A cost-effectiveness analysis of heroin detoxification methods in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD)

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared five methods of detoxification from opioids. The methods compared were:

- rapid opioid detoxification under anaesthetic (RODA);
- rapid opioid detoxification under sedation (RODS);
- "conventional" clinidine-based inpatient detoxification methods (CID);
- "conventional" outpatient detoxification methods (COD); and
- a buprenorphine-based (BUP) outpatient detoxification method.

Type of intervention
Treatment (detoxification methods of heroin dependent users).

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adults (18 years and above) who were (DSM-IV) heroin-dependent users and had not received treatment before or during the last 3 months. All patients were in quest of treatment. Pregnant women, or adults with unstable psychiatric conditions, with related serious medical conditions, and those who were dependent on other illicit drugs besides heroin, were excluded from the study.

Setting
The settings were primary care (general practitioner setting) and secondary care (public hospitals and drug and alcohol clinics, including intensive care units). The economic study was carried out in Australia.

Dates to which data relate
The effectiveness data were derived from four parent clinical studies published between 2001 and 2003. The cost data were derived from sources published between 1999 and 2004. All costs were reported for the price year 1999.

Source of effectiveness data
The effectiveness data were derived from four published randomised detoxification trials included in the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project and conducted by the authors. Data from these four studies were pooled in two other completed studies also conducted by the authors.
Link between effectiveness and cost data
It seems that the costing has been carried out prospectively on the same sample of patients as that used in the effectiveness studies.

Study sample
It was not reported in the current paper whether the sample size was based on power calculations, nor were any details of the sample selection methods reported. The authors used four parent randomised detoxification trials (Gibson et al. 2003, Lintzeris et al. 2002, Mattick et al. 2001, McGregor et al. 2002, see 'Other Publications of Related Interest' below for bibliographic details). Overall, 365 patients were included in the analysis, of which 76 received RODA treatments, 25 received RODS treatment, 50 patients received CID, 158 patients received BUP-based outpatient detoxification and 56 patients received COD.

Study design
The analysis of the four parent studies was based on randomised detoxification trials, whereas the current economic evaluation was reported to be a multi-centre quasi-experimental cohort study. The duration of follow-up, loss to follow-up and randomisation methods were not reported. For relevant details, the reader is referred to the parent studies (Gibson et al. 2003, Lintzeris et al. 2002, Mattick et al. 2001, McGregor et al. 2002).

Analysis of effectiveness
It was reported that the analysis was conducted on an intention to treat basis. The primary outcomes used were the proportion of participants who completed detoxification and reached a minimum of 7 days' abstinence, and the proportion of participants who entered post-detoxification pharmacotherapy (using methadone, BUP or naltrexone) regardless of initial abstinence. Abstinence was derived from participants' self-reports related to heroin use and, if available, the use of urine tests or naltrexone challenges. The authors reported that previous studies have demonstrated the validity of self-reports of heroin use for evaluating such treatments.

The authors compared demographic characteristics of the sub-groups of the parent studies using an analysis of variance for continuous data or chi-squared tests for categorical variables. It was reported that the patient groups were comparable at baseline and in demographic characteristics such as age, gender, number of DSM-IV opioid dependence criteria satisfied, percentage who had no heroin-free days during the preceding 28 days, number of drug classes used, and the number of previous entries to prescribed methadone treatment. On the other hand, employment status and number of previous detoxification attempts varied statistically significantly between groups. It was reported that these two characteristics did not affect the abstinence outcomes, whereas the number of previous detoxifications significantly predicted entry to post-detoxification treatment (Spearman rho = 0.14).

