

## A pilot study of buprenorphine–naloxone combination tablet (Suboxone<sup>®</sup>) in treatment of opioid dependence

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### Abstract

*In Australia, maintenance treatment for opioid dependence involves supervised daily administration of a dose of methadone or buprenorphine. A sublingual tablet combining buprenorphine and naloxone in a 4:1 ratio (Suboxone<sup>TM</sup>) has been developed, designed to deter diversion and intravenous misuse, and may be suitable for unsupervised administration. The aim of this study was to investigate the tolerability of Suboxone, and investigate whether unsupervised administration can be effective in stabilized patients. Employed patients on buprenorphine maintenance, who had ceased heroin use, were switched to Suboxone and provided with weekly supplies of medication to take without supervised administration. Subjects were monitored closely with weekly clinical reviews, and research interviews at baseline, 3 and 6 months. Only 11% of people receiving buprenorphine met eligibility criteria. Seventeen subjects were recruited. Fifteen were retained for the full 6 months. No subject appeared destabilized by unsupervised dosing. Suboxone was well tolerated. The current trial demonstrated that unsupervised administration with regular clinical monitoring can be effective in selected patients. However, using access to unsupervised dosing to promote abstinence from heroin probably limits the potential benefits of unsupervised administration to a very small proportion of patients. [Bell J, Byron G, Gibson A, Morris A. A pilot study of buprenorphine–naloxone combination tablet (Suboxone<sup>®</sup>) in treatment of opioid dependence. *Drug Alcohol Rev* 2004;23:311–317]*

**Key words:** buprenorphine–naloxone, heroin, maintenance, qualitative research.

### Introduction

A new formulation of buprenorphine, sublingual tablets combining buprenorphine and naloxone in a 4:1 ratio (Suboxone<sup>TM</sup>), has been registered in the United States for the treatment of heroin addiction. Buprenorphine is an effective maintenance drug in the treatment of opioid heroin addiction [1,2]. The rationale for adding naloxone to buprenorphine is to deter intravenous use of this medication. Naloxone administered sublingually is less than 10% bioavailable, and it has a plasma half-life of less than 1 hour [3]. Taken sublingually with buprenorphine, the combination drug has actions which are said to be indistinguishable from buprenorphine alone [4]. However, administered intravenously to an individual dependent on heroin or methadone, the combination product precipitates withdrawal [4].

Supervised administration has been the defining characteristic of agonist maintenance treatment for heroin addiction in most countries. The primary reason

for this is that supervised administration reduces the diversion and misuse of drugs prescribed in the treatment of addiction. In Australia, even with a programme based on supervised administration, there has been a brisk black market in diverted methadone, largely from takeaway doses [5]. Diversion to the black market, and intravenous injection, has been shown to rise and fall in proportion to the extent of provision of take-away doses for unsupervised consumption [6]. The most serious consequence of diversion has been that deaths have resulted from administration of diverted methadone [7]. Despite supervised administration, buprenorphine diversion and injection is being observed increasingly in Australia, and in a recent survey 30% of injecting drug users (IDU) in the state of Victoria reported having injected buprenorphine [8]. In France, where buprenorphine treatment is delivered without supervised administration, there has been a substantial amount of injecting of buprenorphine, and calls for a more regulated way to administer the drug [9].

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By reducing the risk of intravenous misuse of diverted medication, combination buprenorphine–naloxone may reduce the need for supervised administration in maintenance programmes. Due to the presence of naloxone there is less risk that the combination tablets will be crushed and injected. In addition, there appears to be limited respiratory depression with overdose of buprenorphine [10]. French data on fatal opioid overdoses confirm that despite widespread diversion of buprenorphine to people who are not opioid-tolerant, there is substantially less risk of fatal outcome compared to diversion of methadone [11].

‘Unsupervised administration’ is not the same as ‘unsupervised treatment’; it merely means that the daily administration of the dose is not supervised, rather than that patients in treatment do not receive supervision and monitoring. One of the problems which arises with supervised administration of methadone and buprenorphine is that the immediate task of delivering a daily dose to patients tends to become the focus of treatment, displacing concerns over patients’ well-being and functioning. The potential benefits of reducing the requirement for supervised administration are substantial. Supervised administration contributes to the expense of treatment, and to problems of congregation around clinics where people attend daily. For consumers, the requirement to attend daily deters many people from entering or remaining in treatment, limits geographical access to treatment, contributes to the stigma associated with treatment and makes social reintegration (particularly employment) more difficult. For health professionals, supervised administration creates a treatment system in which, inevitably, the focus becomes the logistics of administering daily doses to large numbers of people, and much clinical interaction becomes a process of haggling over take-away doses. Potentially, unsupervised administration can make treatment more accessible, more effective and less frustrating for all involved.

