A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine–naloxone for heroin dependence

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ABSTRACT

Aims To compare the effectiveness and cost-effectiveness of unobserved versus observed dosing of patients seeking treatment of heroin dependence. Design Randomized controlled trial and cost-effectiveness analysis. Setting Specialist out-patient drug treatment centres in Australia. Participants Heroin users seeking maintenance treatment. Intervention Participants were allocated randomly to observed or unobserved dosing for 3 months. All subjects received buprenorphine–naloxone and weekly clinical reviews. Measurements Primary end-points were retention in treatment and heroin use at 3 months. Costs of treatment were measured (in Australian dollars, AU$) and cost-effectiveness compared. Secondary outcomes included quality of life, psychological symptoms and use of non-opioid drugs. Findings A total of 119 subjects were randomized and analysed. At 3 months, 33/58 (57%) randomized to unobserved treatment, and 37/61 (61%) observed were retained (log-rank $\chi^2 = 0.04$, df = 1, $P = 0.84$). On an intention-to-treat analysis, reductions in days of heroin use in the preceding month, from baseline to 3 months, did not differ significantly; 18.5 days (95% CI: 21.8–15.3) and 22.0 days (95% CI: 24.3–19.7), respectively (Mann–Whitney $U = 807.5$, $P = 0.13$). The mean cost for the unobserved group was AU$1663 (95% CI 1308–2017) per treatment episode, significantly less than the mean cost for the observed group at AU$2138 (95% CI 1713–2562). Conclusions Retention and heroin use was not significantly different between observed and unobserved dosing groups. Attendance for observed dosing was not associated with worse retention. Treatment with close clinical monitoring, but no observation of dosing, was significantly cheaper and therefore significantly more cost-effective.

Keywords Buprenorphine–naloxone, heroin dependence, medical maintenance, suboxone, supervised dosing.

INTRODUCTION

Until recently, direct observation of dosing has been a defining characteristic of opioid substitution treatment programmes, particularly in the United States and Australia [1]. The primary reason for direct observation has been to ensure that medication is taken as prescribed, rather than injected by the patient or sold on the black market. In addition, the requirement to attend a treatment centre daily may improve treatment outcomes by providing a structure for people making the transition from obtaining and using illicit drugs, and bringing people into contact with medical, welfare and counselling services [2].

However, the experience in France in the 1990s has challenged the assumption that effective treatment requires direct observation. Commencing in 1994, after many years with almost no access to substitution treatment, the introduction of high-dose buprenorphine saw more than 60 000 in treatment within a few years. Treatment required almost no infrastructure, being prescribed by general practitioners (GPs). Although the expansion of
buprenorphine availability was not without problems, including widespread injecting of medication [3], there appears to have been a substantial reduction in fatal opioid overdose [4].

In the United States, since 2000 federal legislation has allowed for treatment without direct observation of dosing using a new medication, combination buprenorphine–naloxone (Suboxone™). The rationale for development of this combination was to minimize the risk of intravenous misuse. Taken sublingually, naloxone undergoes extensive first-pass metabolism and has negligible bioavailability; thus, when used as prescribed, the combination product produces effects of buprenorphine alone. However, if injected, the naloxone will precipitate withdrawal in subjects dependent on full opioid agonists [5]. It is anticipated that the drug will be less susceptible to diversion and injection, reducing the requirement for direct observation of dosing.

The availability of preparations with reduced abuse potential has the prospect of making treatment more accessible and less expensive. However, the effectiveness of unobserved administration needs to be tested in clinical trials. Evidence for the effectiveness of buprenorphine in the treatment of opioid dependence has been established in three placebo-controlled clinical trials, each involving direct observation [6–8].

Initial randomized trials establishing the effectiveness of methadone treatment all involved direct observation [9–11]. Subsequent trials comparing buprenorphine and methadone also involved observed administration of medications [12–18]. The evidence of these trials is that buprenorphine, administered with observation, is comparable to methadone in effectiveness.

There is limited evidence of the effectiveness of maintenance treatment without observed dosing. The first controlled trial investigating unobserved buprenorphine was a study investigating counselling support schedules [19]. This study reported no differences in outcome between subjects randomized to thrice-weekly versus weekly counselling.

