,172</td>
<td>450</td>
<td>$89.36</td>
</tr>
<tr>
<td>LAAM – specialist clinic (N=12, 58%)</td>
<td>$24,974</td>
<td>212</td>
<td>$117.98</td>
</tr>
<tr>
<td>Methadone overall (N=287, 50%)</td>
<td>$381,593</td>
<td>2191</td>
<td>$174.15</td>
</tr>
<tr>
<td>Methadone – GP setting (N=61, 66%)</td>
<td>$55,353</td>
<td>520</td>
<td>$106.38</td>
</tr>
<tr>
<td>Methadone – specialist clinic (N=226, 46%)</td>
<td>$326,240</td>
<td>1671</td>
<td>$195.26</td>
</tr>
<tr>
<td>Buprenorphine overall (N=250, 38%)</td>
<td>$428,234</td>
<td>1571</td>
<td>$272.52</td>
</tr>
<tr>
<td>Buprenorphine – GP setting (N=37, 48%)</td>
<td>$51,307</td>
<td>386</td>
<td>$132.85</td>
</tr>
<tr>
<td>Buprenorphine – specialist clinic (N=213, 36%)</td>
<td>$376,928</td>
<td>1185</td>
<td>$318.02</td>
</tr>
<tr>
<td>Naltrexone overall (N=151, 5%)</td>
<td>$372,363</td>
<td>1054</td>
<td>$353.13</td>
</tr>
<tr>
<td>NTX post rapid detoxification under anaesthesia (N=76, 8%)</td>
<td>$235,091</td>
<td>644</td>
<td>$364.79</td>
</tr>
<tr>
<td>NTX post rapid detoxification under sedation (N=25, 4%)</td>
<td>$60,061</td>
<td>59</td>
<td>$1,017.98</td>
</tr>
<tr>
<td>NTX post conventional inpatient (N=50, 0%)</td>
<td>$77,211</td>
<td>351</td>
<td>$219.97</td>
</tr>
</tbody>
</table>
• Buprenorphine ranks third overall in cost-effectiveness at both three and six months with completion rates of 50% and 38% respectively. The caveats placed around buprenorphine in Section 6.4 and in particular the issues of pricing and dosing time apply equally to this section. It is anticipated that any reductions in the price of buprenorphine and efficiencies gained in the administration of the medication (such as reduction in dosing time) may impact significantly on the total cost associated with buprenorphine and hence cost-effectiveness values.

• From Tables 16 and 17, naltrexone appears to be the least cost-effective pharmacotherapy costing approximately $350 per additional heroin-free day in one month at both three and six months. Although the number of patients randomised to receive naltrexone post-detoxification are relatively high in comparison to other pharmacotherapies, the percentage of patients completing treatment are consistently lower than other groups with only 14% of naltrexone patients overall completing three months of treatment and 5% completing six months.

• It is important to note that NTX (50mg) and NTX program+counselling have not been included in Tables 16 and 17 as patients randomised to these studies had already completed detoxification prior to induction into the trial. As the costs of detoxification were not available and baseline outcomes were collected post-detoxification the comparison would not have been valid.

• Across treatment modalities, treatment in the GP setting appears to be more cost-effective than the clinic setting at both three and six months. While every effort to include all costs pertaining to the cost of treatment provision in the GP setting have been made, there may be other costs such as outside counselling, support costs by the clinic and the Division of GPs that have not been captured. While inclusion of these components may not cause the results to change, it is important to recognise that this was the setting in which treatment was provided. It is also important to note that these GP trials have been provided within an environment of support from drug and alcohol treatment centres.

6.5.3 Cost-effectiveness results: main findings and caveats

• In general, agonist maintenance therapies using methadone, LAAM and buprenorphine appear to be more cost-effective and achieve higher rates of completion than antagonist treatments.

• Specifically, methadone and LAAM appear to be the more cost-effective pharmacotherapies with results for methadone being more stable and hence reliable than LAAM. Both LAAM and methadone are cheaper per daily cost of pharmacotherapy than either buprenorphine or naltrexone and also result in a higher proportion of patients completing three and six months of treatment.

• Across treatment modalities, treatment in the GP setting appears to be more cost-effective than the clinic setting at both three and six months. While every effort to include all costs pertaining to the cost of treatment provision in the GP setting have been made, there may be other costs such as outside counselling, support costs by the clinic and the Division of GPs that have not been captured. While inclusion of these components may not cause the results to change, it is important to recognise that this was the setting in which treatment was provided. It is also important to note that these GP trials have been provided within an environment of support from drug and alcohol treatment centres.

6.6 Health economic summary

• The data used in conducting the health economic analyses presented in this section are based on the findings of clinical trials. It is important to note that interventions occurring within clinical trials may differ from actual clinical practice in terms of intensity and resource use.
• The health economic methodology adopted for this evaluation has been developed to facilitate a meaningful comparison of pharmacotherapy interventions for opioid dependency that do vary across treatment modalities, duration and timing.

• The results presented in this section shed light on the most cost-effective treatments for opioid dependence in Australia. However, it is important to consider the caveats placed around the results when interpreting the main findings.

• In summary, the results indicate that rapid detoxification under sedation is the most cost-effective detoxification treatment while methadone is the most stable cost-effective maintenance treatment.
7. REFERENCES


Gooberman, L. L., Bradway, D. W., & Bartter, T. Pellets vs. oral therapy 30 day relapse rates (unpublished).


8. APPENDICES

8.1 Literature reviews

8.1.1 Opioid detoxification

Rationale for linking people undergoing detoxification to ongoing treatment. The goal of detoxification is not necessarily long term abstinence but rather detoxification programs provide supervised withdrawal from a drug so that the severity of withdrawal and medical complications are managed. Detoxification is not necessarily a complete treatment in itself but is more appropriately regarded as a process that aims to achieve safe and humane withdrawal from a drug of dependence (Mattick & Hall, 1996). A reason that detoxification should not be regarded as a treatment as such is that prospective controlled studies have shown patients that have undergone detoxification were equally likely to relapse to illicit drug use as those who did not enter any treatment (Gerstein & Harwood, 1990; Simpson, Joe, & Bracy, 1982). However, detoxification is a necessary step to achieve abstinence, is a required first step in the treatment process (Kleber & Riordan, 1982) and may also signify an end to longer-term treatment such as methadone. Therefore detoxification is an essential component of the treatment system.

As rates of completion of withdrawal (Milby, 1988) are low and relapse to opioid use is common (Gossop, Bradley, & Phillips, 1987; Milby, 1988), it is important to provide patients with the opportunity to enter other treatments. People may enter detoxification programs with the aim of abstinence or reduction of opioid use and find these to be unattainable goals. This is often an opportunity to link them into other treatments, such as maintenance treatment, which they previously may not have considered entering. This link into a further treatment, which is known to reduce illicit drug use, improve health and enhance social functioning, is an important point to consider when evaluating detoxification outcomes.

Overview of opioid detoxification. The opioid withdrawal syndrome is rarely life threatening (Fishbain, Rosomoff, Culter, & Rosomoff, 1993; Mattick & Hall, 1996). However, completion of withdrawal is difficult for most people (Frank & Pead, 1995; Mattick & Hall, 1996) and subsequent rates of relapse to opioid use are high (Gossop, Green, Phillips, & Bradley, 1989).

There has been a gradual improvement in rates of completion of detoxification over the years due to an increased use of medications (including methadone, clonidine and naltrexone) to ameliorate symptoms and shorten the length of treatment (Milby, 1988). Gradual methadone reduction was the routine method for many years, as the withdrawal syndrome was found to be milder, though more protracted, than morphine withdrawal (Kleber & Riordan, 1982). However, discovery of the ability of clonidine, an alpha-2-adrenergic agonist, to alleviate withdrawal symptoms led to its widespread use as a non-opioid alternative for managing withdrawal (Gossop, 1988).

Detoxification initially occurred in inpatient settings although more recently outpatient or home detoxification has become more common. The proportion of patients who complete withdrawal has been reported to be between 50-80% for inpatient detoxification and around 20% for outpatient detoxification (Gossop, Johns, & Green, 1986; Lipton & Maranda, 1983).
Several investigators have found inpatient detoxification to be superior to outpatient detoxification in terms of the proportion of people who complete the process. Factors that may influence this difference include: reduced ability to obtain illicit drugs while inpatients, the potential for greater support in an inpatient setting, greater capacity to adjust and administer symptomatic medication, increased capacity to administer high doses of medication without increased risk, and separation from social contacts and environments that may trigger use (Gowing, Ali, & White, 2000b).

Clonidine has been shown to be as effective in alleviating withdrawal symptoms as reducing doses of methadone. The comparison of the withdrawal syndrome of clonidine and gradual methadone reductions show that peak withdrawal is similar, or marginally higher for clonidine, but appears earlier and resolves more quickly with the use of clonidine (Kleber et al., 1985; San, Camí, Peri, Mata, & Porta, 1990; Washton & Resnick, 1980). Clonidine has side effects of hypotension (low blood pressure) and sedation. As adverse effects are more common with clonidine than with gradual methadone reductions (hypotension, dizziness, drowsiness, lethargy and dry mouth), investigations of other alpha-2-adrenergic agonists (lofexidine, guanfacine, guanabenz acetate) and buprenorphine have been conducted in an attempt to find a drug that is equivalent to clonidine in its capacity to alleviate withdrawal symptoms with fewer side effects (Gowing et al., 2000b).

Buprenorphine Withdrawal. Buprenorphine is a partial, rather than a full, agonist at the mu opioid receptor. It has a slow rate of dissociation from opioid receptors, which results in a long duration of action. Due to the unique pharmacology of buprenorphine, it has been considered for use in the treatment of opiate withdrawal. The rationale for using buprenorphine is that its agonist effects can alleviate withdrawal symptoms, but as it is only a partial agonist the symptoms will be less severe than from a full agonist (Banys, 1994) and slow dissociation from receptors also reduces symptom severity. Buprenorphine has been reported to have a milder withdrawal syndrome than other opiates, however there are few direct comparison studies of buprenorphine with other withdrawal treatments.

Gowing et al (2000a) recently reported a review that assessed the effectiveness of interventions involving short-term buprenorphine use to manage opioid withdrawal. Their Cochrane review of controlled trials compared the use of buprenorphine with other forms of treatment, and found that of the five studies included in the review, all reported withdrawal to be less severe in the buprenorphine group (Gowing, Ali, & White, 2000a).

One study in the review used buprenorphine in an outpatient setting (O’Connor et al., 1997), comparing buprenorphine, clonidine alone or clonidine plus naltrexone. The authors found no difference in retention between the three groups, but significantly lower withdrawal scores in the buprenorphine group when compared with the clonidine and clonidine plus naltrexone groups. There have been a few other studies that have used buprenorphine in withdrawal on an outpatient basis. These were not included in the review as there were no control groups, but in combination with the O’Connor study, they provide preliminary evidence to suggest the feasibility of buprenorphine in outpatient withdrawal (Diamant et al., 1998).

Completion of withdrawal using buprenorphine has ranged from 76% (Umbricht et al., 1999) to 85% (Janiri, Mannelli, Persico, Serretti, & Tempesta, 1994) and 81% in an outpatient buprenorphine group (O’Connor et al., 1997). Cheskin (1994) reported completion rates of 72% overall for the clonidine and buprenorphine groups.
Although the literature is limited, the authors of the Cochrane review concluded that buprenorphine has the potential to ameliorate the signs and symptoms of withdrawal from heroin and possibly from methadone. The reviewed studies varied in terms of the type of buprenorphine used (one study used intramuscular injection whereas the others used sublingual solution or tablets), the range of doses, length of time on buprenorphine and the use of additional medications. Additional research is required to further investigate aspects of the treatment protocol and relative effectiveness in a range of withdrawal treatments (Gowing et al., 2000a).

