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Buprenorphine-Naloxone Versus Methadone Maintenance Therapy: A Randomised Double-Blind Trial With Opioid-Dependent Patients

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Summary

This is the first randomised study comparing buprenorphine-naloxone with methadone for maintenance treatment of opioid dependence. A 17-week, double-blind, double-dummy trial of daily dosing compared buprenorphine-naloxone (8/2 mg and 16/4 mg) with methadone (45 mg and 90 mg) in 268 participants. The percentage of opioid-free urine samples over time did not differ by drug or dosage. The percentage of patients with ≥12 consecutive opioid-negative urine samples did not differ by drug and was significantly greater for patients receiving higher doses of either agent. Induction success, compliance, nonopioid drug use, retention and Addiction Severity Index scores did not differ among groups. Buprenorphine-naloxone is a viable alternative to methadone in clinical practice.

Key Words: Buprenorphine; Buprenorphine-naloxone (Suboxone®); Methadone; Opioid dependence; Treatment outcome.

1. Introduction

Opioid dependence is a chronic medical condition and serious international public health problem. An estimated 13 million injection drug users worldwide are dependent on opioids [1], but more than 70% of injection drug users remain untreated in Europe [24] and the United States [52, 53]. Untreated injection drug users are exposed to the significant adverse medical, social and psychological consequences of drug misuse, including heightened risk for human immunodeficiency virus (HIV) and hepatitis viral infection from using contaminated syringes and needles.

Methadone maintenance therapy has been the mainstay of medication-assisted treatment for opioid dependence; such therapy reduces illicit opioid use and substantially reduces morbidity and mortality rates associated with opioid dependence [11, 46]. However, limited access to methadone treatment in many countries, high numbers of untreated injection drug users, increased health service costs for treatment of addiction-related diseases and cost to society of drug-abuse–related behaviour have prompted international interest in additional medications for managing opioid dependence [15, 54].

Buprenorphine, a μ-opioid receptor partial agonist and a kappa-opioid receptor antagonist, has been useful in expanding access to effective opioid-dependence

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treatment [15, 37]. The partial μ-agonist pharmacology of buprenorphine is unique and its clinical pharmacology and application for managing opioid dependence has been reviewed comprehensively [13, 37]. The clinical efficacy of buprenorphine for maintenance treatment also is well established [29, 35, 39, 43, 45].

The sublingual tablet formulation of buprenorphine (Subutex®) is a maintenance treatment for opioid dependence approved for this indication within a framework of medical, social and psychological treatment. The global availability of buprenorphine has steadily increased, and its successful use as a treatment for opioid dependence has warranted its inclusion in the 15th World Health Organization Model List of Essential Medicines [65]. Subutex is available in Europe, the United States and more than 30 other countries worldwide.

A combination tablet containing buprenorphine and naloxone in a 4:1 ratio (Suboxone®) was developed to mitigate abuse and diversion of buprenorphine [16, 17, 30]. Because injection of the opioid antagonist naloxone will precipitate withdrawal in individuals who are opioid dependent, naloxone in the combination tablet is expected to reduce, but not entirely eliminate, parenteral abuse associated with buprenorphine [18, 19, 30, 33, 48, 50, 58, 61]. Clinical and laboratory-based studies of the buprenorphine-naloxone combination formulation have supported its efficacy and safety [29] and reduced abuse potential [4, 9, 58] relative to buprenorphine alone. Features of the buprenorphine-naloxone combination tablet that make it attractive for treating opioid dependence include its efficacy during less-than-daily dosing [7, 8], safety in direct dose induction [10, 25, 39], usefulness for short-term opioid withdrawal [10, 42], use as a take-home therapy [12, 25, 29], use as a frontline primary care therapy [25, 39], promise as a medication that can attract new patients to treatment [63] and ability to be integrated with care for HIV infection [62]. Additionally, health economic studies have shown comparable cost-effectiveness among buprenorphine-naloxone, buprenorphine alone and methadone [21]. Suboxone is available in Europe, the United States, Canada, Australia and several other countries worldwide.

The efficacy of buprenorphine and of methadone has been compared directly several times. These comparative evaluations used the sublingual liquid formulation (studied during the earlier stages of the therapeutic development of buprenorphine) or the buprenorphine-only tablet subsequently developed for clinical use. Although numerous methodologic differences exist across studies, buprenorphine has generally had comparable efficacy [43] and cost-effectiveness [22] to methadone. The current study is the first to directly compare the efficacy of the buprenorphine-naloxone sublingual tablet with that of methadone for maintenance treatment of opioid dependence.

2. Methods

2.1 Participants

The study was conducted at the Vine Street Center in Denver, Colorado, a licensed, outpatient opioid-treatment facility for adults aged 18 years and older. The clinic offered a range of pharmacotherapies for the treatment of opioid dependence, including methadone,

