

Buprenorphine treatment for opioid dependence: the relative efficacy of daily, twice and thrice weekly dosing

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Abstract

This randomized clinical trial evaluated the relative efficacy of three buprenorphine dosing schedules. Opioid-dependent adults were randomly assigned to receive buprenorphine seven, 3 or 2 days per week for 24 weeks. Daily maintenance doses were 4, 8, 10, or 12 mg of the sublingual buprenorphine solution. Participants who attended the clinic daily received a maintenance dose of buprenorphine daily. Participants who attended the clinic thrice weekly received double their maintenance dose on Monday and Wednesday, followed by a triple dose on Friday. Participants who attended the clinic twice weekly received quadruple their maintenance dose of buprenorphine on Monday and triple their maintenance dose on Friday. Results demonstrated that all dosing regimens were of comparable efficacy in promoting treatment retention, opioid and cocaine abstinence, and reductions in HIV risk behavior (especially as related to drug use) and severity of life problems. Predictor analyses identified sub-populations of opioid-dependent individuals that may have a more positive treatment outcome under each buprenorphine dosing condition. Less-than-daily dosing schedules may provide the opportunity for treatment programs to serve a greater number of opioid-dependent patients and reduce the risk of medication diversion, which may, in turn, have a positive impact on community support of science-based treatment for opioid-dependence.

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1. Introduction

Buprenorphine is a partial mu-agonist that is used in the treatment of opioid dependence in numerous countries, including much of Europe and Australia, and was approved in 2002 by the Food and Drug Administration for the treatment of opioid dependence in the United States. Like the full mu opioid-agonist, methadone, buprenorphine stabilizes the brain neurochemistry of opioid-dependent individuals and prevents opioid-withdrawal symptoms. Also, like methadone, buprenorphine can block the effects of exoge-

nously self-administered opioids (e.g., heroin) due to its affinity and cross-tolerance for the mu-opioid receptor (e.g., Dole, 1988; Dole et al., 1966; Jasinski et al., 1978; Ling et al., 1976).

Numerous clinical trials have demonstrated that, when equi-effective doses are provided, buprenorphine is as efficacious as the full mu-agonist methadone in the treatment of opioid dependence (see Johnson et al., 2000 for an overview). Specifically, buprenorphine has been shown to be as effective as methadone and significantly better than placebo in reducing both illicit opiate use and opiate craving and promoting treatment retention among opioid-dependent individuals. Buprenorphine, however, has a unique profile of effects which are of considerable clinical utility, and may make it an appealing alternative to the daily administered, full agonist,

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methadone (see Bickel and Amass, 1995 for a review). As a partial agonist, buprenorphine has been demonstrated to have a ceiling effect on its agonist activity, such that increases in dose will increase the drug's physiological and subjective effects only to a certain level, after which time dose increases produce no additional effects (Lewis, 1985; Kenakin, 1987; Walsh et al., 1995).

Several studies have investigated the extent to which buprenorphine's unique pharmacological profile enables it to be safely and effectively administered on a less-than-daily basis to opioid-dependent individuals. These studies have demonstrated that, due to the ceiling effect on buprenorphine's agonist activity, as well as its long duration of action, longer interdosing intervals between buprenorphine administration (relative to daily administered methadone) are viable. Indeed, in a series of studies, our research group has demonstrated buprenorphine can safely and effectively be administered every 48 h by doubling the maintenance dose (Amass et al., 1994), every 72 h by tripling the maintenance dose (Bickel et al., 1999) and every 96 h by quadrupling the maintenance dose (Petry et al., 1999, 2000). Importantly, alternate-day dosing schedules have been shown to be preferred to a daily dosing schedule by patients (Amass et al., 1998; Petry et al., 2001).

Although the findings from this series of studies investigating less-than-daily dosing with buprenorphine have provided an abundance of clinically important information, none of these trials explicitly assessed the long-term efficacy of less-than-daily dosing in promoting treatment compliance. That is, various less-than-daily dosing maintenance schedules were typically provided to participants for an average of about a month in these trials, which is shorter than the typical 1-year or longer duration of treatment for opioid dependence (Ball and Ross, 1991). Additionally, the primary outcome measure of interest in these studies was typically observer and subjective ratings of opioid agonist effects and withdrawal. Moreover, to ensure that these measures were collected at critical timepoints during the study without the potential confounding influence of illicit opioid use, participation in these studies was typically contingent upon clinic attendance and opioid abstinence. While these contingencies helped ensure the accuracy of observer and subjective ratings of opioid effects and withdrawal in these prior studies, they may have contributed to higher levels of treatment compliance than these dosing schedules alone may have generated in the absence of such contingencies. Finally, in some prior trials, participants were given the opportunity to choose or earn less-than-daily dosing. This procedure identified that less-than-daily dosing schedules can function as a reinforcer; however, it also allowed for participant exposure to various schedules to vary in unsystematic ways; thereby complicating interpretation of study results.

