A placebo-controlled study of high dose buprenorphine in opiate dependents waiting for medication-assisted rehabilitation in Oslo, Norway

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ABSTRACT

Aims To evaluate whether buprenorphine, even without additional control and psychosocial treatment and support, alleviates the problems faced by patients waiting for medication assisted rehabilitation (MAR).
Design A randomized, double-blind, 12-week study of Subutex® versus placebo without additional support as an interim therapy.
Participants One hundred and six patients, 70 males and 36 females, waiting for MAR in Oslo. The average age was 38 years with an average history of heroin use of 20 years. Fifty-five patients were assigned to buprenorphine and 51 to a placebo.
Intervention Subutex® or placebo sublingual tablets were given under supervision in a daily dose of 16 mg with the exception of a double dose on Saturday and no dose on Sunday.
Measurement Retention, compliance, self-reported drug-abuse, wellbeing and mental health.
Findings The average number of days of participation was significantly higher in the buprenorphine group, 42 (median: 29) compared to 14 (median: 11) for the placebo group ($P < 0.001$). The retention of patients after 12 weeks was 16 patients in the buprenorphine group and one patient in the placebo group. The buprenorphine group had a larger decrease in reported opioid use ($p < 0.001$) and in reported use of other drugs, tablets and alcohol abuse ($p < 0.01$). The group also showed a stronger increase in wellbeing ($p < 0.01$) and life satisfaction ($p < 0.05$). None of the participants died.
Conclusion The patients waiting for MAR benefited significantly from the buprenorphine as an interim therapy according to retention, self-reported use of drugs and wellbeing. However, the patients had difficulties in remaining in treatment over time without psychosocial support.

KEYWORDS Addicts, drug users, heroin, maintenance treatment, Subutex®.

INTRODUCTION

At present, opioid maintenance is generally accepted in the treatment of heroin addiction and other types of opioid dependency. Research demonstrating the benefits, however, rests largely on high-threshold programmes with control procedures to prevent diversion of medication and secure compliance with treatment goals. Additionally, programmes are expected to meet the psychosocial needs of the patients with adequate therapeutic measures (Ball & Ross 1991; Arndt *et al.* 1997). These approaches limit treatment availability and lead

to insufficient capacity and the development of waiting lists. Despite the limitations of high threshold programmes, the potential benefits of low threshold programmes are less researched, and some countries with high availability such as Great Britain, Australia and Denmark have reported troublesome mortality figures concerning both patients in treatment and due to diversion of medication. Mortality seems to decrease with appropriate control procedures and supervised intake (Steentoft *et al.* 1996; Zador *et al.* 1996; Williamson *et al.* 1997; Hall *et al.* 1998). Consequently, there is a need to develop approaches that increase capacity and diminish the waiting list problems while at the same time avoiding the weaknesses associated with low-threshold programmes. The US Food and Drug Administration in 1993 (Nightingale 1993) approved interim methadone maintenance for addicts waiting for entrance to standard comprehensive methadone programmes. In a randomized study with a control group by Yancovitz *et al.* (1991), this type of programme has been shown to increase the percentage entering treatment and to decrease heroin use. The generalizability, however, was limited by lack of placebo design. Another objection might be that the interim programme suggested in our work demands a level of resources that brings the cost–benefit ratio into doubt. Another approach is 'methadone on demand' (Wenger & Rosenbaum 1994), according to which patients are admitted to treatment as they present themselves to the programme and when they are prepared to follow programme rules. This, however, would be expected to involve some of the problems of low-threshold programmes. Buprenorphine has been suggested as an alternative based on lower toxicity. France registered Subutex on the basis of up to a 28-day prescription by general practitioners without special authorization in 1996. At that time the overdose mortality rates had dropped from an all-time high in 1994 (Ministère De l'Interieur 1997). Consequently, the contribution of greater buprenorphine availability is unclear. In a report to the French Ministry of Health (l'Inserm 1998), a working group noted that an elevated level of buprenorphine injection by drug addicts was widespread. However, this does not seem to be reflected in any noticeable increase in overdose deaths by buprenorphine (Auriacombe *et al.* 2001).

In Norway the use of methadone was generally accepted as late as in 1997, when the parliament mandated a nation-wide system on a high threshold basis (Norwegian Ministry of Social Affairs 1996–97). The official programme was launched in 1998 based on an approach involving cooperation between municipal treatment teams and regional centres. This system was expanded particularly from 1999. By April 2001 about 1200 patients were in treatment. Nevertheless, waiting-list problems are rising.