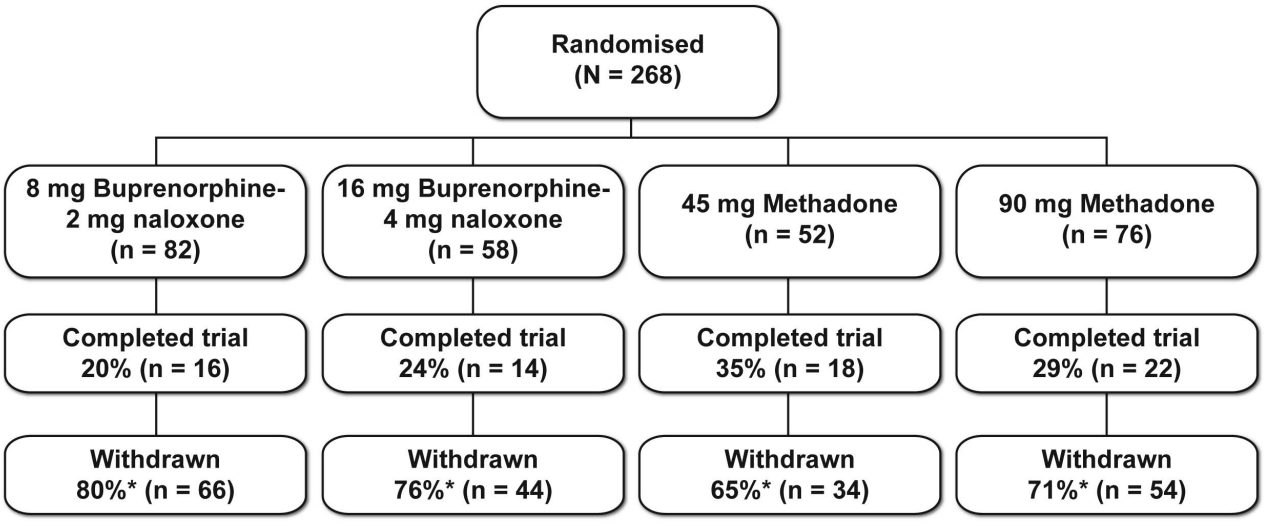

Figure 1. Patient disposition during the trial.

levo-alpha acetyl methadol and naltrexone, along with comprehensive counselling services. Participants were recruited through newspaper and poster advertisements and referred from local treatment programmes. Two hundred sixty-eight individuals participated in this trial (Figure 1).

To be included in the study, participants were at least 18 years old, were in good health and met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for opioid dependence and the Food and Drug Administration (FDA) criteria for methadone maintenance treatment and were using heroin or prescription opioids or receiving methadone maintenance treatment. Exclusion criteria included evidence of active psychosis, manic-depressive illness, organic psychiatric disorders or serious medical illness (e.g. liver or cardiovascular disease). Codependence on other drugs (e.g. cocaine, ethanol or sedative-hypnotics) did not exclude participation. The study was approved by the Colorado Multiple Institution Review Board for human research. Before enrolment, participants provided written informed consent after receiving a full explanation of the procedures. After enrolment, participants completed a comprehensive intake interview to determine study eligibility.

The intake interview included online computerised versions of the psychoactive substance abuse disorder sections of the modified DSM-IV Criteria Checklist [34] and the fifth edition of the Addiction Severity Index [47]. Urine samples were obtained under observation and analysed for opioids, cocaine metabolites, amphetamines, benzodiazepines, barbiturates and cannabinoids using the enzyme-multiplied immunoassay technique (Behring Corporation, San Jose, California, United States). Additional questionnaires were completed to provide information about demographics and drug history. Health status was determined by medical history, physical examination and laboratory evaluation (including complete blood count, clinical chemistry profiles and urinalysis).

Participants were enrolled from 17 July 1997 to 3 September 1999. The study was stopped before achieving the targeted enrolment of 300 participants due to a university-wide mandate to discontinue enrolment of new participants in any experimental drug trial, resulting from sanctions imposed by the FDA on the University of Colorado Health Sciences Center.

2.2 Design

The study was a 17-week, double-blind, double-dummy, randomised clinical trial comparing 4 groups: 8 mg buprenorphine-2 mg naloxone (8 mg buprenorphine-naloxone), 16 mg buprenorphine-4 mg naloxone (16 mg buprenorphine-naloxone), 45 mg methadone and 90 mg methadone. Doses were selected based on relative potency comparisons from controlled trials that compared oral methadone with sublingual buprenorphine available at the time of the study [36, 44, 59]. The methadone doses were chosen to be representative of or higher than those typical of US methadone programmes at the time of the study [11]. Minimum likelihood allocation was used to randomly assign the participants sequentially to 1 of the 4 groups [3] while controlling for sex, methadone and/or Vine Street Center treatment history and duration of regular opioid use (< or ≥15 years).

2.3 Medication supplies and preparation

Buprenorphine-alone, buprenorphine-naloxone and placebo tablets were manufactured by Reckitt Benckiser Pharmaceuticals (Hull, United Kingdom) and supplied free of charge through the National Institute on Drug Abuse and Research Triangle Institute. Buprenorphine-alone tablets containing 2 mg buprenorphine or 8 mg buprenorphine and matching placebo tablets were used during dose induction. Buprenorphine-naloxone tablets containing 8 mg buprenorphine and 2 mg naloxone and matching placebo tablets were used during maintenance.

Methadone solution was purchased from Roxane Laboratories (Columbus, Ohio, United States) in 946-ml bottles at a concentration of 10 mg/ml. Doses less than 90 mg were prepared in 9-ml volumes by diluting methadone solution with sterile water. Undiluted 9-ml methadone solution comprised the 90-mg doses. Methadone doses were placed in break-resistant, amber, 15-ml plastic unit-dose vials and masked for taste with 2 drops of peppermint spirits and a Bitrix granule solution (6 μg/ml; Macfarlan-Smith Ltd., Edinburgh, United Kingdom) and sealed with tamper-evident caps. Placebo solutions were prepared as 9-ml sterile water for irrigation (Baxter Healthcare, Deervale, Illinois, United States) and masked for taste in the same manner as the methadone. Both the methadone and the placebo solutions were coloured with 5 drops of blue food colouring per 946-ml methadone solution or 1000-ml sterile water.

2.4 Medication administration

Participants were required to attend the clinic 7 days per week for medication; take-home medication was not provided. Before receiving the first day's dose, all participants were required to be experiencing mild abstinence signs and to provide a urine sample in which methadone was undetectable, unless the participant was transferring directly from a methadone treatment programme. Participants transferring directly from

methadone treatment were required to wait at least 24 hours from the time of their last verified methadone dose. Mild abstinence signs were assessed by the dispensing nurse using an observer rating scale [5–7, 14]. Specific procedures for buprenorphine and methadone induction follow.

