A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal

Nicholas Lintzeris¹, James Bell², Gabriele Bammer³, Damien J. Jolley⁴ & Louise Rushworth⁴*

Correspondence to:
Nicholas Lintzeris
National Addiction Centre
Institute of Psychiatry
King College London
5 Windsor Walk
London SE8 5AF
UK
Tel: +44 20 7848 0438
Fax: +44 20 7701 8454
E-mail: N.Lintzeris@iop.kcl.ac.uk

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ABSTRACT

Aim To determine whether buprenorphine is more effective than clonidine and other symptomatic medications in managing ambulatory heroin withdrawal.

Design Open label, prospective randomized controlled trial examining withdrawal and 4-week postwithdrawal outcomes on intention-to-treat.

Setting Two specialist, out-patient drug treatment centres in inner city Melbourne and Sydney, Australia.

Participants One hundred and fourteen dependent heroin users were recruited. Participants were 18 years or over, and with no significant other drug dependence, medical or psychiatric conditions or recent methadone treatment. One hundred and one (89%) participants completed a day 8 research interview examining withdrawal outcomes, and 92 (81%) completed day 35 research interview examining postwithdrawal outcomes.

Interventions Participants randomized to control (n = 56) (up to 8 days of clonidine and other symptomatic medications) or experimental (n = 58) (up to 5 days of buprenorphine) withdrawal groups. Following the 8-day withdrawal episode, participants could self-select from range of postwithdrawal options (naltrexone, substitution maintenance, or counselling).

Measurements Retention in withdrawal; heroin use during withdrawal; and retention in drug treatment 4 weeks after withdrawal.

Secondary outcomes Withdrawal severity; adverse events, and heroin use in the postwithdrawal period.

Findings The experimental group had better treatment retention at day 8 (86% versus 57%, P = 0.001, 95% CI for numbers needed to treat (NNT) = 3–8) and day 35 (62% versus 39%, P = 0.02, 95% CI for NNT = 4–18); used heroin on fewer days during the withdrawal programme (2.6±2.5 versus 4.5±2.3, P<0.001, 95% CI = 1–2.5 days) and in the postwithdrawal period (9.0±8.2 versus 14.6±10, P<0.01, 95% CI = 1.8–9.4); and reported less withdrawal severity. No severe adverse events reported.

Conclusions Buprenorphine is effective for short-term ambulatory heroin withdrawal, with greater retention, less heroin use and less withdrawal discomfort during withdrawal; and increased postwithdrawal treatment retention than symptomatic medications.

KEYWORDS Ambulatory, buprenorphine, clonidine, detoxification, heroin withdrawal, randomized controlled trial.
INTRODUCTION

Withdrawal (‘detoxification’) services utilize a considerable proportion of resources allocated to the treatment of heroin addiction, but have limited success. Most heroin-dependent people attempting ambulatory detoxification do not complete it; residential or in-patient detoxification has better completion rates but is expensive and less accessible; and in both cases, most people who successfully detoxify quickly relapse to heroin use (Mattick & Hull 1996). New approaches to withdrawal management are required that will enhance completion rates and reduce symptoms, drug use and complications during withdrawal. However, these outcomes alone may be insufficient to improve longer-term outcomes greatly, and increased participation in ongoing treatment may be required to achieve this goal.

One such approach incorporates the use of buprenorphine, a partial opioid agonist registered recently for the treatment of opioid dependence (Bickel & Amass 1995; Barnett et al. 2001; Lintzeris et al. 2001; West et al. 2000). Its pharmacological properties make it well suited for the management of heroin withdrawal—it alleviates or prevents withdrawal symptoms and reduces cravings in dependent heroin users (Johnson et al. 1989); the withdrawal on ceasing buprenorphine appears to be less severe than from heroin or morphine (Jasinski, Pevnik & Griffith 1978); and short courses of buprenorphine appear to be associated with minimal ‘rebound’ withdrawal (increase in withdrawal severity) upon ceasing buprenorphine (Cheskin, Fudala & Johnson 1994). Importantly, there is a range of postwithdrawal treatment options available following the use of buprenorphine. The commencement of naltrexone during or soon after the cessation of buprenorphine has been described (Kosten & Kleber 1988; O’Connor et al. 1997; Umbricht et al. 1999) or, alternatively, buprenorphine can be continued on a long-term basis as substitution maintenance treatment for those who fail to complete withdrawal or relapse quickly to heroin use (Vignau 1998; Lintzeris et al. 2001).