There are several critical, unresolved issues around unsupervised administration in general and the use of combination buprenorphine–naloxone in particular. Three issues are: (1) is the combination product acceptable; (2) for whom should it be available, and (3) how should it be monitored? Before designing clinical studies to test specific hypotheses, it was decided to explore these issues in a pilot study of unsupervised administration. The pilot study was to investigate tolerability, effectiveness and responses of patients and staff to providing unsupervised doses.

Proposed New South Wales treatment guidelines for methadone and buprenorphine recommend that to receive take-away medication, patients need to have discontinued regular heroin or other injecting drug use, be employed or in education and be stable psycholo-

gically and socially. The rationale for restricting take-away medication to people in these categories is twofold. First, restricting takeaways to stable individuals reduces the likelihood that the drug will be injected or diverted to the black market, and assists people who are socially reintegrated by reducing attendance requirements. Secondly, the lure of receiving take-away medication may function to encourage people to abstain from heroin use. It was decided to apply such eligibility criteria, accepting onto the pilot study of unsupervised dosing people who demonstrated that they had discontinued use of drugs other than buprenorphine and who were employed and socially stable.

### Subjects and methods

It was proposed to recruit 30 subjects. Subjects were drawn from patients receiving buprenorphine maintenance treatment at Langton Centre. All potential subjects who were judged psychologically stable were informed of the study by case managers, and of the requirements of the study:

- (i) Ceased heroin use, not using stimulants (cocaine or amphetamines), not dependent on alcohol or benzodiazepines. Subjects using cannabis were not excluded.
- (ii) Employed at least 20 hours per week (and to present pay slips as evidence), or studying, or full-time carer.

Those expressing an interest in the study were required to go through an observation phase of 2 months, during which time they submitted urine tests twice weekly. They were also asked to provide documentary evidence of employment or study (pay slips or student cards).

When subjects met criteria for participation, they were switched to Suboxone and were then reviewed daily for 3–7 days. During this time symptoms of withdrawal were monitored, and their dose was adjusted if necessary. Then, subjects were supplied with 1 week’s supply of medication. Thereafter, monitoring was by weekly appointment for 3 months. At each visit subjects completed a brief interview, submitted a urine specimen, and collected their next week’s supply of medication. A condition of participation was that participants would be called at random on two occasions during the first 3 months, and asked to submit a urine specimen for toxicology.

After 3 months’ treatment, appointments were changed to fortnightly. Research interviews were conducted at baseline, 3 months and 6 months. At the completion of 6 months, stable subjects were allowed to continue in open-label treatment, picking up Suboxone every 2–4 weeks.

Participants were also invited to talk about their experiences while on unsupervised Suboxone. This was conducted in a 1-hour semi-structured in-depth interview. The data collected from the transcripts of these conversations were then analysed and collated into thematic categories. This qualitative component of the study allowed researchers to explore changes in participants' views in relation to drug use, the Centre and their own 'addict' identity, and will be reported separately.

The study was approved by the Ethics committee, South Eastern Sydney Area Health Service. The study was funded by NSW Health. Suboxone was supplied by ReckittBenckiser Pty Ltd. The company was not involved in the design of the trial, the analysis, nor in the decision to submit for publication.

## Results

At the time of commencement of recruitment for the trial, 17 people were in buprenorphine treatment at the Langton Centre. During the period of recruitment for the trial, 138 individuals commenced a total of 238 episodes of buprenorphine treatment. Thus, the potential pool of eligible subjects was 155. Of these, 31 (20%) commenced surveillance urine tests and 17 (11% of potential subjects) were commenced on Suboxone.

Two subjects might have qualified, but for a brief period during the recruitment phase there was a shortage of Suboxone supply, and it was considered prudent not to initiate new people into treatment until continuity of supply could be guaranteed. During that time, these two eligible subjects dropped out of treatment rather than wait until Suboxone was available. Apart from that, the reason so few people were recruited was that few met the eligibility criteria. Most subjects were not employed. Among the employed people who expressed an interest and began submitting urine samples, persisting use of heroin was common.