**Rapid opiate detoxification under sedation (RODS) or anaesthesia (RODA).** The international literature regarding the effectiveness of rapid opiate detoxification under sedation (RODS) and rapid detoxification under anesthesia (RODA) is limited due to the small numbers of patients included in relevant studies, variation in treatment protocols, lack of randomised designs and control groups, and limited information on long-term outcomes (Mattick et al., 1997; O’Connor & Kosten, 1998).

The available evidence, however, suggests that both techniques have good short-term outcomes, with the majority of patients completing the detoxification protocol and thereby being inducted onto naltrexone. The nature of the RODA procedure means that 100% of patients who begin the treatment can be inducted onto naltrexone. Completion of the detoxification protocol and induction onto naltrexone for RODS ranges from 75% (Gerra et al., 2000), to 80% (Bell et al., 1999), to 100% (Cucchia, Monnat, Spagnoli, Ferrero, & Bertschy, 1998; London, Paul, & Gkolia, 2000).

Average lengths of inpatient stay in recent studies have ranged from one to eight days, with a median of 3-4 days (Bell & Kimber, 2000) and does not appear to be systematically different for RODS patients compared with RODA patients. However, length of inpatient stay tends to be longer for patients on methadone compared with shorter acting opioids (Bell et al., 1999; Hensel & Kox, 2000).

Long-term outcomes point to poor compliance with naltrexone treatment and high rates of relapse to heroin use (see naltrexone treatment), with the majority of patients in recently published rapid detoxification studies relapsing to heroin use in the first two months after detoxification (Bell & Kimber, 2000). There is little information available on relative relapse rates. Gerra and colleagues (2000) report similar relapse rates at six months between outpatient RODS (47%) and conventional outpatient detoxification using clonidine (56%) while 74% of patients in the methadone-tapering group had returned to heroin use.

There do not appear to be systematic differences in long-term outcomes between RODA and RODS patients, however risks and costs associated with RODA may be greater than those for RODS (Bell & Kimber, 2000).

### 8.1.2 Effectiveness of opioid agonist treatments

Generally studies have shown that the agonists methadone and LAAM and the partial agonist buprenorphine reduce illicit drug use, reduce criminal activity, retain people in treatment, reduce the risk of blood borne virus and improve general health and social functioning. The literature on the relative efficacy of the treatments with regards to retention and illicit drug use is discussed below.
Methadone Maintenance. Methadone maintenance was first introduced in the 1960’s (Dole & Nyswander, 1965) and is the most common treatment for opioid dependence in Australia. Due to the ethical problems of allocating people to untreated control groups and denying a treatment that may be of benefit, there have been only three randomised controlled trials conducted that have compared methadone maintenance with a control condition over a substantial time period (Dole et al., 1969; Gunne & Grönbladh, 1981; Newman & Whitehill, 1979). These studies have all demonstrated the effectiveness of methadone maintenance (Ward et al., 1998). Ward et al (1998) reviewed a study investigating opioid dependent men released from prison, and found the risk of returning to heroin use was four times higher for the control group than for the methadone group and risk of being reincarcerated was 2.7 times greater for the control group (Dole et al., 1969). A randomised controlled trial that compared methadone maintenance to placebo found retention in treatment to be significantly greater in the methadone group than in the placebo group (Newman & Whitehill, 1979). Gunne and Grönbladh (1981) found that after two years in methadone maintenance treatment twelve of seventeen patients in the methadone group were no longer regularly using opiates or other drugs compared with only one out of seventeen in the control group (Gunne & Grönbladh, 1981). These early studies gave evidence to support the effectiveness of methadone maintenance.

There have been numerous controlled and observational studies of variations of methadone dose levels (Strain, Stitzer, Liebson, & Bigelow, 1993), intensity of treatment (Yancovitz et al., 1991), length of treatment (Vanichseni, Wongsuwan, Staff of the BMA Narcotics Clinic No. 6, Choopany, & Wongpanich, 1991) and comparisons with other treatments. The literature has consistently shown methadone maintenance to decrease illicit drug use, criminal activity, injection-related risk behaviour (and therefore the risk of blood borne infection), and also improves health and social functioning (Ward et al., 1998).

LAAM Maintenance. Levo-alpha acetylmethadol (LAAM) is a long-acting derivative of methadone that can be taken every second or third day. LAAM was approved by the FDA for maintenance treatment of opioid dependence in the US in 1993. A marketing authorisation of Orlaam was granted in the European Union in 1997. In April 2001, the European Agency for the Evaluation of Medicinal Products issued a public statement recommending a suspension of the marketing authorisation. This was due to reports of ten cases of life threatening cardiac disorders in patients treated with Orlaam currently under investigation (EMEA, 2001). Currently, LAAM is not registered in Australia, and is used as an investigational drug only.

Early work (Fraser & Isbell, 1952) helped to establish the ability of LAAM to alleviate withdrawal symptoms. Several studies (Jaffe et al., 1972; Ling, Charuvasta, Kaim, & Klett, 1976; Ling, Klett, & Gillis, 1978; Savage, Karp, Curran, Hanlon, & McCabe, 1976), and one meta-analysis (Glanz, Klawansky, McAullife, & Chalmers, 1997) have been performed comparing LAAM maintenance to methadone maintenance without showing a consistent difference in the relative efficacy. There have been relatively few studies of LAAM since the 1980s. A Cochrane review is in progress to determine the relative efficacy of LAAM (Clark et al., 2001).

A meta-analysis (Glanz et al., 1997) of 14 randomised controlled trials comparing LAAM with methadone maintenance noted significantly greater treatment retention for methadone. The authors found that medication compliance (reflected in the proportion of patients that discontinued treatment because of side-effects) was significantly greater for LAAM compared with methadone.
Although not significant, there was a trend toward a greater decrease in illicit drug use with LAAM compared to methadone (Glanz et al., 1997). Tennant et al (1986) suggest that LAAM may be preferable to methadone for a select group of individuals, with almost 40% of their patients reporting they would return to heroin use rather than re-enter methadone treatment if LAAM was unavailable (Tennant, Rawson, Pumphrey, & Seecof, 1986). Given the potential practical benefits of LAAM compared to methadone in certain situations, LAAM is a possible alternative to methadone (Glanz et al., 1997).

**Buprenorphine Maintenance.** Buprenorphine hydrochloride, a drug with unique pharmacological properties, has been registered in Australia since October 2000 for the treatment of opiate dependence, including maintenance and detoxification within a framework of medical, social and psychosocial treatment. Buprenorphine is a partial, rather than full, agonist at the mu opioid receptor. In combination with its safety profile, this allows for alternate day dosing, by doubling the daily dose and missing every second day. Buprenorphine has been reported to have a milder withdrawal syndrome, less potential for abuse, respiratory depression and overdose.

Buprenorphine has been shown to be effective when compared to placebo (Johnson et al., 1995a; Ling, 1998). Randomised controlled trials have shown buprenorphine to be as effective as methadone in terms of retention in treatment and reduction of illicit opiate use (Bickel et al., 1988; Johnson et al., 1995b; Strain, Stitzer, Liebson, & Bigelow, 1994). However, other studies (Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993; Ling, Wesson, Charuvastra, & Klett, 1996) found that retention and reduction in opiate use were lower in the buprenorphine groups. The authors concluded that the fixed doses of buprenorphine used in their studies were inadequate, and that future research needed to use higher buprenorphine doses. The early studies of buprenorphine maintenance used buprenorphine as an ethanol-based solution, which has a slightly higher bioavailability than the tablet preparation that is available in Australia.

More recent studies have used sublingual buprenorphine tablets. Fischer et al (1999) compared buprenorphine (maximum 8mg) with methadone (‘no upper limit’ on dose). They found that the buprenorphine group had significantly fewer opiate positive urines but the retention was significantly lower than the methadone group. This may be due to the maximum buprenorphine dose having been set too low (Fischer et al., 1999). Uehlinger et al (1998) found that urine results were similar in the methadone and buprenorphine groups, however retention was lower in the buprenorphine group, with many drop-outs occurring in the induction phase (Uehlinger et al., 1998). Another study reporting lower retention in the buprenorphine group also noted that many patients dropped out in the induction phase (Gessa, Tagliamonte, Pani, Pirastu, & Maremmani, 1998).

A recently published double blind randomised trial of short-term (six week) buprenorphine and methadone maintenance (Petitjean et al., 2001) found that although methadone retention was better in this study (90% compared to 56% in the buprenorphine group), possibly due to inadequate induction doses in the buprenorphine group, both methadone and buprenorphine were effective in reducing opiate use.

A recently published meta-analysis that compared the effectiveness of buprenorphine and methadone found equivalent efficacy of buprenorphine and methadone in terms of illicit drug use (West, O'Neal, & Graham, 2000). In addition, it has been shown that daily and alternate-day buprenorphine dosing have equivalent effects on opioid withdrawal symptoms (Amass, Bickel, Higgins, & Badger, 1994; Fudala, Jaffe, Dax, & Johnson, 1990; Johnson et al., 1995b) and illicit opioid use (Johnson et al., 1995b).
Recent comparison study – methadone, LAAM and buprenorphine. A recent randomised comparison study (Johnson et al., 2000) of LAAM, buprenorphine, high-dose methadone (60-100mg) and low dose methadone (20mg) concluded that LAAM, buprenorphine, and high-dose methadone are significantly better at reducing the use of illicit opioids and retaining people in treatment compared to low-dose methadone.

The mean number of days that a patient remained in the study was significantly higher for those receiving LAAM (89), buprenorphine (96), and high-dose methadone (105) than for those receiving low-dose methadone (70). Retention was also significantly greater among patients receiving high-dose methadone than among those receiving LAAM. The percentage of patients with 12 or more consecutive opioid-negative urine specimens was significantly lower in the low dose methadone group.

8.1.3 Effectiveness of opioid antagonist treatments

Naltrexone treatment. Naltrexone is an opioid antagonist, this means it blocks the effects of opioids. Although naltrexone has been found to be a safe and effective opioid antagonist, the research literature points to poor treatment patient acceptance and poor retention in naltrexone treatment (Tucker & Ritter, 1997). A lack of rigor in the naltrexone literature was identified in a recent Cochrane review (Kirchmayer, Davoli, & Verster, 2001), which concluded that naltrexone cannot be considered to be a treatment that has been scientifically proven to be superior to other kinds of treatment.

Average retention in treatment has ranged from about six weeks (Lewis et al., 1978) to eight months (Ling & Wesson, 1984) and appears to depend on the type of patient studied and the addition of adjunctive therapies. In a recent review by Tucker and Ritter (1987), the average retention across reviewed studies was approximately three months. Early attrition from naltrexone treatment is also common, with reports of 40-50% dropping out within the first week of treatment (Tucker & Ritter, 1997).

The highest retention rates have been reported for patients who are highly motivated to remain abstinent, such as business executives and physicians facing job loss (Washton, Pottash, & Gold, 1984) and participants in prisoner work release programs (Brahen, Henderson, Capone, & Kordal, 1984). In studies comparing retention in naltrexone to retention in methadone maintenance, retention in methadone is greater (Grey, Osborn, & Reznikoff, 1986; Osborn, Grey, & Reznikoff, 1986). The probability of a positive outcome in naltrexone treatment, as for other treatments for drug dependence, is increased by stable social contacts (e.g., spouse, family, and friends) and employment.

Although retention in naltrexone treatment is poor, the majority of studies suggest that those patients who remained in treatment had lower levels of craving, higher abstinence rates and longer periods of abstinence than patients who were treated with placebo or standard treatments (Tucker & Ritter, 1997).

