Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine–naloxone tablet

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Abstract

This study evaluated the efficacy of a combination tablet formulation of buprenorphine containing 8 mg of buprenorphine and 2 mg of naloxone for every other day treatment and whether increasing the daily maintenance dose was essential for maintaining an efficacious alternate-day treatment. Twenty-six opioid-dependent outpatients completing a 16-day baseline entered a double-blind, placebo-controlled, triple crossover trial. Twenty-one days of daily combination tablet administration were compared to two different 21-day periods of alternate-day buprenorphine administration where subjects received either 8 or 16 mg of the combination tablet every other day with placebo on the interposed day. Fifty-four percent (14/26) of subjects completed the study, but only two subjects dropped out during the 16-mg alternate-day condition. Rates of medication compliance, illicit opioid use and subject- and observer-rated measures of opioid effects did not distinguish daily from alternate-day treatments in subjects completing the study. However, pupillary diameter was significantly increased during 8-mg alternate-day compared to the 8-mg daily or 16-mg alternate-day treatment. These data replicate earlier findings describing the acceptability of alternate-day buprenorphine treatment using multiples of the daily maintenance dose and extend these findings by establishing the clinical efficacy of daily and alternate-day dosing regimens with the combination buprenorphine–naloxone tablet. This study also suggests slightly improved outcomes during alternate-day treatment using multiples of the daily dose. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Alternate-day dosing; Buprenorphine; Buprenorphine–naloxone; Heroin treatment; Human; Methadone treatment

1. Introduction

Buprenorphine is a high affinity, partial μ-opioid agonist pending FDA approval as a pharmacotherapy for opioid dependence (see Bickel and Amass, 1995). Buprenorphine’s utility as a pharmacotherapy results from a unique profile of effects related to its partial agonist character and slow dissociation from μ-opioid receptors. Buprenorphine’s ceiling on agonist activity decreases the danger of overdose, may limit its abuse liability (Walsh et al., 1994, 1995) and confers low toxicity even at high intravenous doses (Lange et al., 1990; Huestis et al., 1999), increasing the dose range over which it may be safely administered. Buprenorphine can also produce sufficient tolerance to block the effects of exogenously administered opioids (Bickel et al., 1988a; Rosen et al., 1994; Walsh et al., 1995), suggesting that it may help reduce illicit opioid use. Finally, buprenorphine’s slow dissociation from μ-opioid receptors (Rance and Dickens, 1978) not only results in a long duration of action but also diminishes withdrawal signs and symptoms upon its discontinuation (Jasinski et al., 1978; Seow et al., 1986; Fudala et al., 1990; Amass et al., 1994b; Bickel et al., 1995, 1997; Cheskin et al., 1994), making it particularly useful for opioid detoxification.

Controlled clinical evaluations confirm buprenorphine’s utility for opioid dependence treatment. Studies comparing the relative efficacy of a sublingual buprenorphine solution to oral methadone have reported comparable retention and abstinence rates for up to 25 weeks of maintenance and detoxification treat-
tablet dosages will be 8 mg of buprenorphine and 2 mg of naloxone, respectively. The combination tablet was developed to help mitigate potential diversion and abuse of buprenorphine once it becomes available for widespread clinical use and is expected to be particularly useful sublingually because of the different parenteral to sublingual potencies of buprenorphine and naloxone. While buprenorphine has an approximately 2:1 parenteral to sublingual potency ratio (McQuay et al., 1986), studies with opioid-dependent subjects indicate a parenteral to sublingual potency ratio up to 20:1 for naloxone (Preston et al., 1990). A sublingual naloxone dose up to five times greater than the intravenous dose that reverses toxic opioid overdose can be administered safely to opioid abusers without precipitating withdrawal (Preston et al., 1990). Thus, this combination tablet may permit buprenorphine’s agonist effects to be expressed when administered sublingually, in essence, permitting the combination tablet to behave like buprenorphine alone, while precipitating withdrawal if administered parenterally by opioid-dependent individuals.