We have undertaken a randomized trial to compare the effectiveness of treatment with observation of dosing by randomizing heroin users seeking treatment to either usual care (regular attendance for observed dosing), versus picking up medication once per week, for administration at home (unobserved dosing). In keeping with usual care, subjects in the observed group could attend daily, second-daily or thrice-weekly (using 2- or 3-day dosing schedules) depending on their stability. Treatment was for 13 weeks, and all subjects received combination buprenorphine–naloxone. In addition to monitoring treatment effectiveness, we undertook detailed costing of treatment in order to compare cost-effectiveness. Our hypothesis was that retention in treatment would be superior in the group randomized to unobserved dosing, as the requirement to attend a clinic for supervised administration of medication would be a deterrent to remaining in treatment.

METHODS

Participants

Prospective subjects were people aged over 18 years who were seeking treatment for heroin addiction at four specialist out-patient drug treatment centres in Australia: two centres located in Sydney, one in Newcastle and one in Melbourne. The study was approved initially by the Human Research Ethics Committee (Northern Sector), South-eastern and Illawarra Health Service, and was subsequently approved by the institutional ethics committees of each of the participating sites.

Each centre maintained a log of all people presenting for treatment of opioid dependence and documented reasons for non-recruitment to the trial. Patients were not eligible if they: (i) had a contraindication to buprenorphine; (ii) had been in maintenance treatment for the previous month (to prevent people dropping out of current treatment to enter the study in the hope of receiving unobserved treatment); (iii) were pregnant; (iv) had unstable medical or psychiatric illness; (v) were concurrently dependent on alcohol, benzodiazepines or stimulants; (vi) were at risk of incarceration; (vii) did not have stable accommodation (as it was considered unsafe to provide supplies of medication to people living in homeless shelters or on the streets); (viii) had a drug-using partner who was not in treatment or were living in a household where people were actively using opioids; and (ix) had current or impending involvement with child protection services.

Where couples sought treatment, only one of the couple was randomized. The other partner was allocated to the same treatment group and excluded from the analysis.

Procedures

Opioid-dependent subjects meeting jurisdictional criteria for entry to maintenance treatment (opioid-dependent, with a history of at least 12 months’ opioid use) were initiated on buprenorphine, usually on the day of presentation (day 1). Over the first 4 days a treatment plan was developed, usually involving a choice between detoxification or maintenance. Those interested in maintenance were informed of the trial and invited to participate. Consenting subjects were allocated randomly to either observed dosing or unobserved dosing, with medication dispensed weekly and taken at home.
Subjects switched to buprenorphine–naloxone on day 8. All subjects met weekly with their nurse case-manager, underwent a structured interview relating to heroin and other drug use and were asked to submit a urine sample. Subjects who failed to attend for 8 days (or who missed successive scheduled clinical reviews) were removed from the trial. All subjects were advised that after 3 months’ treatment, treatment allocation would be revised based on a case conference between the doctor and case manager. Each subject remaining in treatment would be allowed access to unobserved dosing at that point, unless during weeks 9–13 they met specified criteria of instability (predominantly, continued injecting drug use). Patients who met criteria of instability could remain in treatment, but had to attend daily for observed administration.

A pharmacist, not involved in the study and off-site to the study sites, generated a randomization list prior to study commencement. The sequence was generated in blocks of 66 by drawing cards marked ‘observed’ or ‘unobserved’ from a container. After subject enrolment the study research assistants faxed the pharmacist for group allocation. Subjects and clinicians delivering treatment could not be blinded to group assignment.

**Primary outcomes**

The primary measures of effectiveness were retention in treatment at 3 months and heroin use at 3 months, as measured by the change in number of self-reported days of heroin use and the drug use scale of the Opiate Treatment Index (OTI).

The OTI drug use scale is a validated questionnaire designed to assess heroin and other drug use. The drug scale examines recent use and produces index of drug involvement—the ‘Q score’—for each substance. The Q score is a measure of average use over the past 28 days and is calculated on the basis of recent consumption [20].

**Cost effectiveness analysis (CEA)**

The CEA involved a systematic identification of resources used and outcomes of the alternative treatments and then an estimate of the incremental cost effectiveness ratio (ICER). An ICER allows comparison of the efficiency of different interventions that are designed to produce a given outcome [21,22].