The literature regarding the use of buprenorphine in the management of heroin withdrawal in comparison to other medications has been summarized recently in a Cochrane review (Gowing, Ali & White 2000a), and MEDLINE and EMBASE were searched for more recently published controlled trials comparing buprenorphine to other withdrawal medication. Five randomized trials were identified. Short courses of buprenorphine are more effective than clonidine (Nigam, Ray & Tripathi 1993; Cheskin et al. 1994) or benzodiazepines (Schneider et al. 2000) in reducing withdrawal severity in in-patient settings; and completion rates for buprenorphine subjects were higher in all three studies (although not statistically significant).

The evidence from randomized trials regarding ambulatory heroin withdrawal is less clear. Bickel and colleagues (Bickel et al. 1988) reported comparable but poor outcomes in 45 heroin users undergoing gradual reduction regimes (7 weeks) of methadone or buprenorphine. O’Connor and colleagues (O’Connor et al. 1997) examined induction onto naltrexone following short buprenorphine, clonidine or naltrexone–clonidine regimes. The buprenorphine group reported less severe symptoms, suggesting a possible advantage, although the study failed to report rates of continued heroin use, thereby confounding the use of withdrawal severity as a key outcome measure; and there were no significant differences in naltrexone uptake.

A serious limitation of previous studies has been the failure to investigate postwithdrawal outcomes such as treatment retention or drug use. Another limitation of previous randomized trials has been the use of either buprenorphine solution (with a higher bioavailability than the marketed tablets (Nath et al. 1999; Schuh & Johanson 1999) or low-dose tablets (0.2 mg) with low buprenorphine dose regimens. The current study was designed to examine the efficacy of buprenorphine (using the marketed Subutex® preparation) compared to clonidine and other routinely used symptomatic medications for short-term ambulatory heroin withdrawal on the following outcomes:

• heroin use during and after the withdrawal programme;
• retention in treatment during the withdrawal programme and in the postwithdrawal period;
• severity of opiate withdrawal symptoms during the withdrawal programme, and
• adverse events during the withdrawal programme.

METHODS

Protocol

This was an open-label randomized controlled trial in which 114 heroin-dependent people were assigned to one of two regimes during an 8-day out-patient withdrawal programme. The conditions were: (a) control group receiving clonidine and other symptomatic medications; (b) experimental group: a 5-day sublingual buprenorphine tablet regime. At day 8, subjects were able to self-select from a range of postwithdrawal treatment options, with participants monitored over a subsequent 4-week period. Research interviews were conducted with a research assistant at days 8 and 35. The study was conducted concurrently at two sites—Turning Point (n = 64) in Melbourne, and the Langton Centre (n = 50) in Sydney, Australia. Both sites are specialist multimodal drug treat-
ment centres located in inner-city neighbourhoods that do not require referral and did not charge patients for services at the time of the study. Relevant Human Research Ethics Committees approved the research.

The sample size was calculated against the outcome of ‘completion of withdrawal programme without heroin use’. Clinical experience at both sites indicated ∼5% of patients receiving out-patient symptomatic treatment completed withdrawal without using heroin. An earlier buprenorphine out-patient withdrawal study using the same dosing regime (Lintzeris 2002) reported that 28% of patients completed withdrawal without using heroin. Approximately 61 subjects were required in each group (∝ = 0.05, β = 0.10).

Subjects were recruited voluntarily from consecutive patients seeking ambulatory withdrawal at the treatment sites. Selection criteria were: aged ≥18 years; heroin dependent (DSM-IV) with positive urine drug screen for opiates on presentation; not in methadone treatment in the past 8 weeks (confirmed with government records); no concurrent dependence on alcohol, benzodiazepines, amphetamines or cocaine; not homeless; not pregnant; no significant medical or psychiatric conditions; no adverse events. Urine drug screens were collected on days 5 and 8. To encourage active engagement in the withdrawal programme, participants who did not attend or contact the clinic for 2 or more consecutive days were discharged from the study treatment procedures, but followed-up for research interviews.