Naltrexone implants. As noted above, published data on naltrexone treatment have found that long-term compliance is an issue for treatment effectiveness (Chiang, Kishimoto, Barnett, & Hollister, 1985). Sub-cutaneous slow release preparations of naltrexone, known as implants are currently receiving attention as a possible way of improving compliance in naltrexone treatment. Implants can provide effective blockade for up to 60 days compared with approximately 24 hours with a single 50mg oral naltrexone dose (Gooberman et al., unpublished).
There has been interest in the development of naltrexone implants since the early 1980s (Chiang, Hollister, Kishimoto, & Barnett, 1984). However, evidence about naltrexone implants is scarce. There have been no published peer-reviewed studies on the effectiveness of naltrexone implants for the treatment of opioid dependent patients. In an unpublished retrospective study, Gooberman, Bradway and Bartter found naltrexone implants resulted in significantly higher abstinence rates compared with oral naltrexone at 30 days post rapid detoxification. The majority (72%) in the implant group stated that they were not using opiates compared with 47% of the oral naltrexone group (Gooberman et al., unpublished). Foster & Brewer (1989) followed up 55 patients who had naltrexone implants at 12 weeks post detoxification. Eleven patients (21%) reported they had resumed opiate use and none had relapsed to regular opiate use during the first month post detoxification (Foster & Brewer, 1998).

Currently there is no regulation on the manufacture of naltrexone implants and this device is not registered for use in Australia.

The use of implants creates a higher threshold for naltrexone treatment than the oral preparation in that the placement of the implant requires minor surgery. The use of implants also raises ethical issues relating to coercion of patients into treatment and forced abstinence.

The published data on naltrexone implants is limited and therefore conclusions on the relative efficacy and safety of the treatment cannot be made in the absence of well-designed randomised controlled trials.

8.1.4 Models of treatment delivery

There is limited evidence on the comparative effectiveness of treatment delivered in primary health care versus specialist settings. It appears, however, that for patients with comparable baseline characteristics there is no difference in outcomes across these types of settings.

Gossop et al (1999) examined six-month outcomes of methadone patients who received treatment at a specialist clinic or a general practice setting. There was no difference in treatment outcomes between the two groups, with heroin use in the previous month averaging 7.8 days for GP patients and 9.0 days for clinic patients. However, the authors noted that the GPs in this study were unrepresentative of GPs more generally in terms of their willingness and experience in providing treatment to drug users (Gossop, Marsden, Stewart, Lehman, & Strang, 1999).

Similarly, Lewis & Bellis (2001) compared methadone treatment outcomes in a specialist drug clinic and a general practice operating a shared-care policy (with a specialist clinic). They found that retention and abstinence rates in the shared-care model of care in general practice were at least as good as those of a specialist clinic (Lewis & Bellis, 2001).

The role of the specialist drug clinic is an essential component of the shared-care model and the importance of this role is unlikely to diminish in the future. Treatment by GPs in a shared-care model relies on an effective specialist service to provide easy access to experience and advice from drug treatment specialists. Considering that many GPs may never want to treat drug dependence and that some chaotic patients may not be appropriate for treatment in the GP setting, the need for both specialist services and a shared-care approach to treatment is evident.
8.1.5 Criminal behaviour

Australian data indicate a clear association between heroin use and criminal behaviour. Heroin use appears to be more prevalent among police detainees than among the general population. A study involving urinalysis found that approximately 43% of police detainees in Australia had recently used opioids, the great majority of which were probably heroin (Makkai, Fitzgerald, & Doak, 2000). This compares with an estimated 2.2% of the Australian population over the age of 14 years who report ever having used heroin (Australian-Institute-of-Health-and-Welfare, 1999), and an estimated 0.7% of adults aged 15-54 years who could be classified as heroin dependent (Hall et al., 2000). Another Australian national survey found that 1.2% of the general population aged 18 years or more reported having used opioids in the past 12 months, including 0.2% classified as dependent (Hall, Lynskey, & Degenhardt, 1999).

Rates of criminal behaviour among heroin users appear to be high. Among a sample of more than 300 Australian heroin users who were seeking entry to methadone treatment in Australia, approximately 75% self-reported ever having been involved in criminal behaviour (Bell et al., 1992b). Another study, based on police records, found that 90% of heroin users had convictions (Hall et al., 1993). Two Australian studies have found that treatment-seeking heroin users self-reported high rates of criminal behaviour during the month prior to their interviews: 29% (Darke, 1992) and 32% (Bell et al., 1997). Among heroin users in Australia who are not necessarily seeking treatment, these estimates increase even further to approximately 54% (Topp et al., 2001).

The existence of an association between heroin use and criminal behaviour is evident, however, the nature of the causal relationship between them is less clear. Explaining this relationship has fundamental policy implications, as it facilitates appropriate targeting of resources to impact optimally upon the nexus between heroin use and crime. There are at least three possibilities: (1) heroin use may lead to involvement in criminal behaviour; (2) being involved in criminal behaviour may lead to heroin use; or (3) other factors may promote involvement in both criminal behaviour and heroin use. There are Australian data that support all three possibilities.

Heroin use can occur prior to involvement in criminal behaviour as suggested by a finding that women were significantly more likely than men to commit an offence after their first opioid use (Hall et al., 1993). This finding is consistent with a finding that females were more likely to be introduced to heroin use by a heroin-using male sexual partner (Hser, Anglin, & McGlothin, 1987). Alternatively, there is also evidence that criminal behaviour occurs prior to heroin use, and increases once heroin dependence becomes established (Dobinson & Ward, 1985; Dobinson & Ward, 1987; Hall et al., 1993; Kaye, Darke, & Finlay-Jones, 1998; Weatherburn & Lind, 1999). Finally, the possibility that other factors may promote both heroin use and criminality is suggested by Australian findings that those who qualify for a diagnosis of Anti-Social Personality Disorder (ASPD) are more likely both to be involved in criminal behaviour and to begin opioid use subsequent to a criminal conviction (Bell et al., 1997; Darke, Hall, & Swift, 1994; Kaye et al., 1998).

Given the plausibility of all three of the above possibilities, it is reasonable to surmise that the causal relationship between criminal behaviour and heroin use may differ between individuals. From a population perspective, this conclusion implies a need for public policy to address all three broad issues simultaneously in order to achieve maximum benefit. For
example, in the case of people who use heroin before becoming involved in crime, there will be benefit from policies that aim to prevent or reduce heroin use, essentially to minimise the subsequent need for criminal activity to support heroin dependence.

In the case of people who are engaging in crime before starting heroin use, one aim would be to prevent or reduce heroin use among people in the criminal justice system. Such policies might effectively target the prison system, particularly juvenile detention centres, as males with the youngest ages of first conviction have been found to engage in higher rates of criminal behaviour (Bell et al., 1992b; Hall et al., 1993). Finally, identifying and targeting risk factors for the development of personality or mental health disorders, such as ASPD, may help to prevent or reduce levels of both crime and heroin use. Specific risk factors include poor school performance, alcohol and tobacco use in early teens, and greater social deviancy and nonconformity than peers (Hall et al., 1999).

Of these three complementary approaches, the most relevant to clinical services is the aim of directly reducing heroin use. Australian data support the contention that provision of effective treatments for heroin dependence can achieve concomitant reductions in criminal activity. Bell et al. (1992b) found that remaining in treatment was associated with a progressive reduction in the rate of convictions. More specifically, Bell et al. (1997) found that, after entering treatment, patients’ level of criminal behaviour was reduced to about one-eighth of that reported during their most recent period of heroin dependence. Another, more recent, Australian study found that 60% of heroin users self-reported a reduction in criminal behaviour or legal issues (Ezard et al., 1999).

The complexity of the causal relationships between heroin use and criminal behaviour suggests the provision of clinical treatment services is likely to reduce, rather than eliminate, heroin-related criminal behaviour. This expectation is consistent with Australian data demonstrating that frequency of heroin use was positively correlated with frequency of committing crime (Bell et al., 1992b).

The extent to which heroin-related criminal behaviour in Australia could be reduced by provision of treatment services is determined by a number of factors, including: the quality of treatment provided; the proportion of dependent heroin users who participate in treatment; the length of time for which they are retained in treatment; the extent to which patients are required to pay for their treatment (with treatment possibly needing to be funded by some continuing crime); patients’ levels of co-existing social dysfunction and other illicit drug use; their age of first exposure to the criminal justice system; and whether they have ever habitually derived income from illegal sources (Bell et al., 1992b; Bell et al., 1997; Hall et al., 1993; Joseph & Woods, 1995; Killias & Uchtenhagen, 1996; Marsch, 1998; Nurco, Cisin, & Ball, 1985; Rosenbaum et al., 1996; Rothbard et al., 1999).

From a population perspective, the extent to which treatment services will impact on overall levels of heroin-related criminal behaviour will also be limited by the extent to which other effective programs are able to simultaneously target individuals who come into contact with the criminal justice system prior to developing heroin dependence, as well as target individuals who are at increased risk of mental health disorders.

### 8.1.6 Treatment safety – serious adverse events

An examination of the international literature regarding the safety of pharmacotherapies for opioid dependence identifies large variations in the rates of reporting serious adverse events
(SAE). For example, the proportion of patients who report having experienced an SAE ranges from 1% (Broers, Giner, Dumont, & Mino, 2000) to 50% (Garcia-Alonso et al., 1989).

Similarly large variations are apparent when data are considered as mean numbers of SAEs reported per patient, ranging from 10 (Ling et al., 1998) to 100 (Pani, Maremmani, Pirastu, Tagliamonte, & Gessa, 2000) per 100 patients treated. There are several possibilities that may help to explain this apparent variation, each of which has implications for pharmacotherapy related SAEs.

Firstly, this variation may reflect different types of patients in treatment. With regard to the opioid agonist methadone, for example, there appears to be a difference between long and short-term users, whereby the latter have a greater degree of opioid use naivety and are, therefore, at increased risk of experiencing an SAE (Clark, Milroy, & Forrest, 1995). Another study reported that three out of four patients that died had taken the antagonist naltrexone for less than two weeks (Miotto, McCann, Rawson, Frosch, & Ling, 1997). The possibility that differences between patients might explain the reported variation in SAEs is plausible, but most likely accounts for a minor proportion of this variation. These data primarily emphasise the need to alter doses of pharmacotherapies as tolerance develops (Farrell et al., 1994).

Secondly, it may be that SAE rates vary substantially for different pharmacotherapies. That is, different pharmacotherapeutic medications may be associated with different rates of SAEs. The international literature provides some support for this possibility. A meta-analysis of randomised controlled trials demonstrated the risk of discontinuing a study treatment specifically because of side-effects was approximately 4% greater among patients receiving LAAM as opposed to methadone (Glanz et al., 1997). However, this possibility is far from clear as other studies have shown no statistically significant differences in the number of reported SAEs for different pharmacotherapies.

Two previous studies have shown no differential rate of reporting SAEs among patients receiving methadone versus buprenorphine (Ling et al., 1996; Pani et al., 2000), while a third showed no differences as a result of different doses of buprenorphine (Ling et al., 1998). The lack of difference reported in these three studies might reflect that they are comparisons between pharmacologically similar classes of medications: either opioid agonists (methadone) or partial agonists (buprenorphine). If this is the case, then medications with more clearly distinct pharmacological actions might be more likely to be associated with different rates of SAEs. That is, variations in the occurrence of SAEs may be less dependent on individual medications and more dependent on the classes of different medications.

There is some evidence for this from published data. An antagonist medication (naltrexone) has previously been associated with unusually high rates of heroin overdose and suicidal behaviour, as well as mortality rates higher than for patients in methadone treatment (Miotto et al., 1997). Naltrexone does not necessarily increase reported SAEs relative to untreated control patients. Rather, this association is based on the observation that, unlike methadone treatment, for example, there is no associated reduction in reported SAEs for naltrexone (Miotto et al., 1997).