The Centre for Medication Assisted Rehabilitation in Oslo (MARIO) is responsible for all use of methadone for maintenance purposes in Oslo and is also a national competence centre. When the study examined here was initiated, MARIO had a waiting list of 420 applicants. Many of the patients were in bad health, often with physical injuries inflicted by many years of heavy drug abuse. At the same time the centre lacked the capacity to include those on the waiting list while still complying with official principles and guidelines. It was therefore decided to develop a project for interim maintenance combined with standard social welfare assistance (treatment as usual) without extra resources. As there are very few adequately controlled studies that demonstrate the value of maintenance, particularly from an 'intention-to-treat' perspective (Hermstad *et al.* 1998), it was decided that strict scientific evaluation methods would be applied. The study was designed to evaluate whether the use of medication in and of itself, without additional control and psychosocial support, alleviates waiting-list problems. The measures utilized were retention and compliance, wellbeing, life satisfaction, mental health and self-reported drug use.

METHODS

Choice of drug

Both methadone and high-dose buprenorphine (Subutex) are available for treatment of opioid addiction in Norway. Methadone is a full μ-receptor agonist, whereas, buprenorphine is a partial agonist. One effect derived from buprenorphine is diminished respiratory depression and therefore reduced risk of death due to overdose. Methadone is administered dissolved in a strong juice, making it well suited for oral but not for intravenous administration, whereas buprenorphine is administered as sublingual tablets that dissolve in water and are therefore attractive for intravenous injection. Methadone requires daily dosing while buprenorphine may be taken on alternate days. Furthermore, it appears to be easier to quit using buprenorphine than to quit methadone (Eissenberg *et al.* 1996). In an overall evaluation it was judged that high-dose buprenorphine (Subutex) was the natural choice, given that sufficient control procedures could prevent diversion.

Design

A 12-week, randomized double-blind study of buprenorphine versus placebo without additional rehabilitation or support from MARIO was performed. The patients started medication on Mondays in the presence of the project leader, a medical doctor. All participants were offered

buprenorphine after the 12-week period. The staff's only responsibilities were to administer the tablets at the appointed time (Monday–Saturday) and provide supervision for their intake, and to observe any possible side effects. No urine samples were collected. Patients and staff were asked which treatment they thought had been given to each of the patients at the end of the 12-week period.

Participants

The 420 patients on the waiting list of MARIO were eligible for the study. The offer was presented to the patients by mail and through their social service offices. All patients who responded within 3 months were accepted if they fulfilled the inclusion criteria: at least 25 years old, more than 10 years of opioid dependence and a written plan for the rehabilitation process. In addition, traditional drug-free treatment should already have been attempted and the patients were to have a current opioid dependence. Serious illness and pregnancy were exclusion criteria.

The patients were formally informed that:

- They should be free of opioid and other drug intake 24 hours before the start of treatment.
- The use of benzodiazepines and large amounts of alcohol would increase the risk of respiratory depression.
- They should not feel intoxication or abstinence, but normality during the buprenorphine treatment.
- In the case of intake of any opioid, buprenorphine would partially or totally obstruct its effect.
- Intoxicated patients would be denied that day's dosage.
- Patients would be excluded from the programme if they acted in a threatening manner, were violent or if they tampered with the tablets.

In the presence of their social worker, patients signed a statement that indicated that all criteria were fulfilled and the roles were accepted. Medical examinations and pregnancy tests were not offered routinely.

Demographic and baseline characteristics of the 106 patients assigned to placebo (n = 51) or buprenorphine (n = 55) treatment are shown in Table 1. The gender distribution was 70 males and 36 females. The mean age was 38 years with an average history of heroin use of 20 years. All patients met DSM-IV criteria (APA 1994) for opioid dependence and they had injected heroin for more than 10 years. Moreover, all of the patients in our study also had a polysubstance dependence, most commonly with benzodiazepines and/or cannabis.

Table 1 Demographic and baseline characteristics of 106 patients assigned to placebo (n = 51) or buprenorphine (n = 55) treatment. No significant differences between the groups in any of the variables.