The main medication for the control group was clonidine, used in doses consistent with the published literature and usual practice for both sites (standard regime was 100–150µg four times per day as required) (see Table 1 for doses dispensed). Other (oral) medications available to the control group included metoclopramide (10 mg tablets, daily mean dose dispensed = 17 ± 7 mg); diazepam (5-mg tablets) or temazepam (10-mg tablets) (diazepam equivalent dose = 14 ± 8 mg); quinine sulphate (300-mg tablets, 380 ± 190 mg); hyoscine butylbromide (20-mg tablets, 34 ± 18 mg); and ibuprofen (400-mg tablets, 940 ± 370 mg). Medications were dispensed daily from the clinic pharmacies. The experimental group received buprenorphine dispensed once a day under supervision. The 5-day regime was developed in an earlier trial (Lintzeris 2002), and doses are shown in Table 1. The routine day 1 dose of buprenorphine was 6 mg, given at least 6 hours after the last reported use of heroin. A lower initial dose (4 mg) was prescribed for one patient who had only minor features of withdrawal at the time of dosing, and dosing could not be delayed due to clinic closing times. Buprenorphine doses ceased on day 5 to allow a ∼72-hour washout (‘opiate-free’) period prior to outcome assessment on day 8.

The 8-day withdrawal programme had similar conditions for both groups with the exception of their medication regimes. Participants were reviewed daily before dosing, during which supportive counselling was provided and the following data collected: (a) withdrawal severity (Subjective and Objective Opiate Withdrawal Scales (SOWS, OOWS) (Handelsman et al. 1987); (b) drug use; (c) patient rating of dose adequacy; and (d) adverse events. Urine drug screens were collected on days 5 and 8.

### Table 1. Doses of medications dispensed during withdrawal programme (mean ± SD).

<table>
<thead>
<tr>
<th>Day</th>
<th>Experimental group buprenorphine (S/L) mg</th>
<th>Control group clonidine (oral) mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.0 ± 0.6</td>
<td>0.75 ± 0.24</td>
</tr>
<tr>
<td>2</td>
<td>9.3 ± 1.6</td>
<td>0.74 ± 0.19</td>
</tr>
<tr>
<td>3</td>
<td>9.6 ± 3.0</td>
<td>0.90 ± 0.83</td>
</tr>
<tr>
<td>4</td>
<td>8.8 ± 2.0</td>
<td>0.71 ± 0.20</td>
</tr>
<tr>
<td>5</td>
<td>3.6 ± 1.3</td>
<td>0.61 ± 0.25</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0.63 ± 0.26</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0.51 ± 0.23</td>
</tr>
<tr>
<td>Total</td>
<td>37.2 ± 5.3</td>
<td>3.11 ± 1.51</td>
</tr>
</tbody>
</table>

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Addiction, 97, 1395–1404
All patients were reviewed at day 8, with a discussion of the available treatment options. These included substitution treatment (methadone or buprenorphine for experimental subjects, methadone only for the control group to reflect a treatment system without buprenorphine; naltrexone treatment; or counselling services (involving at least weekly sessions using a relapse prevention framework). Patients could also choose to re-attempt withdrawal using symptomatic medications.

The primary outcomes and related measures for the study were as follows.

1. **Heroin use**: self-reported use in the preceding month was collected at baseline using the Drug Use Section of the Opiate Treatment Index (OTI) (Darke et al. 1991), which measures the frequency of recent use within the preceding 28 days as a Q score (higher Q scores reflect more frequent use). Drug use during the withdrawal episode was measured by (a) self-report at the day 8 research interview recalling the number of times and the number of days of heroin use since day 1; and (b) urine drug screens (UDS) collected on days 5 and 8. Drug use in the postwithdrawal period was assessed using the OTI at day 35.

2. **Retention in withdrawal treatment** was measured as the number of (consecutive) days each subject participated in the withdrawal episode. Subjects were deemed to have completed the withdrawal programme if they did not miss 2 or more consecutive days during the 8-day episode.

3. **Participation in postwithdrawal treatment** was measured as (a) the number of days subjects were enrolled in any treatment during the 4-week follow-up period; and (b) the number of subjects retained in some form of drug treatment at day 35.

The secondary outcomes and related measures were as follows.

1. **Severity of withdrawal** was a ‘secondary’ outcome as continued heroin use during out-patient treatment confounds the interpretation of withdrawal severity. Measured daily using the SOWS and OOWS prior to dosing.

