The Cost Effectiveness of Buprenorphine in a Primary Care Setting: A Randomised Controlled Trial

Anthony Harris
Senior Lecturer, Health Economics Unit, Monash University

Elena Gospodarevskaya
Research Fellow, Health Economics Unit, Monash University

Alison Ritter
Head of Research, Turning Point

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The Co-ordinator
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Abstract

Introduction

Buprenorphine offers an alternative to methadone in the treatment of heroin addiction, and has the advantage of allowing alternate day dosing. However the comparative effectiveness and cost effectiveness of buprenorphine in practice has not been extensively studied. This study is the first to examine the cost effectiveness of buprenorphine as maintenance treatment for heroin addiction in a primary care setting using economic and clinical data collected within a randomised trial.

Study design and methods

The study was a randomised open-label trial with data collection at baseline, 3, 6 and 12 months following treatment commencement. Patients were dosed buprenorphine or methadone at community pharmacies and the pharmacy of a specialist drug and alcohol centre. The final total sample size was 139. Patients were assessed and treated by their general medical practitioners according to clinical guidelines for methadone and buprenorphine. Individual treatment regimes were used and doses tailored to individuals. Participants were aged between 18 and 65, heroin dependent, and able to give informed consent. Two subgroups were identified before the analysis. Those who were currently on a methadone program n=57 (continuing therapy subgroup) were analysed separately from new treatment recipients n=82 (initial therapy subgroup). The trial took place in Melbourne in 1999/2000.

The study took a broad societal perspective and included health, crime and personal costs. Data on resource use and outcomes were a combination of clinical records and self report at interview. The incremental costs per additional day free of heroin use and per QALY were chosen as the outcomes in the study. An analysis of uncertainty calculated the likelihood of net benefits for a range of acceptable money values of outcomes. All costs were in 1999 Australian dollars.

Results

There was a small difference in average quality of life of 0.03 QALYs over the 52 weeks of the trial that favoured methadone. In the initial therapy subgroup those randomised to buprenorphine had an average of 0.65 QALYs (95% CI 0.56 to 0.73) while those randomised to methadone had an average of 0.61 QALYs (95% CI 0.52 to 0.70). During the year of the trial the estimated mean number of heroin free days did not differ significantly between those randomised to buprenorphine, 222 (95% CI 194 to 250), or methadone, 225 (95% CI 91 to 266). The total economic cost during the year of the trial was $17,736 (95% CI –2,981 to 38,364) and $11,916 (95% CI $7,697 to $16,135) in those randomised to methadone or buprenorphine. If crime is excluded, the costs were $4,513 (95% CI 3,495 to 5,531) and $5,651 (95% CI 4,202 to 7,100)

Discussion

The trial found no significant differences in costs or outcomes between methadone and buprenorphine maintenance. Although some of the results suggest that methadone may have a cost advantage, it is difficult to infer from the trial data that offering buprenorphine as an alternative would have a significant effect on total costs or outcomes. The point estimates of costs and outcomes suggest that buprenorphine may have an advantage in those initiating therapy although the confidence intervals were wide and the likelihood of net benefits from substituting one treatment for another was close to 50%.
Introduction

Methadone has been the mainstay for the treatment of opiate dependency for many years. Its personal and social popularity have been due to its success in reducing heroin use and the crime associated with addiction [1]. Not everyone is successful on methadone. Some cannot tolerate its side effects, some dislike the prolonged withdrawal, and some patients find the need for daily dispensing too restrictive. Most people have more than one episode of treatment and relapse to continuous heroin use is common. This has led many to consider other treatments for heroin addiction.

Buprenorphine has been shown to be a safe and effective alternative to methadone, and is registered in a number of countries for the treatment of heroin addiction[2-8]. A number of randomised controlled trials have examined the efficacy of buprenorphine maintenance compared to methadone maintenance[9,10]. A systematic review of the literature found that buprenorphine given in flexible doses was statistically significantly less effective than methadone in retaining patients in treatment (RR= 0.82; 95% CI: 0.69 to 0.96). High dose buprenorphine did not retain more patients than low dose methadone, but suppressed heroin use better. There was no advantage for high dose buprenorphine over high dose methadone in retention (RR=0.79; 95% CI: 0.62 to 1.01), and high dose buprenorphine was inferior in suppression of heroin use [11].

Buprenorphine has the advantage that it suppresses withdrawal symptoms for longer than methadone allowing less frequent clinic visits. A number of studies has shown that buprenorphine results in fewer withdrawal symptoms, and its use has been recommended in a primary care setting due to it being less toxic, less prone to diversion and easier to withdraw [12]. As a consequence buprenorphine became the first narcotic drug for the treatment of opiate dependence that can be prescribed in an office setting under the US Drug Addiction Treatment Act of 2000. This is expected to provide patients with greater access to treatment. However buprenorphine is considerably more expensive per dose than methadone. It is therefore not obvious that buprenorphine represents value for money as a treatment for heroin dependence. There have been numerous suggestions that because of its less than daily dosing, buprenorphine might be less expensive overall if all patient costs are considered [13]. Barnett et al. [14], in a modeled evaluation of the cost effectiveness of buprenorphine compared to methadone in the US, claimed that buprenorphine had an acceptable incremental cost per QALY as a substitute for methadone at a price of $5 per dose. However their analysis was not based on trial evidence of resource use and the perspective that they took meant that they excluded all non-health costs. In short the evidence for claims that the price premium of buprenorphine over methadone represents value for money is weak. To date there have been no trials of buprenorphine versus methadone that evaluate simultaneously the effectiveness and the resource implications of offering buprenorphine to either those newly entering a maintenance program or those who are current methadone users. Consequently the cost effectiveness of buprenorphine compared to methadone is unknown.