One recent clinical trial, conducted in Spain (Pérez de los Cobos et al., 2000), evaluated the relative efficacy of daily dosing with 8 mg of buprenorphine to thrice weekly buprenorphine dosing (10 mg on Mondays and Wednesdays

and 24 mg on Fridays). Results from this 12-week study indicated that the retention rates were similar across the two groups; however, the percentage of opioid-positive urine tests were significantly higher among participants who received buprenorphine thrice weekly compared to the daily dosing schedule (58.5% versus 46.6% opioid-positive results, respectively). Although these results are clinically meaningful, there were a number of procedures followed in this study that did not directly mimic how less-than-daily dosing schedules would likely be used in clinical practice. Specifically, the study protocol, although methodologically sound, required an inpatient, hospital-based induction phase onto buprenorphine and also required all participants to attend the clinic daily even if they were in the thrice weekly dosing group. Additionally, the authors identified several concerns regarding the doses of buprenorphine used in the study and proposed that administration of higher, therapeutic doses of buprenorphine with these less-than-daily dosing schedules may have produced more positive outcomes.

Another recent 12-week clinical trial (Schottenfeld et al., 2000) also compared the relative efficacy of daily (average of 16 mg/70 kg body weight daily) versus thrice weekly (average of 34 mg/70 kg body weight on Fridays and Sundays and 44 mg/70 kg body weight on Tuesdays) buprenorphine dosing. Unlike in the study conducted by Pérez de los Cobos et al. (2000), this study found that both dosing schedules were efficacious and comparable in their ability to promote treatment retention and opioid-abstinence (57% and 58% opioid-positive results in the daily and thrice weekly dosing groups, respectively). The higher, clinical doses of buprenorphine used in this study may have largely contributed to the comparable efficacy of the daily and thrice weekly dosing schedules evaluated in this study. Nonetheless, this study also required all participants to attend the clinic daily despite their dosing schedule.

The primary purpose of the present clinical trial was to expand on prior research to enhance our understanding of the clinical efficacy of less-than-daily dosing schedules with buprenorphine. Specifically, this trial was designed to evaluate the relative efficacy of three buprenorphine dosing schedules in promoting treatment compliance in the absence of confounding behavioral contingencies, when the dosing schedules were provided for longer periods of time relative to prior studies (24 weeks versus 12 weeks) and when participants were asked to attend the clinic only on days they were scheduled to receive medication. Depending upon random assignment to treatment condition, participants were required to attend the clinic to receive buprenorphine medication 2, 3, or 7 days per week. Participants who attended the clinic twice weekly received quadruple their maintenance dose of buprenorphine on Monday and triple their maintenance dose on Friday. Participants who attended the clinic three times weekly received double their maintenance dose on Monday and Wednesday, followed by a triple dose on Friday. Participants who attended the clinic daily received a maintenance dose of buprenorphine daily. All dosing schedules remained

in effect for 24 weeks. Primary outcome measures included treatment retention and both opiate and cocaine abstinence as measured via objective urinalysis testing.

Less-than-daily dosing regimens with buprenorphine may be of considerable clinical utility for a number of reasons. First, as described above, such dosing schedules have been shown to be safe, effective and preferred by patients over daily dosing schedules. Second, these dosing schedules reduce the need for patients to attend a treatment program on a daily basis, which is particularly useful to those patients who live far distances from a treatment clinic and for whom travel is a barrier to treatment. Third, less-than-daily dosing regimens may be cost-effective for clinics and may enable a larger number of patients to be treated at each clinic. Fourth, less-than-daily dosing schedules eliminate the risk of diversion of take-home medication, as, unlike with methadone, no take-home doses of buprenorphine are necessary (e.g., Bickel and Amass, 1995). Fifth, less-than-daily dosing schedules may be offered as an incentive to participants contingent on abstinence from illicit drugs and compliance with treatment (e.g., Stitzer et al., 1992).

2. Method

2.1. Participants

Participants were adult (≥ 18 years of age) outpatients who met DSM IV criteria for opioid dependence. Co-dependence on cocaine, ethanol or sedative-hypnotics did not exclude individuals from participating in the study. Participants received a full medical evaluation prior to participation in the study. Exclusionary criteria included evidence of a significant active psychiatric disorder (e.g., psychosis, organic psychiatric disorders), a medical illness (e.g., liver or cardiovascular disease), or pregnancy. Individuals who sought treatment but who did not meet the necessary inclusion criteria were either referred to an appropriate outpatient or inpatient substance abuse treatment center. The study was approved by the University of Vermont's Institutional Review Board, and all participants provided informed consent to participate. Based on these inclusionary criteria, a total of 134 individuals participated in this randomized, controlled trial ($n = 45$ daily dosing; $n = 44$ thrice weekly dosing; $n = 45$ twice weekly dosing).