2. **Adverse events** were reported daily during withdrawal programme.

**Statistical analysis**

Key outcomes were analysed for between-group differences on an intention-to-treat basis using Pearson χ² tests for categorical data and Student’s t-tests for continuous data. Where significant group differences were identified for key outcomes, estimations of the effect size are presented using numbers needed to treat (NNT) with 95% confidence intervals (CI) for categorical outcomes; and 95% CI for difference of the means for continuous variables.

**Assignment**

Individual subject randomization was conducted by an independent organization, the Randomization Service of the National Health and Medical Research Council Clinical Trials Centre (NHMRC-CTC). A computerized schedule was developed by the NHMRC-CTC using the technique of dynamic balanced randomization (Signorini et al. 1993), balancing treatment allocation within each site and across the study as a whole (with the aim of a 1:1 ratio between groups at each site). Subjects were allocated by the NHMRC-CTC after the completion of all enrolment and baseline data collection.

**Masking**

The study was open-label with patients, treatment providers and outcome assessors aware of group allocation. The option of blinding patients to their medication under double dummy conditions was considered unfeasible as the control group protocol involved take-home medications, and patients would have determined quickly whether they had ‘dummy’ or ‘active’ symptomatic medication [simply by taking their tablets (e.g. diazepam or placebo) and seeing if there was any effect]. Indeed, the only other out-patient, randomized trial comparing buprenorphine to symptomatic withdrawal medications attempted to blind subjects; however, the authors concluded that blinding had not been achieved for most subjects (O’Connor et al. 1997).

**RESULTS**

**Characteristics of subjects at intake**

Baseline demographic characteristics and measures of heroin use are shown in Table 2.

Subjects (103/114, 90%) were injecting, and 11 reported smoking (four randomized to the experimental, seven to control group). In the preceding month, 53/114 (47%) subjects reported using alcohol; 62 (54%) reported cannabis use, and 44 (39%) reported benzodiazepine use. Amphetamines, cocaine, hallucinogens were each used by fewer than 10% of subjects. There were no significant group differences at baseline on demographic characteristics or measures of heroin or other drug use; nor were there significant differences between the study sites.
Participants reported (mean ± SD) 6.9 ± 8.6 previous treatment attempts (median = 4). Withdrawal programmes had previously been attempted by 89 subjects (78%), and accounted for over 60% of all previous treatment attempts. Sixty-nine per cent of all previous withdrawal attempts had been as out-patients. Fifty-six subjects (49%) reported previous methadone treatment, 46 (40%) had previous out-patient counselling, 16 (14%) had been in residential rehabilitation and 11 (9%) had previous naltrexone treatment. Fourteen subjects (12%) had no previous treatment experience. There were no significant group differences.

Withdrawal outcomes

Treatment retention

Experimental participants (50/58, 86%) completed the withdrawal programme, compared to 32/56 control subjects (57%), representing a significant difference (χ²(1) = 11.92, P = 0.001, NNT = 4, 95% CI, NNT = 3–8). The experimental group remained in withdrawal treatment for a mean of 7.3 ± 1.9 days, the control group for a mean of 5.6 ± 3.1 days (t (91.4) = 3.59, P = 0.001, 95% CI = 0.8–2.7).

Heroin use

Twenty-five experimental subjects (43%) and four control subjects (7%) provided at least one opiate negative UDS (χ²(1) = 19.4, P < 0.001, NNT = 3, 95% CI, NNT = 2–5). Twelve experimental participants (21%) provided opiate negative UDS on both days 5 and 8, compared to two (4%) from the control group (χ²(1) = 7.75, P = 0.005; NNT = 6; 95% CI, NNT = 4–18).

Self-reported heroin use at the day 8 research interview is shown in Table 3. Experimental participants reported using heroin on significantly fewer days compared to control participants (t (99) = 3.95, P < 0.001, 95% CI = 1.0–2.5 days). Significantly more experimental...
used additional benzodiazepines. Twenty experimental
patients reported any benzodiazepine use (nine reported using one tablet during the week, four reported using two tablets, three reported using three tablets and four patients reported using four or more tablets).