Resource use was valued in 2005 Australian dollars (AU$) with a total cost estimated for each individual and then each treatment group. Detailed costings of medication, medical, counselling and dispensing costs, other health care costs (hospital admissions, ambulance service, dental services, emergency visits, allied health professionals, pathology tests, prescriptions), travel costs and travel time were undertaken. Additional information on the resource use categories and their unit costs is available from author Marian Shanahan; space availability precluded their inclusion.

The perspective taken for economic evaluation was that of the health care sector. Costs of providing the intervention (observed and unobserved administration) were estimated, as were the costs of other treatments for substance misuse, including any treatment taken up by those who dropped out of treatment and any other use of the health care system. The personal costs of travel to treatment were also collected.

Information on resources used in providing treatment, including time and frequency of direct clinical contacts and diagnostic tests, was recorded on a form placed in clinical files; an audit of clinical files was undertaken to ensure completeness of data collection. Dispensing information was obtained from pharmacy records, and cost of buprenorphine–naloxone obtained from the Australian Pharmaceutical Benefits Schedule. Indirect clinical time, the time spent related to patient care but not directly in contact with patients such as case conferencing, formal and informal consultations, preparing and updating clinical records, was measured using a survey questionnaire administered to the clinic staff providing treatment to participants. Direct and indirect time was combined to obtain the total time spent with each participant. Staff time was valued using actual staff salaries and benefits.

Costs related to overheads were estimated and allocated based on time in treatment (again, further details can be obtained from author Marian Shanahan).

Information on other health service use, including medications, hospital stays or other contacts with health professionals, were collected from the participants for the previous 28 days during the baseline and 3-month interviews. The costs for these two periods were extrapolated to estimate costs for the 3 months using two times the third month plus baseline.

To estimate travel costs, participants were asked about the costs, time taken and type of travel used most commonly to attend for dosing or dispensing. Once the cost to attend for an individual treatment episode was estimated this was multiplied by the number of attendances.

Costs were estimated for 3 months and include study treatment up to and including 91 days or dropout, whichever came first, other health services use and any other treatment costs plus travel costs to obtain treatment. For those who were not followed-up, other health services use costs were imputed from the average of those who were followed-up. Travel costs were based on self-report and extrapolated to 3 months.

The analysis of costs of the intervention and travel costs took account of the censoring of cost data (as a result of treatment dropout) [23]. The mean costs for
3 months, including the cost of intervention, travel, other health services costs and other treatment costs, were estimated. Given the skewed nature of the cost data, traditional statistical methods are not valid, thus bootstrapping methods were used to estimate 95% confidence intervals. A total of 1000 replicates were taken of each sample and 95% confidence intervals about the sample estimate were reported.

The ICER in this study is the incremental cost per additional day free of opioid use from baseline to the 3-month follow-up. The non-parametric bootstrap method was used to estimate the distribution for the ICER. When the confidence interval includes zero (either because there is no significant difference in outcomes or there is no significant difference in costs) a negative ICER occurs, making the CI difficult to interpret [24].

Secondary outcomes

Changes in non-opioid drug use, quality of life and psychological symptoms at 3 months and reports of medication diversion and injection were documented. Injecting sites were inspected monthly by the attending doctor.

Quality of life was assessed using the WHOQoL BREF [25], a self-report inventory that contained 26 items covering the preceding 2 weeks. Four domains of quality of life were assessed: physical, psychological, social and environmental [26,27].

Psychological symptoms were assessed using the Depression, Anxiety and Stress Scales—21 items (DASS21) [28]. This self-report inventory assesses severity of depression, anxiety and stress experienced over the proceeding week.

Each participating clinic kept a log of all reports of trial medication being diverted or injected by trial subjects and a record of adverse drug reactions. Participants were also asked about injection and diversion at 3-month research follow-up.

Outcomes were assessed at research interview by four research assistants, who were trained to administer the questionnaires and were blind to randomization. However, during follow-up interviews subjects frequently revealed which treatment condition they had been in.