2.2. Medication administration

Buprenorphine hydrochloride (Reckitt & Colman; Hull, England) was prepared as a stock concentration of 16 mg/ml in 35% ethanol (vol/vol). Stock solutions containing 2, 4, 8, 10 and 12 mg/ml in 35% ethanol (vol/vol) were prepared from serial dilutions of the 16 mg/ml stock. Buprenorphine placebo consisted of the ethanol vehicle. The maximum volume (ml) necessary for the highest dose was calculated on an individual basis, and then doses were delivered in a constant

volume throughout the study. All medication was administered sublingually with a Ped-Pod Oral Dispenser (SoloPak Laboratories, Franklin Park, IL, USA) under double blind conditions. Participants then held the medication under their tongues for a period of 5 min without speaking.

For the first 14–18 days of treatment (depending on intake day), participants completed an induction phase, when all participants' attended the clinic daily and their buprenorphine dose was gradually increased to their maintenance dose. In this process, participants were initially given a 2 mg induction dose of the sublingual buprenorphine solution at intake. Each participant's dose was then generally increased to 4 mg on the second day, and this dose was usually maintained throughout days 2–7. Final dose increases were typically made on treatment day 8. Daily maintenance doses were 4, 8, 10, or 12 mg of the sublingual buprenorphine solution, depending upon the severity of the participant's dependence (as determined by self-reported level of opiate use, participant weight, and participant and observer reports of withdrawal/agonist effects during the first week of treatment).

After the dose induction phase, participants were randomly assigned to one of the three treatment groups, with participants stratified for maintenance dose, previous treatment history, and daily commute time to the study site (≤ 30 , 31–60 or ≥ 61 min of commute time). Participants were stratified on daily commute time, because the study site was the only outpatient clinic in the state of Vermont to provide pharmacotherapies for opioid dependence at the time of this study, and thus, a notable number of patients traveled from various locations across the state in order to attend treatment at the research clinic. None of the three variables on which participants were stratified differed significantly across the three dosing conditions. Participants in the three conditions were maintained on buprenorphine in accordance with either a daily, twice weekly, or thrice weekly dosing scheduled for 24 weeks determined by random assignment. During this maintenance phase, participants who attended the clinic twice weekly received quadruple their maintenance dose of buprenorphine on Monday and triple their maintenance dose on Friday. Participants who attended the clinic three times weekly received double their maintenance dose on Monday and Wednesday, followed by a triple dose on Friday. Participants in the third condition received a maintenance dose daily. After the 24-week maintenance phase, participants' buprenorphine dose was gradually reduced (1 mg decrease every 4 days) over the following 8 weeks.

2.3. Laboratory safety assessment

All participants were required to participate in a laboratory session after the period of dose stabilization (approximately treatment day 10), in order to demonstrate that they could safely tolerate the largest dose of buprenorphine to which they would be exposed during the study (either a daily, triple or quadruple maintenance dose, depending on condition assignment). We have successfully employed this procedure in

numerous prior studies conducted with buprenorphine (e.g., Amass et al., 1994; Petry et al., 1999, 2001). Participants assigned to the daily dosing condition received their maintenance dose at Time 0, and placebo doses at Times 2 and 4 h. Participants in the 3 days per week dosing condition received their maintenance dose at Times 0, 2 and 4 h. Participants assigned to the 2 days per week dosing condition received double their maintenance dose at Time 0, and then received their maintenance dose at Times 2 and 4 h. All participants were monitored for 3 h after receiving their last dose of medication. If a participant were to exhibit signs of acute opioid intoxication, s/he would not be permitted to participate in the study and would be referred to an appropriate outpatient or inpatient substance abuse treatment center; however, no participant had to be withdrawn from treatment in this study because of failing this procedure. Note that buprenorphine was administered in divided doses during the laboratory safety assessment only, but was given in single dose administrations for all groups throughout the study.

2.4. Behavioral treatment

All participants received standard lifestyle counseling during the course of treatment, based on the results of a survey of standard counseling in methadone clinics (Ball and Ross, 1991). All participants met with one of three, master's-level substance abuse therapists at least 1 h per week throughout treatment, during which time therapists helped participants make lifestyle changes in areas of employment, education, family interactions, social/recreational activities and relapse prevention. Participants also received HIV/AIDS education as part of this counseling.

2.5. Urinalysis procedures

All participants provided urine samples twice weekly (Monday and Friday), which were screened immediately on-site with the enzyme-multiplied immunoassay technique (Syva Corp., San Jose, CA). All specimens were screened for methadone, opiates, propoxyphene and cocaine, with one randomly selected specimen per week also screened for benzodiazepines. All urination procedures were observed by a research staff member. Participants were discharged from treatment if they missed three consecutive urinalysis dates. If a participant was terminated from treatment, s/he was offered a standard gradual buprenorphine taper or a clonidine-assisted detoxification and referred to an appropriate treatment facility. Blood alcohol levels were also analyzed via a breathalyzer at the time when urine specimens were collected. Blood alcohol levels had to be less than or equal to 0.05 g/ml for participants to receive medication.

