Cessation of methadone maintenance treatment using buprenorphine: transfer from methadone to buprenorphine and subsequent buprenorphine reductions

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Abstract

Background: Buprenorphine is used in the treatment of opioid dependence. Due to its pharmacology, the transfer from methadone to buprenorphine may precipitate withdrawal symptoms. Methods: Methadone maintained patients with clinical indicators of stability who were seeking withdrawal from methadone were recruited from three Australian states. Patients on methadone doses between 30 and 40 mg were randomised to transfer to buprenorphine by a fixed dose (transfer at 30 mg methadone) or by a variable dose induction (transfer when ‘uncomfortable’). A third group of patients with methadone doses less than 30 mg were transferred to buprenorphine at their entry methadone dose. Fifty-one patients were inducted onto buprenorphine using the same dosing protocol with the first dose of 4 mg buprenorphine. Following stabilisation on buprenorphine, patients gradually reduced the buprenorphine dose to 0 mg. Withdrawal severity and drug use was monitored. Results: There were no significant difference between the transfer at 30 mg and transfer when ‘uncomfortable’ dosing protocols in severity of withdrawal on transfer from methadone to buprenorphine. Those on doses less than 30 mg reported significantly less withdrawal discomfort at transfer. All but one patient stabilised on buprenorphine. Thirty-eight of the 51 patients inducted onto buprenorphine reached 0 mg. Conclusions: Transfer from methadone to buprenorphine can safely occur from doses of around 30 mg of methadone. Buprenorphine dose reductions were well tolerated. Thirty-one percent of patients were not using heroin or methadone at 1-month follow-up.

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1. Introduction

The benefits of methadone maintenance treatment, including the reduction in heroin use, criminal activity, spread of HIV, and improved health and social functioning are well documented (Ward et al., 1998). However many methadone maintained patients experience difficulty in ceasing methadone maintenance treatment. Research into methadone withdrawal suggests that completion rates, reaching 0 mg methadone, range from about 40 to 100% depending on factors such as staff approval, rate of reduction, psychosocial support and medication provided (Milby, 1988). Buprenorphine, a partial agonist at the mu opioid receptor, has been reported to have a mild withdrawal syndrome (Jasinski et al., 1978; Bickel et al., 1988) and may be a useful agent in assisting methadone maintenance patients seeking cessation of maintenance therapy.

The feasibility of using buprenorphine to assist methadone withdrawal is complicated by difficulties in
transferring from methadone to buprenorphine. Specifically, abrupt transfer from methadone to buprenorphine may precipitate withdrawal symptoms, subject to the methadone maintenance dose at transfer and the initial buprenorphine dose (Walsh et al., 1995). This discomfort may occur as buprenorphine has a high affinity for opioid receptors; therefore if too high a buprenorphine dose is given it may displace the full agonist methadone from the receptors and precipitate withdrawal symptoms. Alternatively, if the initial buprenorphine dose is too low it will not adequately substitute for methadone and result in spontaneous withdrawal symptoms.

This study was designed to investigate different methadone transfer regimes, examining (a) the extent of withdrawal severity during the transfer in stable methadone maintained patients that wished to withdraw from maintenance treatment; and (b) the withdrawal symptoms throughout the buprenorphine reductions and outcomes post-withdrawal. The study aimed to develop a transfer protocol for use in a subsequent randomised controlled trial examining the efficacy of buprenorphine compared to methadone in the cessation of methadone maintenance treatment.

2. Methods

The pilot study was conducted in 1999 at four clinics in Sydney, Melbourne, Brisbane and the Gold Coast. Ethics approval was granted in each state. Buprenorphine (Subutex®) was not registered in Australia at the time of the study.

2.1. Recruitment

Methadone patients on doses of 40 mg of methadone or less who were interested in withdrawal from methadone maintenance treatment were considered for the study. The inclusion criteria for the study were: at least 6 months in methadone treatment, eligibility for methadone take-home doses, no heroin use in the last 2 weeks (by urine and self-report), daily attendance for 2 weeks and a Global Assessment of Functioning (GAF) (Jones et al. 1995) score of 61 or greater. Exclusion criteria were: serious medical or psychiatric conditions, pregnancy, breast-feeding or concurrent alcohol or benzodiazepine dependence. A rationale for these selection criteria are provided in Lenné et al. (2001).