Double-blind and double-dummy dosing conditions were applied. All participants received an oral solution first, followed by the tablets. Masking agents in the liquids were designed to also mask the taste of the tablets [5, 6, 8]. The dispensing nurse gave the participants the day's methadone or placebo solution to drink, then the day's tablets in a plastic cup. Patients were instructed to place the tablets under their tongue and hold them there until the tablets dissolved.

To assess the adequacy of the double-blind and double-dummy procedure, on the last study day participants were asked, "Which medication do you think you were taking during the last 17 weeks?" Most participants responded that they had been taking methadone (buprenorphine-naloxone: 81.5%; methadone: 70.3%; p=NS), which suggested that the double-blind and double-dummy procedures were adequate to keep the participants from knowing which drug they were receiving. To the best of our knowledge, neither the counselling nor the dispensing staff had any knowledge of the study blind and neither was able to discern dosing assignments.

2. 5 Buprenorphine induction and maintenance

A 2-day, rapid-induction procedure used buprenorphine alone [7, 8]. On the first day, the buprenorphine-naloxone groups received 2 sublingual tablets that each contained 2 mg buprenorphine, for a total dose of 4 mg buprenorphine. On the second day, the buprenorphine-naloxone groups received 1 tablet containing 8 mg buprenorphine. On the third and all subsequent days, the 8-mg buprenorphine-naloxone group received 1 placebo tablet and 1 sublingual tablet that contained 8 mg buprenorphine and 2 mg naloxone, whereas the 16-mg buprenorphine-naloxone group received 2 sublingual tablets that each contained 8 mg buprenorphine and 2 mg naloxone, for a total dose of 16 mg buprenorphine-naloxone.

2.6 Methadone induction and maintenance

On the first day, the methadone groups received 15 mg methadone. Doses of methadone were then increased daily by 15 mg until the target dose of 45 mg or 90 mg was reached on day 3 or day 6, respectively. On all subsequent days, the methadone groups received either 45 mg or 90 mg methadone.

2.7 Urine sample collection and analysis

Urine samples were collected 3 times weekly under observation (Mondays, Wednesdays and Fridays) before administering medication and were analysed on site for the presence of opioids using the enzyme multiplied immunoassay technique. Urine samples also were analysed for the presence of cocaine metabolites, amphetamines, benzodiazepines, barbiturates and cannabinoids on 1 randomly chosen day per week using the same method. Cut-off calibration concentrations of 300 ng/ml were used for testing for opioid and cocaine metabolites, 200 ng/ml for benzodiazepines and barbiturates, 50 ng/ml for cannabinoids and 1000 ng/ml for amphetamines. The percentage of missing samples was similar in all 4 groups (12% [8 mg buprenorphine-naloxone], 14% [16 mg buprenorphine-naloxone], 12% [45 mg methadone] and 16% [90 mg methadone]). Breath alcohol samples were collected on urine testing days as part of routine clinical procedure; participants were not permitted to attend the clinic intoxicated.

2.8 Counselling

Participants received 1 hour of individual, manualised behavioural counselling with a trained therapist every other week for the duration of the study. Therapy sessions focused primarily on helping participants make lifestyle changes in regard to drug use, employment, family interactions and social/recreational activities. Participants also received AIDS education. Strong oversight and mandated counselling (enforced by withholding doses until a patient saw his or her counsellor) ensured that the amount and quality of counselling did not differ across groups.

2.9 Safety monitoring

Before dosing each day, the dispensing nurse conducted a brief assessment to determine whether adverse events had occurred. Complaints were noted in the participant's chart but were not systematically recorded for data collection purposes because this study was not a formal safety evaluation. All serious adverse events were immediately reported to the project investigator.

2.10 Study withdrawal and post-study treatment options

If participants failed to obtain their medication for 3 consecutive days or did not provide urine samples on 5 consecutive occasions, they were withdrawn from the study and offered alternative treatment in the centre's clinical programme or referred to other local treatment agencies. Because buprenorphine was not

available outside of research parameters at the time of this trial, participants who completed the study were offered continued care under a compassionate extension of treatment [40]. Participants who elected this alternative agreed to remain blind to the medication and dose until the randomised clinical trial was complete. All participants were evaluated for progress and evidence of clinical stability before being transferred to the compassionate extension phase. Doses for participants who consistently provided opioid-positive urine samples during the study were increased in a blind fashion to either 16 mg buprenorphine-naloxone or 90 mg methadone at entry to the compassionate extension phase. Participants in the compassionate extension phase were also offered take-home medication for Tuesdays, Thursdays and weekends if opioids were undetectable in their 3 previous consecutive urine samples. Only descriptive data (percentage of participants entering and average duration of participation) for this phase are described in this report.

2.11 Participant debriefing

When the study ended, investigators met with each remaining participant, revealed the participant's study drug and dose and made arrangements for continued care. Letters offering to meet for debriefing purposes were sent to enrolees no longer participating in the study or receiving services in the clinic.

2.12 Outcome measures

The primary outcome measure was the amount of opioid abstinence achieved over time. On average, each participant was scheduled for a total of 51 urine tests for the presence of opioids (thrice weekly for 17 weeks). Missed samples were considered positive for the purposes of analysis. The secondary outcomes included the proportion of participants who achieved 12 consecutive opioid-negative samples, the proportion of participants with successful inductions, medication compliance, nonopioid illicit drug use, treatment retention and changes in overall functioning. A successful induction was defined as at least 1 dose of medication on the sixth day of the study or later. Medication compliance was measured by the number of medication doses ingested by each participant. Retention time was measured by the percentage of participants active in the study over time, calculated from the day of first dose to the day of the last dose actually received. Functioning in several psychosocial domains was assessed by examining Addiction Severity Index (ASI) scores at the end of treatment, controlling for intake ASI scores.

2.13 Statistical analysis

To examine baseline differences among the groups, we used analysis of variance (ANOVA) or chi-square tests. Given the nature of the longitudinal data and multiple data points, hierarchical linear modelling (HLM) was used to examine opioid abstinence and use of nonopioid drugs over time [51]. HLM has increasingly been used in studies of interventions and clinical trials and has been advocated as an important tool in examining complex relationships between outcomes and their covariates [66].

