Buprenorphine dosing regime in the management of out-patient heroin withdrawal

NICHOLAS LINTZERIS

Turning Point Alcohol and Drug Centre and Australian National University, Victoria, Australia

Abstract
This study aimed to establish a buprenorphine regime suitable for the short-term management of out-patient heroin withdrawal using an open-label, single-group case series. Eighteen dependent injecting heroin users underwent an 8-day withdrawal episode with supervised dosing of sublingual Subutex® tablets. Buprenorphine doses were titrated daily over a 5-day period. Fifteen subjects (83%) completed the 5-day regime, and 14 (78%) completed the 8-day withdrawal episode. The mean doses (SD) were 6.1 (1.2) mg on day 1; 9.6 (1.7) mg on day 2; 10.1 (1.9) mg on day 3; 8.9 (2.0) mg on day 4; 4.1 (1.5) mg on day 5; and a total regime dose of 38.9 (5.8) mg. Withdrawal severity was mild, with minimal rebound upon the cessation of dosing. Five subjects reported no heroin use, and five subjects reported using on only one occasion during the 8 days. An out-patient buprenorphine regime is recommended. [Lintzeris N. Buprenorphine dosing regime in the management of out-patient heroin withdrawal. Drug Alcohol Rev 2002;21:39–45]

Key words: buprenorphine, detoxification, dose regimes, heroin withdrawal.

Introduction
In recent years, sublingual buprenorphine tablets (Subutex®) have been registered internationally for the management of heroin dependence as a maintenance substitution medication, and for the management of heroin withdrawal. Buprenorphine has a number of properties that suggest it to be a promising medication for heroin withdrawal: it alleviates features of opiate withdrawal and reduces cravings for heroin[1–3]; it reduces the euphoric effects of additional heroin use thereby reducing continued heroin use[4,5]; and there is minimal 'rebound' withdrawal upon the cessation of short courses of buprenorphine, thereby not significantly prolonging the duration of withdrawal[1,6]. Furthermore, buprenorphine can be dosed once a day, thereby reducing diversion or abuse; and post-withdrawal treatment with the opioid antagonist naltrexone can be commenced within days of ceasing buprenorphine[7,8], or clients can be maintained on maintenance buprenorphine programmes.

Previous withdrawal research has predominately examined the use of buprenorphine in in-patient settings, where it has been found to be superior to clonidine in reducing withdrawal severity[6,9]. Most in-patient withdrawal studies have utilized sublingual buprenorphine solution[6,8] or low dose tablets[9–11]. More recently, an in-patient regime using the commercially available Subutex® preparation has been described[12], titrating daily doses in the range of 4–9 mg per day at the outset of withdrawal, with reductions over 10–12 days.

There has been limited clinical research in the use of buprenorphine in out-patient withdrawal settings[13,14], which is the context in which many heroin users undergo withdrawal. In particular, there is little clarity regarding suitable dosing regimes for out-patient heroin withdrawal using the commercially available tablet preparation Subutex®. It is difficult to draw conclusions from prior out-patient studies that have utilized sublingual solution[13] of different bio-availability[15], or have used multiple daily doses of low dose (0.2 mg) sublingual tablets[14]. In-patient regimes may not be appropriate for out-patient settings—the primary role of medication in in-patient settings is to relieve the more severe discomfort of
Methods

This single-group, open-label study recruited heroin users presenting to a specialist out-patient treatment service in Melbourne. Recruitment was voluntary, with no active promotion for the study. Selection criteria were: heroin dependent (DSM-IV 304.0); opiate positive urine screen on assessment; not in methadone treatment within last 8 weeks; no concurrent dependence on alcohol, benzodiazepines or psychostimulants; aged 18 or over; not homeless; no major active medical or psychiatric conditions; and willing to provide informed consent. Thirty-four consecutive heroin users seeking out-patient heroin withdrawal were assessed for the study—six (18%) were ineligible [medical or psychiatric reasons (two); concurrent benzodiazepine dependence (two), under 18 (one); and unstable social environment (one)]. Ten clients were assessed as eligible but chose conventional out-patient withdrawal services. Eighteen subjects were recruited to the study (53% of those screened).

Subjects attended the out-patient clinic for review on a daily basis over an 8-day period. Buprenorphine doses were available during the first 5 days, corresponding to the period of peak discomfort of heroin withdrawal. Doses were titrated daily in order to achieve a comfortable withdrawal, with daily monitoring of withdrawal features (subjective and objective opiate withdrawal scales [16]), drug use (self-report and urine drug screens conducted on days 1, 5 and 7 or 8); adverse events (self-report and examination) and client perception of dose adequacy. The titration schedule and the possible range of daily doses are shown in Table 1. No other medications were available routinely. All buprenorphine was dispensed as 2 mg sublingual tablets from the clinic under supervision, and subjects received routine case management and supportive counselling [17].