Among the 14 subjects who commenced urine testing in the hope of receiving Suboxone, 68/142 urine samples (52%) were positive for morphine. In contrast, among the 17 accepted subjects, 185/193 urine tests showed no heroin use. Six of the eight tests positive for morphine were submitted by one subject; the other two positive tests occurred early in the urine screening period.

Characteristics of recruited subjects are shown in Table 1. Nine subjects reported having no periods of abstinence for 2 months or longer outside time spent in maintenance treatment or in a controlled environment. The other eight subjects reported periods ranging from 3 months to 4 years of continuous abstinence at times during their heroin-using careers. As shown in the table, some subjects commenced urine screening from the moment they entered buprenorphine treatment, and were switched to Suboxone after 2 months treatment; however, most had been in prolonged treatment.

The switch from buprenorphine (Subutex<sup>TM</sup>) to the combination product (Suboxone<sup>TM</sup>) was associated with mild withdrawal symptoms for 24 hours in the first subject. Thereafter, 13 subjects had about a 50% increase in dose when switching (from an average dose of 8.5 mg Subutex<sup>TM</sup> to day 1 Suboxone<sup>TM</sup> average of 12.2 mg); in no cases were there complaints of either intoxication or withdrawal. Two subjects, both of whom had been on very low doses of Subutex (1.2 and 4 mg, respectively) increased their dose further slightly by day 8 to 4mg and 8 mg, respectively. Dosage changes during the trial are displayed in Table 2.

In total four subjects were transferred at the same buprenorphine dose; two reported mild withdrawal symptoms and in one case, patient no. 13, the subject requested to return to Subutex<sup>TM</sup> rather than continuing with the combination product. This subject had used heroin regularly; six of seven tests were positive for morphine prior to commencing Suboxone<sup>TM</sup>, and this may have contributed to her withdrawal symptoms.

**Table 1.** Characteristics of trial subjects

	M	F	Total
<i>N</i>	11	6	17
Age	31 (21–42)	37 (19–56)	33 (19–56)
Years of dependence	8 (2–22)	16 (1–30)	11 (1–30)
Total months opiate maintenance treatment (OMT)	53 (3–180)	57 (11–96)	54 (3–180)
Months this episode OMT	11 (2–32)	10 (2–36)	11 (2–36)
Education			
< year 10	2	1	3
SC	5	1	6
HSC	1	2	3
Tertiary	3	2	5

**Table 2.** Dose changes during treatment

Subutex dose	Day 1 Suboxone	Day 8 Suboxone	3 months Suboxone	6 months boxone
1.2	2	4	4	4
2	4	4	4	4
2.8	4	4	4	4
4	6	8	8	8
6	8	10	12	14
6	8	8	8	8
6	8	8	6	6
7	10	10	8	8
8	8	12	10	8
12	18	18	18	Discontinued
10	10*	16	16	8
10	10*	Discontinued		
12	18	18	18	18
12	16	16	16	16
12	12	8	12	12
16	24	24	24	24
24	32	32	30	30

\*These two patients reported some withdrawal symptoms in the 24 hours after their first dose of buprenorphine–naloxone; one subject requested return to buprenorphine.

One subject who switched at the same dose reported feeling slightly intoxicated, and reduced his dose before day 8; the other reported no withdrawal symptoms, but requested a dose increase by day 8. Once on a stable dose most people did not make changes, although a few subjects who were planning to withdraw had dose decreases by 6 months.

Overall, retention in treatment was high. One subject dropped out after 1 day, and has had several subsequent episodes of detoxification. The only other subject to leave treatment within 6 months moved interstate and dropped out. He subsequently returned to Sydney and is continuing on standard buprenorphine. A third subject dropped out after 6 months, remained abstinent for several months, then recommenced heroin use and re-entered treatment with buprenorphine. The fourth subject to leave treatment dropped out after more than a year when she found she was pregnant. She has remained drug-free for 10 months, and was drug-free at the time of writing.

Most subjects submitted approximately one urine test per week during the first 6 months. Fourteen of the 15 subjects who remained in treatment for 6 months submitted a total of 362 urine tests (mean 24, range 20–34); the remaining subject, who was undertaking work-place supervision, submitted 42 urine samples in the 6 months. Five subjects had at least one urine positive for morphine (total 18 positive, range 1–5). Eight subjects reported continuing cannabis use during treatment, and two subjects each had one urine test positive for cocaine and ecstasy, respectively.