To estimate retention time, the Kaplan-Meier statistic was used with 95% confidence intervals. Log rank chi-square test was used to determine if there were significant group differences in retention time.

3. Results

3.1 Demographic characteristics

Two-hundred sixty-eight (268) participants were randomly assigned to receive medication. Selected baseline characteristics are shown in Table 1. A malfunction of the minimum-likelihood-allocation computer software used for stratifying subject assignments resulted in uneven numbers being assigned to the 4 groups. Treatment groups did not differ according to gender, previous history of methadone treatment, history of treatment at the Vine Street Center, ethnicity, age, years of opioid use or years of education. Participants primarily used heroin daily, and approximately two thirds had a history of methadone maintenance treatment. Ten participants transferred directly from a methadone maintenance programme into the study (methadone dose range, 30–85 mg/day). Fifty-three participants received treatment at the Vine Street Center previously.

3.2 Opioid abstinence

Two-level HLM analyses demonstrated that the percentage of opioid-free urine samples over time among drug groups ($p=0.81$) or among drug doses ($p=0.46$) did not differ significantly (Figure 2). Overall, the results of the HLM analyses demonstrate that whereas, in general, study participants increased their percentage of opioid-negative urine samples over the course of the trial, this increase was not predicted by drug type or drug dose.

3.3 Consecutive opioid-negative urine samples

Ten percent (10%) of the 8-mg buprenorphine-naloxone group, 17% of the 16-mg buprenorphine-naloxone group, 12% of the 45-mg methadone group

Table 1. Demographic characteristics.

	Buprenorphine-Naloxone		Methadone	
Characteristic	8 mg (n=82)	16 mg (n=58)	45 mg (n=52)	90 mg (n=76)
Male, n (%)	58 (70.7)	41 (70.7)	42 (80.8)	50 (65.8)
Age, years*	37.2 ± 1.2	38.9 ±1.4	40.3 ± 1.5	38.1 ±1.2
Race, n (%)				
White, non-Hispanic	41 (50.0)	30 (51.7)	25 (48.1)	35 (46.0)
Black, non-Hispanic	14 (17.1)	9 (15.5)	12 (23.1)	15 (19.7)
Hispanic	26 (31.7)	16 (27.6)	13 (25.0)	26 (34.2)
Asian	0	1 (1.7)	1 (1.9)	0
Other	1 (1.2)	2 (3.4)	1 (1.9)	0
Education, years*	11.7 ± 0.2	12.6 ± 0.3	12.1± 0.3	12.1 ± 0.2
History of methadone treatment, n (%)	50 (61.0)	39 (67.2)	35 (67.3)	49 (64.5)
Transferred from methadone maintenance, n (%)	4 (4.8)	2(3.4)	1 (1.9)	3 (3.9)
Methadone maintenance dose at time of transfer, mg/d*	54.5 ± 12.3	40.0 ± 0.0	30 ± 0.0	44 ± 10.2
History of Vine Street Center treatment, n (%)	10 (12.2)	10 (17.2)	14 (26.9)	9 (11.8)
Years of regular opioid use*	9.2 ± 1.1	10.2 ± 1.3	12.4 ± 1.4	10.0 ± 1.2
Days of using heroin in the last 30 days*	26.9 ± 0.9	26.3 ± 1.1	26.7 ± 1.1	26.3 ± 0.9
DSM-IV abuse or dependence, n (%)				
Cocaine	22 (26.8)	17 (29.3)	19 (36.5)	17 (22.4)
Cannabis	16 (19.5)	12 (20.7)	5 (9.6)	10 (13.6)
Amphetamines	7 (8.5)	8 (13.8)	4 (7.7)	10 (13.1)
Sedatives	4 (4.9)	4 (6.9)	3 (5.8)	1 (1.3)
Nicotine	37 (45.1)	21 (36.2)	26 (50.0)	37 (48.7)
Alcohol	20 (24.4)	16 (27.6)	14 (26.9)	24 (31.6)
Hallucinogens	2 (2.4)	3 (5.2)	0	1 (1.3)
Inhalants	3 (3.7)	2 (3.4)	1 (1.9)	0
PCP	4 (4.9)	4 (6.9)	3 (5.8)	1 (1.3)

*Mean ± the standard error of the mean. There were no significant differences across groups by drug or by dose

and 16% of the 90-mg methadone group had at least 12 consecutive opioid-negative urine samples. Results of the homogeneity of proportions test found that the percentage of participants with at least 12 consecutive opioid-negative urine samples differed by dose (8 mg vs. 16 mg buprenorphine-naloxone, p<0.001; 45 mg vs. 90 mg methadone, p=0.02), but not by drug (8 mg buprenorphine-naloxone vs. 45 mg methadone, p=0.18; 16 mg buprenorphine-naloxone vs. 90 mg methadone, p=0.22). Those receiving higher doses of methadone or buprenorphine-naloxone were more likely to have at least 12 consecutive opioid-negative urine samples than those receiving lower doses.

3.4 Induction

The homogeneity of proportions test was used to determine if the percentage of participants who had successful induction differed significantly among the 4 groups. Successful inductions occurred in 80.5%, 81.0%, 82.7% and 82.9% of the participants receiving 8 mg buprenorphine-naloxone, 16 mg buprenorphine-naloxone, 45 mg methadone and 90 mg methadone, respectively. No significant differences were detected between any 2 treatment groups (p=0.22–0.98).