2.6. Outcome measures

The primary outcome measures for assessing the relative efficacy of the three dosing regimens were: (1) opiate ab-

stinence examined as both number of weeks abstinent and longest period (in weeks) continuously abstinent, (2) cocaine abstinence examined in a similar manner as opiate abstinence, (3) combined opiate and cocaine abstinence examined in a similar manner as opiate abstinence, (4) treatment retention examined as time retained in treatment and percent of participants who completed the maintenance phase of the study, (5) HIV risk behavior as measured by drug and sex risk composite scores (past month) on the HIV risk behavior scale (HRBS) (Darke et al., 1991, 1992) and (6) addiction severity index (ASI) composite scores (McLellan et al., 1980).

2.7. Statistical analyses

Comparisons between treatment groups on baseline characteristics were performed using either analysis of variance or Kruskal–Wallis tests for continuous measures and chi-square tests for categorical variables. Analysis of variance was also used to compare treatment groups with respect to mean duration of documented continuous and non-continuous abstinence. Time to event analysis, utilizing a logrank test, was used to compare treatment groups on retention time. Additionally, a chi square test was used to compare groups on the percentage of subjects retained through the 24-week maintenance phase. Repeated measures analyses of variance were used for treatment comparisons corresponding to past month drug and sex risk composite scores on the HRBS collected at intake and every 4 weeks during the maintenance phase of treatment and ASI composite scores collected at intake, week 12 and 24 at the end of the maintenance phase of treatment. Means presented for the HRBS composite represent least square means, which adjust for the missing data due to incomplete follow-up. Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC).

Stepwise regression was used in a retrospective manner to identify participant characteristics that were significant predictors of continuous abstinence from opiates and cocaine and retention in treatment. Analyses were performed within each of the three dosing conditions, and across dosing conditions. The across-treatment analyses utilized interaction terms between predictors and treatment to potentially identify differential predictors of outcome for the three dosing conditions. Specifically, predictors included were participants': (1) gender, (2) education (in years), (3) marital status (currently married or other), (4) employment status (currently employed full-time or other), (5) age, (6) cocaine dependence (as measured by the DSM-IV), (7) travel distance to the research clinic, (8) history of previous treatment for opiate use, (9) number of years of regular opiate use, (10) score on the Michigan Alcohol Screening Test (MAST; Selzer, 1971), (11) score on the Beck Depression Inventory (BDI) (Beck et al., 1961), and (12) maintenance buprenorphine dose. The goal of these exploratory analyses was to identify specific sub-populations of opioid-dependent patients who may have more successful treatment outcome under specific dosing conditions. Such

Table 1
Participant characteristics by buprenorphine dosing condition

Characteristic (% of M ± S.D.)	Daily (n = 45)	Thrice weekly (n = 44)	Twice weekly (n = 45)
Demographics			
White	96	100	98
Male	67	68	56
Never married	49	41	44
High school education	84	80	78
Employed full-time	53	41	42
Age (in years)	33.44 ± 9.47	32.82 ± 9.51	33.76 ± 8.67
Monthly income (in dollars)*	970 (420, 1640)	842 (581, 1600)	800 (400, 1300)
Opioid use			
Prior treatment	64	73	56
Years of regular use	8.90 ± 8.38	8.44 ± 7.42	6.15 ± 5.38
Age of first use	20.98 ± 7.09	21.07 ± 6.41	22.61 ± 8.02
Dollars spent weekly on opioids*	350 (117, 840)	350 (68, 495)	467 (163, 700)
Preferred route			
Intravenous	62	64	71
Intranasal	29	20	20
Oral	9	16	9
Other drug dependence			
Alcohol	24	41	33
Cocaine	33	27	47
Sedative	18	9	9
Cannabis	27	30	23
ASI composite scales			
Medical	.23 ± .30	.26 ± .34	.30 ± .32
Employment	.54 ± .31	.52 ± .33	.54 ± .30
Alcohol	.10 ± .21 ^a	.15 ± .21 ^{ab}	.05 ± .08 ^{ac,a,**}
Drug	.38 ± .10	.36 ± .11	.37 ± .09
Psychiatric	.31 ± .25	.29 ± .25	.41 ± .23
Legal	.20 ± .24	.13 ± .20	.23 ± .27
Family social	.22 ± .23	.24 ± .22	.33 ± .27
Beck Depression Inventory Score	18.47 ± 13.76	21.33 ± 11.63	21.53 ± 10.70
Michigan Alcoholism Screening Test Score	14.44 ± 15.04	14.98 ± 14.20	9.82 ± 13.30
Mean Daily Buprenorphine Dose	7.2 ± 2.4	7.5 ± 2.4	7.4 ± 2.2

* Median (interquartile range).

