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## Buprenorphine dosing regime for inpatient heroin withdrawal: a symptom-triggered dose titration study

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### Abstract

The study aimed to identify the range of buprenorphine doses required to comfortably alleviate symptoms in patients undergoing inpatient heroin withdrawal using a symptom-triggered titration dosing regime, and to identify the patient characteristics that impact upon the buprenorphine dose requirements. The study was conducted in two Australian inpatient withdrawal units, recruiting 63 dependent, injecting heroin users with no recent methadone treatment, dependence on other drugs, or other active medical or psychiatric conditions. In a single (patient) blinded case series, placebo or 2 mg sublingual buprenorphine tablets was administered four times a day according to severity of withdrawal (assessed with Subjective Opiate Withdrawal Scale). Up to 16 mg buprenorphine was available over the first 4 days of the admission, up to 8 mg on day 5, and placebo continued until day 6. Thirty-two subjects completed the dosing regime, with mean ( $\pm$ S.D.) daily doses of  $3.8 \pm 2.8$  on day 1,  $5.8 \pm 3.2$  on day 2,  $4.8 \pm 3.3$  on day 3,  $2.3 \pm 2.6$  on day 4,  $0.8 \pm 1.3$  on day 5, and a total dose of  $17.4 \pm 9.7$ . Higher buprenorphine doses were required by those patients with more severe psychosocial dysfunction, women, those with more frequent heroin use, and those with more severe dependence on heroin at intake. A dosing regime using sublingual buprenorphine tablets for short inpatient heroin withdrawal is proposed.

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**Keywords:** Buprenorphine; Heroin withdrawal; Detoxification; Inpatient titration regime

### 1. Introduction

Buprenorphine is a partial opioid agonist that is increasingly being used both for maintenance substitution treatment and for detoxification, the subject of this paper. Buprenorphine can be used for managing heroin withdrawal in gradual reduction regimes over several weeks, or in short courses of up to 7–10 days. In clinical practice, the duration of buprenorphine treatment for withdrawal is often determined by the availability of resources. In particular, many inpatient detoxification

units are limited to between 3- and 14-day admissions, and hence short-term regimes are generally favoured. This paper examines the development of short buprenorphine dosing regimes for inpatient heroin withdrawal.

There has been considerable variation in the types of doses and preparations previously studied in the short-term (less than 14 days) inpatient management of heroin withdrawal (Table 1). Doses have varied from as low as 1 mg per day (e.g. Nigam et al., 1993) to as high as 32 mg in a single dose (Kutz and Reznik, 2001). The diversity in doses may reflect the differences in preparations, routes of administration, ancillary medications, or clinical 'end-points' used to titrate doses. Almost all of these studies have reported favourable clinical outcomes, making it difficult to decide how a dosing regime should be chosen.

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Table 1  
Study dosing regimens used in previous inpatient studies of heroin withdrawal

Study	Preparation, number of subjects	Dosing regime	Equivalent total dose in S/L tablets (mg)
Nigam et al. (1993)	S/L tablet, $N = 22$	Range of daily doses: 0.6–1.2 mg over 10 days	10
Liu et al. (1997)	Not specified, $N = 63$	Three groups, doses titrated; doses commenced between 3 and 6 mg per day, and tapered to 0 over 7–8 days	~ 14–26
Parran et al. (1994)	Subcutaneous injection <sup>a</sup> , $N = 22$	Doses titrated; 0.9–2.7 mg per day $\times$ 2 days, 0.45–1.35 mg per day $\times$ 2 days, and 0.2–0.7 mg per day $\times$ 2 days	6.6–20
Cheskin et al. (1994)	S/L solution <sup>b</sup> , $N = 11$	Day 1: 8 mg, day 2: 6 mg, day 3: 3 mg; total dose: 17 mg	~ 24
Schneider et al. (2000)	S/L not specified, $N = 4$ (heroin only)	Days 1–7: 3 mg per day, day 8: 2 mg, day 9: 1 mg, day 10: 0.4 mg; total dose: 24.5 mg; carbamazepine also used, 21-day admission	24.4
Kutz and Reznik (2001)	S/L tablet, $N = 10$	Single dose of 32 mg administered on day 1	32
Vignau (1998)	S/L tablet, $N = 36$	Doses titrated daily; day 1, mean: 6.1 mg (range: 4.4–9.0); day 2, mean: 6.4 mg (range: 5–9); day 3, mean: 5.5 mg (range: 4–7.6); then, progressively reducing to 0 mg by day 12	Total mean: ~ 35 (data presented graphically)
Umbricht et al. (1999)	S/L solution <sup>b</sup> , $N = 28$	Day 1: 12 mg, day 2: 8 mg, day 3: 4 mg, day 4: 2 mg; total dose: 26 mg	~ 36

