1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial

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Summary

Background The partial opiate-receptor agonist buprenorphine has been suggested for treatment of heroin dependence, but there are few long-term and placebo-controlled studies of its effectiveness. We aimed to assess the 1-year efficacy of buprenorphine in combination with intensive psychosocial therapy for treatment of heroin dependence.

Methods 40 individuals aged older than 20 years, who met DSM-IV criteria for opiate dependence for at least 1 year, but did not fulfil Swedish legal criteria for methadone maintenance treatment were randomly allocated either to daily buprenorphine (fixed dose 16 mg sublingually for 12 months; supervised daily administration for a least 6 months, possible take-home doses thereafter) or a tapered 6 day regimen of buprenorphine, thereafter followed by placebo. All patients participated in cognitive-behavioural group therapy to prevent relapse, received weekly individual counselling sessions, and submitted thrice weekly supervised urine samples for analysis to detect illicit drug use. Our primary endpoint was 1-year retention in treatment and analysis was by intention to treat.

Findings 1-year retention in treatment was 75% and 0% in the buprenorphine and placebo groups, respectively (p=0·0001; risk ratio 58·7 [95% CI 7·4–467·4]). Urine screens were about 75% negative for illicit opiates, central stimulants, cannabinoids, and benzodiazepines in the patients remaining in treatment.

Interpretation The combination of buprenorphine and intensive psychosocial treatment is safe and highly efficacious, and should be added to the treatment options available for individuals who are dependent on heroin.

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Introduction

Heroin dependence is a major cause of morbidity and mortality.[1] In the absence of effective treatment, Swedish heroin addicts have a mortality rate 20-fold to 50-fold higher than their sex and age matched peers who are not dependent on heroin.[2] Abstinence-oriented treatment continues to be the most commonly offered treatment option in Scandinavia and many other parts of the world; however, this approach is not supported by evidence. Beneficial effects of psychosocial support and psychological treatment for heroin dependence have been reported,[3,4] but their efficacy has always been tested in individuals who are in methadone-maintenance programmes. Without parallel agonist treatment, psychosocial interventions have consistently failed to show effectiveness, mainly because of low retention in treatment programmes despite long detoxification periods and intensive psychosocial interventions.[5]

By contrast, a large amount of published work shows that maintenance treatment with methadone, a long acting full opiate receptor agonist, can greatly increase adherence to treatment, lessen illicit drug use, and reduce mortality.[2,6,7] On the basis of this evidence, guidelines implying that methadone maintenance treatment should be expanded have been published.[1] Nevertheless, many restrictions remain on the use of methadone in Scandinavia, because of unsubstantiated fears of primary methadone addiction and leakage from treatment programmes to uncontrolled street use. However, although the proportion of patients receiving methadone should increase in accordance with published guidelines, a specific threshold for inclusion does seem to be medically warranted.

Buprenorphine might, therefore, be a useful complementary or alternative option to methadone. The partial opiate-receptor agonist profile of this compound is, in theory, attractive, and this drug could be used to suppress heroin craving and, antagonise heroin effects, while having a limited potential for dose escalation and, toxicity. Individual comparative studies of buprenorphine in heroin dependence[8–13] and meta-analyses of these[14,15] show that this compound is efficacious in comparison with other available options, and observational data from France lend support to the notion of reduced toxicity.[16] Because it is a partial agonist, buprenorphine could be especially useful for patients who need only a limited degree of agonist action.

Interpretation of results of published studies of the effectiveness of buprenorphine has long been limited by features of trial design. For example, there are only a few placebo-controlled studies that assess the efficacy of buprenorphine (a 14-day[17] and a 12-week trial,[18]) and with the exception of one study in which the outcome of buprenorphine treatment was clearly inferior to 80 mg methadone maintenance,[10] follow-up has been limited to 3–6 months. Furthermore, few attempts have been made

to benefit from the increased retention in buprenorphine programmes to deliver concurrent evidence based, behaviour-oriented, psychosocial treatment. Although improved retention in treatment and reduced illicit drug use have been associated with buprenorphine, there has been little structured assesment of the effects of this treatment on other difficulties of heroin addiction. From a practical point of view, several studies have used an alcohol solution of buprenorphine, whereas the marketed product is a sublingual tablet.

