

Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial

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Summary

Background Expansion of access to effective treatments for heroin dependence is a worldwide health priority that will also reduce HIV transmission. We compared the efficacy of naltrexone, buprenorphine, and no additional treatment, in patients receiving detoxification and subsequent drug counselling, for maintenance of heroin abstinence, prevention of relapse, and reduction of HIV risk behaviours.

Methods 126 detoxified heroin-dependent patients, from an outpatient research clinic and detoxification programme in Malaysia, were randomly assigned by a computer-generated randomisation sequence to 24 weeks of manual-guided drug counselling and maintenance with naltrexone (n=43), buprenorphine (n=44), or placebo (n=39). Medications were administered on a double-blind and double-dummy basis. Primary outcomes, assessed by urine testing three times per week, were days to first heroin use, days to heroin relapse (three consecutive opioid-positive urine tests), maximum consecutive days of heroin abstinence, and reductions in HIV risk behaviours over 6 months. The study was terminated after 22 months of enrolment because buprenorphine was shown to have greater efficacy in an interim safety analysis. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00383045.

Findings We observed consistent, linear contrasts in days to first heroin use ($p=0.0009$), days to heroin relapse ($p=0.009$), and maximum consecutive days abstinent ($p=0.0007$), with all results best for buprenorphine and worst for placebo. Buprenorphine was associated with greater time to first heroin use than were naltrexone (hazard ratio 1.87 [95% CI 1.21–2.88]) or placebo (2.02 [1.29–3.16]). With buprenorphine, we also recorded significantly greater time to heroin relapse (2.17 [1.38–3.42]), and maximum consecutive days abstinent than with placebo (mean days 59 [95% CI 43–76] vs 24 [13–35]; $p=0.003$); however, for these outcomes, differences between buprenorphine and naltrexone were not significant. Differences between naltrexone and placebo were not significant for any outcomes. HIV risk behaviours were significantly reduced from baseline across all three treatments ($p=0.003$), but the reductions did not differ significantly between the three groups.

Interpretation Our findings lend support to the widespread dissemination of maintenance treatment with buprenorphine as an effective public-health approach to reduce problems associated with heroin dependence.

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Introduction

Heroin and injection drug use are worldwide problems that substantially increase HIV transmission in Malaysia, many other developing and transitional countries (including China, India, Indonesia, Iran, Pakistan, and Russia), and in high-income countries (USA, England, Europe, and Australia).^{1–7} Until recently, Malaysia, along with many other developing countries, implemented a largely punitive approach to drug problems, relying on imprisonment or long-term detention in so-called rehabilitation programmes and prohibiting medical treatments for heroin dependence.^{3,7} In Malaysia, the failure of this approach to stem drug problems and HIV transmission led to the introduction in 1996 of some medical treatments, which were limited to medically-supervised detoxification, drug counselling, and maintenance treatment with the opioid antagonist naltrexone.⁷

Malaysia continued to prohibit maintenance treatment with opioid agonists, however, until the start of this study, which introduced maintenance treatment with buprenorphine and led to the subsequent approval of maintenance treatment with methadone. Concerns about the potential abuse liability of methadone, misconceptions about the therapeutic mechanisms of maintenance treatment with opioid agonists (some believe that it simply substitutes one addiction for another), and poor understanding of its effectiveness contributed to prohibition of this treatment approach. Notably, maintenance treatment with an opioid agonist remains prohibited in some countries, including Russia,^{3,8} and is provided only to an estimated 240 000 of 800 000 or more heroin addicts in the USA.⁹ Dissemination of medical treatments will partly depend on assessment of the comparative efficacy of the different treatments.

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Heroin detoxification followed by drug counselling or referral to self-help groups is a common treatment approach in the USA, Malaysia, and elsewhere, despite little strong empirical evidence to lend support to this approach.¹⁰ Naltrexone, a fairly long-acting (24–72 h after oral administration) opioid antagonist, was approved by the US Food and Drug Administration for the treatment of opioid dependence in 1984, on the basis of its safety and pharmacological efficacy at blocking effects of opioids, and it was introduced in Malaysia in 1996. Several meta-analyses and reviews concluded, however, that placebo-controlled studies have provided insufficient evidence to support the efficacy of naltrexone,^{11,12} although two placebo-controlled studies undertaken in St Petersburg, Russia, showed significantly larger retention and reductions in relapse with naltrexone.^{8,13} However, poor treatment retention and difficulties with patient acceptance have restricted its effectiveness in clinical practice.¹¹

Strong and consistent findings from randomised, placebo-controlled clinical trials and observational and quasi-experimental studies indicate the effectiveness of maintenance treatment with a partial opioid agonist, buprenorphine, or a full agonist, methadone, in reduction of illicit opioid use and risk of HIV transmission.^{3,14–16} Studies directly comparing buprenorphine and methadone report comparable or greater efficacy of methadone.^{15,17} Advantages of buprenorphine—including decreased overdose risk, possibly reduced risk of abuse (especially when provided as a tablet containing naloxone), and potential for dosing three times per week^{18,19}—facilitated its introduction in Malaysia at a time when methadone was still prohibited. No studies have directly compared the efficacy of treatment with an opioid agonist (either buprenorphine or methadone) and maintenance treatment with naltrexone. The absence of direct comparisons could contribute to policy makers' assumption that the introduction of maintenance treatment with opioid agonists has no advantages, if maintenance treatment with naltrexone is available. Additionally, not very many placebo-controlled clinical trials of maintenance with either buprenorphine^{18,20–23} or naltrexone^{8,11–13,24} exist.