Characteristics	*Placebo*		*Buprenorphine*	
Sex %				
Male	67		65.5	
Female	33		34.5	
Age, years				
Total				
Mean	38		38	
Range	29–53		26–49	
Males				
Mean	40		38	
Range	31–53		28–49	
Females				
Mean	35		37	
Range	29–44		26–46	
Family situation %				
Single	59		51	
Married/live together	16		11	
Partner, but do not live together	12		16	
Divorced	14		16	
Widowed	0.0		6	
Partner also addicted %	12		17	
Education %				
Primary school not finished	6		2	
Primary school	52		54	
High school	30		23	
Vocational training	8		14	
College/university	2		6	
Income %				
Employed	2		0	
Pension	35		36	
Social welfare	63		64	
Accommodation %				
Homeless/shelter	26		16	
Institution	13		20	
With relatives	18		23	
Permanent resident	44		41	
Previous maintenance treatment %	12		15	
Drug history	Mean	SD	Mean	SD
Age starting i.v. use (years old)	18	4.0	18	5.1
Age starting heroin (years old)	18	4.6	18	4.1
Years of heroin addiction	20	5.6	20	5.6

Treatment procedure

Patients were assigned randomly to buprenorphine (group A) or a placebo (group B). The randomization code was kept in the pharmacy and was available only to the pharmacy staff. Buprenorphine was administered as Subutex® sublingual tablets of 2 mg and 8 mg. Both Subutex® and the placebo were produced by the Subutex® manufacturer (Reckitt and Colman Products Ltd,

Dansom Lane, Hull, UK). Every week (Monday–Saturday) patients were given the tablets sublingually by a nurse/counsellor in groups of 10. They had to come at the appointed time. Two staff members observed the patients until the tablets were absorbed, approximately 10 minutes. On Saturday the patients received a double dose. No take-home doses were allowed. On the first day both groups A and B received 4 mg Subutex. During the course of the first 8 days the dose for group A was increased to 16 mg/day. At the 12th week of the period the dosage was scaled down to 4 mg/day. This was necessary because both groups would have the opportunity to continue with buprenorphine after the study period and at that time we did not know to which group the patients had been assigned. Group B's dosage was decreased to 0 mg in 9 days, and thereafter replaced by the placebo. Thus all patients had to start with the same dose, 4 mg after the placebo-controlled period. The randomization code was revealed when all patients had finished the 12-week period.

Intake of Subutex was consecutively registered. If a patient came to the appointment time obviously intoxicated, the medication for the corresponding day was withdrawn. For patients who missed 4 consecutive days of dosing, further medication was withdrawn and they were considered non-completers. We considered it too risky to give a patient 16 mg buprenorphine if he or she had been without medication for more than 4 days.

Seven non-completers (two males and five females) were not available for the follow-up evaluation, four in the buprenorphine group and three in the placebo group. All of them dropped out during the first week due to missing 4 consecutive days of medication.

Measures

Primary outcome variables were retention (is the patient still in the project?) and compliance (how many of the total number of doses had been taken?). Reasons for not completing the project time were recorded. A visual analogue scale (VAS) from 0 to 10 was used for self-reported drug use. 'Daily heavy drug abuse' was recorded as 10 and 'drug free' was recorded as 0. Abuse of opioids was calculated separately and other drugs, benzodiazepines and alcohol were registered collectively. Subjective well-being was measured with a VAS (10 = very bad, 0 = very well) and with the temporal satisfaction with life scale (TSLS) (Pavot *et al.* 1998). Mental health (i.e. anxiety and depression) was measured with the symptom checklist (SCL-5) (Tambs & Moum 1993). Patients were questioned about potential adverse effects (i.e. sweating, oedema, nausea and exanthema). Additional symptoms were also recorded.

Statistical methods

Survival analysis was applied to study participation and attrition of patients. The effect of the intervention upon the other outcome variables was analysed by comparing change in the placebo group with the buprenorphine group. Differential scores were calculated for all participants; that is, changes from initial scores (last week before start of treatment) to scores obtained at the 12-week mark for the entire period; *t*-tests were used to compare the differential scores of the two groups. In addition, *t*-tests were used to compare the side-effects in the groups.

Approval

The study was approved by the Norwegian Medicines Control Authority (SLK NR 99–5497) and the Regional Ethics Committee for Medical Research (249/99–99107). Informed consent forms were signed by all participants.

RESULTS

Study design

The estimate of which treatment was given to the 78 patients who fulfilled ≥ 10 days is reported in Table 2. As can be shown, 80% of the patients and 71% of the staff gave a correct answer. The majority of the patients giving a wrong answer (92%) had been given buprenorphine. The staff answered incorrectly more often about the patients who had been given placebo.