Less than daily dosing strategies have not been evaluated using the buprenorphine–naloxone combination tablet and no studies have been published in which the two different alternate-day dosing strategies noted above have been directly compared to each other and to daily dosing. The purpose of the present study was to establish the clinical efficacy of alternate-day buprenorphine treatment using the combination buprenorphine–naloxone tablet and determine whether using multiples of the daily dose during alternate-day dosing was essential for providing an efficacious alternate-day treatment. Daily dosing with the combination tablet was compared to alternate-day combination tablet dosing during which either the daily dose or a multiple of the daily dose was dispensed every other day.

2. Methods

2.1. Subjects

Forty-seven opioid-dependent subjects (33 male, 14 female) participated in an 11-week outpatient study. Subjects were recruited through newspaper and poster advertisements and referred from local treatment programs. To be included in the study, subjects had to be at least 18 years old, in good health, and meet DSM-IV criteria for opioid dependence and FDA criteria for methadone treatment [i.e. a history of opioid dependence and either significant current opioid use (i.e. opioid-positive urines) or signs of opioid withdrawal (i.e. gooseflesh, sweating, lacrimation, excessive yawning, etc.)]. Eligibility was determined via a comprehen-
The interview included online administration of computerized versions of the psychoactive substance abuse disorder sections of the DSM-IV Criteria Checklist (modified from Hudziak et al., 1993) and the fifth edition of the Addiction Severity Index (McLellan et al., 1985). Additional questionnaires were also completed to provide information about demographics and drug history. Health status was determined by medical history, physical exam and laboratory evaluation (including complete blood count, clinical chemistry profiles and urinalyses). Exclusion criteria included evidence of active psychosis, manic-depressive illness, organic psychiatric disorders or serious medical (e.g. liver or cardiovascular disease) illness. Co-dependence on other drugs (e.g. cocaine, ethanol or sedative-hypnotics) did not exclude individuals from participation.

The study was approved by the Colorado Multiple Institution Review Board for human research. Subjects provided written, informed consent after receiving a full explanation of the procedures prior to their inclusion in the study. Participants were required to pay a fee averaging $60/month to help support clinic services; no subjects were discharged due to non-payment of fees.

Subjects’ mean age was 42.4 years (range 22–64). Subjects reported using opioids regularly for an average of 16.5 years (range 1–45) and spending $386.49 (range $105–1750) per week on opioids. Thirty-eight subjects reported primarily intravenous, seven reported primarily intranasal and two reported primarily intramuscular opioid use. Forty subjects reported having received methadone treatment previously. Eleven subjects transferred from a methadone maintenance program directly into this study. Weekly pregnancy tests (urine hCG, Abbott Laboratories) for the 14 female subjects were negative throughout the study.

2.2. Buprenorphine induction and stabilization

A 2-day, rapid induction procedure was used in accordance with published guidelines for transitioning patients onto buprenorphine (Bickel and Amass, 1995). On the first day of participation, the first 29 subjects enrolled in the study received two combination tablets that each contained 2 mg of buprenorphine and 0.5 mg naloxone, comprising a total dose of 4 mg of buprenorphine and 1 mg of naloxone. On the second day of participation, these subjects received one tablet containing 8 mg of buprenorphine and 2 mg of naloxone. Following complaints of withdrawal symptoms by seven (24%) of the 29 subjects on the second day of participation, the induction procedure was changed so that the next 18 subjects were induced with buprenorphine alone rather than the combination tablet. On the first day of participation, these latter 18 subjects received two tablets that each contained 2 mg of buprenorphine, comprising a total dose of 4 mg buprenorphine. On the second day of participation, these 18 subjects received one tablet containing 8 mg of buprenorphine. Only two (11%) of the 18 subjects inducted with buprenorphine alone complained of withdrawal symptoms on the second day of treatment.

Following buprenorphine induction, subjects received one placebo tablet and one combination tablet containing 8 mg of buprenorphine and 2 mg of naloxone each day for the next 14 days (days 3–16) to establish a treatment baseline. The purpose of this baseline was (1) to stabilize subjects on a 24-h dosing schedule of the buprenorphine–naloxone tablet and (2) to allow a period during which early treatment dropouts could be identified and culled from the final target study sample of at least 24 participants as determined by a prior power analysis. On day 2, subjects were told “This is your maintenance dose” by the dispensing nurse. On all subsequent days, subjects were not instructed regarding what doses they were receiving.