Consequently, we undertook a double-blind, double-dummy, placebo-controlled randomised clinical trial to compare the efficacy of detoxification followed by drug counselling alone (placebo), or combined with maintenance treatment with naltrexone or buprenorphine, for maintenance of heroin abstinence, prevention of relapse, and reduction of HIV risk behaviours.

Methods

Patients and study setting

Patients met criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM IV)²⁵ for present opiate dependence, and had a urine toxicology test that was positive for opioids. Patients were ineligible if they

were dependent on alcohol, benzodiazepines, or sedatives; had concentrations of liver enzymes (alkaline phosphatase or alanine transaminase) greater than three times the upper limit of normal; were dangerous to themselves or others; were psychotic or had major depression; or had life-threatening medical problems. Enrolment for the study began on July 8, 2003, and ended on May 14, 2005. Patients were recruited from the community and completed a residential detoxification programme before entering an outpatient research clinic in Muar (Malaysia), that was established for the study. During the 22-month enrolment period, 215 patients made at least one contact for initial screening; 18 made only an initial contact; 23 did not complete the assessment; 12 were not eligible because of high liver-enzyme concentrations; 19 completed the assessment but did not enter the detoxification programme; and 17 did not complete detoxification phase. Thus, 126 patients were randomly assigned to the different treatments. We obtained written informed consent from all patients. The study was approved by the Human Investigation Committee, Yale University School of Medicine, and the Malaysian Ministry of Health Human Subjects Review Board.

Procedures

Before randomisation, all patients completed a 14-day detoxification protocol²⁶ in a residential setting, during which they were given sublingual buprenorphine (Reckitt Benckiser Healthcare; Hull, UK) for the first 3 days (8 mg, 4 mg, and 2 mg), and oral naltrexone (Duopharma (M) Sdn Bhd; Bangi, Malaysia) on days 4 (12.5 mg), 5 (25 mg), and 6 (50 mg). Withdrawal symptoms were treated, as needed, with oral clonidine, diazepam, naproxen, and metoclopramide.

On day 14 in the residential detoxification centre, drug counselling started, and patients were randomly assigned to maintenance treatment with placebo, naltrexone, or buprenorphine. A simple, complete randomisation sequence was generated by a computer programme (SPSS version 11), and maintained in the USA (by MCC). 2 days before completion of detoxification, the treatment group assignment for each study participant was disclosed only to the study pharmacist in Malaysia, to allow sufficient time for preparation of double-blind, double-dummy drugs. All other study personnel were blind to treatment assignment throughout the entire study duration.

All patients were given manual-guided individual and group drug counselling every week in the outpatient research clinic. Group therapy, which was led by a psychiatrist with advanced training in addictions (MM), provided education about heroin addiction, HIV/AIDS, and the recovery process. Specific modules included relapse prevention and training in coping skills—between four and six sessions specifically targeted reducing HIV risks associated with injection drug use, sharing of