Subjects underwent a research interview at induction (day 1), measuring demographics, frequency of drug use in the preceding month (drug section of the Opiate Treatment Index (OTI) [18]) and expected severity of withdrawal using a (0–100) visual analogue scale (VAS). A discharge research interview examined sever-
ity of withdrawal experienced (VAS) and measures of client satisfaction with buprenorphine and their dosing regime.

Results

Ten subjects (56%) were male, 89% were Caucasian, mean age (SD) was 25.3 (4.5 years (range 21–37), 50% were currently employed (part or full-time), and 78% were receiving some social security benefits. The average duration of opioid dependence was 3.9 (4.6 years (range 1–19). All reported injecting heroin, using on average 2.9 (1.1 times a day in the preceding month (range 1.5–4.5) as measured by the OTI Q score.

Completion rates

Fifteen subjects (83%) completed the 5-day dosing regime and 14 (78%) completed the 8-day withdrawal episode and discharge research interview. Two subjects (a couple) failed to attend after the third day, and one subject terminated buprenorphine after day 1, transferring to a methadone maintenance programme.

Buprenorphine doses and client satisfaction with dosing regime

The doses dispensed to the 15 subjects completing the dosing schedule are shown in Table 2. The mean total buprenorphine dose dispensed was 38.9 (5.8 mg (range = 29–47 mg).

Subjects rated the adequacy of their doses at discharge interview using a five-point Likert scale (‘much too low’; ‘too low’; ‘about right’; ‘too high’; ‘much too high’). Eleven of the 14 subjects rated their dosing regime as ‘about right’. Three subjects rated their doses as ‘too low’, despite the total doses for these three being above the 50th percentile, and the peak withdrawal severity (SOWS) for these subjects were 18, 20 and 15, indicative of mild withdrawal severity.

<table>
<thead>
<tr>
<th>No. of subjects receiving</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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<tbody>
<tr>
<td>0 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
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<tr>
<td>3 mg</td>
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<td>4</td>
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<tr>
<td>6 mg</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>2</td>
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<td>8 mg</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>–</td>
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<td>7</td>
<td>5</td>
<td>6</td>
<td>–</td>
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<td>4</td>
<td>2</td>
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<td>–</td>
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<td>1</td>
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<td>–</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.1 ± 1.2</td>
<td>9.6 ± 1.7</td>
<td>10.1 ± 1.9</td>
<td>8.9 ± 2.0</td>
<td>4.1 ± 1.5</td>
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</tbody>
</table>

Drug use during withdrawal episode

Five subjects (28% of the 18 recruited) reported no heroin use over the 8-day withdrawal episode; five (28%) reported using heroin on one day; two (11%) reported using on 2 days; three (17%) reported using on 3 or more days; and data were unavailable for three subjects (17%) (missing data ×2; transfer to methadone ×1).

Nine subjects had a negative urine drug screen for opiates at day 5 (50% of total sample, 60% of those in treatment), five subjects had positive urine test results, three were no longer attending, and results were missing for one subject. Urine tests for opiates at day 7 (or 8) revealed that four subjects had negative results (22% of total sample, 29% of those in treatment), four subjects had positive results, four were no longer attending, and results were unavailable for six subjects (usually due to self-reported heroin use). Four subjects (22%) provided opiate negative urine results throughout the episode.

Subjects described the circumstances surrounding and their reasons for using heroin. Several subjects reported heroin use in response to withdrawal discomfort prior to their day 2 dose. Otherwise, all but one subject reported that their use of heroin was volitional (e.g. using for intoxication) or situational (e.g. partners or friends using around them), rather than to relieve withdrawal discomfort. Those subjects who used heroin all reported that buprenorphine considerably reduced the effects of heroin, serving as a barrier to further use. There appeared to be no clear relationship between the use of heroin and dose of buprenorphine dispensed. The mean total dose for those subjects not using heroin (39.8 mg) was comparable to those using heroin on one or more occasions (38.3 mg).
Withdrawal severity

Subjects generally reported minimal withdrawal discomfort throughout the withdrawal episode (Fig. 1). The interpretation of withdrawal scores is difficult for those individuals who used heroin regularly, and consequently this figure includes data for those subjects (n = 13) reporting no or minimal heroin use (five reported nil use and five reported using once over 8 days; one subject reported no heroin use prior to ‘dropping out’ after day 5; and two subjects used heroin on days 2 and 8 but completed the withdrawal scales on day 8 prior to their heroin use that day).