Withdrawal severity
Mean (±SD) daily SOWS scores for all subjects with data are shown in Table 4. Experimental group reported significantly less withdrawal severity on days 3–7 inclusive (see Table 4 for details). However, the interpretation of withdrawal scores in an out-patient context is compromised by the use of heroin during the withdrawal programme, and there were too few abstinent control subjects (n = 2) to enable comparison across the two groups. Hence, data were examined for subjects who described heroin use on 2 days or less (such levels of heroin use were unlikely to dramatically alter the withdrawal profile). The mean daily SOWS scores (±95% CI for mean) are shown in Fig. 2 for these 45 subjects (12 control, 33 experimental). A repeated-measures analysis reveals that the experimental group reported significantly less total withdrawal severity than control patients (F = 9.17, P < 0.01).

The mean (±SD) peak SOWS score for all experimental participants was 19.9 ± 11.7, significantly lower than the control mean of 29.7 ± 15.0 (t (86) = 3.40, P < 0.005, 95% CI = 4.0–15.4). The magnitude of this difference (SOWS of −10, 50% higher score in the control group) suggests this to be of clinical as well as statistical significance. Most subjects in both groups reported their peak withdrawal discomfort during the first 3 days. Of the 53 experimental participants in treatment at day 8, five (9%) experienced mild and/or transient withdrawal after ceasing buprenorphine on day 5; and four (8%) reported a moderately severe ‘rebound’ withdrawal, which remained unresolved by day 8.

Table 3 Heroin use during withdrawal and postwithdrawal periods.

<table>
<thead>
<tr>
<th></th>
<th>Experimental</th>
<th>Control</th>
<th>Sg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. days used heroin during 8 day withdrawal program</td>
<td>(n = 53)</td>
<td>(n = 48)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.6 ± 2.5</td>
<td>4.5 ± 2.3 days</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>No. subjects with opiate negative UDS on days 5 and 8</td>
<td>12/58 (21%)</td>
<td>2/56 (4%)</td>
<td>P = 0.0005</td>
</tr>
<tr>
<td>No. subjects reporting no heroin use during 8 day withdrawal program</td>
<td>13/58 (22%)</td>
<td>3/56 (5%)</td>
<td>P = 0.013</td>
</tr>
<tr>
<td>No. days used heroin during 28 day postwithdrawal period</td>
<td>(n = 48)</td>
<td>(n = 43)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.0 ± 8.2</td>
<td>14.6 ± 10.0</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6.5</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>No. subjects reporting no heroin use in 4-week postwithdrawal period</td>
<td>5/58b (9%)</td>
<td>1/56b (2%)</td>
<td></td>
</tr>
</tbody>
</table>

*The n reported in this table reflect the number of patients completing interviews at days 8 and 35, respectively.

Table 4 Daily SOWS scores during withdrawal episode.

<table>
<thead>
<tr>
<th>Day</th>
<th>Experimental</th>
<th>Control</th>
<th>Sg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>16.2 ± 1.5 (58)</td>
<td>15.7 ± 14.5 (56)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>16.0 ± 1.6 (55)</td>
<td>21.7 ± 14.0 (31)</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Day 3</td>
<td>12.3 ± 1.0 (50)</td>
<td>19.7 ± 15.6 (29)</td>
<td>P = 0.008</td>
</tr>
<tr>
<td>Day 4</td>
<td>9.3 ± 0.7 (52)</td>
<td>22.5 ± 14.3 (31)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Day 5</td>
<td>7.9 ± 6.9 (48)</td>
<td>16.2 ± 13.7 (25)</td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>10.0 ± 8.0 (32)</td>
<td>18.4 ± 12.3 (24)</td>
<td>P = 0.003</td>
</tr>
<tr>
<td>Day 7</td>
<td>9.0 ± 1.0 (34)</td>
<td>15.5 ± 12.5 (24)</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>Day 8</td>
<td>8.0 ± 7.3 (43)</td>
<td>12.0 ± 11.9 (25)</td>
<td></td>
</tr>
</tbody>
</table>

* n reflects the number of patients with SOWS data each day.

Day 1: (t (43.7) = 2.25, 95% CI = 0.8–14.0); day 2: (t (38.7) = 4.81, 95% CI = 7.4–18.7); day 3: (t (30.5) = 2.85, 95% CI = 2.4–14.3); day 6: (t (54) = 2.90, 95% CI = 2.9–13.9); day 7: (t (56) = 2.13, 95% CI = 0.4–12.7).