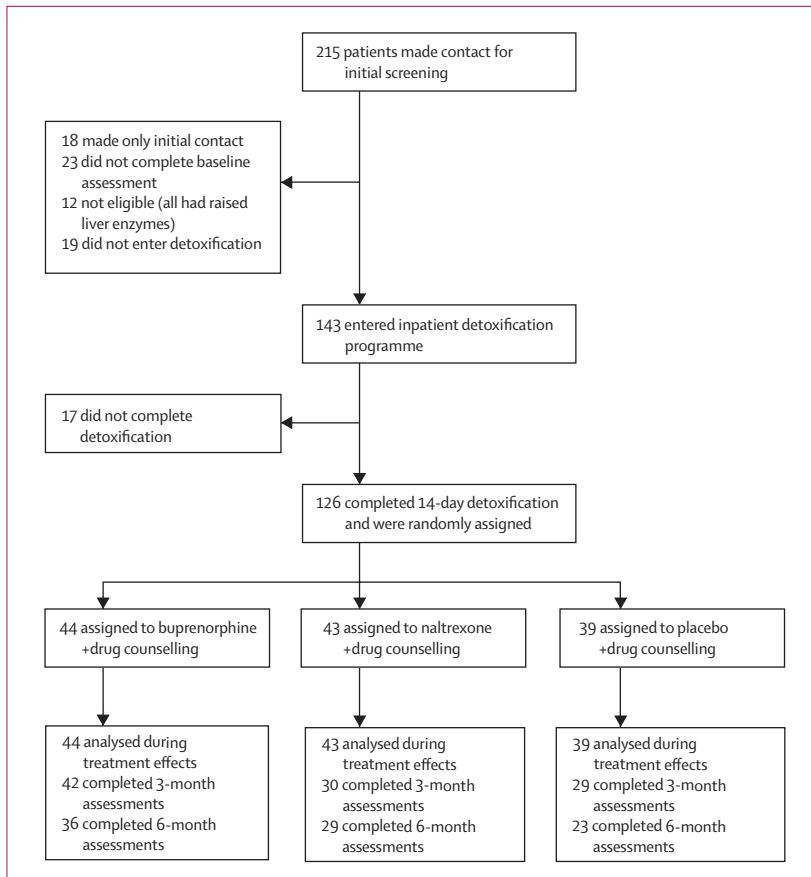


Figure 1: Trial profile

injection equipment, and sexual activity. The treatment manual was adapted for use in Malaysia, and took advantage of the importance of family in Malay and Chinese culture, and the ethos of respect for parents (particularly for one's mother). As part of the recovery process, group therapy discussed the notion of "locked doors"—ie, closing off the heart from recognising the importance of others and accepting advice—and the importance of "turning over" to a higher power (eg, God/Allah for Malay Muslims, or one's family), being humble, and seeing one's parents (especially mother) or children as being more important than the satisfaction of one's own immediate needs or craving.

Training components in communication skills were modified to take into account that being outspoken is considered arrogant in Malaysian culture. Instead, patients were encouraged to cope with disagreement with others by lowering their expectations (recognising that they can only change what is within their power to change—ie, themselves—and that they cannot change someone else). Manual-guided individual drug counselling was provided by nurses, and used a treatment manual that was adapted from an earlier study undertaken in a US primary-care clinic, providing enhanced counselling to patients maintained on

buprenorphine.¹⁹ The nurses had no experience of treating addictions before receiving 4 days of didactic training and then treating, under close supervision, at least three training cases during the pilot phase of the study. Individual counselling sessions lasted about 45 min. These sessions reviewed recent drug use or efforts at abstinence, urine test results, and self-help group attendance; and provided support and advice about prevention of relapse. The nurses attempted to encourage patients who resumed heroin use or relapsed to remain in treatment and curtail heroin use, and to re-engage patients who missed appointments for counselling or medication.

Study medications were prepared by a research pharmacist, who had no direct contact with participants. Buprenorphine mono tablets (containing only buprenorphine) and placebo tablets that appeared identical were provided by the manufacturer. Naltrexone was purchased for the study: tablets were crushed, and the study pharmacist placed naltrexone or placebo inside capsules that appeared identical. All patients ingested oral capsules (containing either naltrexone or placebo) and dissolved sublingual tablets (containing either buprenorphine or placebo), under the direct observation of a study nurse who verified ingestion of the capsule and absorption of the tablet. To mask slight taste differences between active and placebo buprenorphine tablets, participants gargled with a mentholated antiseptic mouthwash before taking the sublingual tablets.

One 8-mg tablet of buprenorphine (or matching placebo) and one 50-mg tablet of naltrexone (or placebo) were given every day during the first week of maintenance. Subsequently, patients received two 8-mg tablets of buprenorphine (or placebo) and two 50-mg tablets of naltrexone (or placebo) every Monday and Wednesday, and three 8-mg tablets of buprenorphine (or placebo) and three 50-mg tablets of naltrexone (or placebo) every Friday. For patients who reported craving or withdrawal symptoms, or had persistent heroin use, the dose of buprenorphine or matching placebo was increased to 24 mg (three 8-mg tablets) on Mondays and Wednesdays and to 36 mg (four 8-mg tablets and two 2-mg tablets) on Fridays. The success of the patient blind was assessed by asking patients at week 12 which medication they thought they were receiving: 30 (94%) of 32 patients receiving buprenorphine, 16 (76%) of 21 patients receiving naltrexone, and four (20%) of 20 patients receiving placebo, correctly identified their medication ($\chi^2=31.8$, $df=2$, $p<0.0001$).

Outcome measures

As specified in advance, the primary outcome measures were assessed for 24 weeks after randomisation, and were: days to first heroin use (first opiate-positive urine test after randomisation); days to heroin relapse (three consecutive opiate-positive urine tests, or an opiate-positive test followed by two consecutive positive or missing tests); the maximum consecutive days of

abstinence from heroin (the longest period of opioid-negative urine tests); and reductions in self-reported HIV risk behaviours. Secondary outcomes were adverse events and treatment retention, which was defined as time to treatment completion or to last clinical contact, to protective transfer for unremitting heroin use (3 consecutive weeks of opioid-positive tests), or to referral to an alternative treatment because of a substantial medical or psychiatric problem, as assessed by the study psychiatrist.

We measured illicit drug use by urine testing three times per week during treatment, with use of a semiquantitative homogenous enzyme immunoassay for opioids (Microgenics Corp, Fremont, CA, USA), with a cut-off set at 300 ng/mL. Trained research assistants, who were not involved in the treatment of patients, administered the AIDS risk inventory²⁷ to assess drug-related and sexual risk behaviours associated with HIV transmission, before patients began detoxification and at 3 months and 6 months after randomisation. Concentrations of liver enzymes were assessed every month in the Hospital Muar Clinical Laboratory. We recorded serious adverse events (ie, admission to hospital or death) at the time of occurrence. Self-reported adverse effects were gathered every week with a structured questionnaire that assessed the severity of 32 symptoms (eg, headache, constipation, drowsiness) on a 4-point scale (none, mild, moderate, or severe).