** Significant difference between groups on alcohol ASI composite score, ANOVA letter $P < 0.05$. Means sharing a common are not significantly different and indicate that the 3 ×/ week dosing group had on this higher mean composite score measure compared to the 2 ×/ week dosing group.

information may be beneficial for matching opioid-dependent patients to buprenorphine dosing regimens in which they may have the greatest likelihood of a successful treatment outcome.

3. Results

3.1. Participant characteristics

A summary of the demographic characteristics of participants by treatment group is provided in Table 1. Participants in the three treatment conditions were well-balanced on all measured baseline characteristics with the exception of the alcohol composite score in which participants in the 3 × per week dosing condition had a significantly higher mean composite score on this measure compared to those in the 2 × per week dosing condition. However, scores on the Michigan Alcoholism Screening Test (MAST) did not significantly differ

across groups. Mean daily buprenorphine dose also did not significantly differ across groups.

3.2. Treatment retention

The percentage of participants retained in treatment for the entire 24 weeks of the maintenance phase was 69%, 73%, and 64% for the daily, 3 × per week and 2 × per week dosing conditions, respectively. The percentage of participants retained in treatment for the duration of maintenance treatment did not significantly differ across dosing conditions ($\chi^2_{(2)} = 0.71$; $P = 0.70$). The time-to-event distributions associated with retention for each group, presented in Fig. 1, were also not statistically significant across groups (log rank test $\chi^2_{(2)} = 0.58$; $P = 0.74$).

3.3. Opioid abstinence

No significant differences were detected in opioid abstinence across the three treatment groups. Percent of scheduled

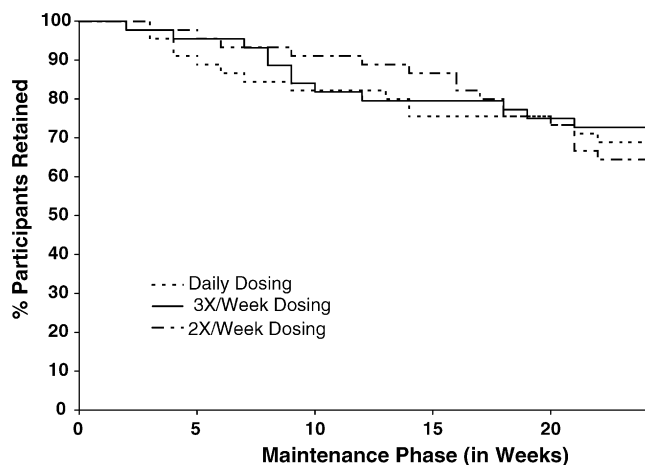


Fig. 1. Participant retention in maintenance treatment by buprenorphine dosing condition.

urines that were opioid-negative was 73%, 70% and 73% in the daily, 3× per week and 2× per week dosing conditions, respectively. As shown in Fig. 2, participants in the daily, 3× per week and 2× per week dosing conditions achieved an average of 12.3 (S.D. = 8.0), 10.2 (S.D. = 8.1) and 10.9 (S.D. = 8.3) weeks of continuous opioid abstinence while in maintenance treatment. This measure did not significantly differ

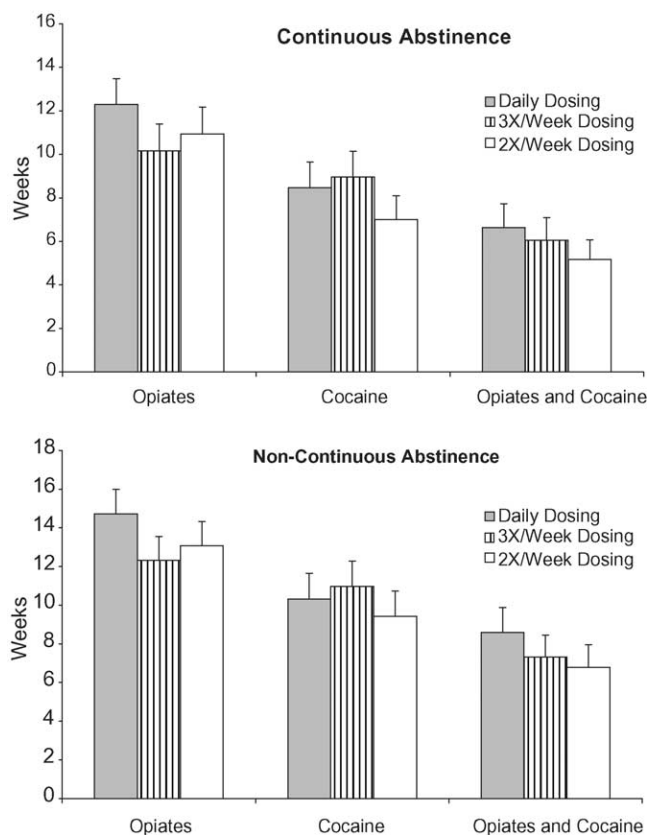


Fig. 2. Number of weeks continuously and non-continuously abstinent by buprenorphine dosing condition.