Retention and compliance

The proportion of patients still in treatment by number of days in the 12 week-period is shown in Fig. 1. The mean number of days of participation was 14 (median: 11) for the placebo group and 42 (median: 29) for the buprenorphine group ($p < 0.001$). When considering only the patients who remained in the study after the first 9 days, the mean number of days of participation was 20 (median: 14) for the placebo group and 52 (median: 56) for the buprenorphine group ($p < 0.001$). Log-rank tests of equality of survival distributions also showed that the two groups were significantly different, both when including the total groups ($p < 0.001$) and when including only patients who remained in the study after nine days ($p < 0.001$).

Looking at the retention of patients after 12 weeks, 16 patients in the Subutex group completed the programme and one patient in the placebo group. Ninety-nine of the

Table 2 The estimate of which treatment was given in the 78 patients who fulfilled 10 days of treatment.

	Patients' estimate			*Staff estimate*		
Medication	*Answer correct*	*Answer wrong*	*Don't know*	*Answer correct*	*Answer wrong*	*Don't know*
Subutex (n = 44)	30 (69%)	12 (27%)	2 (5%)	38 (86%)	4 (9%)	2 (5%)
Placebo (n = 34)	32 (94%)	1 (3%)	1 (3%)	17 (50%)	16 (47%)	1 (3%)
Total (n = 78)	62 (80%)	13 (16%)	3 (4%)	55 (71%)	20 (26%)	3 (4%)
	χ^2: 35.86; df = 2; $p < 0.001$			χ^2: 16.33; df = 2; $p < 0.001$		

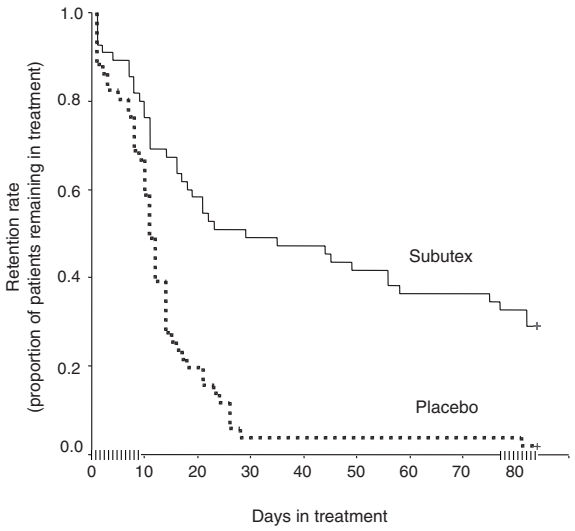

Figure 1 Proportion of 106 patients assigned to placebo (n = 51) or buprenorphine (n = 55) remaining in treatment as a function of time. Kaplan–Meyer plot. Log-rank tests of equality of survival distributions showed that the two groups were significantly different, both when including the total groups and when including only patients who remained in the study after nine days ($p < 0.001$). Shaded area on the x-axis indicates the initial period of 9 days when both groups received buprenorphine (the dosis was increased from 4 mg to 16 mg in the buprenorphine group and decreased from 4 mg to 0 mg in the placebo group), and the final week during which the daily dose of the buprenorphine group was scaled down from 16 mg to 4 mg

106 patients who were included came back for follow-up and buprenorphine treatment after 12 weeks. The most common reason for dropping out before 12 weeks was missing 4 consecutive days, 44/50 (88%) in the placebo group and 33/39 (85%) in the buprenorphine group. The others discontinued for other reasons, five (10%) in the placebo group and four (10%) in the buprenorphine group. Six did not finish because they thought they were taking the placebo (one did not), three dropped out because they wanted to continue drug abuse for one more period (all in the Subutex group) and one patient in the placebo group discontinued treatment because of hospitalization for a collum femoris fracture.

With regard to the seven patients who dropped out during the initial phase and who did not return for evaluation after 12 weeks, there were no significant differences between this group and the remaining participants (n = 99) for any of the psychological variables, or for heroin use according to the initial score. However, there was an initial difference ($p < 0.01$) in use of 'other drug', with the dropouts reporting a higher level of drug use, thus indicating a potential contributing factor in their attrition.

Compliance (percentage of doses taken per day of participation) was equal in the two groups for the period the participants remained in the study: 85% in the placebo group and 83% in the buprenorphine group.