Statistical analysis

Findings from an unpublished pilot study of naltrexone maintenance in Malaysia showed that 72% of patients were abstinent at 6 months; data from a US study noted that 42% of patients given buprenorphine at doses comparable with those planned for our study, and 12–24% of patients given low doses (to estimate the effects of placebo), achieved sustained abstinence.²⁸ On the basis of these findings, we anticipated a medium effect size difference (equivalent to $h=0.50$) between naltrexone and buprenorphine (favouring naltrexone) in the longest consecutive number of days abstinent, and a larger difference in effect size between drug counselling only (placebo) and either of the two maintenance treatments (favouring the two drugs). We needed a total sample size of 180 to provide a power greater than 0.80, with a two-sided type I error of 0.05, to detect similar or larger differences in effect size, in mean maximum consecutive days of abstinence or the other primary outcome measures, in the three groups.

Statistical analyses were planned in advance, and were by intention to treat. We assessed days to first heroin use, days to heroin relapse, and number of patients remaining in treatment (all truncated at 168 days) with the Life Table method²⁹ and the Wilcoxon test. This approach is similar to the Kaplan-Meier survival analysis and Cox regression procedures, and we recorded the same pattern of results with all three approaches.

	Buprenorphine (n=44)	Naltrexone (n=43)	Placebo (n=39)
Age (years)	36.3 (9.3)	38.2 (9.3)	37.6 (8.2)
Malay ethnic origin	31 (71%)	28 (65%)	27 (69%)
Single	35 (80%)	32 (74%)	23 (59%)
High-school education or above	2 (5%)	3 (7%)	5 (13%)
Unemployed	23 (52%)	14 (33%)	14 (36%)
Lifetime history of incarceration	28 (64%)	30 (70%)	23 (59%)
History of previous drug treatment	21 (48%)	30 (70%)	24 (62%)
Heroin use (years)	14.5 (8.0)	16.4 (9.0)	14.8 (8.0)
Heroin use in past 30 days (days)	27.0 (6.6)	26.0 (8.3)	28.3 (6.2)
Lifetime ATS abuse	26 (59%)	18 (42%)	16 (41%)
Current ATS abuse	20 (46%)	17 (40%)	13 (33%)
Lifetime benzodiazepine abuse	26 (59%)	25 (58%)	26 (67%)
Current benzodiazepine abuse	24 (55%)	21 (48%)	23 (59%)
Lifetime IDU	33 (75%)	36 (84%)	31 (80%)
Current IDU	20 (46%)	16 (37%)	16 (41%)
Lifetime needle sharing	22 (50%)	13 (30%)	22 (56%)
Current needle sharing (past 30 days)	14 (32%)	8 (19%)	12 (31%)
HIV seropositive*	11 (26%)	11 (26%)	5 (13%)
Hepatitis C	39 (89%)	41 (95%)	36 (92%)
Hepatitis B	0	2 (5%)	5 (13%)
Pulmonary tuberculosis	5 (11%)	10 (23%)	6 (15%)
Consistent condom use	3 (7%)	4 (9%)	2 (5%)
Multiple concurrent sex partners (lifetime)	17 (39%)	15 (35%)	9 (23%)

Data are mean (SD) or number (%). ATS=amphetamine-type stimulant. IDU=injection drug use. *Results are based on 43 patients in the buprenorphine group, 42 in the naltrexone group, and 38 in the placebo group.

Table 1: Baseline patient characteristics

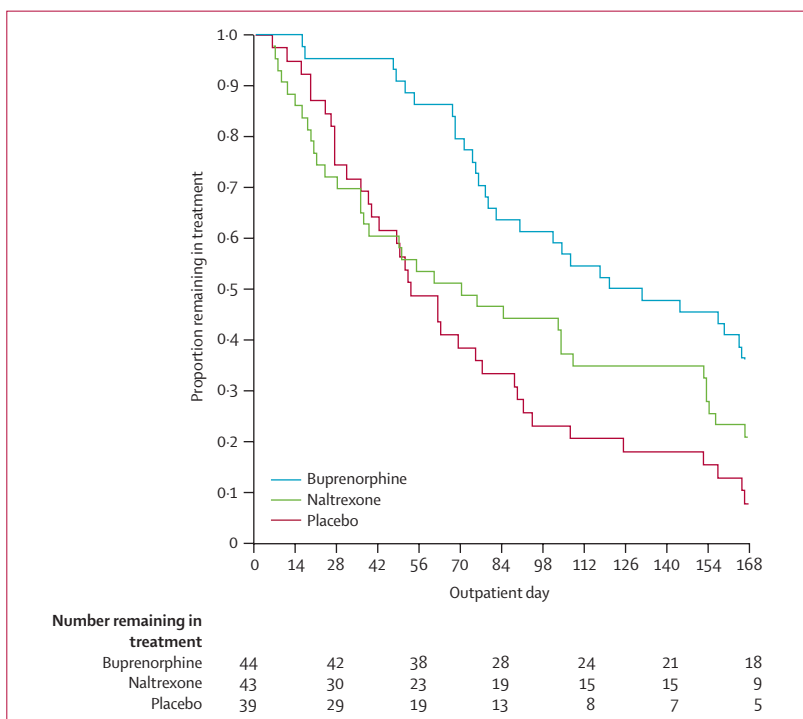


Figure 2: Proportion of patients in each treatment group who remained in treatment on each study day after detoxification