We aimed to assess the efficacy of a highly structured, integrated treatment package that consisted of buprenorphine in a daily sublingual dose of 16 mg, relapse-prevention group therapy,[19,20] weekly counselling sessions, and thrice weekly urine screens.

Methods
Pilot phase
In the pilot phase in September, 1999, we recruited five individuals who were moderately heroin dependent (ie, had a mean addiction severity index [ASI] composite score of 2·5 [SD 1·76, range 1·9–3·8]) to an open-label pilot trial. The 4 men and 1 woman were aged between 27–34 years at the onset of treatment, had fullfilled DSM-IV criteria for heroin dependence for at least 1 year, and had had repeated admissions to a chemical-dependence unit in central Stockholm. Procedures during the first 6 months were the same as those described for the main trial, but after this time, treatment for patients in the pilot study was individualised.

All five patients remained in treatment for at least 3 years, although three of the five chose to increase their dose from 16 mg buprenorphine to 24 mg after the first 6 months in the trial. No serious adverse events were recorded. During the first year, we noted a significant reduction in ASI category severity ratings and composite score (mean composite scores at baseline, 2·5 [SD 1·76]; 3 months, 1·5 [1·0]; 6 months, 1·4 [2·26]; 9 months, 1·2 [1·52]; 12 months, 1·2 [0·96]; repeated measures ANOVA for time effect; p=0·0004). On the basis of results from this pilot study, the Swedish medical products agency and Stockholm-south human subjects ethics committtee gave approval for the placebo-controlled randomised trial.

Patients
In the randomised controlled phase, done between May, 2000, and April, 2001, we screened newly admitted inpatients in the chemical-dependence unit of Maria Clinic, Addiction Centre South for trial eligibility. We included individuals with an opiate dependence who were seeking admission for medically-assisted heroin withdrawal, had a history of heroin dependence (as defined by DSM-IV criteria), for at least 1 year, and were aged 20 years or older. We excluded individuals who fulfilled eligibility criteria for methadone maintenance treatment in Sweden (ie, at least 4 years of multiple daily heroin use that had been objectively documented in hospital records, and three or more unsuccessful treatment attempts in abstinence-oriented treatment programmes), and those with a codependence on alcohol, amphetamines, cannabinoids, or benzodiazepines. Sporadic use or abuse of these substances was not a reason for exclusion. Other exclusion criteria were: any neurological disorder; dementia; cognitive impairment; psychosis; any state which compromised a patient's ability to comprehend, consent to, or follow the study protocol; any other psychiatric or somatic disorder, unless the patient was stable and without treatment that is contra-

indicated with buprenorphine. We gave eligible patients written as well as oral information, and obtained their written informed consent before inclusion, as stipulated by the permit from the Stockholm-south human subjects ethics committee.

Procedures
Participants were randomly assigned to either the treatment group or to placebo by the clinical trials unit of the Hospital Pharmacy, Huddinge University Hospital, with use of a random number table from a standard textbook. Randomisation was in blocks of eight participants, with all blocks consisting of four placebo and four buprenorphine patients, because patients started relapse-prevention therapy in groups of eight.

At inclusion, patients were assigned a consecutive number between one and 40, and then given medication from individual patient packs that had been preassembled by the trials unit of the pharmacy, and labelled with the corresponding patient number. Packs contained active or control medication regimens (table 1) as predetermined by the randomisation procedure, but were of identical appearance, as were placebo and buprenorphine tablets. The preparation of the patient packs was done in isolation from any personnel working in the study or with patients. The code-translation table was retained in a safe at the trials unit, to which only the pharmacists who participated in the randomisation procedure had access. In the case of a medical emergency, the medical trial leader (MH) could have had access to the codes through the pharmacist on duty, but we did not encounter any serious adverse events that necessitated the code being broken. A signed copy of the code translation table was delivered to the trial leader after the last patient had completed the predetermined 365 day treatment period. The original version is kept on file at the hospital pharmacy.