Other drug use
Use of other drugs during the withdrawal episode was self-reported at the day 8 research interview. Of the experimental group, 34/53 (64%) reported any cannabis use, 24/53 (45%) reported alcohol use, and 7/53 (13%) reported the use of any other opiates. In the control group, 26/48 (54%) reported any cannabis use, 18/48 (38%) reported alcohol use and 8/48 (17%) reported the use of any other opiates. There were no significant group differences, and the proportion of patients reporting any use of these drugs is comparable to the baseline reports. All control patients were prescribed (and in some cases used additional) benzodiazepines. Twenty experimental participants reported no heroin use during the withdrawal period ($\chi^2 (1) = 6.10, P = 0.013; NNT = 6; 95\% CI, NNT = 4–21).
An RCT of buprenorphine in brief heroin withdrawal

Adverse events

Adverse events are shown in Table 5. Excluded from the table are symptoms that were assessed as being part of the underlying withdrawal syndrome, or those considered unrelated to the medication or the condition being treated. Similar proportions of subjects in each group reported no adverse events. Some degree of buprenorphine-induced precipitated withdrawal (defined as the patient reporting a transient increase in withdrawal symptoms in the hours immediately after buprenorphine dosing) was reported in 12% of cases despite attempts to prevent it (see Methods). In most cases this was mild and required no specific treatment, although clonidine and diazepam were prescribed for one patient.

Post-withdrawal outcomes

Treatment retention

Thirty-seven control (66%) and 47 experimental (81%) participants engaged in some form of treatment in this period ($\chi^2 (1) = 2.80, P = 0.09$). The experimental group participated in treatment for significantly more days in the 28-day postwithdrawal interval (mean = 19.0 ± 11.2) than the control group (11.0 ± 11.0) ($t (112) = 3.83, P < 0.001, 95\% CI = 3.8–12.1$).

More experimental participants (36/58 or 62%) were retained in some form of treatment at day 35 compared to the control group (22/56 or 39%) ($\chi^2 (1) = 5.50, P = 0.02, NNT = 5, 95\% CI, NNT = 3–25$). At day 35, 31/58 experimental participants (53%) were in substitution treatment (26 in buprenorphine, five in methadone); four (7%) were in naltrexone treatment, and one (2%) was in drug-free counselling. In comparison, 15/56 control participants (27%) were in methadone treatment; five (9%) were in naltrexone treatment, and two were re-attempting withdrawal.

Heroin use

The mean self-reported frequency of heroin use in the 4-week period (OTI Q score) for the experimental group ($n = 48$) was 0.68 ± 0.92 (median = 0.38), compared to 1.21 ± 1.13 (median = 1.0) for the control group ($n = 43$) ($t (80.8) = 2.45, P = 0.017, 95\% CI = 0.10–0.97$). The self-reported number of days of heroin use (Table 3) yielded similar findings ($t (89) = 2.94, P = 0.004, 95\% CI = 1.8–9.4 days$).

DISCUSSION

This is the first randomized study to demonstrate that buprenorphine has greater efficacy than clonidine plus other symptomatic medications for the outcomes most relevant to out-patient withdrawal services: reductions in heroin use during withdrawal and enhanced treatment retention during the withdrawal and postwithdrawal periods. Consistent with previous studies (Nigam et al. 1993; Cheskin et al. 1994; O’Connor et al. 1997), patients using buprenorphine reported significantly less severe withdrawal symptoms than those using clonidine.
The effect sizes on key outcome measures between the two groups were considerable, suggesting a marked clinical advantage in using buprenorphine over combination symptomatic medication.

The most significant potential limitation of the study was the open-label design—blinding of subjects was unfeasible as subjects could easily identify the medication to which they had been allocated. The open-label design may have biased outcomes, given the tendency for some participants to assume that ‘new’ or ‘investigational’ medications are likely to be ‘better’. Other study limitations were less important: follow-up rates of subjects were adequate (89% day 8, 81% day 35), without significant differences in follow-up rates for the two groups. Drug use measures in the postwithdrawal period were limited to self-report; however, self-report data are usually considered reliable when collected by research assistants not involved in clinical services, and with no punitive consequences for subjects reporting heroin use (Darke 1998). Self-reported heroin use during the withdrawal programme was consistent with UDS findings.