Four subjects did not attend for random call-in, all on the grounds that work commitments made it impossible to do so. One subject was not required to attend as he was undergoing twice-weekly urine tests in the work-place as part of the conditions of his returning to work.

At 6 months, three subjects had become unemployed. One had lost job her following a cerebrovascular accident and the others gave up work for unspecified reasons; both also dropped out of treatment, one at 4 months and the other after completing 6 months. Two subjects who had been studying had ceased studying and not found work.

#### *Clinical observations*

One feature of the study was that it provided potential participants with an incentive to discontinue heroin use in order to gain access to Suboxone without the requirement to attend daily for supervised administration. Case managers judged that three patients, two of whom had been in treatment for years, discontinued occasional heroin use for purposes of participating in the trial. Two of the three continued to use heroin episodically once they were on Suboxone, and together accounted for seven of the 16 positive urines submitted during treatment.

One subject, no. 13, was recruited despite urine tests prior to recruitment being positive for morphine. There was a substantial delay between submitting samples and receiving test results. When this patient, who was employed full time, indicated that she would have to

leave treatment due to work commitments she was offered Suboxone before the results of the tests were available.

### *Qualitative findings*

Qualitative interviews explored changes associated with taking medication without direct supervision. In particular, changes in the participants' relationship with staff and with themselves (in terms of their 'addict' identity, and their relationship to drug use) were explored. Although several strong and consistent themes emerged from the interviews, the main theme expressed was that of freedom. Freedom from the anxiety and shame associated with daily attendance at the clinic for dosing was identified consistently as a major benefit. For example, one woman commented:

'I don't feel so anxious and stressed out about coming to Langton on a weekly basis. This, it frees me. . . [while being daily dosed] I would walk around to see if I knew anyone who has seen me. I've always hidden it from my family. The freedom that Suboxone gives people like us is amazing. We only have to be here once a week, we can tolerate that.'

Many of the participants' accounts associated the clinic with illicit drug use and their past drug-using identity. Therefore it was not surprising that freedom from the clinic also contributed to the sense of having 'moved on'. Receiving medication to self-administer without supervision was also seen as an expression of trust and responsibility, and contributed to a changed (and much improved) relationship with clinic staff.

Some people expressed a long-term wish to eventually cease Suboxone, but also recognized the value of remaining in long-term maintenance treatment. One respondent, who had experienced many different forms of treatment, commented:

'Since I've been on Buprenorphine and Suboxone I actually don't really think about heroin much at all. . . during naltrexone you know it was periods of just abstinence with no drugs, I'd think about heroin you know daily or even hourly, whereas for this maybe twice a week, just sort of think about it for a few minutes. . . I do sort of miss the old days [of heroin use] but most of the time it's just sort of self satisfaction of where I am now as to where I used to be, no more a prisoner of heroin.'

### *Adverse events*

There was one serious adverse event: a subject who after many months on Suboxone had a cerebrovascular accident, with transient loss of speech and limitation of

movement in her right arm. This resolved fully in time. Investigation revealed a left carotid stenosis. The subject was 54 years of age, on treatment for hypertension and was a smoker. The event was judged as not related to Suboxone treatment, and she continues on Suboxone.

One subject became pregnant after many months in treatment. All subjects had been warned to avoid pregnancy, and she discontinued Suboxone on the diagnosis of pregnancy, at 2 months. She had a full-term delivery of a healthy infant.

### **Discussion**

This pilot study suggests that Suboxone can be given without supervised administration in highly selected subjects. The combination product was well tolerated, and retention in treatment was 15/17 at 6 months. Most subjects were still in treatment 18 months after the commencement of the trial. Heroin use during treatment was very uncommon, as was use of drugs other than cannabis.

There are few data currently available on the efficacy of unsupervised administration of Suboxone, or on the appropriate patient selection. A previous large-scale study from the United States [12] treated subjects for a year, demonstrating the safety of the combination product. The study allowed up to 10 days of 'carry' medication (medication to be taken from the clinic and taken without supervision) at the discretion of the investigators, but there was no report of how many subjects received unsupervised administration. The trial had liberal entry criteria, and two urine samples were collected per month for toxicology; the report states that the percentage of urine tests negative for opiates 'ranged from 35.2% to 67.4%', although quite what this means was not made clear. Self-reported use of heroin and other drugs was not reported.