Adverse events

None of the patients who had taken part in the study died during 2000 and no serious side effects were observed. The side effects that patients were asked about during the 12-week treatment period were reported as follows: (a) sweating, 15 in the placebo group and 13 in the buprenorphine group; (b) oedema, two in the placebo group and three in the buprenorphine-group; (c) nausea, nine in the placebo group and nine in the buprenorphine group; (d) exanthema, six in the placebo group and one in the buprenorphine group. The two groups were statistically similar, with one exception. There was a significantly greater number of subjects with exanthema in the placebo group ($p < 0.05$). Additional self-reported physical symptoms included: decreased appetite, joint pain, dizziness, headache, feeling cold or hot, pain, general abstinence feeling, leg cramps and gastrointestinal disturbances. Additional psychological symptoms were: anxiety, depression, tiredness, less energy, bad memory and sleeplessness. There was no statistically significant difference between the two groups.

Table 3 Change from initial scores to scores after the 12 weeks' intervention period, for subjective wellbeing, mental health and drug use. Comparison between control group (n = 48) and intervention group (n = 51).

	Placebo		*Buprenorphine*		
	Mean	*CI*	*Mean*	*CI*	*Diff.*
Wellbeing (VAS)	–0.43	(–1.32, 0.45)	–2.00	(–2.95, –1.04)	***
Life satisfaction (TSLS)	–0.24	(–0.57, 0.09)	–0.65	(–1.00, –0.31)	*
Anxiety and depression (SCL-5)	–0.17	(–0.40, 0.07)	–0.30	(–0.52, –0.08)	NS
Heroin use	0.52	(–0.64, 1.68)	–3.21	(–4.29, –2.13)	***
Other drug use	1.11	(0.18, 2.05)	–0.66	(–1.77, 0.44)	**

The rightmost columns indicate p-level for difference between the placebo group and the buprenophine group with regard to change scores. One-tailed t-tests are used. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, NS = not significant.

Drug use

The efficacy results are shown in Table 3. The self-reported use of heroin or other drugs (Fig. 2a) was decreased significantly in the buprenorphine group compared to the placebo group ($p < 0.001$). The16 patients in the buprenorphine group who remained in the study throughout the 12 weeks (completers) were also compared with the 39 patients who did not complete in the buprenorphine group. The completers had a stronger decrease in reported heroin use ($p < 0.01$) and use of other drugs ($p < 0.05$).

Global ratings

Efficacy results based on the patients' reported sense of wellbeing and mental health using a VAS and temporal satisfaction with life scale (TSLS) and symptom checklist (SCL-5) are shown in Fig. 2b,c,d. The statistics are based on mean changes from initial scores to scores after 12 weeks (Table 3). The buprenorphine group showed a stronger increase in wellbeing (VAS $p < 0.001$ and TSLS $p < 0.05$). Regarding anxiety and depression (SCL-5) the change was not significantly different in the two groups.

Furthermore, when comparing the 16 subjects in the buprenorphine group who remained in the study throughout the 12 weeks with the patients who did not complete in the buprenorphine group, further differences were found. The completers had a more favourable change with regard to wellbeing and to life satisfaction (VAS, $p < 0.001$ and TSLS $p < 0.01$). They also showed a stronger decrease in anxiety and depression (SCL-5, $p < 0.05$).

It should be noted that neither for the drug use variables nor for SCL/TSLS were there initial group differences; that is, their initial scores were equal. However, the buprenorphine group scored lower ($p < 0.5$) than the placebo group on well being (VAS). Thus, in order to confirm the above findings of group differences in change-scores, an additional analysis was conducted by means of ANOVA, in which the effect of group (buprenorphine versus placebo) on final wellbeing was tested when controlling for initial wellbeing as a cofactor. Again, significant results emerged for the group variable: $F = 4.4$, df = 1, $p < 0.05$.

Some self-reported positive effects of the treatment were reported significantly more often in the buprenorphine group: 'less craving' (six in the placebo group and 19 in the buprenorphine group, $p < 0.001$), 'a more normal life' (two in the placebo group and 10 in the buprenorphine group, $p = 0.01$) and 'more content to live' (none in the placebo group and four in the buprenorphine group, $p = 0.03$). Other comments were 'better finances' (none in the placebo group and three in the buprenorphine group, $p = 0.05$), 'feels more stable/safe' (three in the placebo group and four in the buprenorphine group, $p = 0.39$), 'no criminal activities' (none in the placebo group and two in the buprenorphine group, $p = 0.09$), 'tries to use less drugs' (two in the placebo group and one in the buprenorphine group, $p = 0.26$) and 'more contact with the children' (one in the placebo group and one in the buprenorphine group). The patients also reported that the first week felt good and that the detoxification was good (10 in the placebo group and six in the buprenorphine group, $p = 0.11$). The staff also received spontaneous comments from the patients in the placebo group, who said that this detoxification was their best ever.