The current study is the first trial of buprenorphine compared to methadone that has collected data on cost and outcomes directly from participants. This has allowed an evaluation of the comparative costs and effectiveness of buprenorphine in a primary care setting. Calculating cost effectiveness in a trial setting has the advantage in that it provides a degree of internal validity not usually found in economic studies of health interventions. This study avoids some of the problems that plague cost effectiveness studies in health care and addiction - that they are often based on cost and outcome
data from a variety sources with unknown biases, compounded by subjective methods of establishing credible intervals around point estimates of cost effectiveness. On the other hand this is a difficult population to study in a randomized controlled trial and the generalisability of the results may be limited to the particular setting and by the quality of the data.

**Study design**

**Recruitment and eligibility**

Participants were aged between 18 and 65, heroin dependent, and able to give informed consent. Potential participants were excluded if they were breastfeeding, pregnant or intending to become pregnant during the trial, had a concomitant severe medical or psychological condition, were currently enrolled in another trial, or were refused treatment by the pharmacist. This study was approved by the Department of Human Services Ethics Committee, and conducted in accordance with Good Clinical Research Practice international guidelines. All participants gave written informed consent.

**Sample size and characteristics**

The study was part of a wider implementation trial testing the feasibility of providing buprenorphine to heroin dependent clients in a community setting, and the sample size was set to develop the necessary infrastructure that would facilitate the safe and effective uptake of these treatments [15]. For that reason the sample size for the economic trial was pragmatic and not chosen on the basis of its power to detect a difference in costs or outcomes. It was originally planned to recruit a maximum of 424 heroin dependent participants to the study including heroin users currently not in addiction treatment (initial therapy subgroup) and patients currently in a methadone program (continuing therapy subgroup). Patients who consented to treatment were randomised to buprenorphine or methadone by an independent telephone randomisation service using a dynamic balancing method to even out numbers in each arm.

**Trial design**

The trial was open-label for 12 months, with data collection at baseline, 3, 6 and 12 months following treatment commencement. The trial had three staggered intakes with one site in Intake I (five doctors at a drug and alcohol specialist clinic), eight sites in Intake II (involving 12 individual general practitioners) and 10 sites in Intake III (involving 11 general practitioners).

**Treatment description**

Patients were assessed and treated by their general medical practitioners according to clinical guidelines for methadone and buprenorphine [16]. Methadone dose, frequency of review and participation in counselling was tailored for each individual patient as per standard practice. Buprenorphine treatment used the sublingual 2 and 8 mg tablet preparations. The guidelines for buprenorphine treatment were structured along similar lines – with flexible doses, reviews and participation in counselling; and with conditions of daily supervised dispensing at induction. The maximum recommended daily buprenorphine maintenance dose was 32 mg. After a period of stabilisation (recommended at least 4 weeks), alternate day and three day buprenorphine doses were allowed (by doubling or tripling the dose, respectively, to a maximum of 64 mg dispensed at a time). Those randomised to buprenorphine were able to transfer to methadone and then back to buprenorphine, if this was clinically indicated, as part of the open label treatment regime. All 28 general medical practitioners were experienced methadone prescribers. All doctors and
pharmacists received training in delivering buprenorphine treatment, lasting approximately 3 to 3.5 hours. Patients in Intake 1 were dosed buprenorphine or methadone at the clinic pharmacy, while all other patients were dosed at community pharmacies (a total of 49 pharmacies across the state of Victoria). In Australia, methadone (and buprenorphine) is provided under supervised dosing conditions and take-home doses are highly regulated. In the state where this study was conducted methadone take-home doses were limited to a maximum of one per week. No buprenorphine take-home doses were permitted in the trial.

Methods

Heroin use and quality of life

The primary outcome measures for the cost analysis were days free of heroin use during the trial and the associated health related quality of life. Total heroin free days were calculated from the self-reported heroin use in the past four weeks reported at each interview. Self-report heroin use data have generally been shown to be reliable and valid. In order to check the validity within this sample, a urine drug screen was conducted on the day of the research interview and then compared to the appropriate self-report window period. The percentage agreement between the urine test and self-report was 76% at 3 months and 85% at 6 months.