Medication was given sublingually on appearance of withdrawal symptoms, but at least 8 h after the last reported heroin intake, in accordance with the regimens shown in table 1.

To provide adequate treatment for opiate withdrawal symptoms, patients allocated to placebo were allowed buprenorphine for the first 6 days of the trial, in accordance with the clinic's standard treatment for heroin withdrawal. Patients were discharged after 1 week in hospital, but were also asked to return to the treatment unit daily for supervised administration of medication for at least 6 months. After this time, the frequency of visits was agreed with individual patients, but the daily medication dose was kept constant throughout the study.

Within 4 weeks of inclusion, patients started sessions every week of therapy in accordance with Marlatt's relapse prevention manual, modified for Project Match,[22] and adapted for group treatment of heroin-dependent participants. Treatment was started in groups of eight people, and was given for ten sessions, followed by two booster sessions. The groups were led by two nurse-practitioners who were trained in this method, and who

	Controls (mg)	Maintenance group (mg)
Day 1	8 + 0	8 + 0
2	8 + 0	8 + 8
3	2 + 2	8 + 8
4	2 + 2	8 + 8
5	2 + 0	8 + 8
6	2 + 0	8 + 8
7+	0 + 0	8 + 8

0=placebo tablets identical to active medication.

Table 1: **Buprenorphine dose regimens for control and treatment groups**

had no knowledge of which drug a patient had been assigned. Relapse prevention focused on identification of craving triggers, and development of novel cognitive and behavioural strategies to cope with craving.[19] An example of this approach is identification of situations and emotional states that produce craving and that are associated with high risk of relapse; behavioural analysis of the relapse process; and role play to develop skills to avoid situations that might trigger relapse; or, if these situations are encountered, to use alternative behaviours that do not lead to relapse.

Furthermore, individual treatment plans were developed in collaboration with social services departments to address issues of housing and occupation (ie, employment, studies, or occupational therapy). Throughout the study period, patients had 45 min individual counselling sessions every week in the treatment unit. We took supervised urine samples thrice weekly under conditions that prevented manipulation of samples. The SWEDAC (Swedish Board for Accreditation and Conformity Assessment) accredited laboratory of clinical pharmacology at Huddinge University Hospital used an Emit kit (Beckman Coulter, Bromma, Sweden) to screen the samples. The cutoff concentrations to define a positive sample were 300 mg/L for opiates (ie, all compounds detected by the Emit Kit, and dextropropoxyphene), 300 mg/L for central stimulants, 300 mg/L for cannabinoids, and 100 mg/L for benzodiazepines. All positive samples were validated and quantified with SWEDAC-accredited liquid chromatography-mass spectrometry (LC-MS).

A contingency management plan was part of the treatment plan, and was thoroughly communicated to the patient during the induction week. If a patient completed a continuous 6-months drug-free (for all drug categories) verified by urine analyses, take-home doses were allowed

so that frequency of visits could be reduced to thrice weekly. If relapse occurred—ie, illicit drug intake was reported, or indicated by urine samples positive for drugs, then daily supervised administration was resumed. If a patient did show signs of relapse (such as a positive urine sample, non-attendance at appointments, or both) we offered additional support, including intensified counselling, and ultimately, admission if needed. More than two positive urine samples within 3-months (for any banned substance) would lead to discharge from the study unless the patient agreed to and complied with intensified support efforts as described previously. Other predetermined criteria for involuntary discharge from treatment were failure to attend for more than 7 days, violent behaviour, or dealing in drugs. Discharged patients were all referred to standard clinical treatment at a different site.

On entry to the study, and after each completed 3-month period, patients remaining in treatment did addiction severity index (ASI) interviews, a validated and widely adopted instrument in many countries to assess patient problem severity in seven dimensions: somatic morbidity, work, alcohol use, illegal drug use, crime, family situation, and psychiatric morbidity. Composite scores were used in addition to severity scores because they are derived from objective data, and have a higher reported degree of psychometric stability than severity scores.[21]

Statistical analysis

The predetermined outcome measures were retention in treatment (primary measure) and reduction in problem severity assessed by the ASI (secondary measure). The a priori determined total number of participants to be included was 40. We chose this sample size of 40 patients, on the basis of available clinical resources, and results of a power calculation (nQuery Advisor Software, Los Angeles, CA), showing that with this sample size the probability of detection of a clinically relevant treatment effect of improvement in 1-year retention from about 20–70% would be 95·7% at two-tailed $\alpha=0·05$.