Thirdly, it may be that a relatively simple association between the occurrence of SAEs and different pharmacotherapies is not precise enough to account adequately for the variability in reported SAE rates. For example, there may be a dose-response relationship between taking a prescribed medication and the occurrence of an SAE. There are two possibilities:
either different doses of the same medication result in different rates of SAEs or different doses of different medications result in different rates of SAEs. Findings from the international literature suggest the former is unlikely. In a study comparing four different dosage levels of buprenorphine (1mg vs 4mg vs 8mg vs 16mg), Ling et al (1998) reported no patient deaths and a comparable proportion of serious medical events in each group. Another study comparing three different buprenorphine dosage levels also found no adverse medical reactions (Bickel, Amass, Crean, & Badger, 1999). Similarly, published data cast doubt on the likelihood that different doses of different medications result in different rates of SAEs. One study found no difference in SAE rates across all three groups (Ling et al., 1996), as did a second study comparing 8mg of buprenorphine with 60mg of methadone (Pani et al., 2000).

A fourth possibility is that the apparent variation in previously reported SAEs is an artefact. There are at least three confounds that might help explain these variations. The first is that published SAE rates may reflect variations in treatment retention rates: presumably the longer patients are retained in treatment, the higher the number of SAEs that are likely to be reported. It is worth noting in passing that reporting of any SAE is dependent upon the event actually being detected and recorded by clinicians or investigators, rather than its actual occurrence.

Therefore, it is probable that, depending on the adequacy of the detection and reporting mechanisms, published SAE rates are an under-estimate of the true SAE rates. However, this first confound refers to the extent to which systematic differences between studies may exist, even though they are probably all under-estimates. If this confound were a major contributor, it would be expected that treatments with better retention rates would also report higher SAE rates.

The second possible confound is that different SAE rates may be associated with different treatment objectives. The most obvious distinction in terms of treatment objectives is induction / detoxification versus maintenance. There is some evidence for this. Pani et al (2000) reported comparable SAE rates between buprenorphine and methadone, but fewer patients reported SAEs during the induction, as opposed to the maintenance, phases of the study.

Although some proportion of this difference may be due to the first confound discussed in the preceding paragraph, that is, that more SAEs are likely to be reported during the maintenance phase of the study because it represents a longer period of time, it is also possible that the induction or detoxification period of treatment is inherently less susceptible to the occurrence of SAEs. For example, it is likely that the majority of induction phases occur in clinical, well-supervised medical settings that would decrease the likelihood of an SAE occurring. In the absence of additional plausible explanations, it may be expedient for future research to report the occurrence of SAEs separately for induction, detoxification and maintenance phases of studies.

Different definitions for what constitutes an SAE is the third potential confound that may help account for variation between studies in the rate of SAEs reported. There is ample evidence from the published literature for this possibility. This is arguably the most influential of the three confounds identified since prevalence of SAE rates are clearly dependent upon the definition used. Intuitively, the most obvious difference in defining SAEs is the distinction between those that are related to the pharmacotherapy itself, as opposed to those that are related to the route of administration or the method of ingestion. For the latter, an increased risk of SAEs is likely to result from the injection of methadone syrup intended for oral
consumption, especially when the methadone is obtained illegally (Clark et al., 1995). It has also been reported that patient mortality is more than seven times higher for methadone tablets versus methadone syrup (Williamson, Foreman, White, & Anderson, 1997). Identifying these SAEs is likely to be relatively reliable, since the majority of patients using a pharmacotherapy will ingest the medication under clinical supervision.

Identifying SAEs related to the pharmacotherapy itself is much more nebulous. There are two major issues that complicate this process. One is the danger that identifying SAEs in relation to a medication may lead to simplistic and erroneous conclusions that a pharmacotherapy causes an SAE. This inference has different degrees of validity and different implications depending on the medication ingested and the type of resultant SAE. For example, a previous study found that six patients experienced an SAE within ten minutes of being administered naloxone for heroin intoxication, after which no further SAEs were observed (Osterwalder, 1996).

This finding clearly implies a causal relationship and suggests additional care is required immediately after administration. A different example of implied causality relates to naltrexone. A previous study found that 11 of 13 patients experienced a heroin overdose after they had either dropped out or had completed naltrexone treatment. This finding implies the failure to continue naltrexone treatment places patients at increased risk of heroin overdose and suggests the importance of alerting patients and their families to the potential risk of heroin overdose if naltrexone treatment is ceased, as tolerance for opioids, such as heroin, will be low.

However, identifying such clear associations between the group of pharmacologically similar agonist medications (e.g., methadone, LAAM, buprenorphine) and the wide-range of conditions that appear to have been reported as either adverse events or SAEs is much more problematic. The types of SAEs reported in the literature represent a continuum of events that range from the relatively benign occurrence of problems generally associated with heroin dependent populations, such as cutaneous reactions and side-effects commonly associated with opioid withdrawal syndrome, through to more potentially serious events, such as precipitated withdrawal, infectious disease, accidents, depression and exacerbation of chronic or pre-existing conditions such as asthma, anaemia, gastritis and dental problems, to life-threatening SAEs such as cardio events, overdoses and suicides, and ultimately to events that result in death (Garcia-Alonso et al., 1989; Ling et al., 1996; Miotto et al., 1997; Pani et al., 2000; Rademaker, Oakley, & Duffill, 1995; Stoller, Bigelow, Walsh, & Strain, 2001). Given this broad range of adverse and serious adverse events, arguably the most obvious observation is that relevant researchers need to achieve greater consensus as to what constitutes an SAE associated with the provision of pharmacotherapy for opioid dependence. This is not to suggest that formal guidelines do not exist. The Therapeutic Goods Administration (TGA) in Australia defines SAEs as those events that result in death or significant disability, are life-threatening, require inpatient hospitalisation or prolonging of an existing hospital stay, or are a congenital anomaly, birth defect or malignancy. However, the existence of such guidelines does not seem to have encouraged the formulation of a widely accepted definition. For the purposes of this report, therefore, it seems reasonable to adopt the definition provided by the TGA.

Clearly the occurrence of an overdose represents one such category and is likely to be most useful if it is sub-divided into heroin overdose, overdose related to any other substance and dosing errors. The latter is particularly relevant given that relatively new pharmacotherapies

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NATIONAL EVALUATION OF PHARMACOTHERAPIES FOR OPIOID DEPENDENCE (NEPOD)
may initially be associated with higher rates of SAEs until physicians become more expert in their prescribing practices. The occurrence of accidents and injuries also seem to have been frequently reported in the literature and represents a category into which SAEs might readily be classified. Suicide, psychiatric, mood and detoxification-related events seem similarly useful categories. The broadest and most difficult SAEs to categorise are represented by those that relate to pre-existing conditions, chronic illness and the multitude of relatively minor side-effects associated with pharmacotherapy. Arguably the most effective approach may be to combine them into a single category. This is not to trivialise the discomfort suffered by patients, but primarily aims to avoid arbitrary distinctions and potentially misleading inferences about the effects of pharmacotherapy. As some researchers have previously suggested that some of these events are commonly associated with opioid withdrawal (Ling et al., 1998), it follows that some SAEs are likely to be predictable and, therefore, managed appropriately. Given that, it would seem useful to have another sub-category for such anticipated SAEs. These might include headaches, photophobia, seizures, vomiting and encephalopathy.

8.1.7 Aftercare

Aftercare was not systematically evaluated in the trials reported herein, as the focus was on the relative efficacy of pharmacotherapies. However, those who have received assistance for a drug problem require assistance for some period of time after the formal intervention has finished. Successful treatment of any chronic condition that is subject to relapse often requires ongoing and extended assistance. The form of this assistance can be "booster sessions" to maintain skills, etc. learnt in treatment, or it can be simple support and monitoring of progress as the client reintegrates into the community. The process of integrating into a normalised personal and community life may throw up unexpected problems that the client needs assistance to deal with.

For opiate-dependent persons, consistent results have been reported. Ward, Mattick, and Hall (1992) in their review of methadone maintenance treatment note that there is evidence that aftercare enhances outcome (Ward et al., 1992). In a randomised controlled trial, a comparison was made of a structured aftercare program against assistance on request for persons who were opiate-dependent and had been treated in methadone maintenance programs, therapeutic communities, and detoxification programs (McAuliffe, 1990; McAuliffe & Ch'ien, 1986).

The structured aftercare program consisted of combined relapse prevention procedures and an unstructured self-help approach. The study found that, compared to the assistance on request, the structured approach significantly reduced the risk of relapse, decreased self-reported crime, and assisted unemployed persons to find employment. The message from this research is clear: structured aftercare is an important component of treatment.

The content of aftercare will depend upon the type of intervention used initially if the follow-up is to take the form of booster sessions, or it will be determined by the problems and issues that arise for the client within the post-intervention period. If the aftercare is run on an individual basis there will be room for tailored problem solving approaches, and this will have advantages. Run on a group basis, aftercare will be less tailored but will allow clients to form important support networks and to learn from each other's mistakes. Relapse prevention strategies can form an important part of this aftercare and will allow lapses to be dealt with without becoming relapses.
Self-help can be integrated, but it is recommended that there be a structure to the aftercare just as there needs to be to the intervention. It has been noted in other reports on the treatment of opioid dependence (Mattick & Hall, 1993) that benefits are to be derived by ensuring that the aftercare component of treatment includes some relapse prevention and skills-based material.

### 8.2 Trials which were monitored and which contributed outcome data to NEPOD

<table>
<thead>
<tr>
<th>Trial No.</th>
<th>Principal investigators</th>
<th>Location</th>
<th>Design</th>
<th>Types of Participants</th>
<th>No. of participants (reported on)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glasgow, Bell, Mattick, Bammer</td>
<td>Canberra</td>
<td>Naltrexone induced detoxification under sedation, followed by NTX maintenance</td>
<td>Methadone Patients</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>Saunders, Lawford, Jones, Young</td>
<td>Brisbane</td>
<td>Naltrexone detoxification under anaesthesia (RODA) vs. sedation (RODS) (followed by naltrexone treatment) vs. best conventional (generally methadone maint. - control)</td>
<td>Heroin Users Methadone Patients</td>
<td>92 RODA – 25H, 42M RODS – 25H</td>
</tr>
<tr>
<td>4</td>
<td>Ali, White, Thomas</td>
<td>Adelaide</td>
<td>Naloxone induced detoxification under anaesthesia vs. conventional detox. Followed by naltrexone treatment</td>
<td>Heroin Users</td>
<td>101</td>
</tr>
<tr>
<td>6</td>
<td>Lintzeris, Bammer, Bell</td>
<td>Melbourne Sydney</td>
<td>Buprenorphine assisted detoxification vs. conventional detoxification. Followed by naltrexone, methadone or buprenorphine maintenance</td>
<td>Heroin Users</td>
<td>114 Recently abstinent Heroin Users 64 Melbourne 50 Sydney</td>
</tr>
<tr>
<td>7</td>
<td>Ritter, Tucker, Kutin, Jackson, Young</td>
<td>Melbourne</td>
<td>Naltrexone treatment with or without 12 weeks counselling</td>
<td>Recently abstinent Heroin Users</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>Mattick, Ali, White</td>
<td>Sydney Adelaide</td>
<td>Buprenorphine vs. methadone maintenance</td>
<td>Methadone Patients</td>
<td>405</td>
</tr>
<tr>
<td>10</td>
<td>Ritter, Lintzeris, Kutin, Clarke</td>
<td>Melbourne</td>
<td>Buprenorphine vs. methadone maintenance (GP setting)</td>
<td>Methadone Patients</td>
<td>153 Stage 1 (Clinic) 35 Stage 2,3 (GP) 118</td>
</tr>
<tr>
<td>11</td>
<td>Ritter, Lintzeris, Kutin, Clarke</td>
<td>Melbourne</td>
<td>LAAM vs. methadone maintenance (GP setting)</td>
<td>Methadone Patients</td>
<td>175 Stage 1 (clinic) 37 Stage 2,3 (GP) 138</td>
</tr>
<tr>
<td>12</td>
<td>White, Ali, Moss</td>
<td>Adelaide</td>
<td>LAAM vs. methadone maintenance</td>
<td>Methadone Patients</td>
<td>66</td>
</tr>
<tr>
<td>14</td>
<td>Bell, Mattick, Bammer, Young</td>
<td>Sydney</td>
<td>Naltrexone induced detoxification under sedation, followed by NTX maintenance</td>
<td>Methadone Patients</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>Ritter, Lintzeris, Mattick, Hawken, Bell, Harris, Lenn</td>
<td>Melbourne Sydney Brisbane Gold Coast</td>
<td>Methadone detoxification using buprenorphine - pilot dosing study</td>
<td>Methadone Patients</td>
<td>55 Victoria – 8; Queensland – 30; NSW –17</td>
</tr>
<tr>
<td>24</td>
<td>Bell, Mattick, Bammer, Young</td>
<td>Sydney</td>
<td>Comparison of 3 dose levels of naltrexone treatment</td>
<td>Recently abstinent Heroin Users</td>
<td>61</td>
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<tr>
<td>29</td>
<td>Bell, Mattick, Lintzeris</td>
<td>Sydney</td>
<td>Buprenorphine detoxification in specialist vs. GP settings</td>
<td>Heroin Users</td>
<td>100</td>
</tr>
</tbody>
</table>
8.2.1 Individual Trial Information