Quality of life was measured using a multi-attribute utility scale (AQoL) and used to calculate QALYs. The AQoL provides a single index of health related quality of life and a health status profile based on four dimensions referring to independent living, social relationships, physical senses and psychological well-being. Each dimension has 3 items and each item has 4-levels ranging from normal health to worst health state. Overall utility was calculated as a weighted multiplicative index of the four dimensions with a score of 1 for perfect health and zero for death. The weights were derived from at time trade-off exercise in the Australian population. In a trial lasting one year the average utility score is the average QALY. Employment status and personal income was reported but not included as a measure of outcome.

Cost of resource use

A broad social perspective on cost was taken and included personal costs of travel as well as social cost of health care and crime. Pharmaceutical and medical services use were taken from the clinical and pharmacy record, supplemented by self-report at interview. Self reported data on pharmaceutical and other health service use, travel and crime in the previous 28 days were reported at each interview (baseline, 3 months, 6 months and 1 year) using a standard questionnaire. All resource use was aggregated and valued at current prices per unit of service to create total costs for each treatment group. The resource categories used and the sources of unit cost data used in the calculation of total costs are shown in Table I. The costs of crime were assumed to consist of the quantifiable social resource consequences of criminal activity and its detection: the health care costs from assault, loss of income by the victims of crime, and the depreciated value of property damaged, stolen or obtained fraudulently, detection, prosecution and imprisonment. This is an understatement of the true costs of crime as it ignores the psychological or physical impacts on crime victims as well as the broader costs of crime prevention associated with perceptions of the prevalence of crime.

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1 The loss in the value of the property was assumed to be 66% of the replacement cost to account for the fact that stolen property has a lower value than property legitimately obtained.
### Table 1: Categories of cost and unit costs, $AU 1999

<table>
<thead>
<tr>
<th>Cost category</th>
<th>Cost per unit</th>
<th>Cost sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>$0.0074 per mg</td>
<td>Commonwealth government program price to pharmacy(^1)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>8mg tablets at $30.10 per pack of 7</td>
<td>Commonwealth government program price to pharmacy(^1)</td>
</tr>
<tr>
<td>Dispensing</td>
<td>Cost per week (range=$20 - $60) (^2)</td>
<td>Pharmacist actual charges in trial</td>
</tr>
<tr>
<td>Cost of prescription drugs</td>
<td>Cost per dose (range = $0.15- $41.3 per day)</td>
<td>Price for maximum quantity on Pharmaceutical Benefits Schedule [19] and MIMS Australia [20]</td>
</tr>
<tr>
<td>Cost of OTC drugs</td>
<td>Cost per dose (range = $0.009- $4.00 per day)</td>
<td>MIMS Australia [20]</td>
</tr>
<tr>
<td>Prescriber visits</td>
<td>Cost of visit by the type of medical consultation(^3) GP=$25.85  Specialist = $65.80.</td>
<td>Items 23 and 104 on Medicare Benefits Schedule [21]</td>
</tr>
<tr>
<td>Inpatient hospital admissions</td>
<td>Inpatient DRG (range = $923.7- $16,865)</td>
<td>Victorian Cost Weights Study (Department of Human Services, 1999-2000) [22]</td>
</tr>
<tr>
<td>Outpatient and emergency services</td>
<td>Outpatient cost (range = $77.6- $323.1 per admission episode) Emergency cost (range = $99- $141.5 per admission episode)</td>
<td>Outpatient mean cost (Department of Human Services, 1998-1999) [23]. Ambulatory cost weights (Department of Human Services, 1999-2000) [24]</td>
</tr>
<tr>
<td>Ambulance</td>
<td>Cost of an ambulance call by the type of call $200 (without transportation) $545(with transportation)</td>
<td>Department of Human services. Personal communication [25]</td>
</tr>
<tr>
<td>Counselling</td>
<td>Psychiatrist = $66.55</td>
<td>Item 302 for Psychiatrists on Medicare Benefit Schedule [21]</td>
</tr>
<tr>
<td></td>
<td>Individual psychologist (range = $50- $120 per hour)</td>
<td>Australian Psychological Society’s recommended fee schedule [26]</td>
</tr>
<tr>
<td>Allied Health</td>
<td>Cost of visit by the category of allied health Range $33-$70</td>
<td>Fee suggested by professional associations</td>
</tr>
<tr>
<td>Pathology</td>
<td>Cost of test by the type of test (range = $9.90 - $41.00)</td>
<td>Medicare Items 73527, 66515 and 66623 for pathology tests [21]</td>
</tr>
<tr>
<td><strong>Non-medical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal travel</td>
<td>Cost of car =$0.30 per km</td>
<td>Vehicle operating cost and depreciation RACV [27]</td>
</tr>
<tr>
<td></td>
<td>Cost of public transport =$2.30 - $7.90</td>
<td>Public transport fare by zone effective from 1 January 1999 [28]</td>
</tr>
<tr>
<td></td>
<td>Travelling time = $6.00 per hour</td>
<td>Value of time for private travel [29] adjusted for CPI.</td>
</tr>
<tr>
<td>Crime committed(^4)</td>
<td>Property crime range =$200 (shoplifting) - $5139 (car theft) Fraud social security =$200 Credit card fraud = $3225 Violent crime =$1518 Police investigation $30 (shoplifting) - $246 (violent crime)</td>
<td>Australian Institute of Criminology, Canberra [30-32] Victorian Police Service Annual Crime Statistics Report [33]</td>
</tr>
</tbody>
</table>