2.2. Assessment

Patients were maintained on their current methadone dose for 2 weeks, during which time they were assessed against the eligibility criteria. All patients underwent a medical assessment and random urine samples were taken. Patients with samples positive for opiates (other than methadone) were excluded from the study. A research interview was conducted examining drug use and treatment history, motivations to cease methadone treatment and goals following treatment. Standard questionnaires including the Opiate Treatment Index (OTI) (Darke et al., 1992), Brief Symptom Inventory (BSI), Subjective Opiate Withdrawal Scale (SOWS) and Objective Opiate Withdrawal Scale (OOWS) (Handelman et al., 1987) were administered.

2.3. Random assignment and masking

Individual patient randomisation was conducted by an independent organisation, the National Health and Medical Research Council Clinical Trials Centre (NHMRC-CTC). A computerised schedule was developed by the NHMRC-CTC using the technique of dynamic balanced randomisation, 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. The study was open-label with patients, treatment providers and outcome assessors aware of group allocation.

2.4. Induction procedure

Patients on doses of 30 mg or more were randomly allocated into a fixed (transfer at 30 mg methadone) or variable transfer protocol (transfer when ‘uncomfortable’). The fixed transfer protocol required patients to reduce their methadone dose by 2.5 mg per week to 30 mg and they remain on 30 mg for 1 week before being transferred to sublingual buprenorphine tablets (Subutex®). The variable dosing protocol involved patients reducing their dose by 2.5 mg a week until they reported withdrawal discomfort. They were then transferred to buprenorphine. A third group (transfer below 30 mg), were not randomised and included patients on methadone maintenance doses of less than 30 mg who sought to transfer to buprenorphine for the purpose of withdrawal. These patients were not eligible for randomisation but they were included to provide a further comparison group. After the 2-week assessment they were transferred to buprenorphine from their entry dose. The induction onto buprenorphine was the same regardless of protocol allocation (see Table 1). At least 24 h after their last methadone dose patients were given 4 mg sublingual buprenorphine hydrochloride. Patients were monitored using the SOWS and OOWS half hourly for 3 h. Supplementary doses of buprenorphine were administered in the afternoon for the first 3 days if required. The dosing schedule was flexible with doses modified according to patient response.
Symptomatic medication including NSAIDs (joint aches), quinine (muscle cramps), metoclopramide (nausea), atropine sulphate and diphenoxylate hydrochloride (diarrhoea) or paracetamol (headaches), was available for withdrawal symptoms as required. Patients were reviewed by a medical officer daily for the first 5 days. The dose of buprenorphine received was dependent on whether the previous dose was considered to be adequate (based upon features of withdrawal, side effects, concomitant drug use and patient report). Intoxicated patients were not dosed.

2.5. Reduction procedure

After reaching a stable dose of buprenorphine, usually by Day 5, patients remained on that dose for a further 2 weeks. Reductions of 2 mg buprenorphine could occur weekly thereafter. Patients could choose to stay on a particular dose for a 2-week period but had to reduce to 0 mg within 16 weeks. Patients were reviewed at least weekly by clinical staff. Patients could choose to terminate from the study and return to methadone treatment at any time; those patients who returned to regular heroin use or became destabilised (medical, psychological or social parameters) were discontinued from the study and returned to methadone maintenance treatment.

2.6. Follow-up

Patients were encouraged to return to the clinic for symptomatic medication or supportive counselling following the cessation of buprenorphine. Transfer to naltrexone (initial dose 12.5 mg) was an option for patients 5 days after ceasing buprenorphine and subject to no other recent opiate use. A research interview was conducted 1 month after ceasing buprenorphine treatment.