	Buprenorphine (n=44)	Naltrexone (n=43)	Placebo (n=39)	p value			
				Linear contrast	Bup vs placebo	Bup vs ntx	Ntx vs placebo
Days in treatment	117 (102–132)	84 (64–103)	70 (54–87)	0.0002	0.0009	0.022	0.55
Days in treatment without heroin use	51 (33–68)	24 (11–37)	18 (8–28)	0.0013	0.0058	0.028	0.82
Days in treatment without heroin relapse	79 (61–98)	64 (44–84)	39 (25–53)	0.0016	0.007	0.46	0.15
Maximum consecutive days abstinent	59 (43–76)	42 (28–57)	24 (13–35)	0.0007	0.003	0.22	0.21

Data are mean (95% CI). Bup=buprenorphine. Ntx=naltrexone. p values are based on analysis of variance.

Table 2: Effects of treatment-group assignment on outcomes of retention and heroin use

Additionally, Cox regression analysis was used to calculate proportional hazard ratios, with their attendant 95% CIs, for the pair-wise comparisons. We used a factorial analysis of variance (ANOVA) procedure, including assessment of polynomial contrasts and post-hoc Scheffe adjusted pair-wise comparisons, to evaluate differences between treatment groups on the maximum consecutive days of abstinence. The mixed-model procedure was used to assess treatment effects on the total score of the AIDS risk inventory, and on the subscales for drug and sexual risk behaviour.

We assessed differences in the frequency of adverse events across the three treatment groups with omnibus χ^2 tests. To compare our results to those of other studies, differences between treatment groups for the average number of days to first heroin use, days to heroin relapse, and number remaining in treatment (up to a maximum of 168) were evaluated with ANOVA. As planned in advance, and consistent with the association between treatment discontinuation and relapse to use of illicit opioids, we coded missing urine tests as positive. Notably, 72 of the 84 patients who discontinued treatment early for reasons other than medical disorders had a morphine-positive urine test before leaving treatment. The completion rate of scheduled assessments was high: we obtained 87% (4301 of 4936) of the scheduled urine tests during the time patients remained in the study, and 82% (311 of 378) of all scheduled assessments with the AIDS risk inventory.

Findings of an interim safety analysis undertaken in June, 2005—including 103 patients who had completed treatment by the time of the interim analysis—showed greater efficacy of buprenorphine than of placebo or naltrexone, and were presented to the data and safety monitoring board. On the basis of the recommendations of the board, the study was terminated on Aug 3, 2005. Ten patients who had been randomly assigned (four to buprenorphine, five to naltrexone, and one to placebo) were still in the treatment phase when the study was terminated. Data from these ten patients are included in the analyses, consistent with an intention-to-treat analysis. The pattern of results does not change if data from these patients are excluded in the analyses (data not shown). However, inclusion of these patients in the analysis resulted in lower reported study completion, retention,

and time to resumption of heroin use or relapse than would have been reported if these patients were excluded from the analyses, since data for these outcomes were truncated at the time of study termination. All analyses used two-tailed tests of significance and were done with SPSS (version 15.0) or, for the Cox Regression analysis, SAS (version 9.1). To adjust for the interim analysis, p values less than 0.025 were considered significant.

This study is registered with ClinicalTrials.gov, number NCT00383045.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 44 patients were randomly assigned to buprenorphine, 43 to naltrexone, and 39 to placebo. Table 1 shows the patients' demographic and clinical characteristics, which did not differ between the three groups.

We recorded significant overall differences in retention ($p=0.0004$), with retention highest for buprenorphine and lowest for placebo (figure 2). In pairwise comparisons, retention was significantly higher with buprenorphine than with naltrexone (hazard ratio [HR] 1.55 [95% CI 1.01–2.37]) or placebo (2.15 [1.38–3.35]). Retention did not differ significantly between naltrexone and placebo (1.32 [0.85–2.05]). Table 2 shows the mean differences between treatment groups for the outcomes of retention and heroin use.

We recorded significant overall differences between treatment groups for days to first heroin use ($p=0.0009$; figure 3) and days to heroin relapse ($p=0.009$; figure 4), and a significant linear trend for the maximum consecutive days of heroin abstinence ($p=0.0007$; table 2). All results were best for buprenorphine and worst for placebo (figures 3 and 4; table 2). In pairwise comparisons, time to first heroin use was significantly greater for buprenorphine than for naltrexone (HR 1.87 [1.21–2.88]) or placebo (2.02 [1.29–3.16]), and did not differ significantly between naltrexone and placebo (1.04

[0.67–1.61]). The outcome of days to heroin relapse was also greater for buprenorphine than for placebo (2.17 [1.38–3.42]) and naltrexone (1.56 [1.01–2.41]), and did not differ significantly between naltrexone and placebo (1.35 [0.86–2.11]). Post-hoc comparisons showed that patients given buprenorphine had longer maximum consecutive days of opiate abstinence than did those given placebo (mean days 59 [95% CI 43–76] vs 24 [13–35]; $p=0.003$); however, the differences between buprenorphine and naltrexone (42 [28–57]; $p=0.22$) and between naltrexone and placebo ($p=0.21$) were not significant.