We analysed data using Statistica version 6.0 for Windows. Retention in treatment and actual survival (ie, number of days staying in treatment, and number of days staying alive, respectively) were analysed with Cox's proportional hazard regression analysis with treatment status as the predictor variable. In both cases, patients who completed 365 days of treatment were regarded as censored observations. ASI severity and composite scores fulfilled criteria of homogeneous variances, and were analysed with repeated measures ANOVA, treating dropouts as missing values. Comparisons between individual timepoints were done with Tukey's honestly significant difference (HSD) test for unequal samples.

Role of the funding source

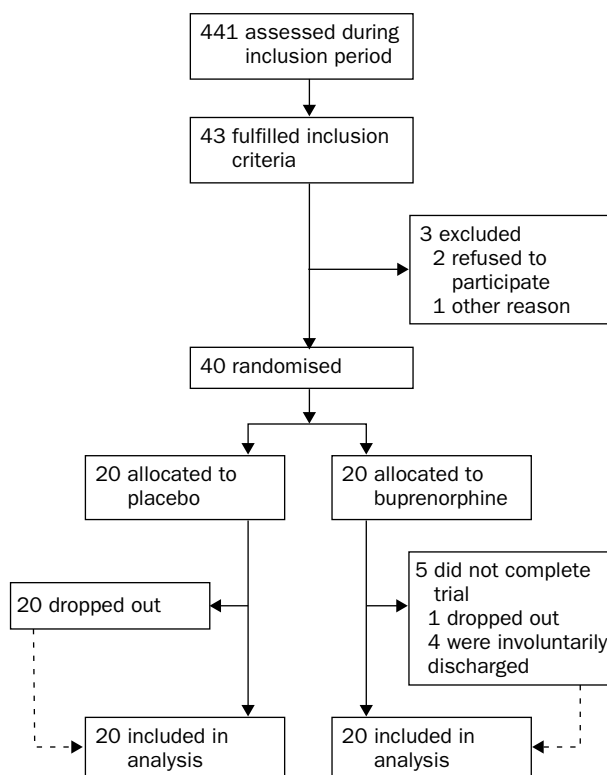The sponsors had no role in study design, data collection, data analysis, or writing of the report.

Figure 1: **Trial profile**

	Placebo (n=20)	Buprenorphine (n=20)
Men	14 (70%)	15 (75%)
Age (years)	31·5 (8·2)	29·2 (12·2)
ASI composite score	1·84 (1·1)	2·11 (0·46)
Years of heroin use	4·8 (3·4)	5·8 (3·6)
Hepatitis B infection	7 (35%)	7 (35%)
Hepatitis C infection	16 (80%)	14 (60%)
HIV-1 infection	0	1 (5%)

Data are number (%) or mean (SD).
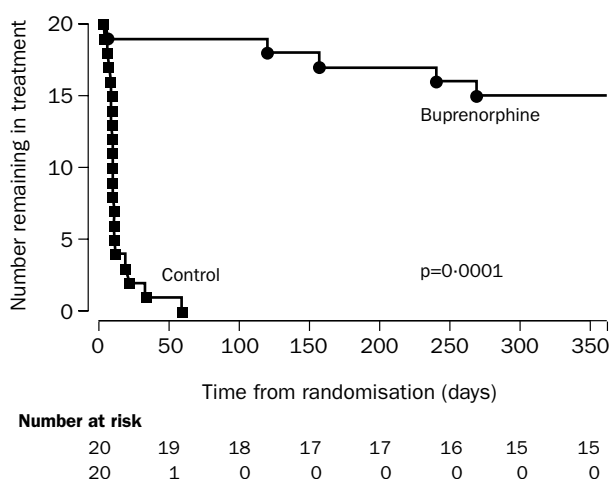
Table 2: **Patients' baseline characteristics**

Figure 2: **Kaplan-Meier curve of cumulative retention in treatment**

Figure 3: **Addiction severity index ratings and composite scores for patients in buprenorphine group**
Data are mean (SD).