An initial power calculation suggested that 86 subjects in each group would be required to detect a 20% difference in retention at the 0.05 alpha level with 80% power. As there were no data on which to estimate the likely retention in unobserved dosing, it was planned to undertake an interim analysis when 60 subjects had reached 3 months’ follow-up, to determine whether the sample size would be appropriate. The planned interim analysis showed virtually identical retention at 3 months in the two conditions, and very similar outcomes in heroin use. To confirm this, and obtain a larger sample for costing data, it was decided to continue recruitment until the medication became registered for general use in Australia.

Statistical analyses were performed using SPSS software, version 14.0. Retention in treatment was analysed using the Kaplan–Meier method, and comparisons made using the log-rank test. Change in heroin use was compared statistically using the Mann–Whitney U-test. All statistical tests used two-sided P-values, with significance set at P < 0.05. All analyses were performed on an intention-to-treat basis, unless it is stated that the analysis is for those who remained in treatment.

RESULTS

Participants were recruited from February 2004 to August 2005. During this time there were 591 assessments of people seeking treatment for heroin use across the four centres. Figure 1 shows the recruitment and flow of subjects through the trial. People seeking different treatment were usually requesting short-term detoxification only.

Of the 131 eligible and consenting subjects 12 were couples, of whom only the index case was randomized, giving 125 randomized subjects. During data analysis, a systematic protocol violation was identified at one site, where randomization occurred more than 2 weeks after commencing an episode of treatment in six subjects. These subjects were excluded from analysis.

The characteristics of participants are listed in Table 1. Most subjects had long histories of heroin addiction and previous episodes of treatment. Four subjects of the 119 were, at the time of enrolment, dependent upon opioids other than heroin. Two were dependent upon illicitly obtained buprenorphine, one upon illicitly obtained methadone, and one was taking large doses of codeine. All had previous histories of heroin use.

On almost all variables, the groups were well-matched—with the exception of their reported heroin use in the month prior to commencing treatment, with subjects randomized to observed treatment reporting a mean of 3 days’ more heroin use, a difference that was statistically significant. For the 3-month observation period, 17/61 (28%) of subjects in the observed dosing group received second-daily or thrice-weekly dosing. Most of these subjects moved to this dosing regime only towards the end of the 3-month period once they had been attending regularly for daily dosing. In keeping with usual care, buprenorphine–naloxone dosage was titrated for each patient. Mean dose for the duration of the treatment was calculated for each group by dividing the total amount of buprenorphine–naloxone dispensed in each group by days of treatment. The mean dose for the duration of treatment was 11 mg in the observed group and 12 mg in the unobserved group.
Assessments booked for trial  = 767
Number of persons  = 627

Booked assessments attended = 591 (77.1%)

Recruited to study  
\( n = 131 \) (includes 6 couples)
Randomised to study \( n = 125 \)

6 protocol violations (late randomisation) 3 in each group

Subjects analysed  
\( n = 119 \)

Observed dosing  \( n = 61 \)

Unobserved dosing  \( n = 58 \)

Followed up at 3 months  
\( n = 49 \) (80%)

Total 3 months  
Follow Up 77%

Followed up at 3 months  
\( n = 43 \) (74%)

Reasons for non recruitment

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable accommodation</td>
<td>117</td>
</tr>
<tr>
<td>Seeking different treatment</td>
<td>105</td>
</tr>
<tr>
<td>Recent OTP participation</td>
<td>43</td>
</tr>
<tr>
<td>Non-attendance 1st week</td>
<td>24</td>
</tr>
<tr>
<td>Polydrug use</td>
<td>27</td>
</tr>
<tr>
<td>Unstable med or psych</td>
<td>22</td>
</tr>
<tr>
<td>Pending incarceration</td>
<td>21</td>
</tr>
<tr>
<td>&lt;12 months heroin</td>
<td>10</td>
</tr>
<tr>
<td>Partner using</td>
<td>8</td>
</tr>
<tr>
<td>&lt;18 years old</td>
<td>5</td>
</tr>
<tr>
<td>Pregnant, child protection</td>
<td>2</td>
</tr>
<tr>
<td>Missing</td>
<td>76</td>
</tr>
</tbody>
</table>