1. The price of buprenorphine and methadone are supplied to pharmacies through a government program. Buprenorphine was not available through this program in 1999 and so the 2002 price of both drugs was used. In the case of methadone the price did not change in this period.
2. As part of the trial protocol patients were charged the same fee for Buprenorphine as the usual methadone fee within each pharmacy. In order to estimate the true cost of dispensing Buprenorphine, we assigned a cost to every dose dispensed based on the average cost of a dose of methadone at that pharmacy. Thus, if methadone was charged at $30 a week, and the average number of methadone doses per week at that pharmacy was 6, we assigned a dispensing fee of $5 per dose for Buprenorphine. Variation in the cost of dispensing between Buprenorphine and methadone was thus restricted to the frequency of dosing and to a lesser extent variation in fees between pharmacies. This does not account for the potentially higher time cost of dispensing sublingual Buprenorphine in some settings.
3. Patient charges were added to fees where reported.
4. Crimes without an immediate victim or direct resource consequence (drug dealing for example) were excluded from the cost calculation. Where the participants admitted to the fact that a crime was detected and prosecution took place the costs of law enforcement procedures and incarceration (if any) were included.

Note: individual unit costs were applied and the table illustrates the range of unit prices used. For example actual DRGs were used for cost hospital inpatient costs, and the range of costs per separation in the study was $932.7- $16,865.
Cost effectiveness analysis

The incremental cost per additional day free of heroin use was chosen as the primary outcome in the economic component of the study, supplemented by the cost per additional health related quality adjusted life year (QALY). The costs and heroin free days were interpolated for the entire 366 day study period using the information reported by the participants for the previous 28 days at each follow up interview. Levels in the intervening months were assumed to be equal to the average of those reported at the adjacent interviews. Differences in mean total costs and outcomes over the 12-month period (with 95% confidence intervals) were described. A t-test was used to calculate p-values for the difference in the mean cost. Regression analysis was used to test for differences in baseline levels of cost and outcomes, and where necessary to adjust costs and outcome results. Where the cost data were severely skewed a number strategies were adopted to infer a difference in mean cost. These included eliminating outliers and a log transformation of the data.

All observations on eligible participants who were randomised and received the first treatment dose were included in the analysis. The reason for not adopting a strict intention to treat approach was that some people had entered the study specifically to gain access to buprenorphine, and when randomised to methadone they did not commence treatment and immediately withdrew from the study. Their exclusion meant that their costs were not included, and so it is not likely to have biased the estimate of the incremental cost effectiveness of buprenorphine compared to methadone.

Given the experience of research in this population it was anticipated that there would be missing data as individuals failed to attend one or more interviews. The approach to missing data was to use a last point carried forward algorithm where there was evidence from other interview data that the individual was still in treatment. We also tested to see if an alternative method of linear interpolation affected the results for the outcome variables. Where the individual had withdrawn from treatment and was lost to follow up there was no firm basis for imputation. Since there was a high expected non-random drop out rate from the study, it would potentially bias the results if they were excluded from the analysis or only their observations while in the trial were included. In fact by 12 months nearly half of the subjects were lost to follow up. The approach taken to these missing data was to impute the baseline observations. This is likely to be conservative with respect to buprenorphine. However some patients who withdraw could be abstinent, in another treatment program, or be daily heroin users, and it is not obvious that baseline imputation would be conservative. A comparison with an analysis of available cases only provided partial evidence on this.

Uncertainty Analysis

The bias corrected nonparametric bootstrap method was used to estimate the distribution of the mean incremental cost effectiveness ratio [34]. This takes account of the joint density of costs and outcomes. There are some well-known problems in interpreting confidence intervals around cost effectiveness ratios [35]. In particular a negative ratio could arise from a treatment that is less expensive and more effective or one that is more expensive and less effective. It is therefore difficult to make inferences using incremental cost effectiveness ratios when the confidence interval includes zero. The cost effectiveness analysis was supplemented by converting the outcomes (heroin use and health related quality of life) into money values and calculating the net benefits of the intervention [36]. Acceptability of buprenorphine is then judged as the probability, based on the
trial evidence, that the net benefit is positive. A cost benefit analysis like this however requires an assumption about the social value of health improvements (in this case a QALY or a heroin free day). It also makes the assumption that a health gain for a given cost is valued the same as a parallel health loss compensated by an equivalent reduction in cost [37]. While there have been some attempts to look at decision makers ceiling cost effectiveness ratios, there is no agreed social cut-off value in Australia or elsewhere [38]. Following Van Hout et al [39] and Briggs [40] we have adopted the simple approach of varying the social cut off value, and then taken a Bayesian interpretation of the percentage of bootstrapped mean net benefits that are positive as the likelihood of net benefits from therapy (with the assumption of prior ignorance).

