

Short communication

Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence

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Abstract

Research suggests that buprenorphine may possess antidepressant activity. The Beck Depression Inventory was completed at baseline and 3 months by heroin dependent subjects receiving either buprenorphine or methadone maintenance as part of a larger, pre-existing, double blind trial conducted by NDARC (Australia). Depressive symptoms improved in all subjects, with no difference between methadone and buprenorphine groups, suggesting no differential benefit on depressive symptoms for buprenorphine compared to methadone.

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1. Introduction

Buprenorphine maintenance demonstrates comparable efficacy to methadone maintenance treatment (MMT) [10] and may have advantages, including alternate day dosing [21], better safety profile, and milder withdrawal syndrome [16].

Another possible advantage of buprenorphine is an antidepressant effect. Comorbid depression is common in opioid dependent patients, and is associated with poor outcomes [23]. Two studies [3,9] report rapid mood improvement using low dose buprenorphine in non-opiate users with refractory depression. Another study [15] reports a rapid improvement in depressive symptoms during an open trial of buprenorphine, which the authors consider to be greater than that typically observed during stabilisation in MMT.

The role of opioids in depression and the mechanism behind this putative antidepressant effect are unclear. Human [11] and animal [26] studies suggest that opiates may have antidepressant effects. Although methadone may inhibit

reuptake of serotonin [4] and displace imipramine from binding sites [7], opiates may also inhibit monoamine activity, which may be relevant to the pathophysiology of depression [8]. Buprenorphine is a partial agonist at μ -receptors, and displays affinity for κ , δ , and nociceptin (ORL1) receptors [14]. The combination of μ agonism and κ -antagonism produces less dysphoria than methadone [22]; animal studies suggest that κ -antagonists may exert antidepressant effects [18]. Buprenorphine may also interact with serotonergic systems [24] or the hypothalamic-pituitary-adrenal axis [12].

This study examined whether heroin users maintained on buprenorphine demonstrate greater improvement in depressive symptoms than those on MMT.

2. Subjects and methods

Recruitment was part of a larger, pre-existing study conducted by the National Drug and Alcohol Research Centre (Australia), comparing sublingual buprenorphine and oral methadone in heroin-dependent patients seeking opioid maintenance treatment [19]. This paper is concerned with the first stage (weeks 1–13) of the larger study. Previous drug treatment history or current depressive disorders were not a basis for exclusion.

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Individuals were randomised to either buprenorphine or methadone. Patients received either buprenorphine sublingual tablets and placebo methadone syrup or methadone syrup and placebo buprenorphine tablets in a double-blind, double-dummy design. Medications were administered daily in the clinic. Dosing was initiated at 30 mg methadone or 4 mg buprenorphine; details of dosing schedules are provided elsewhere [19]. Doses were individually titrated based on patient assessment to optimise response.

Daily dosing occurred for 6 weeks, after which alternate day dosing began. Those on buprenorphine received double their previous daily dose (or increased to the maximum permitted dose of 32 mg) on alternate days and placebo on interposed days. Methadone patients received a corresponding increase in their placebo buprenorphine tablets to maintain the blind.

The Beck Depression Inventory (BDI) [2] is a self-report measure of symptoms and was completed at baseline and 3-months. Drug use was assessed using the Opiate Treatment Index [5].

Baseline group differences were evaluated using independent samples *t*-tests for continuous variables and chi-square tests for categorical variables. Treatment effects data were analysed using a two-way fixed effects analysis of variance. Outcome predictors were examined using regression analyses.

3. Results

Four hundred and five subjects were recruited for the primary study. We had a restricted window of time in which we were able to opportunistically collect data for this secondary study. Within this, 147 subjects were assessed, 54 of which were captured at both baseline and 3-month time-points. Subject characteristics are detailed in Table 1. There were no baseline differences between buprenorphine and methadone patients for the groups of 147 or 54 subjects. There were no baseline differences between completers and dropouts for demographics, drug use, or BDI.

Table 1
Characteristics of subjects included for study

	Methadone (<i>n</i> = 79) (S.D.)	Buprenorphine (<i>n</i> = 68) (S.D.)
Sex	Male = 61%	Male = 63%
Age (years)	29.8 (7.78)	29.2 (7.53)
Duration of heroin use (months)	84.9 (76.1)	86.7 (87.9)
Previous history of treatment for opiate dependence	71%	79%
Days lasted in trial	74 (30)	71 (32)
BDI (Baseline)	22.3 (10.2)	24.9 (11.0)
BDI (3 months)	11.5 (9.7)	13.5 (8.9)
Dose at 3 months (mean daily dose over past 30 days—mg)	50.1 (24.3)	8.6 (4.1)
Dose range (mg/day)	20–150	2–32
Compliance at 3 months (% dose taken in last 30 days)	88%	87%

3.1. Treatment effects on depression

Depressive symptoms significantly improved in both treatment groups over the study period ($F_{1,52} = 45.67$; $P < 0.001$); no differences were observed between those subjects receiving methadone compared to those on buprenorphine ($F_{1,52} = 0.04$; $P = 0.83$). See Table 2. Similarly, when analysed on an intent to treat basis (last observation carried forward): all subjects significantly improved ($F_{1,96} = 28.50$; $P < 0.001$) with no difference between treatment groups ($F_{1,96} = 0.01$; $P = 0.92$).