3.5 Medication compliance

To determine if groups differed in the amount of

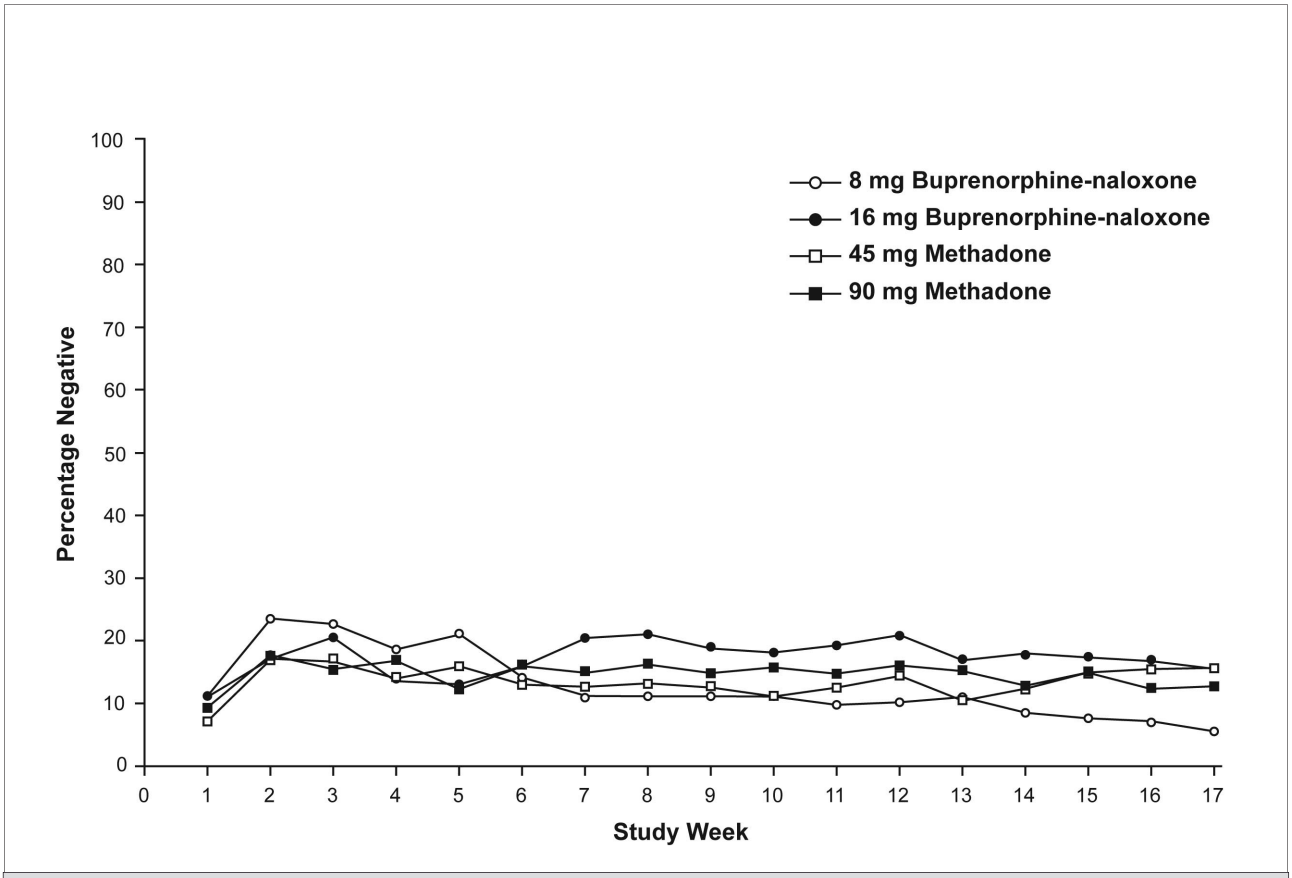

Figure 2. Percentage of opioid-negative urine test results in the 4 treatment groups. Each point represents the percentage of patients with negative urine test results at the end of each week.

medication ingested, ANOVAs were conducted. Of the 119 total possible doses to be ingested, mean ± standard error of mean (SEM) numbers of doses ingested by each group were 38.1 ± 4.7, 37.5 ± 5.6, 48.9 ± 5.9 and 44.3 ± 4.9 for the 8-mg buprenorphine-naloxone, 16-mg buprenorphine-naloxone, 45-mg methadone and 90-mg methadone groups, respectively. Results of the ANOVAs demonstrate that medication compliance did not differ significantly according to drug or dose (p=0.41).

3.6 Nonopioid drug use

Unconditional level 1 HLM models showed that nonopioid drug use neither changed significantly over time nor differed significantly across groups (p=0.32–0.83). The most commonly used drugs other than opioids were cocaine and cannabinoids. The percentage of patients with positive urine samples ranged from 69.8% to 77.6% for cocaine and 65.6% to 77.5% for cannabinoids. Mean percentages of participants with positive urine samples ranged from 57.3% to 68.0% for barbiturates, 57.8% to 68.5% for amphetamines and 62.5% to 69.0% for benzodiazepines.

3.7 Retention

To estimate retention time, Kaplan-Meier survival analyses using 95% confidence intervals and log rank chi-square tests to determine significant group differences were generated (Table 2). Additionally, Kaplan-Meier graphs show that cumulative retention by low dose in Figure 3 with the log rank test (p=0.09), and high dose in Figure 4 with the log rank test (p=0.28) did not differ significantly by drug.

3.8 Overall functioning

To evaluate whether participants differed in psychosocial functioning by group, univariate general linear models were conducted. For these analyses, ASI scores at the end of the trial were the outcome, and intake scores on the ASI were entered as covariates to control for initial levels of functioning. Participants did not vary significantly by group on ASI Alcohol, Cocaine, Drug, Employment, Family, Legal, Medical, Opioid or Psychiatric scales (p= 0.08–0.84). Table 3 shows the self-reported number of days of heroin use in the past 30 days, and the opiate and drug composite scores from the ASI collected at baseline, at week 8 and at week 16.