Non-parametric bootstrapping of the data on cost and outcome in a controlled trial can provide an unbiased estimate of the distribution of the mean incremental cost effectiveness ratio, but it may not do so if the initial sample is unbalanced between groups. The approach in this study was to use regression analysis to adjust for baseline differences where appropriate, and to use the resulting imputed values in the bootstrap process to estimate the distribution of the incremental cost effectiveness ratio. As Briggs et al [41] discuss there are two components to the uncertainty in an imputation process like this. The first is the mean square error of the regression representing the unexplained variation in the estimate from the regression. Second the coefficients in the regression are themselves subject to error. The approach to the first of these two sources of uncertainty was to calculate an adjusted value for each observation from the regression, and then to add a randomly chosen residual from the regression to each observation. The mean annual value for this new sample incorporates the first component of imputation error. The second source of error is handled by repeating the regression 1000 times from a resample of the original data. It should be noted that while we have included an estimate of the error introduced by the imputation of cost due to the unbalanced randomisation, we have not included any estimate of the error due to the imputation of missing data. This means that the width of the confidence intervals is likely to be underestimated.

**Results**

**Sample characteristics**

Of the total of 158 people recruited to the trial, 3 withdrew their consent, and a further 14 did not receive a dose, resulting in a final sample of 139. Follow-up interview rates at 3 months were 75% and 77% for those randomised to buprenorphine and methadone respectively. At 6 months, 77% of the buprenorphine and 67% of the methadone groups were traced for interview. At 12 months, 53% and 50% of those randomised to buprenorphine and methadone were successfully traced and interviewed. Participant flow and research follow-up rates are shown for the sample in Figure 1. Although patients randomised to buprenorphine were able to switch therapies the vast majority of patients who remained in treatment were receiving buprenorphine (86% at 3 months; 93% at 6 months).
The mean age of all patients was 30, and 57% were male. Sixty two percent were unemployed. Those randomised to methadone were more likely to be in a permanent relationship, in employment and have a higher level of education. None of these differences were statistically significant. Previous drug and alcohol treatments, which included inpatient and outpatient detoxification, residential rehabilitation, outpatient counselling, self-help groups and prescribed methadone were common across the sample. For those receiving methadone maintenance, the average daily dose at 3 months was 42mg and at six months 50.3mg. For those on buprenorphine, the average daily dose at both three and six months was 13.8mg. At three months, 70% of the buprenorphine group was on an alternate day or three times per week dosing schedule. This had decreased slightly at six months to 66% on a less than daily dosing schedule.
Outcomes

Table 2 shows the estimated number of days of heroin use and the health related quality of life during the last 28 days at each interview. During the year of the trial the estimated mean number of heroin free days did not differ significantly between those randomised to buprenorphine or methadone. For the sample as whole the estimated difference in days using heroin between those randomised to methadone and those randomised to buprenorphine was only 3 over the whole year. For the continuing therapy subgroup there was an average of 275 (95%CI 230 to 320) reported days without heroin in those randomised to buprenorphine and 277 (95%CI 240 to 314) in those randomised to methadone. In the initial therapy subgroup the mean reported number of heroin free days was 192 (95%CI 157 to 226) and 182 (95%CI 139 to 225) in those randomised to buprenorphine or methadone.

There was a small difference in average quality of life of 0.03 QALYs over the 52 weeks of the trial that favoured methadone. Over the 52 weeks of the trial those randomised to buprenorphine had an average of 0.65 QALYs (95% CI 0.56 to 0.73) while those randomised to methadone in the initial therapy subgroup had an average of 0.61 QALYs (95% CI 0.52 to 0.70). For those in the continuing therapy subgroup the mean was 0.61 QALYs (95%CI 0.53 to 0.70) for those randomised to buprenorphine and 0.58 QALYs (95%CI 0.51 to 0.66) for those randomised to methadone. Maintenance treatment had a slightly greater benefit for the initial therapy subgroup in terms of QALYs measured, but the improvement was similar between those randomised to buprenorphine or methadone.

Table 2: Measures of outcome over time

<table>
<thead>
<tr>
<th></th>
<th>Randomised to Buprenorphine (n=73)</th>
<th>Randomised to Methadone (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days free of heroin use</td>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>Baseline</td>
<td>9.9 (7.4, 12.4)</td>
<td>11.4 (8.5, 14.4)</td>
</tr>
<tr>
<td>Previous 28 days at 3 months</td>
<td>18.2 (15.6, 20.9)</td>
<td>17.9 (15.2, 20.6)</td>
</tr>
<tr>
<td>Previous 28 days at 6 months</td>
<td>18.9 (16.5, 21.3)</td>
<td>18.3 (15.5, 21.0)</td>
</tr>
<tr>
<td>Previous 28 days at 12 months</td>
<td>16.9 (14.2, 19.6)</td>
<td>18.2 (15.5, 20.9)</td>
</tr>
<tr>
<td>During year of the trial</td>
<td>222.4 (194.3, 250.5)</td>
<td>225.0 (91.3, 266.1)</td>
</tr>
<tr>
<td>Utility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.59 (0.53, 0.65)</td>
<td>0.60 (0.54, 0.67)</td>
</tr>
<tr>
<td>Previous 28 days at 3 months</td>
<td>0.63 (0.57, 0.69)</td>
<td>0.61 (0.55, 0.67)</td>
</tr>
<tr>
<td>Previous 28 days at 6 months</td>
<td>0.61 (0.55, 0.68)</td>
<td>0.62 (0.55, 0.69)</td>
</tr>
<tr>
<td>Previous 28 days at 12 months</td>
<td>0.63 (0.56, 0.69)</td>
<td>0.58 (0.51, 0.64)</td>
</tr>
<tr>
<td>During year of the trial</td>
<td>0.62 (0.56, 0.68)</td>
<td>0.59 (0.54, 0.65)</td>
</tr>
</tbody>
</table>