DISCUSSION

The project presented here studied the efficacy of buprenorphine in alleviating problems and suffering encountered by addicts waiting for comprehensive methadone maintenance in a placebo controlled design. The use of a placebo in serious illnesses, when effective drugs are available, might obviously be criticized even

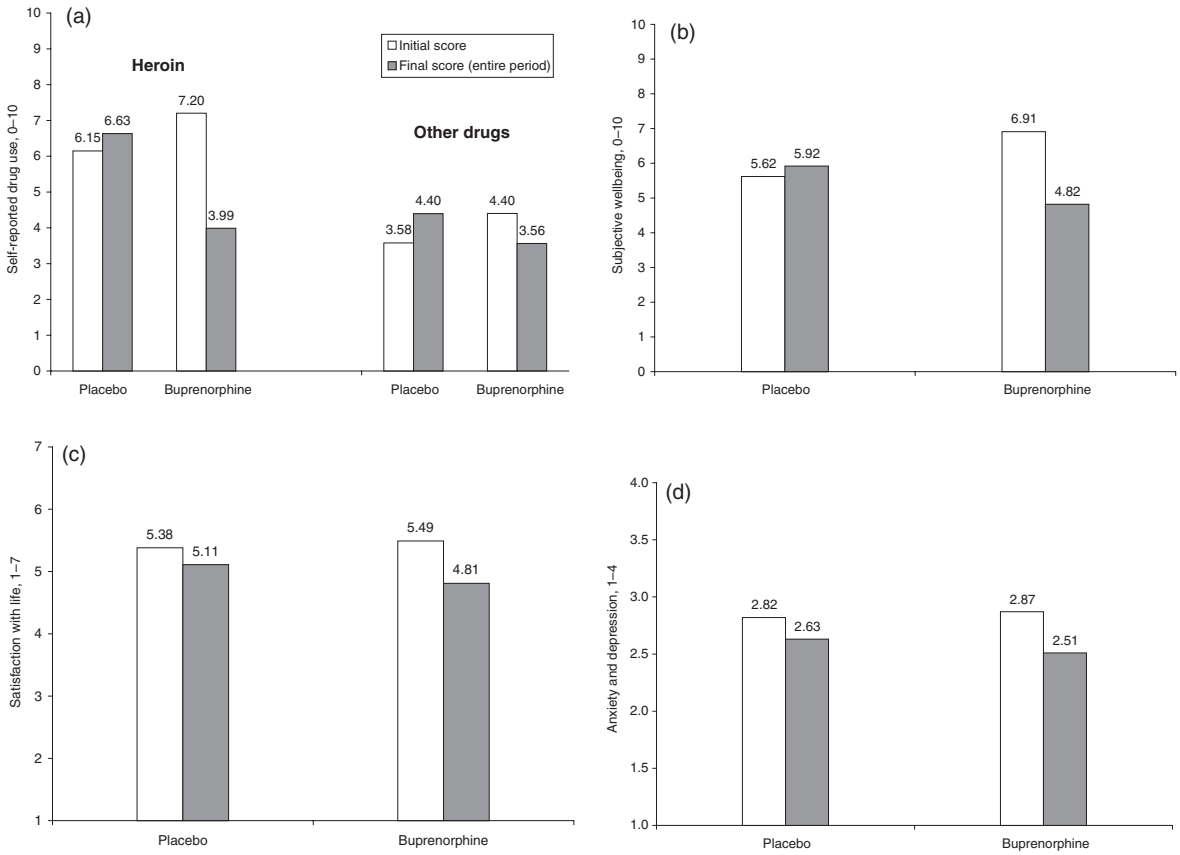

Figure 2 Efficacy results for 99 patients assigned to placebo (n = 48) or buprenorphine treatment (n = 51). Bars represent initial scores and final scores referring to the entire 12 weeks' intervention period. The scales were as follows: (a) VAS on self-reported drug use from 10 = daily heavy drug abuse to zero = drug-free; (b) VAS on subjective wellbeing from 10 = very bad to 0 = very well; (c) temporal satisfaction with life scale (TSLS) from 7 = very bad to 0 = very well; (d) symptom checklist (SCL-5) on anxiety and depression from 4 = very bad to zero = very well. The buprenorphine group had a more favourable change in: (a) heroin use ($p < 0.001$) and use of other drugs ($p < 0.01$); (b) wellbeing (VAS) ($p < 0.001$); (c) satisfaction with life (TSLS) ($p < 0.05$). For anxiety and depression (SCL5) there was no difference