Table 2. Mean and median retention based on Kaplan-Meier survival analyses

	Mean Retention (Weeks)	SE	95% Confidence Interval		Median Retention (Weeks)	SE	95% Confidence Interval	
			Lower Bounds	Upper Bounds			Lower Bounds	Upper Bounds
Low Dose								
8 mg buprenorphine-naloxone	12.125	0.178	11.776	12.1473	13	0.294	12.419	13.584
45 mg methadone	13.214	0.199	12.824	13.604	15	0.470	13.591	15.652
Overall	12.588	0.133	12.327	12.588	14	0.167	13.672	14.605
High Dose								
16 mg buprenorphine-naloxone	12.504	0.196	12.120	12.888	13	0.347	12.319	13.681
90 mg methadone	12.277	0.182	11.919	12.634	13	0.316	12.381	13.619
Overall	12.379	0.134	12.117	12.641	13	0.234	12.542	13.458
Total Trial Retention	12.482	0.094	12.297	12.666	14	0.167	13.672	14.328

SE = standard error

Table 3. Self-reported heroin use and Addiction Severity Index opiate and drug composite scores over time

	Buprenorphine-Naloxone		Methadone	
	8 mg	16 mg	45 mg	90 mg
Self-reported days of heroin use in the past 30 days*				
Intake	26.9 ± 0.8	26.3 ± 1.1	26.7 ±1.2	26.3 ± 0.9
Week 8	7.0 ± 2.0	1.3 ± 0.8	12.1 ± 2.7	5.7 ± 1.6
Week 16[a]	5.8 ± 2.4[a]	3.1 ± 1.7[a]	9.0 ± 2.5	4.3 ± 1.6
Addiction Severity Index Opiate Composite Score*[c]				
Intake	0.70 ± 0.02	0.70 ± 0.02	0.70 ± 0.02	0.68 ± 0.02
Week 8	0.33 ± 0.05[b]	0.16 ± 0.05[b]	0.37 ±0.07[b]	0.34 ±0.04[b]
Week 16	0.28 ± 0.06[b]	0.23 ± 0.06[b]	0.34 ±0.06[b]	0.34 ±0.04[b]
Addiction Severity Index Drug Composite Score*				
Intake	0.24 ± 0.01	0.26 ± 0.01	0.34 ± 0.07	0.27 ± 0.01
Week 8	0.11 ± 0.02[b]	0.11 ± 0.03[b]	0.13 ± 0.03[b]	0.12 ±0.02[b]
Week 16	0.09 ± 0.02[b]	0.14 ± 0.03[b]	0.11± 0.02[b]	0.12 ± 0.02[b]

*Mean ± the standard error of the mean

[a]The combined buprenorphine-naloxone groups reported significantly less heroin use than the combined methadone groups, p=0.05

[b]Significantly different from intake, p<0.00001

[c]The Opiate Composite Score is derived from the drug scale

3.9 Safety monitoring

Five serious adverse events were reported during the trial. All events resulted in hospitalisation and were not related to the study drug. Three hospitalisations were related to treatment for abscesses associated with illicit injection heroin use, 1 was related to high blood pressure and 1 was for a lung mass and shoulder infection. Four events occurred in participants assigned to receive methadone and 1 in a participant assigned to receive buprenorphine-naloxone.