across dosing conditions ($F_{(2,131)} = 0.78$; $P = 0.46$). Additionally, participants in the daily, 3× per week, and 2× per week dosing groups achieved an average of 14.7 (S.D. = 8.4), 12.3 (S.D. = 8.2), and 13.1 (S.D. = 8.4) weeks (non-continuous) of opioid abstinence during the maintenance phase of the study. This measure also did not significantly differ across the three treatment groups ($F_{(2,131)} = 0.98$; $P = 0.38$).

3.4. Cocaine abstinence

No significant differences were detected in cocaine abstinence across the three treatment groups. As shown in Fig. 2, participants in the daily, 3× per week and 2× per week dosing conditions achieved an average of 8.5 (S.D. = 7.8), 8.9 (S.D. = 7.9), and 7.0 (S.D. = 7.3) weeks of continuous cocaine abstinence while in maintenance treatment. This measure did not significantly differ across dosing conditions ($F_{(2,141)} = 0.35$; $P = 0.71$). Additionally, participants in the daily, 3× per week, and 2× per week dosing groups achieved an average of 10.3 (S.D. = 10.5), 10.9 (S.D. = 8.6), and 9.4 (S.D. = 8.8) weeks (non-continuous) of cocaine abstinence during the maintenance phase of the study. This measure also did not significantly differ across the three treatment groups ($F_{(2,141)} = 0.78$; $P = 0.46$).

3.5. Opioid and cocaine abstinence

No significant differences were detected across the three treatment groups when abstinence from both opioids and cocaine were considered. As shown in Fig. 2, participants in the daily, 3× per weekly and 2× per weekly dosing conditions achieved an average of 6.6 (S.D. = 7.3), 6.0 (S.D. = 6.9), and 5.2 (S.D. = 6.1) weeks of continuous abstinence from both opioids and cocaine ($F_{(2,131)} = 0.55$; $P = 0.58$). Participants in the daily, thrice weekly and twice weekly dosing groups achieved an average of 8.6 (S.D. = 8.7), 7.3 (S.D. = 7.5), and 6.8 (S.D. = 7.9) weeks (non-continuous) of opioid and cocaine abstinence during the maintenance phase of the study ($F_{(2,131)} = 0.59$; $P = 0.56$).

3.6. HIV risk behavior scale (HRBS)

Both drug and sex risk behavior significantly decreased from baseline to the end of the maintenance phase, but there was no evidence of differential reduction across groups. Drug-related HIV risk behavior based on the past month drug risk composite scores on the HRBS significantly reduced from a mean score of 6.3 (S.D. = 6.1) at intake to a mean score of 1.4 (S.D. = 3.0) at the end of the maintenance phase of treatment ($F_{(1,749)} = 68.6$; $P < 0.001$). Additionally, sex-related HIV risk behavior measured via past month sex risk composite scores on the HRBS significantly reduced from a mean score of 3.7 (S.D. = 4.4) at intake to a mean score of 3.1 (S.D. = 3.3) at the end of the maintenance phase of treatment. Although the magnitude of change on the sex risk composite scores was less than that for the drug risk com-

posite scores, the change in sex risk composite scores was statistically significant ($F_{(1,749)} = 6.26$; $P = 0.01$).

3.7. Addiction severity index composite scores

Composite scores on the addiction severity index (ASI) at the time of treatment intake were highest on the scales for employment (mean = 0.53; S.D. = 0.32), Drug (mean = 0.37; S.D. = 0.10), and psychiatric (mean = 0.34; S.D. = 0.25); moderate on the scales for medical (mean = 0.26; S.D. = 0.32), family (mean = 0.26; S.D. = 0.24), and legal (mean = 0.19; S.D. = 0.24), and lowest on the scale for alcohol problems (mean = 0.10; S.D. = 0.18). With two exceptions for the alcohol and medical composite scores, all other composite scores significantly decreased from their intake levels during maintenance treatment ($P < 0.05$) ranging from a 6% decrease for the employment composite score to a 47% decrease for the legal composite score. The medical composite score increased 31% (to a mean of 0.34) from its intake level. The alcohol composite score did not significantly change, but rather was low at the time of treatment intake and remained low during the maintenance phase of treatment. No differential reductions in ASI composite scores across dosing groups were detected (all P -values > 0.05).