We noted significant reductions from baseline to the 3-month and 6-month assessments for the overall summary measure of the AIDS risk inventory ($p=0.003$) and the drug-risk subscale ($p<0.0001$), but not for the sex-risk subscale ($p=0.14$) (table 3). We did not record significant differences in reductions associated with different treatment groups for the summary scale ($p=0.14$), the drug-risk subscale ($p=0.14$), or the sex-risk subscale ($p=0.14$) (table 3). Review of subscale scores and individual items on the AIDS risk inventory suggested that the overall reductions were driven primarily by reductions in the recency and frequency of injection drug use; the proportion of patients reporting past month injection drug use in all groups decreased substantially from baseline (table 3).

We recorded no deaths; two patients were admitted to hospital during the detoxification phase (one for oversedation and one for pulmonary infection, both of which occurred before randomisation); and 12 patients were admitted during treatment (eight patients in the naltrexone group, three in the buprenorphine group, and one in the placebo group [$p=0.035$]). Three of the patients given naltrexone were admitted to hospital for disorders considered possibly related to the study drug (severe insomnia and craving during the first week after randomisation, which was consistent with protracted withdrawal symptoms; attempted suicide;³⁰ and psychosis);³¹ all other admissions were for disorders considered unrelated to the study drugs (eg, accidental injury, infections unrelated to injection or respiratory depression, asthma, and chest pain).

Three patients were withdrawn from the study for medical reasons (one given placebo and one given naltrexone with psychosis; one given buprenorphine was withdrawn from the study in advance of surgery for hernia repair). The number of patients who had any rise in liver-enzyme concentrations (13 [30%] in the buprenorphine group, ten [23%] in the naltrexone group, and 11 [28%] in the placebo group; $p=0.79$) or concentrations greater than three times the upper limit of normal (four [9%], three [7%], and five [13%], respectively; $p=0.66$) did not differ significantly between treatment groups. During the course of treatment, we obtained at least one assessment every week of adverse effects on 43 patients given buprenorphine, 35 given naltrexone, and 36 given placebo. More patients given

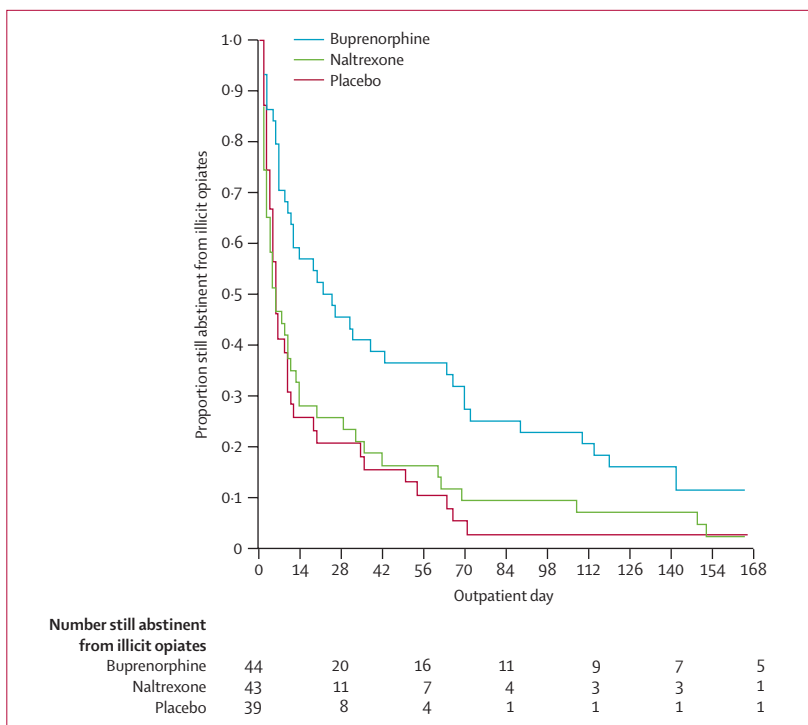


Figure 3: Proportion of patients in each treatment group who remained in treatment and had not resumed illicit opiate use on each study day after detoxification