The peak withdrawal severity was generally experienced as mild, occurring prior to the day 2 dose, with resolution of symptoms thereafter. There was minimal rebound withdrawal evident: withdrawal scores remained low following the cessation of buprenorphine, and only two subjects reported peak withdrawal scores after day 5 (and in both instances the peak SOWS scores were low—15 and 6). Only one of the nine subjects who used heroin after day 5 cited withdrawal symptoms as a major reason.

The mean expected withdrawal severity (VAS 0 = ‘no withdrawal’ to 100 = ‘most severe withdrawal’) for those completing both research interviews (n = 14) at intake was 28 (16), while the mean experienced withdrawal severity was 16 ± 12, indicating that the experience of withdrawal discomfort was significantly less (p < 0.05) than expected (t (13) = 2.29, 95% CI = −2 to −26).

Adverse events and measures of client satisfaction

Subjects were asked to identify ‘good things’ and ‘bad things’ associated with the use of buprenorphine using open-ended questions. The five most common positive responses were: (a) no, minimal or mild withdrawal symptoms experienced (79% of subjects); (b) felt ‘normal’ and could perform daily activities (57%); (c) reduced or no cravings for heroin use (36%); (d) blocks the effects of heroin use (36%); and (e) psychologically comfortable during withdrawal (29%). The most common negative aspects reported when prompted were (a) side effects (57% of subjects); inconvenience of daily dosing (7%); current dosing period too short (7%); sleep disturbance (7%). 36% of subjects could not identify a negative aspect when prompted to do so.

Adverse events were recorded daily, with 16 subjects reporting some adverse events, although differentiating between side effects and withdrawal symptoms was difficult at times. The most common adverse events reported were headache (50% of all subjects), sedation (28%), nausea, constipation and anxiety (21% each). All adverse events were anticipated, mild, and resolved within days. Precipitated withdrawal following the initial buprenorphine dose was not reported in any of the subjects.

Discussion

The first aim of this exploratory study was to examine the range of buprenorphine doses required for a heroin withdrawal episode in an out-patient setting. A number of trends emerged during the study. The first four subjects each received 4 mg on day 1; however, all complained of inadequate relief of withdrawal symptoms and cravings over the 24-hour period; and all subsequent clients were dispensed 6 or 8 mg on day 1. Higher doses (between 8 and 12 mg) were used on days 2–4 in most clients. Despite the reduction in dose on
day 5, most subjects did not report any significant increase in withdrawal discomfort the following day. The majority of subjects (79%) reported at the completion of their episode that their doses of buprenorphine had been ‘about right’. The three subjects who reported that their doses had been ‘too low’ did not experience severe withdrawal symptoms and received higher than average doses of buprenorphine, suggesting the diversity of client expectations as to the role of medication in withdrawal.

Although the titration dose ranging study design was considered most suited to the exploratory nature of this research, dose titration studies do not provide information regarding the efficacy of different dosing regimes. Ultimately, blinded randomized controlled trials, in which subjects are assigned to different doses are required in order to identify optimal dosing regimes. Nevertheless, the outcomes described in this study were generally satisfactory: most subjects completed the withdrawal regime with minimal withdrawal discomfort, and few reported using heroin to alleviate withdrawal; adverse events were mild and well tolerated; and there were high levels of client satisfaction. Given these trends, it is possible to recommend a buprenorphine dosing regime for out-patient heroin withdrawal (Table 3) based upon the majority of clients on day 2 (87%); day 3 (93%); day 4 (87%) and day 5 (80%).

It must be emphasized that a certain degree of flexibility in withdrawal dosing regimes should be available to account for a variety of client factors (e.g. side effects, severity of withdrawal syndrome, psychological factors); and environment and treatment factors (such as level of psychosocial supports). Furthermore, this regime may not be suitable for heroin users with concomitant medical or psychiatric conditions, recent methadone treatment or individuals undergoing withdrawal from multiple drugs, conditions that were excluded from the study.

How does the proposed dosing regime arising from this study compare to previous research? The findings from this study are consistent with the general trend of research literature in which daily buprenorphine doses of 4 mg or more are more effective than lower doses in reducing withdrawal discomfort, cravings and heroin use[19–25]. However, there have been only two descriptions of short-term buprenorphine regimes for the management of out-patient heroin withdrawal reported in the published literature. The first out-patient withdrawal regime[13] used 3 mg sublingual buprenorphine solution dispensed daily for 3 days prior to the initiation of naltrexone and a range of symptomatic medications (clonidine, oxazepam, ibuprofen, ketorolac, prochlorperazine) on day 4. There was no rationale provided for the dosing regime used, and the suitability of the regime is difficult to assess as certain key outcomes were either not reported (e.g. continued heroin use) or difficult to interpret (e.g. withdrawal severity, retention) due to the initiation of naltrexone early in the process.