3.8. Predictors of treatment outcome

Results of the retrospective analyses identified three significant predictors of continuous opioid and cocaine abstinence within specific dosing conditions. Employment status significantly predicted continuous opioid and cocaine abstinence for participants in the daily dosing condition ($F_{(1,43)} = 4.59$; $P = 0.04$; $R^2 = 0.10$). Fulltime employment was associated with an estimated 4.5 weeks of additional continuous opioid and cocaine abstinence under the daily dosing regimen. Number of years of regular use of opioids at baseline significantly predicted continuous opioid and cocaine abstinence for participants in the three times weekly dosing condition ($F_{(1,41)} = 8.64$; $P = 0.005$; $R^2 = 0.17$). Each additional 5 years of regular opioid use at baseline predicted approximately 2.0 additional weeks of opioid and cocaine abstinence under a thrice weekly dosing regimen. Moreover, gender significantly predicted continuous opioid and cocaine abstinence for participants in the twice weekly dosing condition only ($F_{(1,43)} = 3.53$; $P = 0.06$; $R^2 = 0.08$). Females, on average, could expect approximately 3.3 more weeks of continuous opioid and cocaine abstinence compared to males under a twice weekly dosing regimen. No significant predictor of opioid and cocaine abstinence was identified when analyses were performed across the three dosing conditions.

When retention was examined as an outcome measure, no significant predictor was identified within any of the three dosing conditions. Analyses performed across the three dosing conditions indicated that the number of years of regular use of opioids significantly predicted treatment retention ($F_{(1,131)} = 5.66$; $P = 0.02$; $R^2 = 0.04$). Each additional 5 years

of regular opioid use at baseline predicted approximately one additional week of retained in treatment.

4. Discussion

This study was designed to enhance our understanding of the clinical efficacy of less-than-daily dosing schedules with buprenorphine for the treatment of opioid dependence. This clinical trial evaluated the relative efficacy of daily, thrice weekly and twice weekly dosing schedules with buprenorphine in the treatment of opioid-dependence.

Results demonstrated that daily, thrice weekly and twice weekly dosing regimens with buprenorphine were of comparable efficacy in promoting retention in treatment, opioid and cocaine abstinence, reductions in HIV risk behavior and reductions in severity of life problems as measured by the addiction severity index among opioid-dependent individuals. These findings are consistent with and expand on earlier work by our research group, which demonstrated that less-than-daily dosing with buprenorphine is preferred by opioid-dependent patients (Amass et al., 1998; Petry et al., 2001). These findings are also consistent with results reported by Schottenfeld et al. (2000) who compared a daily and thrice weekly dosing schedule of buprenorphine and found them to be equally efficacious in promoting treatment retention and opioid and cocaine abstinence. Moreover, the findings of the present study are also largely consistent with results reported by Pérez de los Cobos et al. (2000), who reported comparable treatment retention of patients in daily and thrice weekly dosing regimens. The finding by Pérez de los Cobos et al. (2000) that the thrice weekly dosing regimen was slightly less efficacious than the daily dosing schedule in reducing illicit opioid use was likely due to lower, sub-therapeutic dosages of buprenorphine used in that study compared to the doses used in the study by Schottenfeld et al. (2000) and in the present study, which employed doses shown to be clinically efficacious in a series of prior studies with buprenorphine (e.g., Johnson et al., 1992; Strain et al., 1994; Ling et al., 1996). The present study expanded this prior research by including a twice weekly dosing schedule in the evaluation, by evaluating the dosing schedules for a longer duration, and by requiring participants to attend the treatment facility only on days they were scheduled to receive medication.

The finding that both thrice and twice weekly dosing schedules are as efficacious as a daily dosing regimen is of great clinical significance. Indeed, by allowing patients to attend a treatment setting less often, they have greater opportunities to engage in alternative, reinforcing activities, such as gainful employment, and make progress toward treatment goals. Additionally, less-than-daily buprenorphine dosing provides the opportunity for treatment programs to expand their number of treatment slots and thereby treat a greater number of opioid-dependent individuals. Moreover, administering buprenorphine on a less-than-daily basis allows for more flexible dosing schedules than provided by

daily dosing with methadone. It also enables the medication to be delivered without an associated risk of diversion, which is sometimes a concern associated with take-home doses of methadone medication. Importantly, this concern regarding medication diversion is frequently cited as a reason for lack of community support of treatment programs for opioid dependence. Thus, less-than-daily buprenorphine administration may have a positive impact on community support of science-based treatment for opioid-dependence.

Due to its pharmacology, buprenorphine was designated a schedule III medication for the treatment of opioid dependence in the U.S. As a result, buprenorphine may be provided to opioid-dependent patients by qualified physicians in both Opiate Treatment Clinics and office-based settings (Drug Addiction Treatment Act of 2000; Fiellin and O'Connor, 2002; Fudala et al., 2003). Although these benefits of less-than-daily dosing schedules with buprenorphine may be best realized when it is prescribed in an Opiate Treatment Clinic, the benefits may also apply to buprenorphine treatment in an office-based setting. That is, patients would not be required to consume the medication on a daily schedule but could follow a less-than-daily schedule. Also, although buprenorphine may be prescribed for up to a month at a time, patients in their early stabilization stages of treatment and/or those for whom medication diversion is a concern could effectively be provided with onsite, observed less-than-daily dosing as needed.