**Trial 1: Naltrexone induced rapid opioid detoxification under sedation – Canberra.**

**Setting:** Between July 1999 and January 2000 a total of 17 Methadone Patients were recruited to receive naltrexone-induced rapid opioid detoxification under sedation followed by naltrexone treatment from a drug and alcohol service in Canberra.

**Design:** To examine the withdrawal severity, acceptability and rate of successful completion for Methadone Patients inducted onto naltrexone treatment for 3 months after naltrexone induced rapid opioid detoxification under sedation.

**Method:**
- **Day 1-2:** Patients were admitted to hospital and monitored for severity of withdrawal while receiving naltrexone and other symptomatic medications.
- **Day 3-7:** Patients received naltrexone 50mgs daily and symptomatic medication (if required) as outpatients. Patients were expected to participate in individual and group counselling.
- **Follow-up phase:** Patients received supplies of naltrexone on a weekly basis and were interviewed at one and three months following detoxification.

**Trial 2: Naltrexone induced rapid opioid detoxification under anaesthetic vs. naltrexone induced rapid opioid detoxification under sedation (vs. conventional detoxification) - Sydney.**

**Setting:** Between February 1998 and July 1998 a total of 150 opioid dependent patients were recruited to receive either naltrexone induced rapid opioid detoxification under anaesthetic followed by naltrexone treatment, naltrexone induced rapid opioid detoxification under sedation followed by naltrexone treatment, or conventional detoxification followed by naltrexone treatment from a special care unit and a drug and alcohol service at a hospital in Sydney.

**Design:** The trial aimed to compare the safety, efficacy, acceptability and cost-effectiveness of three different treatment options for heroin and methadone dependent patients.

**Method:** The study consisted of two phases:
- **Phase 1:** Heroin Users and Methadone Patients were randomised to receive one of two treatments: (1) naltrexone induced rapid opioid detoxification under anaesthetic or (2) naltrexone induced rapid opioid detoxification under sedation. Outcomes from these techniques were compared to outcomes from conventional detoxification.
- **Procedure:** Rapid opioid detoxification under anaesthetic: Patients were admitted to the special care unit at a hospital in Sydney where they received naltrexone induced rapid opioid detoxification under anaesthetic.

  **Rapid opioid detoxification under sedation:** Patients were admitted to the special care unit at a hospital in Sydney where they received naltrexone induced rapid opioid detoxification under sedation.
Conventional detoxification: Patients received clonidine and other symptomatic medications on either an inpatient or outpatient basis. Patients who completed detoxification were offered naltrexone treatment.

Aftercare: Patients were offered naltrexone treatment for 12 months with monthly follow-up assessments.

Results: The trial was not included in the formal NEPOD analyses as it was not monitored by NEPOD nor subjected to health economic evaluation using NEPOD methodology, and a different approach to outcome assessment was employed. Because of these differences in methodology, its results could not be integrated. The information herein was extracted from an unpublished report by Currie et al. (Currie et al., 2000). Selected results were included here to enable some comparisons to be made with NEPOD findings.

The main outcome measure included in the report was current “non-dependence on opiates”, confirmed by a 25mg naltrexone challenge under observation for withdrawal symptoms at each follow-up. In contrast, NEPOD results are reported in terms of the number of heroin-free days and abstinence rates in the past 28 days at each follow-up. The results shown below focus on 107 “metropolitan” patients who went through rapid detoxification under anaesthesia or sedation.

This trial found no significant differences in outcomes between rapid detoxification under anaesthesia versus sedation, an outcome that is consistent with NEPOD findings. As well, of 38 additional Heroin Users who entered conventional inpatient detoxification, 12 (32%) completed the procedure, and were inducted onto naltrexone treatment, and were non-dependent on opiates at a one week follow-up. This result was similar to the 24% of 50 Heroin Users who achieved an initial seven days of abstinence following allocation to conventional inpatient detoxification in NEPOD Trial 4.

### Percentages of patients who were non-dependent* on opiates at each follow-up

<table>
<thead>
<tr>
<th>Type of Patient</th>
<th>Treatment (number of patients)</th>
<th>1 Week</th>
<th>3 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin Users</td>
<td>Anaesthesia (10)</td>
<td>100%</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Sedation (22)</td>
<td>100%</td>
<td>64%</td>
<td>55%</td>
</tr>
<tr>
<td>Methadone Patients</td>
<td>Anaesthesia (32)</td>
<td>100%</td>
<td>66%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>Sedation (43)</td>
<td>98%</td>
<td>69%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Notes * = Patients who dropped out were counted as “dependent” on opioids.
**Trial 3: Naltrexone induced rapid opioid detoxification under anaesthetic vs. methadone maintenance treatment (vs. naltrexone induced rapid opioid detoxification under sedation) – Brisbane.**

**Setting:** Between March 1999 and December 2000, a total of 159 Methadone Patients and Heroin Users were recruited to receive either methadone maintenance treatment, naltrexone induced rapid opioid detoxification under anaesthetic followed by naltrexone treatment or naltrexone induced rapid opioid detoxification under sedation followed by naltrexone treatment from a drug and alcohol hospital and an intensive care unit at a Brisbane Hospital.

**Design:** A randomised control trial aimed to compare the effectiveness of methadone maintenance treatment, naltrexone induced rapid opioid detoxification under anaesthetic or naltrexone induced rapid opioid detoxification under sedation for Methadone Patients and Heroin Users.

**Method:** The study consisted of two groups:

**Group 1:** 79 Heroin Users were randomised to one of three treatments: (1) methadone maintenance treatment, (2) naltrexone induced rapid opioid detoxification under anaesthetic followed by naltrexone treatment or (3) naltrexone induced rapid opioid detoxification under sedation followed by naltrexone treatment.

**Group 2:** 80 Methadone Patients were randomised to one of two treatments: (1) methadone maintenance treatment or (2) naltrexone induced rapid opioid detoxification under anaesthetic with naltrexone treatment.

**Procedure:** Rapid opioid detoxification under anaesthetic: patients were admitted to a drug and alcohol hospital for the first night and then transferred to an intensive care unit in a Brisbane hospital to receive naltrexone induced rapid opioid detoxification under anaesthetic. After the procedure, they were transferred back to the drug and alcohol service. Patients were monitored and followed for 2-3 days post discharge.

Rapid opioid detoxification under sedation: patients were admitted to a drug and alcohol hospital to receive naltrexone induced rapid opioid detoxification under sedation where they were monitored and followed up post discharge.

Patients randomised to methadone maintenance treatment in both groups were offered naltrexone induced rapid opioid detoxification under anaesthetic followed by naltrexone after being in methadone maintenance treatment for 6 months.

**Aftercare:** Patients received naltrexone treatment for 12 months with monthly follow-up assessments.

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**Trial 4: Naloxone induced rapid opioid detoxification under anaesthetic vs. conventional inpatient detoxification – Adelaide.**

**Setting:** Between August 1998 and July 1999 a total of 101 Heroin Users were recruited to receive either naloxone induced rapid opioid detoxification under anaesthetic followed by naltrexone treatment or conventional inpatient detoxification followed by naltrexone treatment from one of three separate drug and alcohol facilities in Adelaide.
Design: A randomised control trial that aimed to compare naloxone induced rapid opioid detoxification under anaesthetic and conventional inpatient detoxification as methods of induction onto naltrexone treatment.

Method: The study consisted of two groups and phases:

Phase 1: Group 1 – Patients underwent naloxone induced rapid opioid detoxification under anaesthetic at the intensive care unit in an Adelaide hospital for 1-2 days.
Group 2 – Patients withdrew from heroin while receiving current conventional inpatient treatment at a drug and alcohol service in Adelaide from 5-14 days.

Phase 2: Both groups received supplies of naltrexone therapy fortnightly from the pharmacy for 9 months. Follow-ups were conducted at 1,3,6,9 & 12 months.

Trial 5: Methadone vs. buprenorphine detoxification – Sydney, Brisbane, Gold Coast and Perth.

Setting: Between May 2000 and May 2001 patients were recruited to receive reducing doses of buprenorphine or methadone from one of four separate drug and alcohol facilities in Sydney, Brisbane, the Gold Coast or Perth.

Design: A double-dummy, double blind randomised control trial aimed to compare the withdrawal from methadone with the withdrawal from buprenorphine.

Method: Methadone maintained patients on 30mg or less were randomised to receive gradual methadone or buprenorphine reductions.

Reduction phase: Both groups gradually reduced their methadone or buprenorphine dose over a period of 2 to 20 weeks until they reached 0mgs.

Aftercare: Patients were given the choice of one of three treatment options: (1) symptomatic medications, (2) naltrexone treatment for a period of up to 3 months or (3) methadone maintenance treatment. Follow-ups were conducted at 1, 3 and 6 months.

Trial 6: Heroin withdrawal using buprenorphine vs. conventional pharmacotherapy – Melbourne and Sydney.

Setting: Between March 1999 and February 2000 a total of 114 Heroin Users were recruited to receive either buprenorphine or conventional symptomatic withdrawal medications at one of two separate drug and alcohol facilities based in Sydney or Melbourne.

Design: A randomised control trial aimed at examining the efficacy, safety and cost-effectiveness of buprenorphine compared to conventional pharmacotherapy for the management of short-term heroin withdrawal in outpatient treatment settings.

Method: The study consisted of two groups:

Experimental group: Received buprenorphine over a 5-day period and were reviewed on days 6 & 7 (allowed symptomatic withdrawal medications that did not include buprenorphine).

Control group: Received a regime of conventional pharmacotherapies including clonidine, buscopan, quinine bisulfate and other symptomatic medications over a 7-day period.

Post-withdrawal treatment (Both groups): On day 8 both groups were allowed to self-select

NATIONAL EVALUATION OF PHARMACOTHERAPIES FOR OPIOID DEPENDENCE (NEPOD)
into one of three post withdrawal treatment options: (1) methadone maintenance treatment or buprenorphine maintenance treatment (for experimental group), (2) naltrexone and counselling or (3) counselling without medication for a period of 4 weeks or buprenorphine maintenance treatment (for experimental group). After this period, patients were followed-up and those on either methadone maintenance or naltrexone were allowed to continue on treatment. Patients on buprenorphine had two options: either (1) transfer to methadone maintenance treatment or (2) withdraw from buprenorphine.

