Buprenorphine, buprenorphine/naloxone and methadone maintenance: a cost-effectiveness analysis

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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
Four different regimens for the treatment of heroin addiction were examined. These were high-dose buprenorphine, a buprenorphine-naloxone combination, low-dose buprenorphine and methadone.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients who were opioid dependent. Patients were eligible for study if they had a current diagnosis of opioid dependence (using the criteria in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders), were aged 18 years or older and lived within commuting distance of a clinic, and appeared mentally competent to give informed consent. The exclusion criteria included pregnancy or likelihood of pregnancy during the study period, an acute medical condition that could make participation in the study hazardous, current use of anticonvulsant or antipsychotic medications, and current opioid treatment. Patients were also excluded if they were unable to attend the clinic daily, or had previously been on a buprenorphine study.

Setting
The study setting was primary care. The economic study was undertaken in Australia.

Dates to which data relate
The effectiveness and resource use data were derived from studies published in 2003. The price year was 1998 - 1999.

Source of effectiveness data
The effectiveness data were derived from published studies and clinical guidelines. The author also made several assumptions to derive the effectiveness of high-dose buprenorphine and buprenorphine-naloxone.

Modelling
Three models were examined. Model 1 compared methadone with low-dose buprenorphine. Model 2 compared methadone with high-dose buprenorphine. Model 3 compared methadone with buprenorphine-naloxone.

The effectiveness data used in the cost-effectiveness analysis were taken from Doran et al. 2003 (see 'Other Publications of Related Interest' below for bibliographic details), and were employed in the current study to extend the original analysis of methadone versus low-dose buprenorphine. The treatment regimen for high-dose buprenorphine
(Fudala et al. 2003, see 'Other Publications of Related Interest’ below for bibliographic details) substituted data from the low-dose buprenorphine treatment used in Doran et al. 2003. The time horizon for each model was 6 months.

Missing follow-up data from the studies were imputed by conservatively assuming that patients who were unable to be contacted for follow-up had returned to pre-trial drug use patterns. The author, therefore, reported outcomes achieved for those patients still in treatment and imputed mean outcomes for all patients.

**Outcomes assessed in the review**
The outcome assessed was the mean number of heroin-free days in the month prior to baseline (i.e. start of the trial) and at 6 months.

**Study designs and other criteria for inclusion in the review**
The study by Doran et al. 2003 used effectiveness data from a randomised controlled trial, conducted by Mattick et al. 2003 (see 'Other Publications of Related Interest’ below for bibliographic details), in which 405 patients were randomised to receive either methadone (n=205) or low-dose buprenorphine (n=200). Further details of the study sample or methodology were not provided in the present study. In addition, there were no details on the study by Fudala et al. 2003.

**Sources searched to identify primary studies**
Not relevant. The author did not conduct a systematic review of the literature.

**Criteria used to ensure the validity of primary studies**
The criteria used to ensure the validity of the primary studies were not reported.

**Methods used to judge relevance and validity, and for extracting data**
The methods used to judge relevance and validity, and to extract the data, were not reported.

**Number of primary studies included**
Two primary studies were included in the review.

**Methods of combining primary studies**
The results of the individual primary studies were not combined.

**Investigation of differences between primary studies**
The author did not report if there were any important differences between the studies by Doran et al. 2003 and Fudala et al. 2003.

**Results of the review**
At baseline, the mean number of heroin-free days in the previous month was 2.59 (standard deviation, SD=5.66) for those receiving methadone, 3.23 (SD=6.26) for those receiving low-dose buprenorphine, and 3.23 (SD=6.26) for those receiving high-dose buprenorphine and buprenorphine-naloxone.