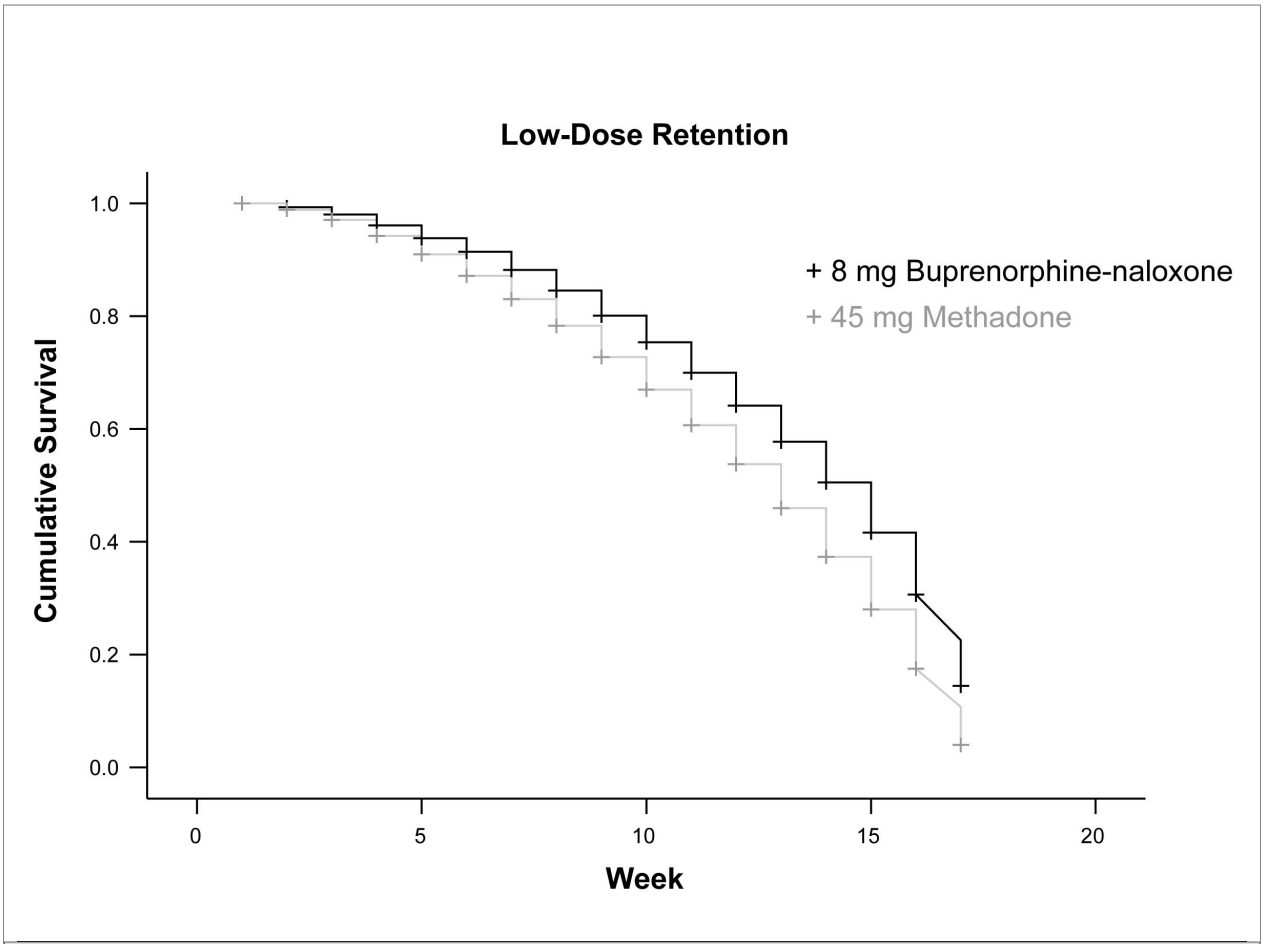

Figure 3. Low-dose retention Kaplan-Meier survival graphs, demonstrating cumulative survival by dose level at each week.

3.10 Poststudy treatment

Ninety percent (63/70) of participants who completed the study elected to continue treatment under the compassionate extension of treatment programme. Similar percentages of participants in each treatment group decided to continue treatment (94%, 79%, 94% and 91% of the 8-mg buprenorphine/naloxone, 16-mg buprenorphine/naloxone, 45-mg methadone and 90-mg methadone groups, respectively). Overall, participants received treatment in this phase for about half a year (mean ± SEM, 184 days ± 19). Medication and doses received during the study did not significantly affect the duration of time participants continued to receive treatment after the study ended. Of the 7 participants who declined to participate in the compassionate extension phase, 6 elected to withdraw from the study during a 30-day dose taper and 1 transferred to methadone maintenance at another facility.

4. Discussion

In the current study, maintenance with buprenorphine-naloxone resulted in opioid abstinence similar to that achieved with maintenance using methadone. In particular, 16 mg buprenorphine-naloxone was noninferior to 90 mg methadone, highlighting the usefulness of this medication for the management of opioid dependence. To our knowledge, no other study has directly compared the marketed buprenorphine-naloxone sublingual tablet to methadone for maintenance treatment of opioid dependence. One study compared these 2 agents in a stepped-care model in which patients began treatment with buprenorphine-naloxone but were transferred to methadone (90–111 mg/day) if 32 mg/day buprenorphine-naloxone resulted in missed visits, reports of craving or withdrawal or illicit opioid use. In that study, the use of methadone and buprenorphine-naloxone similarly retained patients and suppressed illicit opioid use [39]. Both studies used relatively high doses of methadone for comparison, increasing confidence in the suggestion that buprenorphine-naloxone is a viable alternative to methadone for opioid dependence treatment.

Many studies have compared maintenance with sublingual liquid or tablet buprenorphine alone versus maintenance with methadone. Most studies report

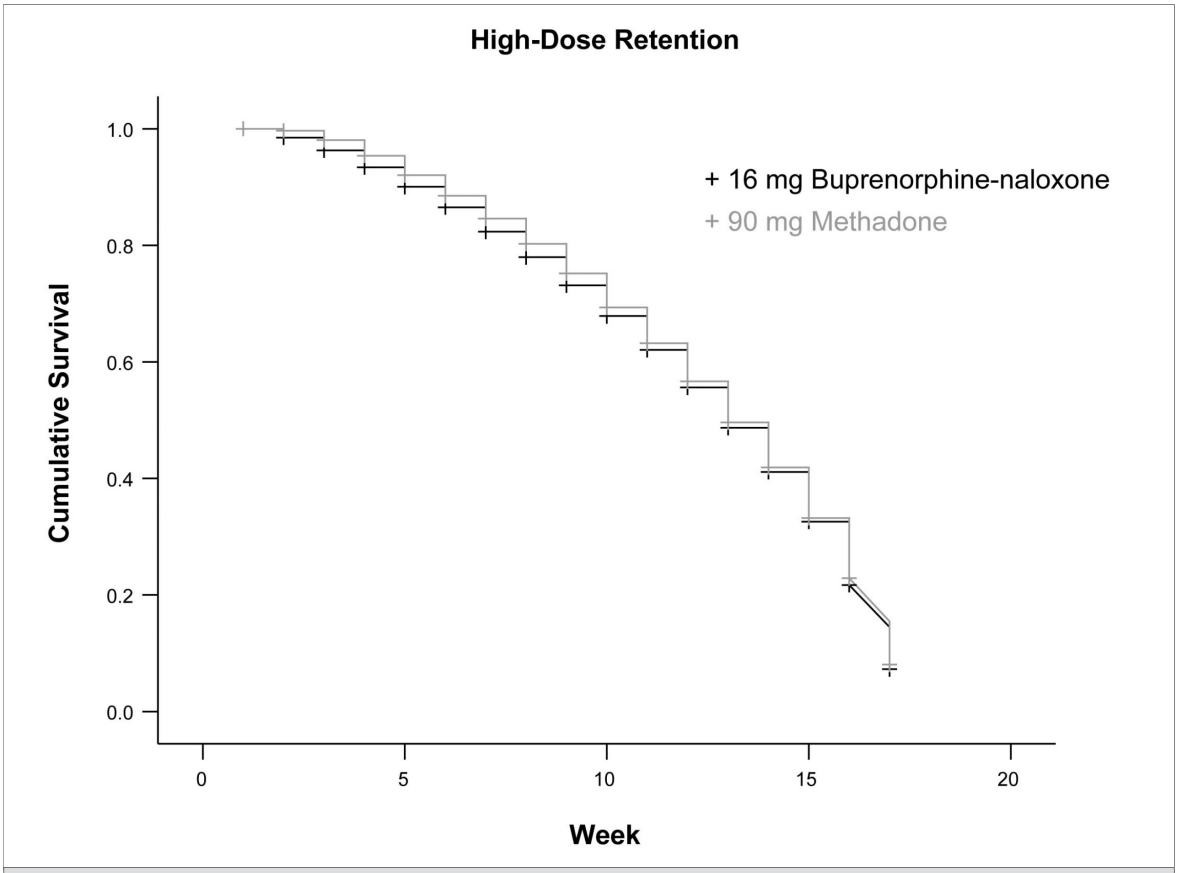

Figure 4. High-dose retention Kaplan-Meier survival graph, demonstrating cumulative survival by dose level at each week.