Results

Of 441 patients admitted between May 1, 2000, and April 1, 2001, 43 were eligible for the study (figure 1). The most common reasons for ineligibility were that patients qualified, or might have qualified, for methadone treatment and were offered referral to the Stockholm methadone programme, or they had codependence on other substances. Two eligible patients declined to participate, and one decided to attempt abstinence-oriented treatment. The remaining 40 participants were all randomly allocated to a treatment group and began receiving study medication.

Table 2 shows patients' baseline characteristics, which did not differ greatly with respect to sex composition, age, duration of heroin use, or problem severity as assessed by composite scores of the ASI or any of its subscales (data not shown for the subscales). No formal criterion of intravenous use was stipulated; however, all but one patient (a heavy smoker of heroin, randomised into active treatment) injected the drug.

The primary outcome retention in treatment was significantly better in the buprenorphine group than placebo (Cox's proportional hazard regression p=0·0001; risk ratio 58·7 [95% CI 7·4–467·4]; figure 2). All 20 patients who discontinued treatment in the placebo group dropped out of treatment, in all cases after urine analysis showed drug use. In the buprenorphine group, one patient dropped out of treatment, and four were involuntarily discharged, again because of positive urine toxicology tests. Thus, both voluntary and involuntary discontinuation of treatment was closely related to relapse.

Data for the secondary outcome ASI problem severity ratings and composite scores could only be obtained while patients stayed in treatment. Because all controls had dropped out before the first assessment at 3 months, the only ass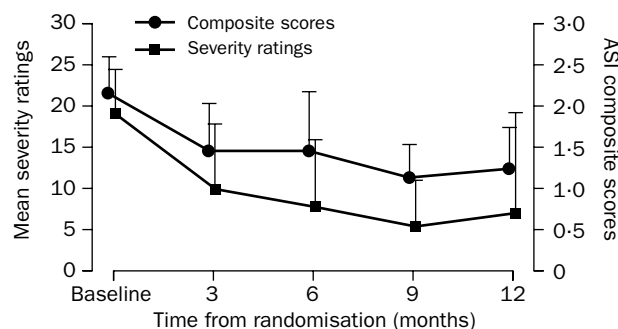essment of the secondary outcome variable was whether baseline problem severity had fallen during treatment with buprenorphine in comparison with baseline untreated scores (table 3). To make this comparison, we did an intention-to-treat analysis, with data from patients who had dropped out as missing values. Results from a repeated measures ANOVA showed a highly significant reduction in ASI scores over time in the buprenorphine group (severity ratings, p<0·0001; composite scores, p<0·0001; figure 3). For both variables, Tukeys HSD test for unequal samples yielded significant reduction versus the baseline value at each time point (p<0·01).

Use of illicit drugs in the buprenorphine group was rare; results from thrice-weekly supervised urine analyses showed that a mean of 74·8% (SD 59·6%) of samples obtained were negative for the substances analysed. We noted a significantly impaired survival in the controls, in which four people died during the treatment period, versus none in the buprenorphine group (Cox's regression, p=0·015).

Discussion

We have shown that the combination of buprenorphine and intensive psychosocial treatment is safe and highly effective in the treatment of heroin addiction.

Although previous studies have indicated a potentially useful efficacy of buprenorphine for heroin dependence,[8–15,23] the placebo-controlled design of our trial provides information not otherwise available. The use of a placebo group in the study was ethically complicated in view of known morbidity and mortality associated with heroin dependence, and the documented efficacy of methadone in people with such addiction.[2] However, the Swedish criteria for admission into the methadone maintenance programme exclude about 90% of heroin addicts from this treatment. Furthermore, although buprenorphine became formally approved for prescription in heroin dependence in Sweden in October 1999, a regulatory gridlock has meant that this treatment is not yet available to patients.