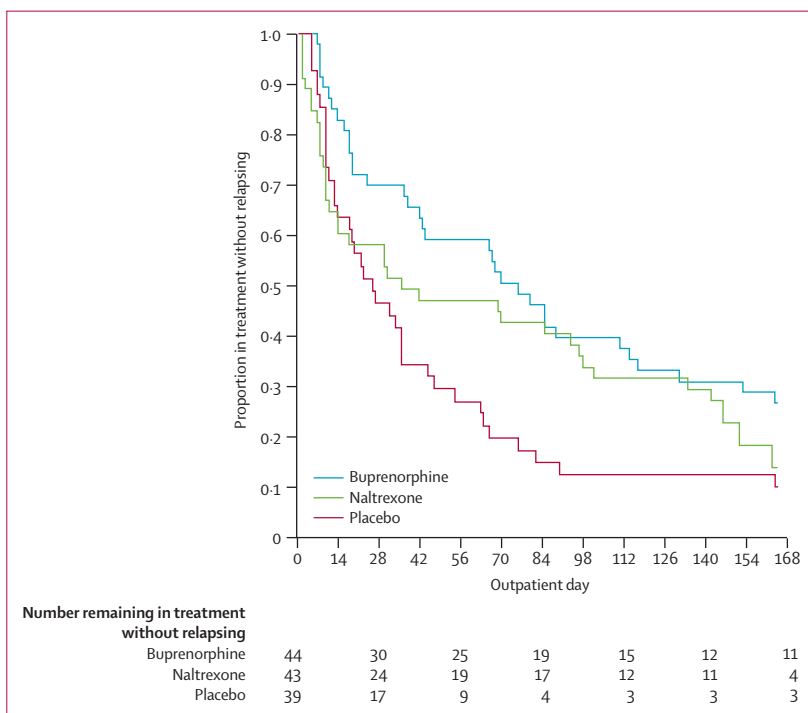


Figure 4: Proportion of patients in each treatment group who remained in treatment and had not relapsed on each study day after detoxification

buprenorphine than naltrexone or placebo made at least one report of severe constipation (22 [51%], eight [23%], eight [22%]; $p=0.007$), drowsiness (20 [47%], six [17%],

	Buprenorphine			Naltrexone			Placebo			p value		
	Baseline (n=41)	3 months (n=42)	6 months (n=36)	Baseline (n=42)	3 months (n=30)	6 months (n=29)	Baseline (n=39)	3 months (n=29)	6 months (n=23)	Time effect	Medication effect	Interaction
ARI total score	56.5 (48.0–64.9)	47.3 (41.7–53.0)	53.7 (44.1–63.4)	46.4 (37.9–54.0)	43.7 (36.7–50.6)	43.1 (33.5–52.7)	57.0 (46.7–67.1)	47.4 (39.5–55.3)	43.6 (34.9–52.4)	0.003	0.14	0.32
ARI drug risks subscore	38.9 (32.7–45.1)	23.1 (19.3–26.8)	25.0 (20.2–29.8)	30.4 (24.0–36.8)	22.5 (18.3–26.8)	21.8 (16.5–27.1)	41.3 (34.2–48.3)	26.4 (22.0–30.8)	25.8 (20.0–31.7)	<0.0001	0.14	0.24
ARI sex risks subscore	15.4 (11.7–19.0)	15.0 (11.7–18.3)	19.1 (15.7–22.6)	11.7 (8.1–15.4)	11.5 (7.9–15.2)	14.4 (10.6–18.2)	13.4 (9.4–17.3)	12.0 (8.0–16.0)	14.2 (9.8–18.6)	0.14	0.14	0.91
IDU past 30 days	20/41 (49%)	1/42 (2%)	5/36 (14%)	16/42 (38%)	2/30 (7%)	2/29 (7%)	16/39 (41%)	2/29 (7%)	2/23 (9%)

Data are mean (95% CI) or n/N (%). ARI=AIDS risk inventory. IDU=injection drug use. The baseline AIDS risk inventory was missing for four participants.

Table 3: Effects of treatment-group assignment on AIDS risk behaviours

ten [28%]; $p=0.0018$), urinary hesitancy (23 [54%], three [9%], eight [22%]; $p<0.0001$), or sweating (14 [33%], four [11%], five [14%]; $p=0.036$). These symptoms were usually transient and were reported in only 1–2.5% of the total number of assessments collected ($n=1460$), and no patient discontinued treatment as a result of these symptoms.

Discussion

The results of this study lend strong support to the efficacy of maintenance treatment with buprenorphine in sustaining abstinence, delaying time to resumption of heroin use and time to relapse, and retaining patients in treatment. HIV risk behaviours decreased significantly from baseline for all three groups, primarily driven by substantial reductions in injection drug use, but did not differ significantly between treatments. Although complete abstinence, elimination of HIV risk behaviours, and recovery of psychosocial functioning would be ideal outcomes, increasing the amount of time abstinent (ie, number of consecutive days abstinent) and delaying the time to resumption of heroin use or relapse—positive outcomes that we noted with buprenorphine maintenance in this study—are important treatment goals. By these measures, maintenance treatment with buprenorphine is significantly more effective than placebo, and significantly more effective on some measures than naltrexone. Since patients generally continue to improve the longer they remain in maintenance treatment with an opioid agonist,³² our finding of significantly greater retention in patients receiving buprenorphine also supports the effectiveness of this medication.

The findings of this study, that buprenorphine is better than placebo for all of our primary outcome measures of drug use and retention, are consistent with the results of other placebo-controlled studies of buprenorphine in the USA,^{18,20,23} Norway,²² and Sweden.²¹ However, the findings of significant superiority of buprenorphine to naltrexone for retention and time to resuming heroin use have not been previously reported. The results for patients given buprenorphine in this study, regarding retention and maximum duration of opioid abstinence, are similar to

those of previous studies of buprenorphine,¹⁹ and results for patients given naltrexone were similar to those from many studies,^{24,33,34} increasing the likelihood that our findings are applicable to other populations and settings.