Since previous studies reporting antidepressant effects utilised low doses (0.2–3.2 mg/day), and some buprenorphine effects are dose dependant, the impact of dose was examined. There were no relationships between dose (average daily dose taken over last 30-days) and final BDI scores in buprenorphine ($t = 0.70$; $P = 0.49$) or methadone ($t = -1.13$; $P = 0.26$) groups.

3.2. Predictors of depression and retention

Baseline BDI scores were unrelated to heroin use duration ($t = 0.81$; $P = 0.42$) and were not predictive of treatment retention in the whole sample ($t = 0.11$; $P = 0.91$), or in either treatment group. Higher baseline depressive symptoms predicted higher symptoms at 3 months in subjects receiving methadone ($t = 3.25$; $P < 0.01$) but not in subjects receiving buprenorphine ($t = 0.90$; $P = 0.38$).

In methadone subjects, there was a significant relationship between compliance (measured as percentage of prescribed dose taken in last 30 days) and BDI at 3 months, where more compliant subjects had lower levels of depression ($t = -2.63$; $P < 0.05$). This was not significant in subjects receiving buprenorphine ($t = 0.56$; $P = 0.58$).

Nine percent of subjects (13/147) reported use of antidepressants during the treatment period. These subjects exhibited a smaller improvement in BDI scores compared to those not receiving antidepressants ($t = -1.74$; $P = 0.088$). Sixteen percent of subjects (24/147) reported regular benzodiazepine use; 26% (38/147) reported occasional use. Use of benzodiazepines was unrelated to treatment group or change in BDI.

Subjects who were abstinent at 3 months had lower BDI scores (mean 7.62) than those who were not abstinent (mean 13.75) ($t = 2.739$; $P < 0.01$). When heroin use was measured as number of heroin using days in previous month, there was a modest but significant relationship between BDI scores and

Table 2
Beck Depression Inventory (BDI) scores in subjects included in the main analysis of treatment effects

	Methadone (<i>n</i> = 30) (S.D.)	Buprenorphine (<i>n</i> = 24) (S.D.)
BDI (baseline)	22.2 (10.5)	24.7 (11.0)
BDI (3 months)	11.6 (10.4)	13.4 (10.2)
Dose at 3 months (mean daily dose over past 30 days—mg)	47.9 (20.1)	8.7 (4.1)

number of heroin using days ($r = 0.21$; $P < 0.05$). There were no observed relationships between changes in BDI scores over time and heroin use outcomes.

4. Discussion

This study found no differential benefit of buprenorphine vs. MMT on depressive symptoms in heroin users engaged in maintenance treatment. The high levels of depressive symptoms at treatment entry and subsequent improvement over time in both groups are consistent with much research [23,25]. Reasons for improvement include both pharmacological and psychosocial stabilisation and may also reflect poorer retention rates for depressed subjects.

Our findings raise the question of why no treatment effects were observed. Study design may have influenced previous positive results. Two were open-label studies with no control arm [3,15]. Emrich et al. [9] used a controlled, crossover design, but subjects were not randomised and the sample size was small. In these studies, improvement was rapid; it is possible that effects may not be sustained over longer periods, or that patients experienced placebo responses. Other studies have reported depression as a side effect of buprenorphine [17], or observed greater symptom improvement with methadone rather than buprenorphine [20].

It is important to note that given our small sample size, our power to detect group differences is low. Power was calculated post hoc to be 0.44 (medium expected effect size), suggesting that larger samples are required in future studies of this nature. It is also important to note that doses of methadone and buprenorphine may not have been equivalent, making group comparisons difficult.

No dose effects were observed. It is possible that the ceiling dose for antidepressant effects is relatively low, and that the doses of buprenorphine used in our study (mean 8.6 mg) were too high to detect any differential effects. Drug liking and opiate-acceptability ratings have been reported to be higher for 4 mg buprenorphine than 8, 16, or 32 mg [13]. The dose–response relationships for many of buprenorphine's effects remain to be established.

Higher baseline symptoms predicted higher symptoms at 3 months in methadone subjects only, raising the possibility that fewer people on buprenorphine remain depressed compared to those on MMT. Higher compliance was predictive of reduction in depressive symptoms in methadone subjects only. In MMT, greater compliance is associated with improved outcomes [1], which may also include mood-related outcomes. It could also be that depressed subjects may be less motivated to attend every day. Why this was not observed with buprenorphine is unclear. Perhaps poor compliance interferes less with the pharmacological effects of a longer acting drug. Some subjects may have been able to break the blind during the alternate day dosing period by experimentation with absent days; however we consider that this would not influence secondary outcomes such as depressive symptoms.

Rates of antidepressant use were lower than reports in other injecting drug use populations [6]. Concomitant medication use may have been underreported; alternatively, new availability of buprenorphine in Australia may have attracted a less problematic group of heroin users into treatment. The smaller improvement seen in those receiving antidepressants may reflect a subgroup with greater symptom severity, which may be less likely to improve during treatment stabilisation.

5. Conclusions

At present there is insufficient evidence to suggest a differential benefit on depressive symptoms for buprenorphine compared with methadone. Due to sample size limitations, results are difficult to interpret, but differential results predicting depressive symptoms at 3 months between methadone and buprenorphine groups suggest that buprenorphine might impact differently on depressive symptoms compared with MMT. Further trials utilizing more frequent symptom monitoring and larger samples are required to establish if this is the case.

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