Diamant and colleagues (1998)[14] reported relatively successful outcomes (70% of subjects completed the regime, and 48% had a negative urine test for opiates on the final day of dosing) in a short-term out-patient withdrawal regime. 0.2 mg sublingual buprenorphine tablets were clinically titrated up to a maximum of 4 mg per day (20 tablets), and then reduced gradually over a 10-day regime. The mean daily dose was between 2 and 3 mg during the first 5 days, with a mean total dose of approximately 15–20 mg: substantially lower than the findings of this study. However, Diamant and colleagues used additional symptomatic medication (prothipendyl and famotidine), with multiple unsupervised doses provided each day as ‘take-away’ medication. The different buprenorphine regimes identified by these two out-patient studies highlights the need for further research comparing the efficacy of high-dose and low-dose regimes.

The second aim of the study was to explore issues more broadly in the use of buprenorphine, with particular emphasis upon its impact upon key withdrawal outcomes. Most subjects reported minimal withdrawal discomfort over the course of the withdrawal: peak withdrawal discomfort generally occurred prior to the second dose of buprenorphine, and with substantial relief of symptoms thereafter. In contrast, patients undergoing heroin withdrawal using symptomatic medication (e.g. clonidine)[6,9,13] typically describe peak withdrawal discomfort 2–4 days after ceasing heroin use. In this regard, the use of buprenorphine appears to have prevented the onset of peak withdrawal discomfort. Furthermore, there appeared to be only minor and brief rebound withdrawal following the cessation of buprenorphine for most subjects. However, a degree of caution should be exercised in drawing this conclusion, as a con-

<table>
<thead>
<tr>
<th>Day of withdrawal regime</th>
<th>Recommended dose of buprenorphine (sublingual tablets)</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>6 mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>8–10 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>8–12 mg</td>
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<tr>
<td>Day 4</td>
<td>6–10 mg</td>
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<tr>
<td>Day 5</td>
<td>3–5 mg</td>
</tr>
<tr>
<td>Total dose</td>
<td>32–42 mg</td>
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siderable proportion of subjects used heroin at least once after ceasing buprenorphine, and it is possible that this was in response to rebound withdrawal, despite the claims by most subjects that their heroin use was either volitional or situational. It is also possible that there was an inadequate period of follow-up and that subjects may have experienced worsening rebound withdrawal symptoms more than 3 days after ceasing buprenorphine. However, this is unlikely, as previous in-patient studies of short buprenorphine regimes suggest that the emergence of rebound withdrawal phenomena occurs within 72 hours of the last dose [6,8], and the day 5 buprenorphine dose (≤6 mg) would not be expected to exert considerable effects for more than 24–48 hours [26,27]. Ultimately in-patient studies with longer follow-up periods are required to discount significant rebound phenomena using such regimes.

Other short-term outcomes during the withdrawal episode were generally favourable for an out-patient setting: there was good retention in withdrawal treatment—83% of subjects completed the dosing regime, 78% were retained throughout the 8-day episode, and one subject (6%) transferred to a methadone maintenance programme. Approximately one-quarter of subjects did not use heroin over the withdrawal episode (28% self-report and 22% confirmed with urine tests), and a further 28% reported using heroin only once during this time. These findings compare favourably with outcomes for clients undergoing conventional out-patient heroin withdrawal at the same treatment agency [28]. However, factors other than the utility of buprenorphine may have impacted upon the findings, including a Hawthorne effect associated with the use of a new experimental treatment [29], and the increased monitoring and enthusiasm by the treatment staff involved in a research project. The study had no control or comparison group with which to evaluate outcomes properly, and randomized controlled trials comparing ‘high dose’ buprenorphine to ‘gold standard’ out-patient treatment are required to assess the efficacy of buprenorphine as a withdrawal medication.

In conclusion, this study is the first to describe a short-term out-patient heroin withdrawal regime using the commercially available sublingual tablet preparation Subutex®. Buprenorphine was easy to use on a once-a-day supervised dosing schedule, was well tolerated by subjects and without the need for additional symptomatic medications. The dosing regime used in this study is consistent with the general trend in the clinical research literature in which buprenorphine doses of greater than 4 mg per day are more effective in reducing withdrawal discomfort, cravings and heroin use, and resulted in generally favourable outcomes.

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References