Outcomes for drug use and retention for patients given naltrexone were consistently better than were those for patients given placebo, although results did not differ significantly. The failure to detect significant differences is consistent with several other placebo-controlled studies of naltrexone and meta-analyses,^{11,12} but contrast with the significant differences that were recorded in the St Petersburg studies,^{8,13} in which maintenance treatment with an opioid agonist was not available, and strong family support encouraged treatment participation. A meta-analysis¹² concluded that retention is the key variable to explain the discrepancies in findings for the efficacy of naltrexone in double-blind clinical trials, and that significant differences in use of illicit opioids are noted between patients given naltrexone and placebo in studies with higher retention. A high retention rate could be achieved by enrolling more highly motivated patients, or by using contingency management (ie, providing incentives to the patient for adhering to treatment), family therapy with behavioural principles, or legal or other pressures to encourage drug adherence and continued treatment participation.^{35–37} The introduction of a long-acting, depot formulation of naltrexone could also improve treatment retention and the effectiveness of naltrexone in clinical practice.³⁸

Despite our favourable findings for buprenorphine, there is still room for improvement, since only two-fifths of patients remained in treatment, and only a quarter continued to receive treatment and avoid relapse throughout the 24-week treatment period. Additionally, as noted in other studies,^{3,39} HIV risk behaviours associated with injection drug use were reduced during treatment in all groups, but sexual risk behaviours, including unprotected sex, did not decrease. The provision of earlier dose increases, higher doses of buprenorphine, or take-home doses of buprenorphine might have improved outcomes for retention and drug use in the buprenorphine group. Training available health-care personnel and nurses

to provide drug counselling is a strength of the study, and improves the relevance of the findings to Malaysia and other developing countries, where very few health professionals have advanced training or experience in treatment for addictions; developing and providing more effective counselling or other behavioural interventions might improve treatment outcomes. The added benefits of improved behavioural interventions would be expected in all treatment groups, however, and would not be expected to change the findings for the superiority of buprenorphine.

Limitations of this study include early termination of the trial because of the findings of significant superiority of buprenorphine for the primary outcome measures of drug use, resulting in a final sample size that was smaller than was initially planned.^{40,41} The negative findings (of no significant differences) in some of the pair-wise comparisons should not be construed as evidence of equivalence between the treatments. The observed effect-size differences, although not significant in this study, might be regarded as clinically important if shown to reach the level of significance in a larger study. Missing data, resulting particularly from the high attrition of patients given naltrexone or placebo, and subsequent loss to follow-up of some patients who did not complete treatment, could have diluted the findings for the efficacy of buprenorphine, since most patients who left treatment prematurely had resumed heroin use before leaving treatment, and early discontinuation of treatment is usually followed by relapse. Outcomes for drug use and retention were based on objective measures, but HIV risk behaviours were assessed by self-reporting, and were not validated by objective measures.

Despite efforts to maintain the medication blind, differences in medication effects allowed most patients given buprenorphine or naltrexone to identify correctly the medication that they were receiving. We think that patients assigned to buprenorphine were able to identify their medication because of the opioid agonist effects of buprenorphine, and that patients assigned to naltrexone were able to identify their medication because it blocked the effects of heroin (for those who used heroin while taking naltrexone). Patients who were assigned to placebo did not have either the opioid-agonist effects of buprenorphine or the opioid-blocking effects of naltrexone and were thus less likely to be able to identify their medication. Criteria for study eligibility—the requirement that all patients complete a residential detoxification before being randomly assigned—and the use of one study site and small sample size restrict the generalisability of the study findings to other patient populations or settings. Buprenorphine could have an even greater effectiveness than could detoxification followed by drug counselling alone or with naltrexone in real-world settings, where patients who are dependent on heroin are given buprenorphine without first needing to undergo detoxification.

This study has important implications for clinical practice and public-health policy. Although maintenance treatment with an opioid agonist remains unavailable in many areas, the findings of this study provide strong support for the efficacy of maintenance treatment with buprenorphine for reduction of illicit opioid use and retaining patients in treatment, compared with either maintenance treatment with naltrexone or drug counselling only, and some support for the potential efficacy of all three treatments to reduce risk of HIV transmission associated with injection drug use.^{3,14,15} Dissemination of this treatment is also supported by the ease of induction onto buprenorphine in ambulatory clinics, the low incidence of serious adverse events or symptoms leading to treatment discontinuation associated with buprenorphine in this and previous studies,^{18,42} and the potential for providing more liberal take-home doses than were provided in the clinical trial. These considerations lend support to dissemination of opioid-agonist maintenance treatment with buprenorphine or methadone (which has at least comparable efficacy, greater ease of induction, and generally lower drug cost than buprenorphine) as an important component of an effective public-health approach for reduction of problems associated with heroin dependence.

Contributors

All authors participated in the design, conduct, and analysis of the study, and have seen and approved the final version of the report.

Conflict of interest statement

We declare that we have no conflict of interest.

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