**Trial 7: Naltrexone +/- counselling – Melbourne and Perth.**

**Setting:** Between April 1999 and October 2000 a total of 97 Heroin Users were recruited to receive either naltrexone + structured group counselling or naltrexone treatment a drug and alcohol facility in Melbourne.

**Design:** A randomised control trial designed to assess the impact of the use of a structured group-counselling program in the treatment of clients participating in naltrexone treatment for heroin dependence.

**Method:** All patients attended daily to receive naltrexone for the first week of treatment. After this period, patients collected naltrexone from the pharmacy on a weekly basis for 12 weeks. The naltrexone + structured counselling group were offered weekly group meetings for 90 mins. Both groups were reviewed at weeks 6 and 12 with a 6-month follow-up.

**Trial 9: Buprenorphine vs. methadone maintenance – Sydney and Adelaide.**

**Setting:** Between July 1996 and April 1998 a total of 405 patients were recruited to receive either buprenorphine or methadone from one of three separate drug and alcohol facilities in Sydney or Adelaide.

**Design:** A double-blind, double dummy randomised control trial aimed to compare the efficacy, safety and cost-effectiveness of buprenorphine and methadone for the treatment of opioid dependent patients.

**Method:** The study involved three stages:

**Stage 1 Double-blind stage (Weeks 1-13)** – Patients were administered an oral liquid and a sublingual tablet (one was a placebo dose) on a daily basis for the first 6 weeks. During this period, doses were titrated and beginning from week 7 active buprenorphine doses were given on alternative days.

**Stage 2 Open stage (Weeks 14-26)** – Staff and patients were informed of the treatment type and a time/motion study was undertaken to identify cost differences between buprenorphine and methadone.

**Stage 3 Observation Stage (27-104 Weeks)** – Patients were allowed to continue with their current study medication or transfer to either buprenorphine or methadone. Follow-ups were conducted at 3 and 6 months.

**Trial 10: Buprenorphine implementation trial – Melbourne.**

**Setting:** Between May 1999 and March 2000 a total of 153 opioid patients were recruited to receive either buprenorphine or methadone from either a drug and alcohol service or community setting in Melbourne.
Design: To examine the implementation of buprenorphine within treatment services focusing on clinical guidelines and training programs. The study assessed the impact upon individuals, health economics and potential markets.

Method: The trial was divided into three intakes:

Intake 1: Compared buprenorphine and methadone treatment at a specialist clinic-based drug and alcohol service. Methadone Patients were from an existing population and Heroin Users were those initiating treatment.

Intake 2: Compared the two treatment options in selected community settings using pharmacies and GP’s. Patients were drawn from methadone prescribers and GP’s.

Intake 3: Compared the two treatment options in broader community settings. Patients were drawn from methadone prescribers and GP’s. Patients were followed-up at 3 and 6 months.

**Trial 11: LAAM implementation trial – Melbourne.**

Setting: Between February 1999 and March 2000 a total of 175 opioid patients were recruited to receive either LAAM or methadone from either a drug and alcohol service or community setting in Melbourne.

Design: To examine the implementation of LAAM within treatment services focusing on clinical guidelines and training programs. The study assessed the impact upon individuals, health economics and potential markets.

Method: The trial was divided into three intakes:

Intake 1: Compared LAAM and methadone treatment at a specialist clinic-based drug and alcohol service. Methadone Patients were from an existing population and Heroin Users were those initiating treatment.

Intake 2: Compared the two treatment options in selected community settings using pharmacies and GP’s. Patients were drawn from methadone prescribers and GP’s.

Intake 3: Compared the two treatment options in broader community settings. Patients were drawn from methadone prescribers and GP’s. Patients were followed-up at 3 and 6 months.

**Trial 12: LAAM vs. methadone crossover – Adelaide.**

Setting: Between July 1998 and May 2000 a total of 66 Methadone Patients were recruited to receive either LAAM or methadone from either a drug and alcohol service or community pharmacies in Adelaide.

Design: A randomised control trial designed to assess the comparative efficacy and acceptability of LAAM and methadone in the treatment of opioid dependence.

Method: The trial comprised of two phases:

Phase 1 (6 months): Group 1 – Received methadone for the first three months followed by LAAM for three months. Group 2 – Received LAAM for the first three months followed by methadone for three months. When commencing LAAM patients from both groups were required to attend the drug and alcohol service pharmacy for a 10 day stabilisation period after which time LAAM was administered on an alternate daily dosing schedule.
Phase 2 (18 months): Patients were free to choose maintenance on either methadone or LAAM. Patients were followed-up at 3, 6, 9 & 12 months.

**Trial 14: Naltrexone induced rapid opioid detoxification under sedation – Sydney.**

**Setting:** Between February 1998 and September 1998 a total of 30 opioid dependent patients were recruited to receive naltrexone-induced rapid opioid detoxification under sedation followed by naltrexone treatment from a Sydney hospital.

**Design:** To examine the withdrawal severity, acceptability and rate of successful completion for opioid patients induced onto naltrexone treatment for 3 months after naltrexone induced rapid opioid detoxification under sedation.

**Method:**

**Day 1-2:** Patients were admitted to hospital and monitored for severity of withdrawal while receiving naltrexone and other symptomatic medications.

**Day 3-7:** Patients received naltrexone 50mgs daily and symptomatic medication (if required) as outpatients. Patients were expected to participate in individual and group counselling.

**Follow-up phase:** Patients received supplies of naltrexone on a weekly basis for four weeks and then monthly for two months. Follow-up interviews were at one and three months following detoxification.

**Trial 16: Methadone detoxification using buprenorphine – Melbourne, Brisbane, Gold Coast and Sydney.**

**Setting:** Between February 1999 and August 1999 a total of 55 *Methadone Patients* were recruited to receive buprenorphine for methadone withdrawal from one of four separate drug and alcohol facilities in Melbourne, Sydney, Brisbane or the Gold Coast.

**Design:** A randomised control trial aimed to assess the efficacy of buprenorphine compared to methadone in assisting patients to withdraw from methadone maintenance treatment.

**Method:** Patients were randomised to one of two protocol groups. A third non-randomised protocol group (C) was included in the trial (patients were unaware of the details for each protocol):

**Protocol A:** Patients reduced methadone dose to 30mgs and were then transferred to buprenorphine.

**Protocol B:** Patients reduced methadone dose until uncomfortable and were then transferred to buprenorphine.

**Protocol C:** Patients whose methadone dose was less than 30mgs at the beginning of recruitment were transferred to buprenorphine.

**Buprenorphine reduction phase:** All groups gradually reduced buprenorphine dose over a period between 7 days to 16 weeks until they reached 0mgs.

**Aftercare:** Patients were given the option of one of three treatment options: (1) symptomatic medications, (2) naltrexone treatment for a period of up to 3 months or (3) methadone maintenance treatment.
**Trial 24: Three dose levels of naltrexone – Sydney.**

**Setting:** Between June 1999 and November 2000 a total of 61 Heroin Users were recruited to receive one of three different doses of NTX (0.05mgs, 0.5mgs, 50mgs) from a drug and alcohol service in Sydney.

**Design:** A double blind randomised control trial designed to investigate whether a partial blockade of the opioid receptors using a low dose of naltrexone (0.5mg), or the use of a non-blocking ultra-low dose of naltrexone (0.05mg), are more effective than a complete blockade (using the conventional 50mg dose), in preventing relapse to dependent opioid use and increasing retention in treatment.

**Method:** All patients were inducted from either accelerated (rapid opioid detoxification) or conventional detox and received a stabilisation dose of naltrexone 50mgs daily for the first 7 days before randomisation on day 8 into one of the three groups (clinicians, researchers and patients were blind to the randomisation group):

- **Group X:** Received naltrexone 0.05mgs.
- **Group Y:** Received naltrexone 0.5mgs.
- **Group Z:** Received naltrexone 50mgs.

Patients attended the clinic on a weekly basis to receive a supervised naltrexone blind dose and weekly takeaways for a period of up to 6 months. Follow ups were conducted at 3 and 6 months post randomisation.

**Trial 29: Buprenorphine withdrawal in specialist and primary care settings – Sydney.**

**Setting:** Between May 2000 and December 2000 a total of 100 Heroin Users were recruited to receive buprenorphine treatment from either a primary care or specialist clinic setting in Sydney.

**Design:** A randomised control trial aimed at comparing the outcomes of buprenorphine-assisted heroin detoxification treatment in primary care and specialist clinic settings.

**Method:** The study involved two stages:

**Stage 1:**
- **Day 1-5:** Patients received buprenorphine in a pre-defined regime for the first 5 days. Day 6: Patients interviewed to address recent drug use, adverse events and satisfaction with their dose.
- **Day 8:** Final interview with treatment provider.

**Stage 2:**
- **Post treatment option:** Patients were able to choose from three treatment options: (1) to continue on buprenorphine for another seven weeks and then transfer to methadone or detox from buprenorphine, (2) methadone maintenance for three months or (3) naltrexone treatment – one month’s free supply and then the patients pay for any ongoing naltrexone. Patients were followed-up at days 8, 35 and 91.
### 8.3 NEPOD core data set

#### Pre-Treatment (Baseline) Assessment

1. Age
2. Sex
3. Use of illicit drugs in past 4 weeks

**OTI: number of heroin-free days**

4. History of heroin use
   - Age at first use of heroin
   - Age at first habit or regular use of heroin

5. Opioid dependence (not for patients initially in methadone treatment)
   - **DSM IV** opioid dependence criteria – total score

6. Methadone dose prior to start of trial (if applicable)

7. Previous D&A treatment history
   - Number of treatment episodes previously started of:
     - Inpatient detoxification
     - Outpatient / ambulatory detoxification
     - Other inpatient or residential treatment / rehabilitation
     - Outpatient counselling
     - Self-help groups
     - Prescribed methadone
     - Total length of time on prescribed methadone

8. Quality of life
   - AQoL - total scaled score
   - SF36 - 8 subscale scores

9. Education and employment
   - Highest level of formal education completed
   - Employment status in past 4 weeks

10. Criminal behaviour in past 4 weeks (OTI Crime scale)

11. Total time imprisoned

12. OTI Social Functioning scale

13. Depression (BSI, SCL-90, or Beck – rescaled to comparable values across studies)

14. Utilisation of non-trial health care services in past 4 weeks (HSU form)

#### Outcome variables

Short-term outcomes (*only assessed in trials involving detoxification from agonists)*:

1. Whether patients (a) completed the basic intervention, (b) achieved initial 7 days of heroin abstinence, and entered post-detoxification treatment.

2. Change in illicit drug use in the past 4 weeks at one month follow-up (Q-scores for each drug type; No. of heroin-free days).