Another novel and clinically important aspect of the present clinical trial was the examination of significant predictors of treatment outcome to identify if specific subpopulations of opioid-dependent individuals may have a more positive treatment outcome under different buprenorphine dosing conditions. Although predictors of outcome in methadone treatment has been studied rather extensively (e.g., Alterman et al., 1998; Hser et al., 1990/1991; Magura et al., 1998; McLellan et al., 1983; Saxon et al., 1996; Strain et al., 1998), research on predictors of outcome in buprenorphine treatment has been limited (Gerra et al., 2004; Petry and Bickel, 1999, 2000). Three significant and clinically meaningful predictors of treatment outcome emerged and differentiated between the three dosing conditions. It is important to note that the analysis of predictors of treatment outcome was retrospective and should be interpreted with caution until the conditions under which these effects can be replicated can be identified.

First, individuals who were employed full-time had more positive outcomes on measures of opioid and cocaine abstinence under a daily buprenorphine dosing schedule relative to those not employed full-time. This finding may suggest that opioid-dependent individuals who are able to maintain stable employment may also be able to maintain the daily requirement of attending a treatment program. The research clinic where this study was conducted offered clinic hours in both the early morning as well as late in the day to best accommodate the schedules of patients who were employed. This procedure likely functioned to support the successful

treatment outcomes of participants who were employed full-time.

Second, males were shown to have poorer outcomes on measures of opioid and cocaine abstinence compared to females under a twice weekly buprenorphine dosing schedule. This finding was not shown to be related to participants' number of prior treatment attempts, years of regular opioid use, or buprenorphine maintenance dose, as male and female participants were shown to not significantly differ on these variables. Although gender has previously been shown to be a weak predictor of outcome for opioid-dependent individuals in methadone treatment (Strain et al., 1998), little research has explored this issue in buprenorphine treatment. This finding may preliminarily suggest that opioid-dependent males entering buprenorphine treatment may best be placed on a dosing schedule that requires greater than twice weekly clinic attendance; however, future studies should assess the extent to which this effect is replicable.

Third, having a greater number of years of regular use of opioids was shown to predict greater opioid and cocaine abstinence under a 3 × per week dosing schedule. Individuals who have used opiates for a greater number of years are clearly more experienced in the use of opioids and may have greater familiarity with the limited treatment options available for the treatment of opioid-dependence, which have typically required daily medication administration. It may be that a thrice weekly dosing may provide an optimal level of contact between an individual seeking substance abuse treatment and the treatment clinic. That is, thrice weekly dosing may enable participants to become sufficiently invested in their treatment attempt, while still allowing them to engage in other reinforcing activities, including interactions with non-drug using contacts, on non-clinic days. This association between having a greater number of years of regular opioid use was not specific to the outcome measures of opioid and cocaine abstinence, however, but rather also predicted (to a lesser degree) greater treatment retention among participants in all dosing conditions. This finding may underscore a "maturing out" phenomenon, such that those individuals with a greater number of years of opiate use and likely more attempts to discontinue their use may be especially invested in treatment with buprenorphine compared to those with a shorter history of opioid use.

One limitation of the present study is that it employed the sublingual buprenorphine solution instead of the sublingual buprenorphine tablets or combined buprenorphine plus naloxone tablets, which are the formulations of buprenorphine that have been approved for use in clinical practice. The findings of the present study should ideally be replicated with the buprenorphine mono and the combined buprenorphine/naloxone combination tablets (when patients consume large doses of naloxone along with buprenorphine); however, there is little reason to think that a different outcome would be achieved in such an evaluation, as long as the lower bioavailability of buprenorphine tablets is considered when selecting doses (the tablets are about half as bioavailable as

the buprenorphine solution with acute administration; however, recent research has shown that the bioavailability of buprenorphine plus naloxone tablets becomes more comparable to the buprenorphine solution after chronic administration (see Mendelson et al., 1996; Nath et al., 1999; Strain et al., 2004) and clinically appropriate, equi-effective doses of the buprenorphine tablet are examined. Also, future studies with the sublingual tablet formulations may assess the extent to which patients may experience challenges with consuming multiple tablets at once due to quantity of tablets and their dissolution time.

In sum, the finding that both thrice and twice weekly dosing with buprenorphine is as efficacious as daily buprenorphine administration in promoting positive treatment outcomes on a wide variety of measures is of considerable relevance to clinical practice. Such less-than-daily dosing schedules may have positive benefits for patients (e.g., less attendance required; more time to initiate new behavioral patterns that do not involve drug use), treatment providers (enables an expansion of treatment slots), and the greater community (no risk of medication diversion), which may cumulatively have a positive impact on expanding the acceptability and reach of science-based treatment for opioid-dependence.

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