TOTAL 460

Figure 1 Flow of subjects through trial

Table 1 Baseline demographics of sample by group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unobserved ( (n = 58) )</th>
<th>Observed ( (n = 61) )</th>
<th>Total ( (n = 119) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>35.3 ± 9.4</td>
<td>34.1 ± 8.3</td>
<td>34.7 ± 8.8</td>
</tr>
<tr>
<td>Gender: male, n (%)</td>
<td>42 (72%)</td>
<td>47 (77%)</td>
<td>89 (75%)</td>
</tr>
<tr>
<td>12+ years education n (%)</td>
<td>32 (55%)</td>
<td>34 (56%)</td>
<td>66 (55.5%)</td>
</tr>
<tr>
<td>Employed, n (%)</td>
<td>20 (35%)</td>
<td>25 (41%)</td>
<td>45 (38%)</td>
</tr>
<tr>
<td>Mean days used opioid, ±SD (in previous 28 days)</td>
<td>22.9 ± 6.3</td>
<td>25.5 ± 5.2</td>
<td>24.2 ± 5.9*</td>
</tr>
<tr>
<td>Years opioid-dependent, ±SD</td>
<td>9.6 ± 8.2</td>
<td>8.1 ± 6.4</td>
<td>8.8 ± 7.3</td>
</tr>
<tr>
<td>Previous opioid treatment, n (%)</td>
<td>46 (79%)</td>
<td>50 (82%)</td>
<td>96 (81%)</td>
</tr>
<tr>
<td>Criminal record, n (%)</td>
<td>35 (60%)</td>
<td>37 (61%)</td>
<td>72 (61%)</td>
</tr>
</tbody>
</table>

*\( P = 0.004 \) (Mann–Whitney U, Z = -2.919, two-sided).
Primary outcomes

Retention in randomized treatment is illustrated in Fig. 2. At 3 months, 33/58 (57%) randomized to unobserved dosing and 37/61 (61%) randomized to observed were retained (log-rank \( \chi^2 = 0.04, \text{ df } = 1, P = 0.84 \)). Survival estimate for the unobserved condition was 70.1 days (95% CI: 62.4–77.9) and in the observed was 68 days (95% CI: 59.6–76.4) Retention did not differ significantly by site.

Overall, self-reported heroin use dropped sharply between baseline and 3 months, with no difference between the randomized groups. Mean reported reduction was 18.5 days (95% CI: 21.8–15.3) in unobserved subjects and 22.0 days (95% CI: 24.3–19.7) in observed subjects (Mann–Whitney \( U = 807.5, P = 0.13 \)). At 3 months, 52% (48/92) of interviewed subjects reported no use of heroin in the month prior to follow-up interview: 61% (26/43) of unobserved and 45% (22/49) of observed subjects (\( \chi^2 = 2.23, \text{ df } = 1, P = 0.14 \)).

When urine results in weeks 9–13 were considered (available only for subjects retained in treatment), 29 of the 36 subjects who reported no heroin use (81%) submitted urine tests consistently negative for opioids. When a requested sample not provided was counted as positive, the number with all tests negative fell to 22/36 (61%) of those reporting abstinence (62% in unobserved subjects, 60% in observed).

Costs of treatment comparison

The mean cost of the intervention treatment for the unobserved group at AU$1663 (95% CI 1308–2017) was less than for the observed group at AU$2138 (95% CI 1713–2562) (see Table 2).

The largest component of these costs for the observed group was the overhead cost category at 41% (which includes administration, clerical support and security as well as depreciated facility and equipment costs) of the total. For the unobserved group the cost of the buprenorphine–naloxone comprises the largest proportion of costs. The category of clinical time (both combined direct and indirect) accounted for 13.1% and 17.4% of the total costs for unobserved and observed.

Table 2 Costs and distribution of intervention treatment (accounting for censoring) (2005 AU$).