Effectiveness results
The percentage of patients who reached initial abstinence was 58% (standard deviation, SD=49%) for RODA, 60% (SD=50%) for RODS, 24% (SD=43%) for CID, 12% (SD=43%) for BUP and 4% (SD=18%) for COD. The Kruskal-Wallis tests demonstrated statistically significant differences in initial abstinence using various detoxification methods (chi-squared 87.39, p<0.001). The Mann-Whitney test demonstrated that RODA and RODS were similar in initial abstinence (z = -0.184, p=0.154), but that the combined mean abstinence rate (59%) was statistically higher than CID (z = -3.974, p<0.001). CID was more effective in achieving initial abstinence than BUP (z = -2.067, p=0.039) but not more effective than COD (z = -3.086, p=0.002). BUP and COD demonstrated comparable initial abstinence (z = -1.823, p=0.068).

The percentage of patients who entered post-detoxification treatment was 42% (SD=50%) for RODA, 68% (SD=48%) for RODS, 12% (SD=33%) for CID, 65% (SD=48%) for BUP and 27% (SD=50%) for COD. The Kruskal-Wallis tests demonstrated statistically significant differences between the detoxification methods (chi-squared 59.8, p<0.001). The Mann-Whitney test demonstrated that RODS was similar to RODA (z = -2.236, p=0.025) and BUP (z = -2.74, p=0.078). However, RODS was more effective than COD (z = -3.483, p<0.001), and BUP was more effective than RODA (z = -3.306, p=0.001). Although RODA was not more effective than COD (z = -1.81, p=0.70), it was more effective than
CID (z = -3.58, p=0.001). Finally, CID and COD demonstrated equal effectiveness in terms of the post-detoxification treatment (z = -1.898, p=0.058).

Clinical conclusions
The authors did not report any clinical conclusions.

Measure of benefits used in the economic analysis
The authors used two clinical outcomes (reported in the 'Analysis of Effectiveness' section) as measure of benefit in the economic analysis. Both outcome measures were derived from the effectiveness analysis.

Direct costs
The following health service costs were used:

the professionals’ time including direct face to face contacts and indirect time (i.e. preparation time, charting case conferences, following up on diagnostics);

the cost of diagnostic procedures;

the cost of medications, including drug costs and dispensing or dosing time;

the facility level costs including supplies, consumables, cost of capital equipment;

the capital costs of each setting and the cost of ancillary support, including administration, management and security.

Indirect professionals’ time was estimated using structured interviews with staff members. Resources used related to the frequency and duration of professional services and tests provided, and were derived from clinical records. The quantities of medications were derived from pharmacy records. Resource use and costs regarding facility level resources were based on each institution's financial data. The unit costs were not reported, while the quantities of resources used were only reported in mean days per episode and mean staff time per episode. As the costs were incurred during a short time (less than 2 years), discounting was not relevant. All the costs were reported for the price year 1999.

Statistical analysis of costs
The authors conducted statistical analysis to investigate the normality of cost distributions. A Kruskal-Wallis test was employed for an overall comparison, while Mann-Whitney tests were employed to conduct multiple comparisons. In addition, the authors used a bootstrapping method to investigate the statistical significance of the incremental cost-effectiveness ratios (ICERs). Five thousand replicates, in total, were conducted for each sample and the bias-corrected accelerated method was used to estimate 95% confidence intervals (CIs).

Indirect Costs
The indirect costs were not included in the analysis.

Currency
Australian dollars (AUD).

Sensitivity analysis
The authors conducted sensitivity analyses to investigate the robustness of the results to variability in the quantities of resources used and cost estimates. The ranges used in the sensitivity analysis were derived from the literature and from official published sources, such as the Australian Pharmaceutical Benefits Scheme and commercial list prices (MIMS).
for drug costs.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The mean costs per treatment episode were reported. This was AUD 491 for BUP, AUD 605 for COD, AUD 1,404 for CID, AUD 1,990 for RODS and AUD 2,689 for RODA.

The differences in costs between the detoxification methods were found to be statistically significant (chi-squared 201.1, p<0.001).