	Baseline	3 months	6 months	9 months	12 months
Somatic morbidity	0·31 (0·66)	0·14 (0·62)	0·22 (0·66)	0·16 (0·60)	0·22 (0·70)
Occupation*	0·94 (0·34)	0·80 (0·20)	0·80 (0·46)	0·73 (0·56)	0·64 (0·50)
Alcohol use	0·06 (0·44)	0·02 (0·16)	0·01 (0·02)	0·01 (0·02)	0·09 (0·50)
Drug use†	0·29 (0·22)	0·09 (0·18)	0·05 (0·16)	0·06 (0·16)	0·03 (0·12)
Criminality‡	0·19 (0·44)	0·07 (0·30)	0·08 (0·36)	0·01 (0·02)	0·02 (0·18)
Family situation	0·20 (0·40)	0·20 (0·46)	0·17 (0·50)	0·11 (0·26)	0·14 (0·38)
Psychiatric morbidity	0·13 (0·42)	0·12 (0·30)	0·12 (0·34)	0·07 (0·18)	0·06 (0·22)

*p=0·0006 for effect over time. †p<0·0001 for effect over time. ‡p=0·02 for effect over time. Data are mean (SD).

Table 3: **Composite scores in the seven subscales of the ASI for patients given buprenorphine**

Against this background, we focused on patients who were not eligible for methadone programmes, and provided all patients in the study with a psychosocial treatment package that extended far beyond that which is normally available. In this manner, we ensured that patients could only benefit from participation in the study, relative to options that would have otherwise been available to them. Despite the intensive psychosocial support offered, and initiation of additional support on relapse, retention was very poor in the controls; no patient in this group remained in treatment beyond 2 months. This outcome accords with results from a Norwegian trial that had placebo controls.[18] The high attrition rate in controls in both these studies is partly as a result of the a priori criterion that participants who continued to use illicit drugs would be involuntarily discharged from treatment. This criterion is similar to clinically available agonist assisted treatment programmes in Scandinavia, and therefore was a realistic design feature to assess clinical efficacy. An important additional consideration is whether withdrawal symptoms in controls contributed to dropout from the study. However, this explanation is unlikely because the initial dose regimen in our control group was identical to that used throughout Sweden for treatment of heroin withdrawal, and seems to be satisfactory in those settings. For example, when comparing a series of patients detoxified with this regimen with a matched series of patients treated with the previously recommended drug, clonidine, a significantly higher proportion of buprenorphine patients successfully complete detoxification and go on to have follow-up treatment. Subjective patient satisfaction data, regularly obtained as a part of the clinic's quality assurance procedures, is also high (unpublished data). However, even if the controls did not have withdrawal discomfort, their high expectations for pharmacological maintenance treatment, followed by a perceived absence of effect with respect to suppression of craving, could lead to disappointment and thus contribute to dropout.

Overall, the dismal outcome for our controls reiterates the grave nature of heroin dependence, and shows the considerable health and social difficulties faced by our patients. Nevertheless, our recruits did not fulfil Swedish criteria for admission to methadone maintenance programmes. However, their exclusion is not surprising; Swedish criteria require objective documentation, such as hospital records, of 4 years of multiple daily heroin use, which actually implies a longer period of heroin dependence because hospital visits rarely begin at the same time as heroin dependence. Accordingly, although we did not include patients who were likely to be eligible for methadone treatment, self-reported duration of heroin use in placebo and active treatment groups was in fact 4·8 (SD 3·4) and 5·8 years (3·6), respectively. Furthermore, the severity of problems in our patient sample is tragically emphasised by the 20% mortality in the controls over the course of a 1-year study. Although our sample size and follow-up were not planned to allow analysis of this variable, this rate is much the same as that reported previously in Sweden,[2,24] and therefore likely to point towards an important clinical reality.