**Primary long-term outcomes (at 3 and 6 month follow-ups):**

3. Change in use of illicit agonists in past 4 weeks (OTI Drug scale ➔ Q-score; heroin-free days)

4. Retention in treatment (number of days up to 3 / 6mo follow-up)

5. Change in criminal behaviour in past 4 weeks (OTI Crime scale)

**Secondary long-term outcome variables (at 3 and 6 month follow-ups):**

6. Change in cost of illicit drug use in past 4 weeks (OTI Drug scale)

7. Change in employment status in past 4 weeks

8. Change in use of other illicit drug types in past 4 weeks (OTI Drug scale ➔ Q-scores)

9. Change in quality of life (AQoL - total scaled score; SF36 - 8 subscale scores)

10. Abstinence from illicit opioids in past 4 weeks

11. Serious adverse events (coded from TGA “Blue Form”)
### 8.4 Other research studies associated with NEPOD

<table>
<thead>
<tr>
<th>Trial #</th>
<th>Principal Investigators</th>
<th>Location</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Currie, Collins, Mudaliar, Cox, Gaunt, Lutz, Ward</td>
<td>Sydney</td>
<td>Rapid detoxification under general anaesthesia or sedation vs. conventional detoxification</td>
</tr>
<tr>
<td>5</td>
<td>Ritter, Lintzeris, Whelan, Mattick, Bell, Hawken, Quigley</td>
<td>Sydney; Brisbane &amp; Gold Coast; Perth</td>
<td>Buprenorphine assisted detoxification vs. gradual methadone withdrawal. Followed by option of naltrexone treatment</td>
</tr>
<tr>
<td>13</td>
<td>Clarke, Khoo, Ritter</td>
<td>Melbourne</td>
<td>Slow release oral morphine maintenance</td>
</tr>
<tr>
<td>17</td>
<td>Ritter et al.</td>
<td>Melbourne</td>
<td>Naltrexone side effects</td>
</tr>
<tr>
<td>18</td>
<td>Dietze et al.</td>
<td>Melbourne</td>
<td>Safety of driving whilst in maintenance treatment</td>
</tr>
<tr>
<td>19</td>
<td>Brearley et al.</td>
<td>Melbourne</td>
<td>Neuropsychological effects of LAAM, Buprenorphine, Methadone</td>
</tr>
<tr>
<td>20</td>
<td>Newcombe et al.</td>
<td>Adelaide</td>
<td>Pharmacokinetics of LAAM</td>
</tr>
<tr>
<td>21</td>
<td>White et al.</td>
<td>Melbourne</td>
<td>Pharmacokinetics of SROM</td>
</tr>
<tr>
<td>22</td>
<td>Kimber, Bammer, et al.</td>
<td>National</td>
<td>Register of pregnancy outcomes</td>
</tr>
<tr>
<td>23</td>
<td>Ritter et al.</td>
<td>Melbourne</td>
<td>ATSI communities and the new pharmacotherapies (outreach)</td>
</tr>
<tr>
<td>25</td>
<td>Dunlop, Ritter, Jorden, Higgs, Bammer</td>
<td>Melbourne</td>
<td>Buprenorphine treatment for Vietnamese Heroin Users. Buprenorphine detoxification; followed by methadone, buprenorphine or naltrexone treatment</td>
</tr>
<tr>
<td>26</td>
<td>Lintzeris, Whelan, Bammer</td>
<td>Melbourne</td>
<td>Inpatient buprenorphine dosing</td>
</tr>
<tr>
<td>27</td>
<td>Lintzeris, Bammer</td>
<td>Canberra</td>
<td>Inpatient buprenorphine detoxification dosing study. Followed by NTX</td>
</tr>
<tr>
<td>28</td>
<td>Lintzeris, Bammer, Whelan</td>
<td>Melbourne</td>
<td>Outpatient buprenorphine detoxification dosing study</td>
</tr>
</tbody>
</table>

**Notes** Data from these studies were not included in any of the analyses in this report.
8.5 Psychosocial functioning at entry to NEPOD trials

NEPOD trials used several questionnaire instruments to measure patients’ psychosocial functioning when they entered the trials, including the Beck Depression Inventory (BDI, BDI-II), the Brief Symptom Inventory (BSI) and the Symptom Checklist–90 (SCL-90). Different instruments were used in different trials.

The BDI and BDI-II are designed to measure severity of depression. The trials that used these instruments involved Heroin Users only (trials 4 and 7, n = 198). Only 12% of those patients were considered to be normal or asymptomatic, 20% had mild to moderate depression, 43% were moderately to severely depressed, and 26% were found to have extremely severe depression.

The SCL-90 (90 items) and its shorter version, the BSI (53 items), are designed to measure nine symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The Global Severity Index (GSI) of both instruments is based on an average of all nine dimensions. When the SCL-90 or BSI are used to screen for psychiatric disorders, an individual is considered a “case” if they have a GSI score, or any two primary dimension scores, which are greater than or equal to a T score of 63 (based on normative samples of adult non-patients). The trials that used the SCL-90 or BSI collected baseline data from 573 Heroin Users and 107 Methadone Patients (trials 1, 3, 9, 16, 24, 29).

Of the Heroin Users who entered the trials, 67% were identified as positive cases on the basis of their Global Severity Index scores, and 79% were identified as cases on the basis of the any-two-dimensions criterion. Significantly fewer Methadone Patients were identified as cases: 22% based on GSI scores and 35% based on individual dimension scores.

Scores for 771 Heroin Users and 107 Methadone Patients on the SCL-90, BSI, BDI or BDI-II were converted into standardized T scores (with a mean of 50 and standard deviation of 10) to enable pooling of the scores on the four instruments. Scores for Methadone Patients (mean = 57, sd =11) were significantly lower than scores for Heroin Users (mean = 68, sd =12). These results showed that both groups of patients were more depressed than “normal” adults, and that Heroin Users were significantly more depressed than patients who were already in methadone treatment when they entered the trials (p<0.001).

Clearly, there are high levels of psychological dysfunction among people seeking treatment for opioid dependence. It is recommended that this issue is considered in the assessment and subsequent treatment of opioid dependent people (Ward et al., 1998). Assessment at entry to treatment should include a psychological screen with a view to address comorbidity and other psychosocial factors in the treatment process.
### Additional data tables

#### Table 18: Characteristics of *Heroin Users & Methadone Patients* of the agonist maintenance treatment trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methadone Maintenance</th>
<th>Buprenorphine Maintenance</th>
<th>LAAM Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H</td>
<td>M</td>
<td>H</td>
</tr>
<tr>
<td>Gender % male</td>
<td>68</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Mean years (S.D.)</td>
<td>30 (7)</td>
<td>33 (8)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Age first used heroin Mean years (S.D.)</td>
<td>20 (5)</td>
<td>20 (5)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Age first heroin habit Mean years (S.D.)</td>
<td>24 (6)</td>
<td>23 (6)</td>
<td>22 (4)</td>
</tr>
<tr>
<td>Employment % unemployed</td>
<td>54</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>% pensioner</td>
<td>5</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>% home duties</td>
<td>7</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>% student</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>% part-time/casual</td>
<td>13</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>% full-time work</td>
<td>15</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>% other</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Highest level of education % Up to Year 10</td>
<td>54</td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td>% Year 11-12</td>
<td>34</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>% Tertiary</td>
<td>12</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Previous methadone dose Mean mg (S.D.)</td>
<td>n/a</td>
<td>60 (34)</td>
<td>n/a</td>
</tr>
<tr>
<td>Total previous time on methadone Mean months (S.D.)</td>
<td>10 (18)</td>
<td>52 (69)</td>
<td>16 (36)</td>
</tr>
<tr>
<td>No. times previously started methadone treatment</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Notes*  

H = *Heroin Users*, M = *Methadone Patients.*
**Table 19: Characteristics of Heroin Users & Methadone Patients of the detoxification trials**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Naltrexone treatment (initially abstinent patients)</th>
<th>Rapid detoxification under sedation or anaesthesia (followed by naltrexone)</th>
<th>Buprenorphine detoxification (followed by maintenance options)</th>
<th>Conventional inpatient detoxification (followed by naltrexone treatment)</th>
<th>Conventional outpatient detoxification (followed by maintenance options)</th>
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<tbody>
<tr>
<td>Gender % male</td>
<td>62 n/a</td>
<td>62 53</td>
<td>61 58</td>
<td>60 n/a</td>
<td>61 n/a</td>
</tr>
<tr>
<td>Age Mean years (S.D.)</td>
<td>30(8)</td>
<td>30(8) 32(7)</td>
<td>30(7) 35(7)</td>
<td>31(7)</td>
<td>29(8)</td>
</tr>
<tr>
<td>Age first used heroin Mean years (S.D.)</td>
<td>20(5)</td>
<td>20(5) 20(4)</td>
<td>21(5) 21(5)</td>
<td>21(5)</td>
<td>21(4)</td>
</tr>
<tr>
<td>Age first heroin habit Mean years (S.D.)</td>
<td>22(5)</td>
<td>23(6) 23(6)</td>
<td>24(6) 24(5)</td>
<td>24(5)</td>
<td>24(4)</td>
</tr>
<tr>
<td>Employment % unemployed</td>
<td>56</td>
<td>53 26</td>
<td>37 31</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>% pensioner</td>
<td>16</td>
<td>14 10</td>
<td>3 15</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>% home duties</td>
<td>1</td>
<td>10 10</td>
<td>3 15</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>% student</td>
<td>6</td>
<td>3 7</td>
<td>8 4</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>% part-time/casual</td>
<td>9</td>
<td>9 16</td>
<td>20 22</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>% full-time work</td>
<td>7</td>
<td>9 28</td>
<td>21 13</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>% other</td>
<td>5</td>
<td>1 1</td>
<td>6 7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Highest level of education % Up to Year 10</td>
<td>29</td>
<td>36 47</td>
<td>26 27</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>% Year 11-12</td>
<td>54</td>
<td>29 20</td>
<td>45 20</td>
<td>16</td>
<td>52</td>
</tr>
<tr>
<td>% Tertiary</td>
<td>16</td>
<td>30 26</td>
<td>25 49</td>
<td>58</td>
<td>20</td>
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<tr>
<td>Present Methadone dose Mean mg (S.D.)</td>
<td>n/a</td>
<td>n/a 47(26)</td>
<td>n/a 38(20)</td>
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<td>n/a</td>
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<tr>
<td>Total previous time on methadone Mean months (S.D.)</td>
<td>11(24)</td>
<td>13(29) 56(45)</td>
<td>8(17) 49(45)</td>
<td>11(19)</td>
<td>1(2)</td>
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<tr>
<td>No. times previously started methadone treatment</td>
<td>1(1)</td>
<td>1(1) 2(3)</td>
<td>1(1) 2(1)</td>
<td>1(1)</td>
<td>1(1)</td>
</tr>
</tbody>
</table>

*Notes*  
H = Heroin Users, M = Methadone Patients.
Table 20: Increase in the number of *heroin-free days of Heroin Users*# at three months and six months compared with prior to entering treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Three months</th>
<th>Six months</th>
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<tbody>
<tr>
<td></td>
<td>Patients remaining in treatment</td>
<td>Total sample**</td>
</tr>
<tr>
<td>Methadone Maintenance</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>n = 158</td>
<td>n = 281</td>
</tr>
<tr>
<td>Buprenorphine Maintenance</td>
<td>19</td>
<td>9</td>
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<tr>
<td></td>
<td>n = 119</td>
<td>n = 250</td>
</tr>
<tr>
<td>LAAM Maintenance</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>n = 25</td>
<td>n = 41</td>
</tr>
<tr>
<td>Naltrexone treatment for already abstinent patients</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>n = 38</td>
<td>n = 117</td>
</tr>
<tr>
<td>Naltrexone treatment after rapid detoxification</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 116</td>
</tr>
<tr>
<td>Buprenorphine detoxification (followed by maintenance options)</td>
<td>19</td>
<td>12*</td>
</tr>
<tr>
<td></td>
<td>n = 61</td>
<td>n = 158</td>
</tr>
<tr>
<td>Naltrexone treatment after conventional inpatient detoxification</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>n = 1</td>
<td>n = 50</td>
</tr>
<tr>
<td>Conventional outpatient detoxification (followed by maintenance options)</td>
<td>12*</td>
<td>9*</td>
</tr>
<tr>
<td></td>
<td>n = 44</td>
<td>n = 56</td>
</tr>
</tbody>
</table>

**Notes**

# = *Heroin Users* were not in receipt of treatment at the time of entering the treatment.

* = includes all Trial 6 follow-ups at 1 month (3 month follow-ups were not conducted).