The high drop out rate in the trial meant that by 12 months a high proportion of data points in Table 2 were imputed (50% of those randomised to methadone and 47% of those randomised to buprenorphine). The similarity of the drop out rates suggests that even if the imputation of heroin use and cost data to missing data has biased the estimate of heroin use it is not likely to have biased the estimate of incremental cost effectiveness in favour of buprenorphine. Table 3 shows the days free of heroin for those who remained in the trial at each interview. It suggests that the imputation algorithm used was conservative in so far as it estimated a greater use of heroin at each
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Data point than available cases suggested. The available cases showed a difference in heroin use of 2-3 days per month at 12 months in favour of buprenorphine, whereas the imputed data showed a difference in favour of methadone. In both cases however the confidence intervals were wide.

Table 3: Days free of heroin using data from cases available at each study interview

<table>
<thead>
<tr>
<th>Days free of heroin use</th>
<th>Randomised to Buprenorphine</th>
<th>Randomised to Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.9 (7.4 12.4) (n=73)</td>
<td>11.4 (8.5 14.4) (n=66)</td>
</tr>
<tr>
<td>Previous 28 days at 3 months</td>
<td>23.4 (15.6 20.9) (n=55)</td>
<td>20.8 (18.2 23.5) (n=51)</td>
</tr>
<tr>
<td>Previous 28 days at 6 months</td>
<td>22.3 (20.3 24.4) (n=56)</td>
<td>20.0 (16.8 23.2) (n=44)</td>
</tr>
<tr>
<td>Previous 28 days at 12 months</td>
<td>23.6 (21.1 26.0) (n=39)</td>
<td>21.6 (18.5-24.7) (n=33)</td>
</tr>
</tbody>
</table>

Costs

Table 4 reports the mean costs over the period of the trial for the sample as whole and the two subgroups by randomisation to buprenorphine or methadone. All prices are in 1999 Australian dollars. The total economic cost during the year of the trial was $11,916 (95% CI $7,697 to $16,135) and $17,736 (95% CI –2,981 to 38,364) in those randomised to buprenorphine and methadone. The data were positively skewed in large part because of the reported crime costs. The average cost of crime was substantial across the sample but these reported costs were associated with just a few participants. Ninety percent of the sample randomised to methadone and 96% of the sample randomised to buprenorphine reported no involvement in property crime in the past 4 weeks. There were no reports of involvement in drug dealing in the past 4 weeks. Indeed the majority of patients reported no criminal activity during the trial. We made some attempts to adjust for the skewed nature of the costs. First the data were transformed into logs and the back-transformed mean cost and confidence intervals were calculated using Cox’s method discussed in Zhou [42]. Second we deleted severe outliers (those above the 75th percentile by at least 3 times the interquartile range). The log-normal mean for those randomised to methadone was $8,647 (95% CI $6,097 to $12,264) and $11,386 (95% CI $7,968 to $16,269) for those randomised to buprenorphine. After removing the 19 observations that were regarded as outliers, the result was that buprenorphine cost $4,463 more than methadone (95% CI -859 to 9,785). In both cases the result of adjusting for skewed distribution of costs was to reverse the apparent cost advantage of buprenorphine, although the difference in the normalized cost between those randomised to buprenorphine or methadone was not statistically significant using either approach.

The combination of the small sample size, a lack of confidence in the reliability of the self reported crime data, and the high positive skew in the results gave rise to concerns about the generalisability of the crime cost data and its suitability for statistical analysis. If crime is excluded altogether the costs were $5,651 (95% CI $4,202 to $7,100) and $4,513 (95% CI $3,495 to $5,531) in those randomised to buprenorphine and methadone.

In the initial therapy subgroup the total economic cost during the year of the trial was $14,185 ($5,442 excluding crime) in those randomised to buprenorphine and $28,595 ($5,245 excluding crime) in those randomised to methadone. When crime costs were excluded the equivalent mean annual cost was very similar between those randomised to buprenorphine and methadone. In the
continuing therapy subgroup crime costs again skew the results, but when they were excluded the annual equivalent cost was higher in those randomised to buprenorphine at $6,006 as compared to those randomised to methadone at $3,634 with a difference of $2,372 (95%CI –$244 to $4988).