S/L, sublingual.

<sup>a</sup> Subcutaneous injection has bioavailability of ~ 1.5 times greater than S/L solution (Jasinski et al., 1989).

<sup>b</sup> S/L solution has bioavailability of ~ 1.4 times greater than S/L tablets (Schuh and Johanson, 1999).

Whilst there have thus far been no published randomised trials comparing different buprenorphine doses for brief inpatient withdrawal, there have been a number of studies, generally of maintenance treatment, that have allocated subjects to different buprenorphine doses and reported measures relevant to detoxification such as severity of withdrawal, cravings, or heroin use (Kosten et al., 1993; Seow et al., 1986; Johnson et al., 1995; Schottenfeld et al., 1993; Kosten and Kleber, 1988; Ling et al., 1998). In summary, the available evidence suggests that daily buprenorphine doses in the range 4–16 mg may be optimal in reducing withdrawal discomfort and heroin use. Although most evidence points toward higher doses being more effective, there are nevertheless concerns that unnecessarily high doses during withdrawal may result in greater ‘rebound’ withdrawal following the cessation of buprenorphine (Kosten and Kleber, 1988; Seow et al., 1986; Resnick et al., 1992). As such, dosing regimes should use the minimum amount of medication necessary to alleviate discomfort and reduce the severity of ‘rebound’ withdrawal after buprenorphine is ceased.

There is also a very limited understanding of the extent to which patient characteristics impact upon the buprenorphine requirements of heroin users undergoing withdrawal. Such an understanding can assist clinicians to better tailor dosing regimes to the needs of patients. Greater withdrawal severity has been significantly related to higher levels of opiate use (Andrews and Himmelsbach, 1944; Smolka and Schmidt, 1999), injecting rather than smoking routes (Smolka and Schmidt, 1999; Strang et al., 1999), expectancy of withdrawal

severity, and psychological profile (Phillips et al., 1986), whilst factors such as age and duration of opioid use appear to be less important (Phillips et al., 1986; Smolka and Schmidt, 1999). It may be expected therefore that similar factors may also contribute to the doses of medication required to alleviate withdrawal severity, although this has not been examined.

This study had two primary aims:

- i) to identify the minimum doses of buprenorphine required to comfortably alleviate withdrawal symptoms in dependent injecting heroin users in an inpatient setting; and
- ii) to examine any association between certain patient characteristics at intake, and the total buprenorphine dose required.

## 2. Methods

### 2.1. General procedures

The study was an exploratory, single-blinded case series using a symptom-triggered titration regime. Sixty-three subjects underwent an inpatient admission for up to 10 days, with buprenorphine available over the first 5 days. The study was conducted in two Australian specialist inpatient withdrawal units: Depaul House, St. Vincent’s Hospital, Melbourne; and the Detoxification Unit of the Canberra Hospital. The project was approved by Human Research Ethics Committees at the relevant institutions.