**Synthesis of costs and benefits**
An incremental cost-effectiveness analysis was performed. For initial abstinence, each detoxification method was compared with COD. RODA resulted in an ICER of AUD 3,859 (95% CI: 3,171 to 5,108), RODS in an ICER of AUD 2,473 (95% CI: 1,799 to 3,657), CID in an ICER of AUD 3,965 (95% CI: 2,650 to 8,882) and BUP in an ICER of AUD -1,265 (95% CI: -5,361 to -131).

For post-detoxification treatment in comparison with COD, RODA resulted in an ICER of AUD 13,893 (95% CI: 6,889 to 98,661), RODS in an ICER of AUD 3,378 (95% CI: 2,312 to 6,446), CID in an ICER of AUD -5,287 (95% CI: -49,609 to -1,666) and BUP in an ICER of AUD -299 (95% CI: -690 to -94).

The sensitivity analyses demonstrated the robustness of the results to variability in the data.

**Authors’ conclusions**
"The buprenorphine-based (BUP) outpatient detoxification method was found to be the most cost-effective method overall, and rapid opioid detoxification under sedation was the most cost-effective inpatient method."

**CRD COMMENTARY - Selection of comparators**
The comparators used were drawn from the NEPOD project carried out in Australia. They seem to have represented the most commonly used detoxification methods in the authors' setting. You should decide if this represents a valid technology in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on published randomised controlled trials (RCTs), which were appropriate given the study question. There was no single RCT that compared all alternatives, so the effectiveness measures were pooled from different RCTs. This requires the RCTs to have comparable protocols and the authors reported that this was the case.

**Validity of estimate of measure of benefit**
The authors used clinical outcomes as initial abstinence rates and the proportion of patients taking up post-detoxification as measures of benefit in the economic analysis. These were derived from the parent clinical studies.

**Validity of estimate of costs**
The perspective adopted in the economic analysis was that of the health care system paying for the intervention. It appears that all the relevant costs have been included in the analysis. The unit costs and the quantities of resources used were not reported separately, which does not enable the analysis to be easily reworked for other settings. The resources used were based on actual data and the costs were derived from official sources. Extensive statistical and sensitivity
analyses were conducted to assess the robustness of the estimates used, which strengthens the interpretation of the study findings. The ranges used in the sensitivity analyses seem to have been appropriate. Discounting was not necessary and the price year was reported.

**Other issues**
The authors compared their findings with those from other studies which, in general, showed their findings to be in agreement with those of other studies. In addressing the issue of generalisability of the results to other settings, the authors seemed hesitant and recommended further research to strengthen the study findings. The authors do not appear to have presented their results selectively and the results from all statistical tests were fully reported. The study enrolled heroin-dependent adult patients and this was reflected in the authors’ conclusions.

The authors reported a number of limitations to their study. First, since only short-term outcome measures were used in the analysis, long-term treatment outcomes could not be estimated. Second, the authors acknowledged that the results reported might not reflect real-life clinical activity since participants fulfilling the trial's inclusion criteria were monitored more carefully, resulting in improved outcomes and higher costs, and treatment was administered in line with established clinical protocols. The authors also acknowledged the problematic nature of the comparisons conducted. For example, outpatient methods were compared with inpatient methods, which are characterised with a limited, immediate, relapse risk of heroin users.

**Implications of the study**
The authors did not make any explicit recommendations for changes in policy or practice. They stressed the need for further research to investigate methods which will result in better compliance with treatment. In addition, their discussion highlighted further areas where more information is needed.

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**Bibliographic details**

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**Other publications of related interest**


to standard inpatient withdrawal as a precursor to maintenance naltrexone treatment in heroin users: outcomes at 6 and 12 months. Drug Alcohol Depend 2002;68(1).

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Analgesics, Opioid /economics /therapeutic use; Analysis of Variance; Buprenorphine /economics /therapeutic use; Chi-Square Distribution; Cost-Benefit Analysis; Female; Heroin Dependence /drug therapy /economics; Humans; Hypnotics and Sedatives /therapeutic use; Male; Methadone /economics /therapeutic use; Naltrexone /economics /therapeutic use; Narcotic Antagonists /economics /therapeutic use

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