that buprenorphine and methadone have similar efficacy in reducing illicit opioid use [23, 35, 36, 56, 59, 64], although some studies report better efficacy for buprenorphine [28, 31, 32] or for methadone [41, 44, 55]. In cases in which 1 drug seemed to be superior to the other, procedural variables, such as an insufficiently rapid buprenorphine induction procedure or inadequate buprenorphine doses, may have influenced the results [20]. A review of 3 meta-analyses comparing buprenorphine and methadone emphasised that induction to buprenorphine should proceed more rapidly than what is safe for methadone induction and should reach maintenance doses within 2 to 3 days [20]. The same review also emphasised that buprenorphine dosing should be flexible and variable according to clinical need. The current study, which used a rapid buprenorphine induction procedure and clinically relevant buprenorphine doses, provides further evidence for the equivalence of buprenorphine to methadone. This finding is of particular importance when considering circumstances in which an alternative to methadone is preferred or necessary because of medical or regulatory restrictions on the patient or limited access to methadone.

That higher maintenance doses of methadone and buprenorphine-naloxone produced greater opioid abstinence than lower doses of these drugs in the current study is not surprising. Greater efficacy of higher doses is supported by other studies of methadone [11, 44, 60] and buprenorphine maintenance [2, 37, 56], but the current study is the first to show that this finding holds true for buprenorphine-naloxone as well. The finding that 16 mg buprenorphine-naloxone produces greater abstinence than 8 mg buprenorphine-naloxone underscores the need for appropriate dose selection and should provide important guidance for countries where maintenance doses for buprenorphine-naloxone average 8 mg or less.

Buprenorphine-naloxone and methadone also had similar effects on other outcome measures. More than 80% of patients were inducted successfully with maintenance drug and dose, regardless of the group assignment. Similarly, high percentages have been successfully inducted with buprenorphine-naloxone using similar procedures [26] and have reached the second week of treatment in other comparisons of buprenorphine and methadone [27, 36, 44, 55, 59]. Medication compliance and retention rates, although low, did not differ by group and are comparable to those found in earlier studies using a similar methodology [27, 36, 44]. Nonetheless, 90% of the patients who completed the current study expressed a desire to continue treatment. In studies where buprenorphine has been made available using

flexible dosing or less stringent attendance requirements, retention rates were substantially higher [26, 35, 39, 49, 59]. Retention rates as high as 75% have been reported over a 1-year period [38].

Buprenorphine-naloxone and methadone produced comparable results for other aspects of treatment performance. Neither drug significantly affected nonopioid drug use, and overall addiction severity decreased over time, paralleling findings in other controlled evaluations of buprenorphine and methadone [29, 39]. Although the current study was not designed to monitor safety per se, very few serious adverse events occurred and none were related to methadone or buprenorphine-naloxone. Therefore, the current results add to the evidence that buprenorphine-naloxone is safe for extended maintenance therapy [57].

The current randomised controlled trial has several strengths that extend the generality of previous research. First, the conservative analytical procedure used in this study, wherein all missing values of urine testing results were extrapolated as positive, controlled for early dropouts and participants who were using opioids and may have decided to be absent for screening. Second, a rapid buprenorphine dose induction procedure and therapeutic maintenance doses of each study medication were used. These features permitted testing the efficacy of buprenorphine-naloxone relative to methadone under best practice induction procedures for buprenorphine, using comparison doses that allowed a fair comparison with methadone. Third, patient participation included those patients previously undergoing maintenance therapy with methadone, those dependent on prescription opioids and those engaging in polysubstance abuse. This demography increases the generality of the findings to the larger international population of opioid-dependent persons seeking treatment with buprenorphine [33, 39]. Finally, the study was conducted in a licensed, community-based opioid treatment programme and exposed patients to buprenorphine-naloxone for a longer period than did most previous efficacy trials (up to 10 months for patients who elected to continue treatment under the compassionate extension phase). These environmental aspects increase the ecological validity of the study and generally underscore buprenorphine-naloxone versatility for use in a multitude of treatment settings [10], for extended maintenance therapy [29] and with a variety of counselling platforms [25] and treatment approaches [39].

Limitations of this study include the uneven numbers assigned to the 4 treatment groups, which potentially decreased the power to detect differences, and the steadily decreasing numbers of patients due to study dropout. The rigorous design of this controlled clinical trial, strict attendance criteria and use of fixed doses naturally contributed to continuous attrition. The finding that buprenorphine-naloxone was not inferior to methadone under these conditions attests to the value of buprenorphine-naloxone as a treatment for opioid dependence and as an alternative to methadone treatment.

5. Conclusions

Maintenance treatment with 16 mg buprenorphine-naloxone reduced opioid use at a rate equivalent to that achieved with 90 mg methadone. Other treatment outcomes were comparable for buprenorphine-naloxone and methadone, including completion of dose induction, treatment retention, greater reductions in illicit opioid use in response to higher doses, low incidence of adverse events and similar decreases in addiction severity. Overall, the comparability of buprenorphine-naloxone with methadone, the lower overdose risk and growing availability should help to significantly expand patient access to safe and effective treatment and reduce the harms associated with untreated opioid dependence.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

Dr. Amass is currently employed by Schering-Plough Corporation, a distributor of buprenorphine. Drs. Kamien and Branstetter report no conflicts of interest.

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