## 2.2. Subjects

Subjects were recruited from eligible consecutive patients presenting to the units seeking heroin withdrawal. Recruitment occurred until 30–35 subjects completed the 5-day buprenorphine dosing regime, the minimum number required to conduct a multiple regression analysis upon six independent variables (describing patient characteristics at intake) (Tabachnik and Fidell, 1983). Selection criteria were as follows: aged 18 or over; heroin dependent (DSM-IV) with injecting as main route of administration (thereby avoiding the potential confounder of different routes of administration); recent heroin use (within 48 h on self-report and positive opiate urine test on admission); not in methadone treatment within past 8 weeks; not dependent on other drugs (excluding tobacco and caffeine); not pregnant (urine  $\beta$ HCG test); no active or unstable medical or psychiatric condition; and providing informed consent. Eligible patients were interviewed by a research assistant for baseline data collection, and then commenced trial treatment procedures.

## 2.3. Treatment procedures

A symptom-triggered dose regime was used to identify minimum effective buprenorphine doses. Symptom-triggered titration regimes involve administering medication doses according to withdrawal severity, and are routinely used in titrating benzodiazepines in the management of alcohol withdrawal, where they have been shown to better match the dose and duration of medication to individual patient needs than fixed dose regimes (Saitz et al., 1994).

Signs and symptoms were monitored four times a day (7 a.m., 12 midday, 5 p.m., and 11 p.m.) from admission until discharge, assessing blood pressure, pulse rate, respiratory rate, severity of withdrawal (using the Objective Opiate Withdrawal Scale (OOWS) and Subjective Opiate Withdrawal Scale (SOWS)) (Handelsman et al., 1987)), state of arousal, speech, and gait.

Doses of buprenorphine were administered against scores on SOWS, as subjective measures of withdrawal severity are more sensitive than objective measures (Handelsman et al., 1987), and are better correlated to treatment outcome, and should be used to guide prescribing practices during withdrawal (Kosten et al., 1985). SOWS assesses 16 common symptoms of opiate withdrawal at a particular point in time, with each item rated on a scale of 0–4 (total score: 0–64). Previous experience with SOWS indicated that scores below the mid-teens generally reflect minimal or mild withdrawal discomfort, scores in the high-teens to low-thirties generally reflect moderate withdrawal discomfort, and higher scores reflect severe withdrawal.

A daily dose of up to 16 mg was considered an appropriate upper dosing limit for the first 4 days of the admission, with doses of 0–4 mg administered after each monitoring point (four times a day). Two milligram was administered if the subject reported moderate withdrawal discomfort (SOWS score: 17–32), and 4 mg for severe withdrawal discomfort (SOWS score: > 32). The blind was maintained by ensuring that all subjects were dosed with two tablets four times a day (containing either placebo and/or 2 mg buprenorphine tablets). The total day-5 dose was administered in two divided doses and was up to half of the total day-4 dose (0 mg if day-4 dose = 0 or 2 mg, 2 mg if day-4 dose = 4 or 6 mg; 4 mg if day-4 dose = 8 or 10 mg, etc.). Subjects received placebos on day 6 in two doses (midday and 11 p.m.).

One concern with this dosing regime was the potential for subjects to over- or under-report the severity of withdrawal symptoms. To minimise gross under- and over-reporting, clinical staff regularly matched subjective (SOWS) with objective (OOWS) ratings of withdrawal, and significant discrepancies prompted a discussion with the subject regarding their scoring. For example, a subject who reported no (0) or minor (1) severity for features such as yawning, sweating, or runny nose that were clearly observable by staff would be prompted to reconsider their score following a re-explanation of the method of scoring of SOWS.

Other medications were not routinely available, although subjects complaining of persistent insomnia were allowed one or two nights of diazepam (5 or 10 mg orally). Subjects were expected to participate in all standard individual and group counselling sessions.

## 2.4. Measures

The primary outcome for the study was the daily and total dose of buprenorphine dispensed to subjects completing the titration regime. Secondary outcomes included (a) the severity of opiate withdrawal; (b) adverse events (elicited from subjects daily and assessed by clinicians); and (c) patient assessment of the adequacy of the buprenorphine dose measured on a Likert scale administered upon discharge (1 = “much too low”, 2 = “too low”, 3 = “about right”, 4 = “too high”, and 5 = “much too high”).