though the study was approved by the appropriate ethical committee. Basically our position was that the project enabled us to alleviate problems for addicts already on a waiting list. More than 400 patients were waiting for MAR, and these patients suffered and some died before they had the opportunity to start treatment. The possibility to offer interim treatment with buprenorphine without psychosocial intervention was a lesser evil. This is an approach that is poorly studied and it was deemed important to apply proper scientific methodology to evaluate the effects. Moreover, the scarcity of solid scientific studies on opioid maintenance has contributed to limited support for this type of programme by Norwegian physicians. Hence it was thought that a methodologically sound project was important for overcoming such resistance. The patients were fully informed that half would have placebo treatment during the first 3 months.

The choice and design clearly increases the significance of the project, as controlled studies of maintenance treatment in opioid dependants are uncommon. A thorough Norwegian review (Hermstad *et al.* 1998) concluded that only two studies met strict scientific criteria (Strain *et al.* 1993; Newman & Whitehill 1979). With regard to buprenorphine, we have found only one study evaluating buprenorphine with patients initially randomized to the placebo condition (Johnson *et al.* 1995). This study spanned only a 14-day study period. The drug was administrated sublingually in a solution and not as tablets, which is currently the standard form for administration. Several studies have focused on comparisons with methadone (Strain *et al.* 1996;Barnett *et al.* 2001), on dosing (Johnson *et al.* 1995) or on doses (Ling *et al.* 1998). These conclude that the effects are comparable when dose-effective dosages are used. One important difference is that methadone gives a higher retention rate (Strain *et al.* 1996; Eder *et al.* 1998; Uehlinger *et al.* 1998; Barnett *et al.* 2001; Petitjean *et al.* 2001). The effect of both methadone and buprenorphine is influenced by

the presence of an adequate psychosocial treatment programme (Ball & Ross 1991; Arndt *et al*. 1997). Programmes that are not accompanied by such treatment have reduced rehabilitation effects and show higher levels of abuse irrespective of the drug used. We conclude that our study contributes to a field with few basic studies of these issues.

Our results demonstrate a marked and significant effect of buprenorphine, as the median number of days of participation was more than twice that of the placebo group ($p < 0.001$). By the end of the first month of the study, only two patients on placebo and roughly half of those on active medication remained in the programme. The level of psychosocial intervention was identical in the two groups, as was the level of patient compliance, as measured by percentage of doses taken. Consequently the results demonstrate beyond any doubt the independent effect of buprenorphine on retention.

In spite of attrition, the study shows that buprenorphine does have a significant effect on self-reported drug use as we found a differential development between the groups also from the intention-to-treat perspective. Those in the placebo group increased their use of drugs while those on active medication reduced their use of heroin as well as of other drugs. These results cannot be explained as a result of selection effects. The positive effects outweigh eventual negative effects among dropouts. The result is valid for the whole group on the average. Further, the results demonstrate the importance of keeping addicts in treatment, as the completers clearly had a more positive status upon evaluation. The dosage level chosen, two tablets of 8 mg/day (16 mg/day), is relatively high. Buprenorphine being a partial μ-receptor agonist has a ceiling effect that is judged to be at 16-mg solution (Walsh *et al*. 1994). It is therefore possible that one would be able to increase effects by increasing dosage. However, the manufacturer did not recommend this.

We also found that buprenorphine has an impact upon alleviating subjective suffering. The life quality factors measured by the VAS scale and TSLS demonstrate two important aspects. The first is the strikingly low level of satisfaction found among all patients in the study, both compared with typical findings for the normal population and findings from samples of patients suffering from illness and disabilities (Pavot & Diener 1993; Diener *et al*. 1999). These findings are not caused solely by abstinence reactions; even these were measured initially upon first encounter. Rather, we find that the low level of satisfaction continued over time, and it might be suggested that addicts are a group characterized by human suffering. The results demonstrate further that use of buprenorphine clearly and significantly increases wellbeing for heroin-dependent addicts. Life is judged to be better, even if it is not regarded as good.