<table>
<thead>
<tr>
<th></th>
<th>Observed (95% CI)</th>
<th>Unobserved (95% CI)</th>
<th>All (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment costs (mean $)</td>
<td>2138 (1713–2562)</td>
<td>1663 (1308–2017)</td>
<td>1993 (1581–2406)</td>
</tr>
<tr>
<td>Direct staff time percentage</td>
<td>13.1%</td>
<td>17.4%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Buprenorphine–naloxone percentage</td>
<td>23.2%</td>
<td>32.2%</td>
<td>25.8%</td>
</tr>
<tr>
<td>Dosing/dispensing percentage</td>
<td>17.5%</td>
<td>11.2%</td>
<td>14.2%</td>
</tr>
<tr>
<td>Diagnostics percentage</td>
<td>9.4%</td>
<td>13.3%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Overhead percentage</td>
<td>41.1%</td>
<td>30.7%</td>
<td>35.1%</td>
</tr>
<tr>
<td>Treatment and travel costs (mean $)</td>
<td>2589 (1829–2777)</td>
<td>1796 (1422–2169)</td>
<td>2303 (1829–2777)</td>
</tr>
</tbody>
</table>
groups, respectively. The direct costs of dosing and dispensing were larger in both relative and absolute values for the observed group at a mean cost of AU$374 compared to AU$186 for the unobserved group.

The mean costs for all treatment, travel and other health care use for 3 months and the 95% CI are found in Table 3. As with the intervention costs only, the total costs as well as each of the components are significantly higher for the observed group.

As there was no statistical difference in outcomes, the incremental cost effectiveness ratio converts to a difference in costs. Bootstrapping methods were used to estimate 95% confidence intervals on the costs and outcomes, and demonstrated that the observed group is more costly than the unobserved group. Once all the costs and outcomes are combined, it costs on average an additional AU$1477 (95% CI 736.41, 2006.52) to achieve an equivalent change in heroin-free days (HFDs) in the observed compared to unobserved subjects.

Secondary outcomes
Non-opioid drug use
Use of non-opioid drugs was infrequent. At baseline, 19.5% (23/118) reported having used benzodiazepines (BZD) in the month prior to interview, but reported use was infrequent (less than daily). At 3 months, 14% (13/92) reported BZD use in the month prior to interview. Similarly, self-reported stimulant use was reported by 21% (25/117) at baseline and 21% (19/89) at 3-month follow-up. Cannabis use was more common, being reported by 64% (75/117) at baseline and by 58% (52/90) at 3-month follow-up. Overall, there was no indication of a change from pretreatment levels of drugs, nor difference between groups.

Psychological symptoms
At baseline interviews, many subjects reported high levels of psychological distress as measured by the depression, anxiety and stress scales of the DASS. The mean depression score at baseline was 16.0 ± 12.1 indicating a moderate level of depression severity, with 35% of respondents obtaining scores falling within the ‘normal’ range (the level of severity reported by 78% of the general population). At 3 months the mean score on the depression scale fell to 11.0 ± 10.5, indicating mild depression severity, a significant difference (Z = −4.58, P < 0.0001), and 54% of subjects scored within the ‘normal’ range. Although less pronounced, improvements were also seen in scores obtained on the anxiety (Z = −2.72, P = 0.23) and stress scales (Z = −3.26, P = 0.001). There was no difference in the degree of improvement between the groups on any of the scales of the DASS (depression t = 0.02, df = 90, P = 0.98; anxiety t = −0.37, df = 90, P = 0.72; stress t = 0.47, df = 90, P = 0.64).

Quality of life
There were significant reported improvements in quality of life from baseline to 3 months as measured by the WHOQoL-Brief. Improvements were significant for physical quality of life (t = 5.4, df = 91, P < 0.001); psychological (t = 3.5, df = 92, P < 0.001); and environmental (t = 3.6, df = 92, P < 0.001). Changes in social quality of life failed to reach significance. However, intention-to-treat analysis comparing unobserved and observed dosing conditions showed no significant differences in change scores.

Serious adverse events
Six serious adverse events were reported, all requiring hospitalization; five of these occurred in the unobserved group. Two patients were admitted with chest pain diagnosed as due to coronary artery disease. Both patients were smokers in their late 40s, and it was not considered that the medication was related to their coronary events. Both recovered and continued on buprenorphine–naloxone. One patient was hospitalized with a urinary tract infection, and one was admitted for a liver biopsy. One patient was admitted to hospital for 4 hours after she was sexually assaulted. She had ongoing counselling after the assault, and ultimately appeared to make a good recovery. In each case the medical problems were judged unrelated to study medication.