Data were collected at intake regarding six patient characteristics thought to possibly impact upon the severity of withdrawal, and hence upon buprenorphine dosing requirements:

- 1) *Quantification of recent heroin use*: measured using the drug use section of the Opiate Treatment Index (OTI) (Darke et al., 1991), which assesses frequency of heroin use within the past 4 weeks, represented as a Q score.

- 2) *Severity of heroin dependence*: measured using the Leeds Dependence Questionnaire (LDQ) (Raistrick et al., 1994). A 10-item scale measuring physical, cognitive, and behavioural components of dependence. Scores of 0–30, with mild ( $\leq 17$  points), moderate (18–23 points), and high ( $\geq 24$  points) degrees of dependence.
- 3) *Expectancy regarding the severity of this withdrawal episode*: measured using a visual analogue scale (0–100 mm) in response to the question: “How severe do you think this withdrawal episode will be?” with 0 = no discomfort, and 100 = the most severe withdrawal symptoms you have ever experienced.
- 4) *Psychosocial distress*: measured using the BASIS-32 (Eisen et al., 1994), a 32-item scale assessing psychosocial functioning in the preceding week including relationship with self and others, depression and anxiety, daily role functioning, impulsive and addictive behaviour, and psychosis. Scoring on a 0–4 scale, with higher scores representing greater dysfunction.
- 5) Body weight (kg).
- 6) Sex (male or female).

### 2.5. Data handling and analysis

The trial was externally and independently monitored. Data entry, and descriptive and regression analysis were conducted using SPSS 10.1 for Windows. Between-group comparisons used Pearson's  $\chi^2$ -tests (categorical data), and Student's *t*-tests (continuous measures) with effect size estimates using 95% CI for difference of the means. Stepwise multiple regression analysis was conducted for associations between patient intake variables and the total buprenorphine dose administered to each subject.

## 3. Results

### 3.1. Participant flow

Sixty-three subjects enrolled in the study. Seventy-seven patients seeking inpatient heroin withdrawal were assessed in Melbourne over a 5-month period. Thirty-two subjects (42%) were recruited, 36 (47%) were ineligible (including dependence on other drugs ( $n = 12$ ), medical or psychiatric conditions ( $n = 13$ ), and/or no recent heroin use ( $n = 6$ )), nine chose not to participate, and one patient acted as a pilot case. Thirty-one subjects were recruited at the Canberra site over a 4-month period. Data regarding the number of eligible and ineligible patients, or the reasons for exclusion, were not available for this site.

### 3.2. Subjects

Most subjects were male (70%), unemployed (81%), and had not completed tertiary education (92%). The mean age at enrolment was  $27.6 \pm 6.4$  years (range: 18.0–46.7), with subjects describing first heroin use at the age  $20.3 \pm 4.9$ , and first regular use at the age  $22.0 \pm 5.1$ . Mean frequency of heroin injecting in the preceding month (OTI Q score) was  $3.69 \pm 2.09$  per day. The group described moderate to high severity of dependence on heroin (mean LDQ =  $23.5 \pm 4.4$ ). The mean total BASIS score was  $1.73 \pm 0.73$ , and mean body weight was  $69.9 \pm 13.1$  kg. The expected severity of withdrawal for this episode was  $51 \pm 27$ , which was the only variable to differ significantly between the two sites ( $t(59) = 3.37$ ,  $P < 0.01$ , 95% CI = 9–35), with the Melbourne subjects reporting a lower mean score.

### 3.3. Completion rates

Thirty-two of the 63 subjects (51%) completed the dosing regime, defined as completing day 5 of the admission. There were no significant differences in baseline variables regarding completers and non-completers; however, 21/32 Melbourne subjects (66%) completed the regime compared to 11/31 (35%) in Canberra ( $\chi^2(1) = 5.72$ ,  $P < 0.05$ ).