By contrast, despite the strict criteria for involuntary discharge, there was an unexpectedly high 1-year retention in treatment in patients receiving the same psychosocial package but who were also given a daily dose of 16 mg buprenorphine. In addition to high retention, results of structured multidimensional assessment showed that problem severity was greatly reduced in the treatment group. A detailed analysis of the ASI subscales in patients who completed treatment revealed robust, significant improvements in the areas of drug use, crime, and occupation. Notably, there was very little change in somatic morbidity, indicating the chronic nature of health problems in this patient group. Psychiatric morbidity only began to fall during the second half year, which lends support to our clinical experience of substance-related psychiatric symptoms being very slow to improve in heroin dependents. Overall, however, treatment outcome for the buprenorphine group was unexpectedly good. The fall in severity of problems, as assessed by the ASI, translates into clinically and practically important improvement for patients. Reductions in drug use and crime, accompanied by improvements in occupation indicate that patients taking buprenorphine not only stayed in treatment and complied with medication, but also embarked on a course to a much altered lifestyle and reintegration into society.

We were careful to adhere to the randomisation protocol correctly, and thus in our opinion, the striking improvements in the active treatment group are unlikely to be a result of any internal bias. However, the relevance of blinding in our study can be questioned. A drawback of blinding in trials of opioid agonists arises through the powerful stimulus for drug discrimination provided by these compounds, especially in patients with much experience of illicit drugs, such as those in our study.[25,26] Therefore, some investigators have used only open-label randomisation, such as active treatment versus waiting-list control.[24] Irrespective of the degree to which blinding was successful in our study, we regarded the use of placebo as important, especially because this design meant that all patients were ensured equal amounts of attention, because the daily supervised administration of medication made up a considerable amount of time spent by the patients in contact with staff. It can be claimed that the treatment effect was, in part, caused by the perception of an opiate-like discriminative stimulus in the buprenorphine group, and an absence thereof in the placebo group. Although this effect would suggest an unsuccessful blinding, it is as a result of intentional pharmacodynamic properties of buprenorphine, and does not, in our opinion, invalidate the finding of clinical efficacy of this compound.

The external validity, or generalisability of our findings might be limited by possible differences in patients' characteristics and other local factors. For example, a high prevalence of concomitant cocaine use or dependence seems common in American populations of heroin dependents, but this pattern of codependence is almost non-existent in Sweden. However, on the basis of ASI scores and mortality in the control group, the overall severity of morbity in our patient sample does not seem to be lower than that reported in American studies.[14,15] Furthermore, although a significant beneficial effect of buprenorphine has been reported in a Norwegian placebo-controlled trial,[18] in which cocaine codependence was not present, it is noteworthy that the retention in treatment after 1 year in our study surpasses that reported over shorter time periods in other trials.[14,15] The improvement in social function also indicates that stable behavioural changes might have arisen as a result of the integrated treatment used in our project. Thus, with the exception of major differences between countries in drug codependence patterns, we are not aware of factors that could greatly affect the generalisability of our findings for other clinical heroin-dependent populations.

The fixed 16 mg dose chosen in our study was intended to take advantage of buprenorphine's partial agonist properties. On the basis of a report that suggested 12·5 mg as the modal dose for clinical effect,[27] we postulated that a somewhat higher dose might add to the efficacy of treatment in case patients sampled illegal opiates, but would not produce undesirable additional agonist action and toxicity. After this protocol was initiated, Nath and colleagues[28] reported that bioavailability of marketed sublingual tablet in the single dose is about 50% of the alcohol solution used in most previous studies. However, relative bioavailability of these preparations could be closer when given over an extended period. Whether higher doses could further improve the efficacy of the drug is not yet clear, but this idea is lent support by results from our pilot group that show that most patients will choose a 24 mg daily dose.

Two other factors might have contributed to the promising outcome in the buprenorphine-assisted group. Our treatment package was designed to take advantage of the expected increase in retention produced by agonist medication to deliver psychosocial support that aims to produce cognitive and behavioural change.[19,20] Surprisingly few other data are available to address whether such a strategy might augment the long-term efficacy of buprenorphine, but our results suggest that it might, and point to development of combined treatments as a promising area for research.

An indication of the mechanisms in buprenorphine assistance might be suggested by one of our clinical observations. Patients who received placebo generally reported a massive heroin craving that was triggered during sessions of relapse-prevention, when trigger stimuli were discussed. This effect might have contributed to the decision to discontinue treatment. By contrast, patients receiving active treatment did not report excessive craving, and found the relapse-prevention sessions useful for development of coping skills.