** = imputed results are based on an assumption that patients who were not followed up had the same level of heroin use at the third and sixth month as they did prior to entering treatment.
### Table 21: Increase in the number of heroin-free days of Methadone Patients\# at three months and six months compared with prior to entering treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Three months</th>
<th>Six months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients remaining in treatment</td>
<td>Total sample**</td>
</tr>
<tr>
<td>Methadone Maintenance</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>n = 85</td>
<td>n = 114</td>
</tr>
<tr>
<td>Buprenorphine Maintenance</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>n = 18</td>
<td>n = 29</td>
</tr>
<tr>
<td>LAAM Maintenance</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>n = 60</td>
<td>n = 82</td>
</tr>
<tr>
<td>Naltrexone treatment after rapid detoxification</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>n = 19</td>
<td>n = 72</td>
</tr>
<tr>
<td>Buprenorphine detoxification (followed by maintenance options)</td>
<td>-4*</td>
<td>-2*</td>
</tr>
<tr>
<td></td>
<td>n = 30</td>
<td>n = 55</td>
</tr>
</tbody>
</table>

**Notes**
- \# = Methadone Patients were already in methadone treatment, and were choosing to enter a new treatment, or be left in methadone.
- *= includes all Trial 16 follow-ups at one month (three month follow-ups were not conducted).
- ** = imputed results are based on an assumption that patients who were not followed up had the same level of heroin use at the third and sixth month as they did prior to entering treatment.
Table 22: Rates of abstinence in the 28 days prior to baseline, and at three months and six months for *Heroin Users*#

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Three months</th>
<th>Six months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients remaining in treatment</td>
<td>Total sample**</td>
<td>Patients remaining in treatment</td>
</tr>
<tr>
<td><strong>Methadone Maintenance</strong></td>
<td>1%</td>
<td>26%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>2 / 282</td>
<td>41 / 159</td>
<td>43 / 282</td>
</tr>
<tr>
<td><strong>Buprenorphine Maintenance</strong></td>
<td>1%</td>
<td>28%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>2 / 250</td>
<td>33 / 119</td>
<td>38 / 250</td>
</tr>
<tr>
<td><strong>LAAM Maintenance</strong></td>
<td>0%</td>
<td>44%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>0 / 41</td>
<td>11 / 25</td>
<td>13 / 41</td>
</tr>
<tr>
<td><strong>Naltrexone treatment for already abstinent patients</strong></td>
<td>0%</td>
<td>66%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>0 / 117</td>
<td>25 / 38</td>
<td>32 / 117</td>
</tr>
<tr>
<td><strong>Naltrexone treatment after rapid detoxification</strong></td>
<td>0%</td>
<td>75%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>0 / 116</td>
<td>15 / 20</td>
<td>22 / 116</td>
</tr>
<tr>
<td><strong>Buprenorphine detoxification (followed by maintenance options)</strong></td>
<td>0%</td>
<td>23%</td>
<td>12%*</td>
</tr>
<tr>
<td></td>
<td>0 / 158</td>
<td>14 / 61</td>
<td>19 / 158</td>
</tr>
<tr>
<td><strong>Naltrexone treatment after conventional inpatient detoxification</strong></td>
<td>0%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>0 / 50</td>
<td>0 / 1</td>
<td>2 / 50</td>
</tr>
<tr>
<td><strong>Conventional outpatient detoxification (followed by maintenance options)</strong></td>
<td>0%</td>
<td>2%*</td>
<td>2%*</td>
</tr>
<tr>
<td></td>
<td>0 / 56</td>
<td>1 / 44</td>
<td>1 / 56</td>
</tr>
</tbody>
</table>

**Notes**  
# = *Heroin Users* were not in receipt of treatment at the time of entering the treatment.  
*= includes all Trial 6 follow-ups at one month (three month follow-ups were not conducted).  
**= imputed results are based on an assumption that patients who were not followed up had the same level of heroin use at the third and sixth month as they did prior to entering treatment.
Table 23: Rates of abstinence in the 28 days prior to baseline, and at three months and six months for Methadone Patients#

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Three months</th>
<th>Six months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients remaining in treatment</td>
<td>Total sample**</td>
<td>Patients remaining in treatment</td>
</tr>
<tr>
<td>Methadone Maintenance</td>
<td>40%</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>46 / 114</td>
<td>39 / 85</td>
<td>52 / 114</td>
</tr>
<tr>
<td>Buprenorphine Maintenance</td>
<td>31%</td>
<td>44%</td>
<td>31%</td>
</tr>
<tr>
<td>LAAM Maintenance</td>
<td>43%</td>
<td>64%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>35 / 82</td>
<td>39 / 61</td>
<td>52 / 83</td>
</tr>
<tr>
<td>Naltrexone treatment</td>
<td>32%</td>
<td>84%</td>
<td>47%</td>
</tr>
<tr>
<td>after rapid detoxification</td>
<td>23 / 73</td>
<td>16 / 19</td>
<td>35 / 74</td>
</tr>
<tr>
<td>Buprenorphine detoxification (followed by maintenance options)</td>
<td>75%</td>
<td>70%*</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>41 / 55</td>
<td>21 / 30</td>
<td>36 / 55</td>
</tr>
</tbody>
</table>

Notes  
# = Methadone Patients were already in methadone treatment, and were choosing to enter a new treatment, or be left in methadone.  
* = includes all Trial 16 follow-ups at one month (three month follow-ups were not conducted).  
** = imputed results are based on an assumption that patients who were not followed-up had the same level of heroin use at the third and sixth month as they did prior to entering treatment.
8.7 Outline of proposal for NEPOD implementation project

Many Heroin Users are reluctant to enter treatment for a variety of reasons. Furthermore, a majority of medical practitioners are reluctant to be involved in providing treatment for opioid dependence due to lack of knowledge about how to do so, lack of time to appraise the relevant scientific literature, and a perceived lack of access to support services. In principle, these barriers to treatment could be addressed by more effective “marketing” of both the currently available and the “new” pharmacotherapies and treatments.

A discussion paper and a proposal for a co-ordinating project that would address this concept have been submitted to the Australian Government Department of Health and Ageing. The proposed process would aim to increase the number of dependent Heroin Users who participate in effective and cost-effective withdrawal or maintenance treatments by:

- Disseminating accurate information about the nature, costs and effects of the pharmacotherapies to the community, medical practitioners, and drug and alcohol workers;
- Encouraging local drug and alcohol services to review and modify their mix of treatment activities, where appropriate;
- Encouraging and supporting GP’s to provide treatment to more opioid dependent patients, and to develop shared-care arrangements with drug and alcohol services.

Summary of Strategy

1. Establish an advisory committee consisting of representatives of the Commonwealth, State and Territory governments, and other key stakeholders including the Australian Divisions of General Practice, ADIS, ADIN, DASC, NCETA, Next Step, Pharmacy Guild, Pharmacy Society, Turning Point, QADREC, Royal Australian College of General Practitioners (RACGP), and relevant pharmaceutical companies.

2. Conduct a baseline survey of Australian methadone clinics and Divisions of General Practice to collect information about their (a) provision of treatment to opioid dependent patients, (b) perceived barriers to implementation of NEPOD recommendations, and (c) interest in participating in the Implementation Project.

3. Provide all methadone clinics and Divisions of General Practice with a copy of the NEPOD final report monograph.

4. Implement a media management strategy, which aims to increase the community’s (and Heroin Users’) knowledge and acceptance of treatment for opioid dependence. The strategy should include (a) a press release and press conference to disseminate NEPOD results and recommendations; (b) a concentrated effort to obtain media coverage of relevant issues through quality current affairs programs, radio and print media; (c) preparation of material for media to which medical practitioners are exposed.

5. Two major aspects of the project (focusing on methadone clinics, general practitioners) could be conducted as an evaluated trial of the advocacy and training process. Relevant material from the NEPOD monograph, including the clinical guidelines which are being developed by DASC in association with NEPOD, will be used as a basis for training seminars. Training and information workshops will be arranged for general practitioners through a random sample of their Divisions. The project will encourage development
of shared-care arrangements between GPs and their local drug & alcohol services. Face-to-face discussions and training presentations will be offered to drug and alcohol service directors and staff at each methadone clinic in an Intervention group. This activity will be supported through discussions with hospital and area health service staff.

### 8.8 Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agonist (Opioid)</td>
<td>An opioid agonist is a type of drug that binds to the opioid receptors, mimicking the actions of the body’s natural chemicals. It provides a substitute for illicit heroin, such that individuals do not experience withdrawal, and have opportunities to restore their physical, psychological and social well-being.</td>
</tr>
<tr>
<td>Antagonist (Opioid)</td>
<td>An opioid antagonist is a type of drug that binds to the opioid receptors and blocks the actions of the body’s natural chemicals. It also blocks the effects of heroin. In heroin dependent individuals it would induce withdrawal; in individuals who have completed withdrawal it may assist in preventing relapse to heroin use.</td>
</tr>
<tr>
<td>Buprenorphine maintenance treatment</td>
<td>A form of opioid maintenance treatment using buprenorphine, a partial opioid agonist, which has a duration of action of 24-48 hours. Buprenorphine is a sublingual tablet preparation, and can be taken every second day.</td>
</tr>
<tr>
<td>Conventional outpatient detoxification</td>
<td>An outpatient detoxification program using clonidine and other symptomatic medications lasting for up to 8 days.</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>The relative cost of achieving a given outcome (effect)</td>
</tr>
<tr>
<td>Detoxification</td>
<td>Detoxification, or withdrawal, is the process of stopping the use of heroin or methadone and reversing neuroadaptation. Detoxification is not a treatment for heroin dependence. Detoxification may be a link to further treatment.</td>
</tr>
<tr>
<td>Heroin detoxification using buprenorphine</td>
<td>A detoxification program using reducing doses of buprenorphine over a five-day period. Symptomatic medications are also used.</td>
</tr>
<tr>
<td>Heroin User</td>
<td>An individual who was not in pharmacological treatment for their opioid dependence when they entered the trial.</td>
</tr>
<tr>
<td>LAAM maintenance treatment</td>
<td>An opioid maintenance treatment using levo-alpha-acetylmethadol, an opioid agonist with a duration of action of 48-72 hours, taken orally 3 times a week.</td>
</tr>
<tr>
<td>Methadone maintenance treatment</td>
<td>A form of <em>opioid maintenance treatment</em> using methadone, an opioid agonist with a duration of action of 15-40 hours which is taken orally on a daily basis.</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Methadone Patient</td>
<td>A patient who was in methadone treatment at the time they entered a trial.</td>
</tr>
<tr>
<td>Naltrexone treatment</td>
<td>An adjunct in the prevention of relapse to heroin use. Naltrexone, an opioid <em>antagonist</em>, when taken daily blocks the effects of heroin and prevents reinstatement of heroin dependence.</td>
</tr>
<tr>
<td>Rapid opioid detoxification</td>
<td>The process of accelerating withdrawal from opioids by the administration of naltrexone or naloxone. This process can occur under anaesthesia with medications provided to relieve symptoms. Individuals are unconscious and may also be mechanically ventilated. The procedure is used for direct induction onto <em>naltrexone treatment</em>.</td>
</tr>
<tr>
<td>under anaesthesia</td>
<td></td>
</tr>
<tr>
<td>Rapid opioid detoxification</td>
<td>A detoxification program that uses naltrexone to speed up the onset of withdrawal combined with sedation and other medications to relieve symptoms. Sedation can be ‘light’ such that individuals are conscious and able to interact or ‘deep’ where individuals sleep and do not recall the experience. The procedure is used for direct induction onto <em>naltrexone treatment</em>.</td>
</tr>
<tr>
<td>under sedation</td>
<td></td>
</tr>
<tr>
<td>Conventional inpatient detoxification</td>
<td>An inpatient detoxification program, also known as standard inpatient detoxification, using clonidine and other symptomatic medications, which may last from 3 to 14 days.</td>
</tr>
</tbody>
</table>