2.7. Outcome measures

Severity of withdrawal (SOWS, OOWS), was monitored half hourly for the first 3 h on the first day of buprenorphine dosing, daily during the first week of transfer and then weekly throughout the buprenorphine reduction phase. The SOWS is a 16-item checklist with common symptoms of withdrawal. Patients rate each item on a scale of 0 (not at all) to 4 (extremely). Scores range from 0 to 64. The OOWS is an objective scale with 13 observable physical signs of withdrawal. A clinician rates the symptom as being absent (0) or present (1). The maximum score is therefore 13. Patients were also asked to rate the severity of this withdrawal episode compared to other withdrawal attempts and discussed the advantages and disadvantages of using buprenorphine. Primary outcomes were the severity of withdrawal, medication use and heroin use during transfer. Secondary outcomes included length of reduction, heroin use during reduction (measured by random weekly urine and self report), ability to reach 0 mg of buprenorphine and outcome at 1-month post discharge.

3. Results

Seventy-five patients started the 2-week assessment process. Twenty were excluded from participation due to opioid positive urines or failure to attend during the 2-week assessment period. Fifty-five patients were recruited; 38 being randomised to the transfer at 30 mg \((n=19)\) or transfer when ‘uncomfortable’ groups \((n=19)\) and 17 who were already on methadone maintenance doses less than 30 mg. Four patients (three

### Table 1

<table>
<thead>
<tr>
<th>Day of buprenorphine dosing</th>
<th>Morning buprenorphine dose</th>
<th>Additional afternoon buprenorphine dose (mg)</th>
<th>Total possible daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 mg (delayed at least 24 h after last methadone dose)</td>
<td>Up to 4</td>
<td>4–8</td>
</tr>
<tr>
<td>2</td>
<td>If intoxicated/severe side effects: Day 1 total dose minus 2–4 mg</td>
<td>Up to 4</td>
<td>0–16</td>
</tr>
<tr>
<td>3</td>
<td>If withdrawal and/or cravings: Day 2 total dose plus 2–4 mg</td>
<td>Up to 4 (to maximum of 24 mg)</td>
<td>0–24</td>
</tr>
<tr>
<td>4 and 5</td>
<td>If intoxicated/severe side effects: Day 3 total dose minus 2–4 mg</td>
<td>–</td>
<td>0–24</td>
</tr>
<tr>
<td></td>
<td>If withdrawal and/or cravings: Day 3 total dose plus 2–4 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

in transfer when ‘uncomfortable’ and one in the transfer at 30 mg group) were randomised but remained in methadone maintenance due to positive urine results indicative of heroin use before transfer to buprenorphine. In total, 51 patients were transferred from methadone to buprenorphine. Patient characteristics for those randomised and those in the transfer below 30 mg group are shown in Table 2.

T-tests were conducted for the randomised groups and showed there was no difference between the groups in gender, number of years of regular opiate use, total number of months in methadone maintenance treatment or number of months in methadone maintenance this treatment episode. The transfer when ‘uncomfortable’ group was significantly younger than the transfer at 30 mg group ($t_{36,0.05} = 3.02, P < 0.05$).

3.1. Transfer dose

The mean methadone maintenance dose for the patients at study entry is presented in Table 2. The mean methadone dose that patients were transferred to buprenorphine from was fixed at 30 mg for the transfer at 30 mg group, 27.0 mg (S.D. 4.5 mg) for the transfer when ‘uncomfortable’ group and 19.1 mg (S.D. 6.0) for the transfer below 30 mg group. The mean dose on which patients stabilised on buprenorphine ranged from 6.0 mg (S.D. 2.7) for the transfer below 30 mg group, to 9.5 mg (S.D. 3.3) for the transfer when ‘uncomfortable’ group and 10.9 mg (S.D. 3.9) for the transfer at 30 mg group. T-tests were carried out to compare the starting methadone dose, transfer dose and buprenorphine stabilisation dose between the randomised groups. There was no difference between patients in the transfer at 30 mg and the transfer when ‘uncomfortable’ dosing protocols on starting methadone dose or buprenorphine stabilisation dose. The methadone transfer dose for the transfer when ‘uncomfortable’ group (27 mg) was statistically significantly lower ($t_{32} = 2.54, P < 0.05$) than the transfer at 30 mg group. However, this difference is not clinically significant.