### 3.4. Buprenorphine doses

The doses administered to the 32 subjects completing the dosing regime are shown in Table 2. Thirteen percent of subjects required no doses beyond day 2, 34% beyond day 3, and 25% beyond day 4, and 28% required dosing into the fifth day. The two sites had a very similar pattern of dosing, with no significant differences in total or daily doses.

There were no statistically significant differences in buprenorphine doses on days 1, 2, and 4 between completers and non-completers; however, the non-completers had a significantly lower mean dose on day 3 compared to the completers ( $t(46) = 2.65$ ,  $P < 0.05$ , 95% CI = 0.6–4.4). This probably reflects the high number (12) of subjects who left during day 3 prior to receiving the full amount of medication for that day.

### 3.5. Dose adequacy

Thirty subjects (27 completers and 3 non-completers) rated the adequacy of their doses of buprenorphine at the discharge research interview. Eighty-seven percent (26/30) indicated that the dose was ‘about right’; 10% ( $n = 3$ ) reported that the dose was ‘too low’; and one subject (3%) reported that the dose was ‘much too high’. The three non-completers those responded all rated their

Table 2  
Doses administered to 32 subjects completing the dosing regime

Buprenorphine dose (mg)	Number of subjects receiving on					Total
	Day 1	Day 2	Day 3	Day 4	Day 5	
0	7	3	4	12	23	
2	6	3	8	11	6	
4	7	8	6	4	3	
6	8	5	3	2	0	
8	3	6	9	3	0	
10	1	7	1	0	0	
12	0	0	1	0	0	
Mean ± S.D.	3.8 ± 2.8	5.8 ± 3.2	4.8 ± 3.3	2.3 ± 2.6	0.8 ± 1.3	17.4 ± 9.7
Median	4	6	4	2	0	17

doses as ‘about right’. Most non-completers left the unit without completing this interview.

generally mild and resolved within 48–72 h without the use of additional medications.

3.6. Withdrawal severity

Fig. 1 displays the range of mean daily SOWS scores (with upper and lower limits of the 95% CI for means) over the first 8 days. The mean peak SOWS (± S.D.) for all subjects was 33.4 ± 11.8. Twenty-seven of 32 (85%) completers reported their peak withdrawal during the first 2 days. There appeared to be only minor rebound withdrawal upon the cessation of buprenorphine dosing. Although many subjects experienced an increase in withdrawal severity after their last dose, this was

3.7. Adverse events

There were no serious adverse events, and most subjects (n = 36) reported no adverse events. Headache (n = 13), constipation (n = 6), dry mouth (n = 2), sublingual irritation (n = 2), dizziness after initial dose (n = 2), and itchiness (n = 1) were all anticipated adverse events. In several cases, it was difficult to differentiate between medication side effects and withdrawal features (stomach cramps (n = 3), anxiety (n = 3), fatigue (n = 3), and hot flushes (n = 2)). With the exception of constipation, adverse events generally subsided within 2 or 3