The current study involved not only selecting stable patients, but also a high level of ongoing monitoring (weekly appointments). The intensity of monitoring of patients appears to be a critical issue in treatment outcomes. In France, methadone administration is supervised but buprenorphine is dispensed for use without direct supervision. However, doctors and pharmacists involved in buprenorphine treatment provide varying levels of monitoring and support. An evaluation suggested that treatment outcomes depended primarily on the level of monitoring rather than which drug patients received [13]; in patients with less monitoring there was more buprenorphine injecting and more illicit drug use.

The pilot study illustrated some of the difficulties that will be encountered in clinical practice with Suboxone. A high-functioning patient who had commenced urine surveillance 3 weeks earlier with a view to

entering the trial announced she would have to cease treatment, owing to pressures of her full-time employment. Rather than have her drop out, she was inducted promptly onto Suboxone. Her urine tests subsequently revealed regular heroin use, and in fact she dropped out of the trial and out of treatment almost immediately. This protocol violation reflected the desire to maintain someone in treatment. Such pressures occur regularly in clinical practice.

This study has limited implications. It appeared that, in stabilized patients, transferring from buprenorphine to the combination product went more smoothly if the dose of the latter drug were increased slightly. However, this would need to be confirmed in blinded studies. The study demonstrated that highly selected patients could be maintained on unsupervised administration without destabilization (and with excellent long-term retention in treatment). However, large-scale efficacy trials of unsupervised dosing are required to assess the impact on overall retention in treatment. Even in subjects who complied with random call-ins, and demonstrated that they had in their possession the tablets needed until their next scheduled visit, it is not possible to exclude a degree of diversion. This will always be a difficult problem to monitor (as it is in treatment programmes involving supervised administration).

Unsupervised administration represents an opportunity to remove the major barrier to participating in treatment, the requirement for daily attendance. This is particularly relevant as one of the key limitations of buprenorphine treatment is poor retention [14]. Removing the requirement for daily attendance is probably the most useful step in attracting and retaining people in treatment. The benefits of maintenance treatment are observed primarily while people remain in treatment and, as has been clearly demonstrated in methadone treatment, relapse after leaving treatment is usual [15,16]. Improving retention can greatly improve the effectiveness of treatment. Unsupervised administration is likely to be less costly, because resources devoted to administration contribute substantially to the cost of buprenorphine treatment [17].

The most important finding of the study lies not in the subjects who participated, but in the very large numbers who were not eligible to participate. Using the restrictive criteria (modelled on guidelines for providing take-away methadone doses), only 11% of subjects were eligible for unsupervised administration. As this pilot study confirmed, many people in methadone and buprenorphine treatment are not employed, and many continue to use heroin occasionally. The assumption that availability of unsupervised administration would be an incentive to abstinence from heroin was not really supported—14/31 potential subjects commenced urine screening but continued heroin use; and of the three

subjects judged by staff to have given up occasional heroin use to enter the trial, two resumed infrequent use once in treatment. As has often been noted in relation to methadone treatment, the paradoxical consequence of an 'orientation to abstinence'—the frame of reference underlying the criteria for entry to the trial—is not to promote abstinence, but to render maintenance treatment less effective [16]. This paradox may apply to unsupervised Suboxone treatment; it is possible that if abstinence-orientated criteria are employed to restrict availability of unsupervised treatment, few people will benefit and the opportunity to improve participation in treatment will be lost. To test this hypothesis, we are now undertaking a study of effectiveness and cost-effectiveness of Suboxone treatment, comparing supervised versus unsupervised administration, and comparing restrictive entry criteria (based on abstinence from heroin) with liberal criteria.

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### Declaration of interest

A/Professor Bell is currently conducting a further clinical trial of Suboxone<sup>TM</sup>, which is partly funded by ReckittBenckiser P/L. He has been funded to conduct a workshop on Suboxone by ReckittBenckiser P/L. A/Professor Bell has been conducting a phase 1 clinical trial of implantable buprenorphine (Probu- phine<sup>TM</sup>) for Titan Pharmaceuticals, and has been funded to attend a conference in the United States by Titan.

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