Attempts to generalize from these findings to broader populations of heroin users and treatment settings must take into consideration that patients with ‘complex’ presentations were excluded; and that the study was conducted in specialist settings. Nevertheless, the almost identical findings for all the principal outcomes at the two sites (in different cities) enhances the extent to which the results can be generalized to similar populations attending specialist treatment settings.

The low abstinence rate among the control group during withdrawal warrants comment. Most previous studies of out-patient heroin withdrawal using clonidine report ‘successful completion’ rates in the range of 20–30% (Gossop 1988; Gowing, Ali & White 2000b). However, previous studies have often used different operational criteria for ‘successful completion’ (e.g. naloxone challenge), or have excluded dropouts from their analysis. Had this study discounted treatment dropouts, and used a negative UDS at day 8 as an operational measure of ‘success’, then 4/32 (13%) of the control group (and 17/50 (34%) of the experimental group) ‘successfully completed withdrawal’, placing outcomes for the control group closer to the range reported in earlier studies.

Side-effects to buprenorphine were generally mild, transient and well tolerated. Headache, nausea, drowsiness, sweating and lethargy were reported by more than 5%, as has been reported previously (Ling et al. 1998). A degree of ‘rebound’ withdrawal was experienced by 17% of patients, highlighting the need for continued monitoring and support of patients beyond the cessation of medication. Precipitated withdrawal was reported by 12% of patients, which in most cases was mild, lasting for several hours and occurred only after the first buprenorphine dose. However, two patients reported moderate to severe symptoms beyond the first day (both continued regular heroin use). Although this can usually be avoided by delaying the first dose until the patient is experiencing withdrawal this may not always be feasible clinically, and education of clinicians and patients in the underlying mechanisms, potential risks and strategies to avoid precipitated withdrawal is required.

The findings suggest that there may be benefits for heroin users (and communities) who engage in withdrawal services even if they do not cease their heroin use completely. Although few patients remained abstinent during the withdrawal or postwithdrawal period, most markedly reduced their heroin use. Importantly, the reductions in heroin use were generally maintained during the follow-up period—frequency of heroin use for the total sample fell by a factor of 3–4 compared to the pretreatment period, with an estimated 4–5-fold reduction in total cost of heroin over the month.

It should be emphasized that the patients entering this study chose—for whatever reason—to attempt a withdrawal episode, and not to enter maintenance substitution treatment initially (methadone maintenance treatment was available at both sites during the course of the study and buprenorphine maintenance treatment was accessible at Turning Point at the time). The fact that most of them end up on a maintenance programme 1 month after attempting withdrawal can be viewed either as a failure (they are not ‘opiate-free’) or as a success (they have been retained in treatment). However, it should also be emphasized that some patients (albeit a minority) were ‘opiate-free’ 1 month after their withdrawal, either in counselling and/or naltrexone programs. To not offer withdrawal services would consign such patients to long-term maintenance substitution treatment. Alternatively, to ‘force’ naltrexone upon all patients entering withdrawal will most likely result in only a minority being in treatment at 1 month, given the poor treatment retention rates associated generally with naltrexone (Tucker & Ritter 2000).

This emphasizes the need for flexible treatment pathways within withdrawal services that can (a) accommodate those patients whose initial attempts at withdrawal prove ‘unsuccessful’ with longer-term substitution treatment; and (b) accommodate those patients who are successful in becoming drug free and may find psychosocial interventions and naltrexone treatment more acceptable. The study demonstrates that reductions in heroin use in the postwithdrawal period were predominately in those patients who remained in (any form of) drug treatment, highlighting the importance of having a range of treatment choices available to account for individual patient preferences and circumstances. In this regard, buprenor-
phine can serve as a valuable ‘gateway’ medication during withdrawal, enhancing retention in a variety of postwithdrawal treatment modalities.

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DECLARATION OF INTEREST

N.L. has acted as a consultant to Reckitt Benckiser (manufacturer and Australian distributor of Subutex®) and Schering Plough (international distributor of Subutex®) in delivering educational sessions and providing clinical advice to health professionals regarding the use of buprenorphine. N.L. was reimbursed by Reckitt Benckiser for attending an international symposium. N.L. and J.B. have been paid by Reckitt Benckiser for attending seminars. L.R. is an employee of Reckitt Benckiser (Australia) in the role of Australian Product Support Manager for Subutex® since July 2000 (appointment commenced after the conclusion of her involvement in the submitted trial).

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