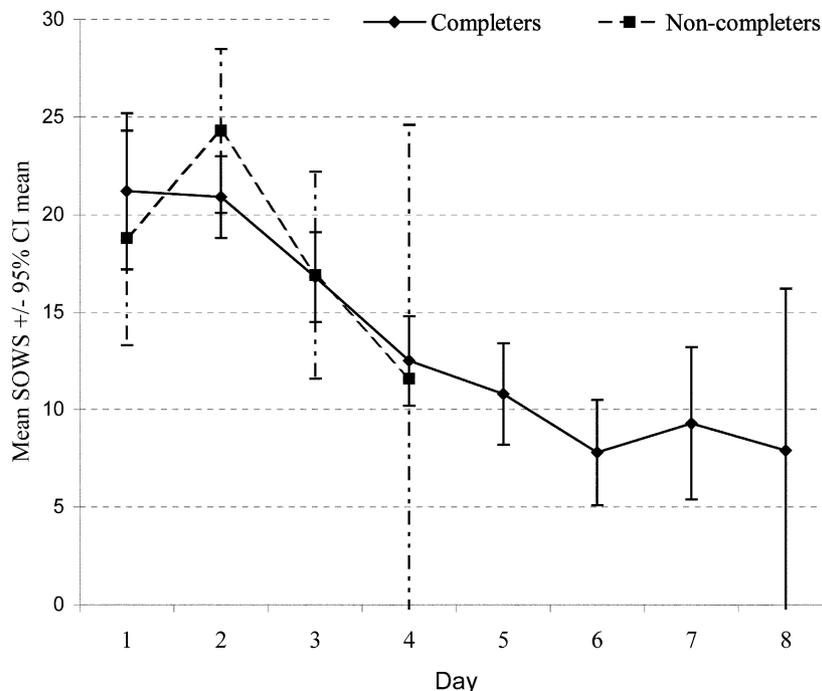


Fig. 1. Mean (± 95% CI of mean) daily SOWS scores. Numbers of completers: days 1–5 = 32, day 6 = 26, day 7 = 18, and day 8 = 12; numbers of non-completers: day 1 = 26, day 2 = 23, day 3 = 16, and day 4 = 4.

days. One subject reported a papular skin rash that emerged on day 2, which may have been related to a concurrent viral upper respiratory tract infection, and subsided with no treatment.

### 3.8. Patient characteristics impacting upon buprenorphine dose

Females received a mean total dose of  $22.4 \pm 8.9$  mg, compared to  $14.9 \pm 9.2$  mg for males ( $t(30) = 2.22$ ,  $P < 0.05$ , 95% CI = 0.6–14.4 mg). A considerable proportion of the variance of buprenorphine dose was accounted for by the six characteristics ( $R^2 = 0.513$ ), with significant variables being BASIS average score ( $F = 10.19$ ,  $P < 0.005$ ), sex ( $F = 10.19$ ,  $P < 0.005$ ), Q score for heroin use ( $F = 6.46$ ,  $P < 0.05$ ), and severity of heroin dependence (LDQ) ( $F = 6.26$ ,  $P < 0.05$ ). Expectancy of withdrawal severity, and body weight were not significantly associated to buprenorphine dose. Using backward stepwise regression, removal of the least significant variables resulted in a marked reduction in  $R^2$ .

## 4. Discussion

This was an exploratory study with two broad aims: to identify the dosing requirements of buprenorphine in the management of inpatient heroin withdrawal; and to identify any associations between patient characteristics and dose requirements. Most subjects required a total dose of between 10 and 26 mg, and daily doses in the range 2–6 mg on day 1, 4–8 mg on days 2 and 3, and 2–4 mg on day 4 were generally sufficient to prevent or alleviate moderate to severe discomfort for most subjects. The majority (87%) rated the adequacy of their buprenorphine doses as being 'about right'.

There appeared to be only minor rebound withdrawal upon the cessation of this short course of buprenorphine. However, some subjects may have experienced rebound withdrawal after discharge, as a considerable number discharged themselves within 24–48 h of their last buprenorphine dose, and therefore caution is required in interpreting these findings. Further research is required which monitors patients for at least 4–5 days after ceasing buprenorphine. Nevertheless, given that the vast majority of heroin users required doses for only 3 or 4 days, and experienced minimal rebound withdrawal in 2–3 days after the last dose, it would appear that buprenorphine is ideally suited to a 7-day inpatient withdrawal episode.

The range of buprenorphine doses used highlights the considerable variation between heroin users as to their experience of withdrawal and their medication requirements. Although this analysis was conducted examining dose requirements rather than withdrawal severity, the

symptom-triggered dosing design would suggest that the same factors that contribute to withdrawal severity should also contribute to amount of medication used. In this regard, the findings are consistent with previous research linking withdrawal severity to psychological profile, frequency of heroin use, and severity of dependence. It should be noted that this study had the minimum number of subjects to conduct such analyses, and larger studies are required to more fully explore the relationships between patient characteristics and dosing needs.