Table 4: Cost during 12 months of trial ($AU,1999)

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>Initial therapy subgroup</th>
<th>Continuing therapy subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methadone</td>
<td>Buprenorphine</td>
<td>Methadone</td>
</tr>
<tr>
<td></td>
<td>(n=66)</td>
<td>(n=73)</td>
<td>(n=36)</td>
</tr>
<tr>
<td>Cost of study medication (including dispensing fee)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (std. err.)</td>
<td>1,122 (85)</td>
<td>1,785 (204)</td>
<td>1,044 (122)</td>
</tr>
<tr>
<td>Annual equivalent cost of travel</td>
<td>890 (108)</td>
<td>550 (87)</td>
<td>892 (168)</td>
</tr>
<tr>
<td>Annual equivalent cost of crime</td>
<td>13,223 (10,209)</td>
<td>6,265 (2,028)</td>
<td>23,349 (3,080)</td>
</tr>
<tr>
<td>Annual equivalent cost of medical and addiction services consumed</td>
<td>2,500 (489)</td>
<td>3,316 (667)</td>
<td>3,308 (838)</td>
</tr>
<tr>
<td>Annual equivalent total cost</td>
<td>17,736 (10,329)</td>
<td>11,916 (2,116)</td>
<td>28,595 (18,851)</td>
</tr>
<tr>
<td>Annual equivalent cost (excluding crime)</td>
<td>4,513 (510)</td>
<td>5,651 (727)</td>
<td>5,245 (878)</td>
</tr>
</tbody>
</table>

The overall cost of medication was higher in those randomised to buprenorphine even with the cost of the drug offset by reduced costs of alternate or 3 day dosing. The less frequent dispensing however did mean that travel costs were significantly lower for those randomised to buprenorphine, particularly in the initial therapy subgroup. The difference in the continuing therapy subgroup may have been due to an imbalance in resource use before the trial. The results of a regression of the log of cost over the year on the log of cost in the pre-study month and a buprenorphine therapy dummy variable are shown in Table 5. Those randomised to buprenorphine had significantly higher costs overall when adjusted for baseline costs. The adjusted cost increase from the regression was $1,182 (95%CI $608 to $1756).
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Table 5: Regression analysis of log total cost (excluding crime) over trial on randomised to buprenorphine and baseline log cost (continuing therapy subgroup) n=56

| log of cost over trial | Coefficient | Robust St. error | T value | P>|t| | 95% CI |
|------------------------|-------------|------------------|---------|-----|--------|
| Randomised to buprenorphine | 0.31 | 0.18 | 1.74 | 0.09 | -0.05 | 0.67 |
| Log pre-trial cost | 0.18 | 0.06 | 2.79 | 0.007 | 0.05 | 0.31 |
| Constant | 6.76 | 0.48 | 14.13 | 0.000 | 5.80 | 7.72 |

F=0.018; adjusted R squared= 0.15; RESET test p=0.67

Cost effectiveness

The point estimates of the incremental cost per extra day free of heroin use and per extra QALY are shown in Table 6. In the whole sample the results are sensitive to the inclusion of crime costs and the choice of outcome measure. With additional heroin free days as the outcome the cost effectiveness of methadone ranges from $5,645 if crime is included to dominance if crime costs are excluded. With additional QALYs as the outcome the cost effectiveness of buprenorphine is $22,760 if crime is excluded, but buprenorphine is dominant if crime is included. Buprenorphine is dominant in the initial therapy subgroup if crime is included and has a cost per additional QALY of $9,850 if crime is excluded. Methadone is dominant in the continuing therapy subgroup if cost per heroin free day is used as an outcome, but buprenorphine has a cost per extra QALY of $26,356 or $37,189 depending on whether crime costs are excluded or included. The absolute difference in outcomes was small and the confidence intervals for both outcome and cost differences were wide. For these reasons the point estimates of the incremental cost effectiveness of buprenorphine or methadone shown in Table 5 should be interpreted with caution. In the subgroup analysis of those who were continuing on therapy, resource use at baseline differed between the groups. We adjusted the estimated mean cost during the trial (excluding crime) using the results of a log-linear regression with a dummy variable for the intervention and cost at baseline as a covariate.

Table 6: Incremental cost effectiveness of therapies ($AU 1999)

<table>
<thead>
<tr>
<th>Total sample</th>
<th>Initial therapy subgroup</th>
<th>Continuing therapy subgroup*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>∆ Cost/</td>
<td>∆ Cost/</td>
</tr>
<tr>
<td></td>
<td>∆HFD</td>
<td>∆QALY</td>
</tr>
<tr>
<td>Including crime</td>
<td>methadone</td>
<td>buprenorphine</td>
</tr>
<tr>
<td></td>
<td>$5,645</td>
<td>dominant</td>
</tr>
<tr>
<td>Excluding crime</td>
<td>methadone</td>
<td>buprenorphine</td>
</tr>
<tr>
<td></td>
<td>dominant</td>
<td>$22,760</td>
</tr>
</tbody>
</table>