One patient, on unobserved medication, was admitted to hospital for treatment of cellulitis of the left hand resulting from an intravenous injection. Hospital files document that he reported having injected heroin, but he...
later told the research interviewer that he had injected buprenorphine–naloxone. He made an uneventful recovery after treatment with antibiotics.

**Diversion and injection of medication**

In 93% of cases in which vein examination showed fresh injecting sites, subjects had urine tests positive for morphine; in the remaining two cases, both gave histories of intravenous use of heroin. There were in total 18 reports of diversion of trial medication logged by the participating clinics. Seven clients seeking treatment reported previously having purchased buprenorphine–naloxone on the street. Five participants reported having injected trial medication, two of whom said it was a pleasant experience, while three reported experiencing precipitated withdrawal. One of the people presenting for treatment reported having been consistently provided with buprenorphine–naloxone for 5 months by a subject on the study. The remaining five incidents of diversion were reported to researchers by local practitioners or, in one instance, a telephone call from a consumer who had purchased the medication from a trial participant and wanted information about it.

**DISCUSSION**

Refuting the trial hypothesis, attendance for observed dosing was not a deterrent to remaining in treatment during the first 3 months. Rather, outcomes in the two groups were strikingly similar, with reduction in heroin use and improved quality of life and psychological state. Treatment without direct observation of administration was as effective as traditional, observed administration. However, as it was significantly less costly, unobserved administration was significantly more cost-effective.

The costs included in this study go beyond the costs of the study treatment and include cost estimates of other treatment, of other health services use and personal travel costs. The data reported provide strong evidence that the observed dosing group has a higher average cost, not just for treatment costs but also for the other treatment and other use of health care services.

The largest component of treatment costs for the observed group was for overhead and indirect costs (41%). The largest category for the unobserved group was the cost of buprenorphine–naloxone (32.2%). However, overhead costs were next (30.7%). Arguably, shifting totally to unobserved dosing would not result in significant savings on overheads, but should allow an increase in the numbers treated. Both groups accessed considerable direct time with staff, illustrating that it was the administration of buprenorphine–naloxone which is unsupervised, not the treatment.

There have been no previous studies comparing supervised and unsupervised treatment. A previous study from the USA compared different frequency of attendance for counselling, finding no differences [19]. A French study has been described, in which it is said that supervision of dosing actually enhanced retention. The authors reported that daily attendance for supervised dosing actually improves retention. The study used quasi-random allocation of 202 patients commencing buprenorphine; subjects received variable periods of supervised dosing—2 weeks, 3 months and 6 months [4]. Retention to 6 months in the three groups was, respectively, 46%, 65% and 80%.

In France, there is substantial variation in the level of clinical monitoring provided by practitioners. Less supervision has been reported to be associated with more heroin use and more injecting of buprenorphine [29]. The current study provided all participants with close clinical monitoring and support. Subjects, including those randomized to unobserved administration, actually received quite intensive treatment, with weekly clinical reviews and frequent medical appointments.

There are two significant limitations to the generalizability of the finding that treatment without observation of doses is of similar effectiveness to observed dosing. First, all participants were aware that at the end of the 3-month efficacy study they could gain access to unobserved administration, and the incentive of unobserved doses may have enhanced retention in the observed group. Secondly, only 131/591 heroin users were recruited. One major reason for non-recruitment was homelessness or unstable accommodation, and in that setting safe storage of medication is difficult.

At the time of the trial, the combination drug was available only from the participating clinics. Despite this limited availability, several reports of diversion for both sublingual and intravenous use were received, and two subjects using the drug intravenously reported a ‘good’ effect. These reports suggest that patient selection and clinical monitoring will still be required to minimize diversion. All participants had monthly inspection of injecting sites on the grounds that people on buprenorphine–naloxone might inject their own medication, with little risk of precipitating withdrawal. No cases were identified with unexplained fresh injecting sites.

In the trial context, where subjects may perceive an incentive to minimize reports of diversion, monitoring based on sporadic reports does not provide an accurate picture of the extent of diversion. An anonymous, large-scale post-marketing study is currently under way to monitor this issue.

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Declarations of interest

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