There was also a significant trend for women to have higher total buprenorphine doses, and this may genuinely reflect higher dose requirements in women undergoing withdrawal. Research with buprenorphine as an analgesic indicates that sex does not affect plasma concentrations, although in one study, women required less buprenorphine than men for postoperative analgesia (McQuay et al., 1980). Research in the addiction field has yielded contradictory findings with regards to treatment outcome, with women reporting less heroin use than men in one maintenance study (Schottenfeld et al., 1998), but more heroin use than men in another (Johnson et al., 1995). Alternatively, the gender difference may reflect a common observation that women routinely report more psychological symptoms than men (Kroenke and Spitzer, 1998), and women may have scored themselves higher on subjective withdrawal severity, thereby receiving higher doses.

Retention rates differed significantly across the two sites. Only four of the first 20 subjects at the Canberra site completed their dosing regime, with many leaving on days 3 or 4. Several factors may have contributed to this low rate. Short admissions (such as 3 days) were not uncommon on the unit, and there was considerable turnover of senior staff during the study. On review, it became apparent to the investigators that clinicians were not emphasising to patients the importance of remaining in treatment for at least several days after ceasing their 'tablets', at which point they could be more confident of having completed withdrawal. After staff training and a review of procedures, greater emphasis was put upon retaining patients for longer in the unit. Retention rates subsequently improved, with seven of the last 11 (64%) subjects completing the regime, comparable to the 66% completion rate at the Melbourne site. The importance of the difference in completion rates across the sites is difficult to interpret, as there were no significant between-site differences on primary or secondary outcomes for those subjects completing the regime across the two sites.

The extent to which subjects remained blinded to the titration dosing procedures and their individual doses was not systematically examined. Nevertheless, the impression on asking subjects at the end of the withdrawal was that many could identify occasions when

they had been dosed with placebo tablets only, however, most were unable to accurately identify the buprenorphine dose they had received, nor the time of last active dose. To this extent, the single-blind design achieved its aim.

There are also limitations in the extent to which the findings can be generalised to patients with concomitant conditions such as dependence on other drugs, medical, or psychiatric conditions. The mild withdrawal syndrome experienced with buprenorphine should be favourable for these patient groups, and it has previously been successfully used in such populations (Parran et al., 1994), however, further investigation is warranted.

The use of a symptom-triggered titration technique allows the capacity to individualise doses according to each patient's needs. Nevertheless, there is the possibility that the study regime was inadequate to accommodate a number of subjects who dropped out of treatment, and that additional buprenorphine doses may have altered the outcome for some patients.

This study design has identified a range of buprenorphine doses that were generally successful in managing inpatient heroin withdrawal. Despite the study limitations, it is possible from the findings of this study to identify a regime for heroin users undergoing brief inpatient withdrawal using 2 mg sublingual buprenorphine tablets (see Table 3). This regime has formed the basis for current Australian clinical guidelines for using buprenorphine in managing inpatient heroin withdrawal (Lintzeris et al., 2001), and can guide future research of buprenorphine in inpatient withdrawal settings. Double-blinded randomised dose efficacy studies are required to compare the efficacy of the doses described in this study to regimes employing lower or higher buprenorphine doses.

Table 3  
Recommended inpatient dosing regime

Day	Buprenorphine S/L tablet regime	Total daily dose (mg)
Day 1	4 mg at onset of withdrawal, and additional 2–4 mg evening dose prn	4–8
Day 2	4 mg mane, with additional 2–4 mg evening dose prn	4–8
Day 3	4 mg mane, with additional 2 mg evening dose prn	4–6
Day 4	2 mg mane prn; 2 mg evening prn	0–4
Day 5	2 mg prn	0–2
Day 6	No dose	
Day 7	No dose	
	Total proposed dose	12–28

prn, as required.

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