At 6 months, the actual mean number of heroin-free days was 22.57 (SD=7.91) for those receiving methadone, 21.88 (SD=8.52) for those receiving low-dose buprenorphine, and 25.25 (SD=4.36) for those receiving high-dose buprenorphine and buprenorphine-naloxone.
At 6 months, the imputed mean number of heroin-free days was 9.43 (SD=11.36) for those receiving methadone, 8.51 (SD=11.03) for those receiving low-dose buprenorphine, and 10.57 (SD=11.75) for those receiving high-dose buprenorphine and buprenorphine-naloxone.

Methods used to derive estimates of effectiveness
The author made a number of assumptions, which were sometimes supported by the published literature.

Estimates of effectiveness and key assumptions
The author assumed that, for high-dose buprenorphine and buprenorphine-naloxone, 85% of all patients would receive takeaways, with the remaining 15% maintained on daily dosing regimens. Missed doses were treated the same. Clinical activity was assumed to be similar to low-dose buprenorphine. Based on the literature, the outcome measure for buprenorphine-naloxone was assumed to be equivalent to that achieved with high-dose buprenorphine.

Measure of benefits used in the economic analysis
The health benefit measure used was the number of heroin-free days gained in 6 months. This was derived from the outcomes.

Direct costs
The direct costs included in the analysis were those to the health care provider. These comprised staff time (counselling, medication review and case management), diagnostic tests (e.g. urine and blood tests), medications and facility-level resources. Facility-level resources included supplies, consumables, capital, equipment, and ancillary services such as general administration and management support. The costs for those receiving low-dose buprenorphine and methadone were derived from the economic analysis undertaken by Doran et al. (2003). In this study, patient-level data were obtained retrospectively for every second patient randomised. Averages were then estimated from those patients whose clinical records were available (i.e. 50% of participants) and applied to those patients whose clinical records were not reviewed, based on the individual patient's number of days in treatment. Diagnostic procedures were valued using standard government charges. Since data were only available for the first 3 months' treatment, medication use was estimated for the remaining time the patient was in treatment. Under the assumptions reported already, and further assuming that the costs of high-dose buprenorphine and buprenorphine-naloxone were similar to low-dose buprenorphine, the author derived the costs for these two treatment regimens. Discounting was not relevant, as all costs were incurred during a short time period, and was therefore not performed. The study reported the mean costs per patient. The price year was 1998 -1999.

Statistical analysis of costs
The costs were treated stochastically. A Mann-Whitney non-parametric test was used to test whether differences in costs between the three groups were statistically significant. Significance was set at p<0.05.

Indirect Costs
The indirect costs were not included.

Currency
Australian dollars (AUD).

Sensitivity analysis
Monte-Carlo simulation, using bootstrapping, was used to obtain the empirical sampling distribution of the incremental cost-effectiveness ratio. Bootstrapping involved sampling with replacement 5,000 times. Sensitivity analyses (one-way and multi-way) were also undertaken by varying resource use and outcomes.
**Estimated benefits used in the economic analysis**
The difference in mean number of heroin-free days in the month prior to baseline and at 6 months was 6.84 (SD=10.90) for methadone, 5.27 (SD=9.96) for low-dose buprenorphine, and 7.34 (SD=10.47) for high-dose buprenorphine and buprenorphine-naloxone. A Mann-Whitney non-parametric test showed no significant difference between the groups, (p=0.172).

**Cost results**
The mean cost per patient over 6 months of treatment was AUD 1,415 (SD=968) for methadone, AUD 1,729 (SD=1,291) for low-dose buprenorphine, AUD 1,867 (SD=1,328) for high-dose buprenorphine, and AUD 1,593 (SD=1,131) for buprenorphine-naloxone.

A Mann-Whitney non-parametric test showed no significant differences between the groups, (p=0.58).

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-effectiveness ratio (i.e. the additional cost per heroin-free day gained). All treatment strategies were compared with methadone.

For model 1, treatment with methadone compared with low-dose buprenorphine was found to be dominant, generating more heroin-free days and being less costly (95% confidence interval, CI: -AUD 2,069 - AUD 1,809).