* unadjusted costs  ∆ = change
Figure 2 plots the bootstrapped incremental mean cost per extra heroin free day (excluding crime) in the four quadrants of the cost effectiveness plane for the whole sample (quad 1 has +ve extra cost and +ve extra outcomes; quad 2 has +ve extra cost and -ve extra outcomes; quad 3 has -ve extra outcomes and -ve extra cost; quad 4 has -ve extra cost and +ve extra outcomes). Forty-two percent were in quadrant 1, 47% in quadrant 2, 6 percent of mean cost effectiveness ratios were in quadrant 3, and 5% were in quadrant 4. If the community willingness to pay per heroin free day is positive, then the likelihood of positive net benefits from buprenorphine is 9.5%. There was a maximum likelihood of positive net benefits of 48% as the willingness to pay threshold for a heroin free day became large (>\$20,000). The exercise was repeated for the whole sample but including the cost of crime. The results in terms of net benefits were very similar with the likelihood of positive net benefits never exceeding 47% even at very high money threshold values for a heroin free day.

A similar picture emerges for the two subgroups whether adjusted for baseline costs or not. If we are prepared to pay at least \$2,000 per QALY then the likelihood of positive net benefits from buprenorphine is 43%, but does not go beyond that even as willingness to pay increases. Including crime costs does not alter that general conclusion. The key result of the uncertainty analysis is that in the sample as a whole, and for both subgroups, the study was not able to show that one therapy was likely to offer better value. In every case there was a high probability that the other therapy had net benefits irrespective of what the community is willing to pay for an improvement in the lives of those dependent on heroin.

Figure 2: Bootstrapped unadjusted mean incremental cost per extra heroin free day from buprenorphine compared to methadone for the whole sample (excluding crime costs)
Discussion

The data do not provide support for a significant difference between buprenorphine and methadone in terms of cost or outcomes in those entering a primary care maintenance program for heroin addiction. The cost data were highly skewed, but the data do seem to suggest that those randomised to buprenorphine have higher associated cost than those randomised to methadone. Most clearly for those who were already on a methadone program, and were seeking an alternative, buprenorphine appeared to be more expensive with a slight gain in health related quality of life, but no more or less effective in reducing heroin use. Although some of the results suggest that methadone may have a cost advantage, it is difficult to infer from the trial data that offering buprenorphine as an alternative would have a significant effect on total costs or outcomes. The point estimates of costs and outcomes suggest that buprenorphine may have an advantage in those initiating therapy although the confidence intervals are wide. The uncertainty analysis showed that the probability of one therapy being better value for money compared to the other is close to 50%. In other words the data could not discriminate between the two treatments in terms of expected net benefits.

There are a number of aspects of this study that limit its generalisability. The most important are the sample size, the wide variation in costs between individuals, and the high dropout rate. Taken together these limit the power of the study to detect a difference between treatments and may have introduced bias in the estimates of that difference. The sample size of 139 meant that the study was underpowered to detect a statistically significant difference in cost or outcomes given the wide variation in cost between individuals and the observed small difference in heroin use or quality of life. A drop out rate of almost 50% by 12 months is a serious limitation on the ability of the study to estimate the longer term net benefits of buprenorphine. We have tried to make efficient use of the data by imputing values in a conservative fashion to limit any bias. Nevertheless the possibility remains that the estimates of net benefit are biased to an unknown extent and in an unknown direction. A further limitation on the study is that measure of benefits may not capture all of the individual and social gains from treatment. The use of health related quality of life as an outcome, even with the money value of time and travel, might be a very narrow measure of the social welfare gain from alternative maintenance treatments. While the impact of criminal activity was considered the data on crime costs were so skewed that we were not confident about their validity. This is a difficult population to study and difficulties in recruitment and a high drop out rate are part of the explanation as to why there are such few large scale trials of treatment alternatives for heroin addiction. However the results of this trial do suggest that there is a potential for buprenorphine to offer a reduction in time and travel costs without any significant deterioration in outcomes at least for 6 months to a year. The savings to patients as calculated here were not sufficient to compensate for an increase in the cost of drug delivery and other medical costs. Whether the potential for savings could be realised more widely depend in part on the generalisability of the study from a general practitioner and community pharmacy program to a larger patient group in other settings.
Conclusion

The trial was not able to show that offering buprenorphine, as an alternative to methadone to everyone who enters a primary care pharmacotherapy program, would change the cost and outcomes of the treatment program, as measured by either heroin use or health related quality of life. Analysis of two sub-groups - those switching from methadone and those newly entering a maintenance program - produced the same result. The data suggest that while buprenorphine might be more expensive than methadone overall, it produces similar outcomes in terms of heroin use and health related quality of life. Any difference in cost is subject to considerable uncertainty.

Is the glass half full or half empty? It is perhaps reassuring to some that buprenorphine affords similar efficacy to that of methadone, with no significant differences in cost. For others it is perhaps disconcerting that including buprenorphine as part of an alternative maintenance treatment for heroin dependence did not afford a clear net advantage over methadone. The study confirmed that entering treatment (with either therapy) led to a reduction in heroin use. An interesting possibility, not analysed here, is whether by including buprenorphine within the range of effective treatment options available for heroin dependence, the total numbers entering treatment could be increased with a consequent reduction in total heroin use at a cost similar to the current methadone program.
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