The second factor that might have contributed to the positive outcome was the intensive and highly structured treatment model, combined with non-confrontational and empathetic staff. That high programme structure leads to low retention rates has been suggested on theoretical grounds,[29] but availabe data do not support this notion. In fact, very high and stable retention rates, as well as striking improvements in social function, have been reported from a non-confrontational, two-phase programme, that had an initially high degree of structure, which was then flexibly relaxed as the patient became stable.[30] We also used this approach. A combination of defined criteria for involuntary discharge, combined with a willingness to mainly initiate support efforts on signs of destabilisation, could have been especially effective in our setting, where the treatment team had access to an inpatient unit which patients could contact at any time to receive support, and where rapid admission could be offered if needed. Ultimately, over the 1-year treatment, this availability resulted in an average consumption of 9·6 inpatient days (SD 31·2) in the actively treated group, but the option of admission provided confidence to patients and treatment staff. However, even this intensive treatment structure was not sufficient to keep unmedicated patients in treatment.

Thus, we believe that our strategy of a highly planned delivery of buprenorphine in combination with structured (ie, manual based) cognitive behavioural treatment, seems to offer a useful complement to methadone maintenance treatment, and should be added to treatment options for heroin dependent individuals.

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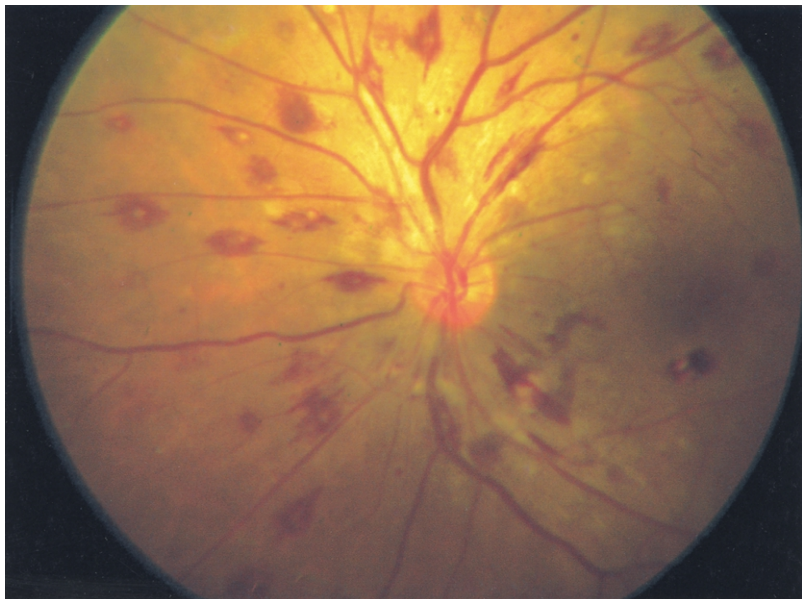
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Clinical picture

Roth spots in diabetes mellitus

Peter Tong, Risa Ozaki

A 45-year-old Chinese woman was admitted to hospital with intermittent blurring of vision, fever, and malaise for 6 weeks. She had a 12-year history of Type 2 diabetes mellitus with good recent glycaemic control (HbA$_{1c}$ 7·4%). Eye examination done 3 months earlier had shown no signs of diabetic retinopathy. On fundoscopy, we found bilateral multiple haemorrhages with white centres (figure). Serial blood cultures did not grow any pathogens. We excluded sub-acute bacterial endocarditis by a transoesophageal echocardiogram. A full blood count showed haemoglobin 4·6 g/dL, platelets 111×10^9/L, WBC 4·4×10^9/L, and reticulocytes 2%. Concentrations of haptoglobin, B12, folate, iron, complement, and immune markers were all normal. Bone marrow aspirate and trephine biopsy showed dysplastic red-cell precursors consistent with myelodysplastic syndrome. The patient was treated with supportive blood transfusions. She developed a fatal intracranial haemorrhage secondary to thrombocytopenia 6 months later. The presence of Roth spots does not necessarily imply sub-acute bacterial endocarditis, and alternative diagnoses should be considered.

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