Compared with methadone, high-dose buprenorphine and the buprenorphine-naloxone combination were found to be more expensive but also more effective than methadone. The additional cost per heroin-free day was AUD 906 (95% CI: -962 - 2,916) for high-dose buprenorphine and AUD 357 (95% CI: -1,520 - 2,367) for buprenorphine-naloxone.

The results of the sensitivity analysis showed that changes in dosing times, price of buprenorphine, and staff time did not change the non-significance of the incremental cost-effectiveness ratios.

**Authors' conclusions**
The observed difference between the cost-effectiveness of methadone and the other treatments was not statistically significant, indicating that high-dose buprenorphine and the buprenorphine-naloxone combination could provide a viable alternative to methadone in the treatment of heroin addiction.

**CRD COMMENTARY - Selection of comparators**
A justification was given for using methadone as the comparator. It represented current pharmacotherapy in Australia. You should decide if this treatment represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
No systematic review of the literature appears to have been undertaken. Although this is common practice with models, in the current study it appears that the studies have been selected from the literature according to convenience or the author’s preferences. Therefore, the effectiveness estimates derived might not be the best available. The author derived the main estimates of effectiveness for methadone and low-dose buprenorphine from a randomised controlled trial. To obtain such estimates for high-dose buprenorphine and buprenorphine-naloxone, the author used what appears to have been a mixture of results from another study and his own assumptions. Consequently, it was not entirely clear how the estimates of effectiveness for these two treatments were derived. The author provided very few details of the sensitivity analysis undertaken and the ranges used to vary the parameters. Therefore, it is possible that the quality of the estimates of effectiveness is poor.

**Validity of estimate of measure of benefit**
The author used the number of heroin-free days gained as the measure of benefit in the economic analysis. He acknowledged that this outcome measure does not provide a sense of wider non-health benefits associated with treatment. The benefits were not discounted given the short time period of the study analysis.

Validity of estimate of costs
All the categories of cost relevant to the health care provider perspective adopted were included in the analysis, as were all major relevant costs. The costs and the quantities were not reported separately, which will limit the generalisability of the author’s results. The costs relating to methadone and low-dose buprenorphine treatment were derived from a published economic evaluation, while those for the other two interventions were not clear. Based on the number of assumptions made, the author does not appear to have performed a thorough sensitivity analysis. In addition, he did not report the ranges over which the parameters were varied. Since all the costs were incurred during a short time period, discounting was unnecessary and was therefore not performed. The price year was reported, which will aid any future inflation exercises.

Other issues
The author did not make appropriate comparisons of his findings with those from other studies. The issue of generalisability to other settings was not addressed. In view of the number of assumptions made, and the fact that it was difficult to understand how the costs and outcomes for two newer interventions were calculated, the results from this study would not appear to be either internally or externally valid.

The author reported a number of further limitations to his study. Some of these limitations were based on the methodological challenges encountered by Doran et al. (2003) in the evaluation of methadone versus low-dose buprenorphine. In particular, data were not collected for 100% of patients and patients of differing degrees of resource intensity might have been omitted. Other limitations highlighted were the method of imputation, which might not accurately capture actual change in heroin use associated with treatment, and the fact that the current study had to make numerous assumptions. Also, actual doses required in the clinical setting may differ from the controlled trial situation that the study was modelled from, and the treatment regimen adopted, once listed, may differ from that used in the study.

Implications of the study
The author gave a brief description of the state of heroin dependence treatment in 5 years time. He suggested that future research should focus on the establishment of a true comparison of methadone versus buprenorphine-naloxone in terms of both efficacy and safety, and cost-effectiveness, to validate the estimates reported in the study. The author envisaged that the use of buprenorphine would continue to expand and that buprenorphine-naloxone would permeate the Australian treatment setting and be considered a first-line treatment.

Source of funding
None stated.

Bibliographic details

Other publications of related interest