All patients but one, transferred successfully to buprenorphine and remained on buprenorphine for the 5 day induction period. One patient (transfer at 30 mg group) did not stabilise on buprenorphine and returned to methadone maintenance after 2 days of buprenorphine (receiving a total of 8 mg buprenorphine on Day 1 and 12 mg the next day).

3.2. Symptomatic medication and heroin use

Eleven patients received symptomatic medication during the 5 day induction period; seven in the transfer at 30 mg group and four in the transfer when ‘uncomfortable’ group. Six patients, two from each group, had positive urine samples or reported heroin/illicit methadone during the 5 day induction period. There was no significant difference between the two randomised groups.

3.3. Withdrawal severity at transfer

Baseline subjective withdrawal scores prior to the first dose of buprenorphine were higher for the transfer when ‘uncomfortable’ group than for the transfer at 30 mg group and the transfer below 30 mg group (reflecting the manipulation of methadone doses in that group to transfer when experiencing discomfort). There was no significant difference in SOWS scores between the randomised groups. Post-hoc analysis found the transfer below 30 mg group had SOWS scores significantly lower than both the other groups SOWS scores ($F_{1,28} = 11.77, P < 0.05$) (Fig. 1).

SOWS scores decreased across the days of induction onto buprenorphine. By Day 5 SOWS scores for all groups were below baseline scores.

There was a significant group by day interaction between the transfer at 30 mg group and the transfer when ‘uncomfortable’ group ($F_{1,19} = 9.26, P < 0.05$). The mean scores of the group that transferred when uncomfortable decreased after the initial buprenorphine dose and declined further towards the end of the week. The transfer at 30 mg group started with lower baseline

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Patient characteristics for each treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transfer at 30 mg</td>
</tr>
<tr>
<td></td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Mean age</td>
<td>38.7*</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>58</td>
</tr>
<tr>
<td>Number years regular opiate use</td>
<td>11.0</td>
</tr>
<tr>
<td>Total months in MMT</td>
<td>53.0</td>
</tr>
<tr>
<td>Months in MMT this episode</td>
<td>39.5</td>
</tr>
<tr>
<td>Maintenance methadone dose on study entry (mg ± S.D.)</td>
<td>34.2 ± 4.9</td>
</tr>
</tbody>
</table>

* Significantly $P < 0.05$. 
scores, increased withdrawal severity for a few days (peaked on Day 2) before declining to below baseline by Day 5.

There was no difference between the fixed and variable dosing groups in OOWS scores over the induction period. Mean scores remained low for all groups (OOWS score < 2.5). The group on doses lower than 30 mg had statistically significantly lower OOWS scores than the other two groups ($F_{1,25} = 10.69$, $P < 0.05$).

3.4. Time to reduce

Thirty-eight of the 51 patients (75%) that transferred to buprenorphine reached 0 mg buprenorphine. On average, patients took 11.1 weeks to reduce to 0 mg with no significant difference between the randomised groups in length of time taken to reduce to 0 mg. The *transfer at 30 mg* group took an average of 12.5 weeks (S.D. 4.7) to reduce to 0 mg buprenorphine, the *transfer when uncomfortable* group took 12.2 weeks (S.D. 3.7) and the *transfer below 30 mg* took 8.3 weeks (S.D. 5.5) to reach 0 mg buprenorphine.

3.5. Heroin use

Random weekly urine samples were collected and patients were asked once a week whether they had used heroin in the past week. On average, patients used heroin once during the reduction. There was no significant difference in heroin use between the randomised groups.

3.6. One-month follow-up

At 1-month follow-up, 17 of the 55 (31%) patients reported no heroin use and had urine results free of heroin (and were not in methadone or naltrexone treatment). Five patients (9%) were in naltrexone maintenance. Eighteen patients (33%), including the four that did not transfer to buprenorphine, were in methadone maintenance treatment within 1 month of study discharge: 8 patients were transferred to methadone during the buprenorphine reductions due to heroin use and 6 patients completed buprenorphine reductions but relapsed to heroin use and re-entered methadone treatment. Seven patients (13%) were using heroin (self-report, urine drug screen) and were not in methadone maintenance treatment. Eight patients (15%) were unable to be contacted.