The findings derived from the SCL-5 point to high levels of anxiety and depression. The score for the intervention group decreased, while it did not for the control group. However, signs of stress remained at a high level in both groups. Over a relatively short period of time, such as the 3 months here, buprenorphine alone cannot reduce the worries connected to real perceived life difficulties nor anxiety and depression from other sources. This is concordant with findings from a large Norwegian study. Lauritzen *et al*. (1997) found that 57% of 2359 addicts in abstinence-orientated treatment were troubled by anxiety and 56% with depression.

The feasibility of the programme is acceptable. Sunday dispensing is both costly and troublesome; therefore, the schedule was 6 days a week with a double dosage on Saturday. Judged by satisfaction level among addicts, most would accept programmes with this schedule. Half preferred double doses on Saturdays and the other half did not. It is also noteworthy that the programme met with no serious incidences. One potential fear was that the placebo approach could lead to overdoses or other difficulties; however, none of this occurred among the 106 participants. Among the addicts on the waiting list who did not partake in the project, there were 12 deaths by overdose (3.8%). It is somewhat difficult to judge this difference, as the overdose number is roughly the same as the expected yearly average for those on the list. The self-selected experiment group might be a population less at risk. What can be said, therefore, is that the experience of being within a project such as this, in and of itself, seems to be protective. This suggestion might reduce objections to the study. Some have felt that the use of placebo in this type of research might be unethical. However, the evidence shows that those partaking in the project have benefited in relation to those remaining on the waiting list, whether they were in the placebo or intervention groups.

The study does, however, demonstrate some limitations in buprenorphine efficacy. The attrition rate was initially relatively high also in the intervention group. The 8-day induction approach may have been too lengthy and caused a high level of dropouts in the first week. After 3 months, the completers in the intervention group were approximately one-third. These results are hard to compare with other studies, as we have found none directly comparable. Johnson *et al*. (1995) found 20% and 27% dropout after 14 days in the two intervention groups in their placebo-controlled study. Here intervention involved buprenorphine, 2 mg and 8 mg, respectively, and allowing patients to request a dose change on day 6 to day 13. The new dose was then chosen randomly from the two to which they had not been originally assigned (0 mg, 2 mg or 8 mg). In a study comparing buprenorphine 10 mg with methadone

60 mg in a double-blind study Petitjean *et al.* (2001) found 56% retention at 1 month. Both these studies combined medication with control and psychosocial interventions, but neither with comprehensive problem-solving. There are differences in dose and design, but it is nevertheless reassuring that the results are on comparable levels. Even at high dosages the effect of buprenorphine is obviously not sufficient to keep the majority of seriously dependent heroin addicts in treatment if one does not attend to psychological and social problems. The finding of a two-thirds dropout rate at 3 months is higher than one would expect in high-dose methadone maintenance (Newman & Whitehill 1979; Wenger & Rosenbaum 1994).

This finding indicates that the value of buprenorphine in a setting without control and proper psychosocial support is limited. Based on French experiences it is likely that office-based prescription represents limited risks with regard to overdoses. However, the likelihood of diversion and of use in injections seem to be high, and the benefits are not obvious. Our findings indicate further that without control and psychosocial intervention, the improvements achieved are modest and the attrition rate is relatively high.

Summing up, this study demonstrates that dispensing buprenorphine without psychosocial interventions beyond daily meetings to receive dosages is feasible and useful for reducing drug use and alleviating suffering. It is feasible to offer this treatment to hard core addicts on a waiting list for a limited time period, as well as possibly to structure programmes that are acceptable to both staff and addicts. The efficiency is limited by a clinically significant attrition rate. The time period in this study is 3 months, a relatively long time period for a placebo-controlled study. However, this makes it possible to demonstrate a gradual decline in retention. Consequently, the finding is that use of buprenorphine without additional control and psychosocial and medical programmes has obvious limitations. A promising approach would be to use the beneficial effects of buprenorphine shown in this study, to reduce abuse of illicit drugs during the waiting period for a treatment programme. The addicts thus have the opportunity to use this period to work out realistic plans for their rehabilitation process in a more comprehensive medication-assisted rehabilitation programme. A probable benefit would be more motivated patients with a greater possibility to succeed in treatment.

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