4. Discussion

The literature on dosing schedules used to transfer patients from methadone to buprenorphine is limited. This study contributes to our understanding of the methods of transfer using flexible dosing schedules in an outpatient setting. Previous studies examining the transfer from methadone to buprenorphine have used fixed dosing protocols and have recommended transfer from lower methadone doses (Walsh et al., 1995). Walsh et al. (1995), reported increased withdrawal symptoms when the final methadone dose is 60 mg compared to patients on 30 mg of methadone (Walsh et al., 1995). A study by Levin et al. (1997) used a fixed dosing schedule to transfer patients from high dose methadone to buprenorphine in an inpatient setting. The authors...
concluded that, within a supportive inpatient setting, patients can be switched from high dose methadone to buprenorphine with an acceptable degree of tolerability (Levin et al., 1997).

The patients in the current study were long-term methadone maintained patients who sought to withdraw from methadone treatment as outpatients. They were transferred to buprenorphine on doses of 30 mg or less of methadone. This study used a flexible dosing regime and the results confirmed that the transfer from methadone to buprenorphine on doses of around 30 mg methadone is feasible, safe and acceptable to both patients and clinical staff. Patients on doses less than 30 mg appear to experience less withdrawal at transfer, although outcomes do not differ. The majority of the patients withdrew safely from buprenorphine.

All but 1 patient who attempted the transfer stabilised on buprenorphine. The majority of patients did not experience substantial precipitated withdrawal discomfort within the 3 h after dosing. Although patients reported some withdrawal discomfort, subjective withdrawal severity scores were generally mild, tolerated by most patients (78%) without symptomatic medication and had resolved to baseline levels by Day 5.

Six people used heroin or illicit methadone to relieve discomfort during the induction week. Heroin use during transfer from methadone to buprenorphine, may be prevented by better control of withdrawal symptoms with medication and better patient education. Clinically it is important to reassure patients that the discomfort is transitory and should resolve within the first few days. It is important to stress that heavy use of heroin or other opiates may result in increased and persistent precipitated withdrawal symptoms, as buprenorphine has a high affinity for opiate receptors and will displace the heroin. This may result in a longer time to stabilise on buprenorphine.

The majority of patients who transferred to buprenorphine (75%) were able to reduce to 0 mg with tolerable withdrawal discomfort. A review of previous research into methadone withdrawal (Milby, 1988) suggests that completion rates are about 60% for gradual methadone withdrawal for stable patients. The transfer to buprenorphine and gradual reductions for methadone patients attempting withdrawal may contribute to improvement in completion rates, although direct comparisons of the two methods of withdrawal would be required to confirm this.

While reductions to 0 mg buprenorphine were tolerated by the majority of the sample, relapse to heroin use was an issue for some. Almost a third of the total initial sample were not using heroin or methadone at 1 month follow-up and a further 5 patients were still in naltrexone treatment. It is worth noting that the patients involved in the study were a selected group of stable methadone patients. The majority (73%) of patients had not used heroin in the month prior to participation in the trial. Return to heroin use remained a problem for over half of all patients attempting to cease methadone maintenance; 7 patients who were no longer in treatment had used heroin in the previous month, 14 were back in methadone treatment due to heroin use during or after buprenorphine reductions and 8 patients were lost to follow-up (presumed to have relapsed). This is comparable to the estimates by Milby (1988) that approximately half of patients who reduce off methadone will promptly relapse to heroin use. This is an issue that needs to be considered when withdrawing patients from maintenance treatment, with frequent monitoring and reconsideration of treatment plans if heroin use is detected.

In summary, transfer from methadone to buprenorphine at doses of 30 mg methadone is tolerable for patients who have been maintained on methadone for long periods. There was no evidence for superior outcomes when patients are transferred at 30 mg or when the transfer is delayed until they begin to feel discomfort during methadone reductions. Patients transferring from lower doses appear to experience less discomfort at transfer, although outcomes were comparable. The majority of patients completed reductions with a third being heroin-free at 1 month follow up. Return to heroin use post-withdrawal remains a problem, but buprenorphine appears to be a useful medication to transfer methadone maintained patients who wish to gradually withdraw from opioid replacement therapy.

Acknowledgements

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