2.3. Medication administration

Placebo, buprenorphine-alone and buprenorphine combination tablets were manufactured by Reckitt and Colman Products (Hull, UK) and supplied through the National Institute on Drug Abuse and Research Triangle Institute. Active tablets were flavored, white, flat and oval-shaped with a beveled edge; placebo tablets were matched in flavor, color, shape and size. Dosing conditions were double-blind and doses were masked for taste with a 1-ml sublingual flavor solution of Bitrex granules (6 µg/ml; Macfarlan-Smith Ltd., Edinburgh, UK) and peppermint spirits (Amass et al., 1994a, 1998). Subjects swished the flavor solution in their mouth for 1 min and discarded it into a cup before receiving medication each day. The dispensing nurse gave the day’s tablet(s) to the subject in a plastic cup and instructed the subject to hold the tablet(s) under the tongue until dissolved.

2.4. Study design

Beginning on day 17, subjects received in randomized order each of three, 21-day dosing conditions: 8 mg/24 h, 8 mg/48 h and 16 mg/48 h. Subjects were instructed before the study that they would receive medication in each of three ways, but would not be told when dosing conditions changed. For ‘24-h dosing’, subjects were told they would receive their daily dose each day. For ‘48-h “single” dosing’, subjects were told they would receive their daily dose (i.e. a single dose) every other day with inactive placebo (blank) doses on the other days. For ‘48-h “double” dosing’, subjects were told they would receive twice their daily dose (i.e. a double
dose) every other day with placebo (blank) doses on the other days. Every subject was scheduled to experience each of the three dosing schedules according to one of six possible sequences. Subjects were randomly assigned to one of these dosing schedule sequences, and the order in which the dosing schedules were received was balanced across subjects.

2.5. General procedures

Subjects were compensated for their study participation according to a contingent compensation schedule designed to reinforce opioid abstinence and clinic attendance. Subjects received $2 for each opioid-negative sample provided and $2 each day they attended the clinic (defined as taking their scheduled dose of medication and completing any questionnaires). Further, if subjects provided three opioid-negative urine samples and attended all 7 days during any given treatment week, they received a bonus of $5. Thus, subjects could be compensated up to $25 per week and could earn a maximum of $275 for completing the 11-week study.

Subjects who did not complete the study for any reason were offered detoxification with buprenorphine, transfer into the methadone or LAAM maintenance programs within our service, or referral to another local treatment facility. Buprenorphine detoxification was accomplished by decreasing the subject’s buprenorphine dose by 2 mg a week until a zero dose was reached. Subjects were withdrawn from the study and offered alternative treatment if they failed to take their medication on three consecutive days and/or failed to provide urine samples on five consecutive occasions.

Urine samples were collected thrice weekly (Mondays, Wednesdays and Fridays) before medication administration under observation and analyzed for the presence of opioids using the enzyme multiplied immunoassay technique (Behring Corporation, San Jose, CA). Samples were also analyzed for the presence of cocaine metabolites, amphetamines, benzodiazepines, barbiturates and cannabinoids on one randomly chosen day per week. Cutoff calibration concentrations of 300 ng/ml were used for tests of opioid and cocaine metabolites, 200 ng/ml for benzodiazepines and barbiturates, 50 ng/ml for cannabinoids and 1000 ng/ml for amphetamines. Missed urine samples were considered drug-positive for the purposes of data analysis. Breath alcohol samples were collected on urine testing days as part of routine clinical procedure and subjects were not permitted to attend the clinic intoxicated.

2.6. Counseling

Subjects received individual, manualized behavioral counseling sessions (L. Amass, unpublished) with a trained therapist every other week for the duration of the study. Additionally, subjects could also participate in weekly group counseling sessions. Therapy sessions focussed primarily on helping subjects make lifestyle changes in the areas of their drug use, employment, family interactions, and social/recreational activities. Subjects also received AIDS education.

2.7. Subject- and observer-rated measures

Subject- and observer-rated measurements were collected every day prior to medication administration using a Macintosh Powerbook 520 computer (Apple Computer, Inc., Cupertino, CA) running custom-designed data acquisition software (BioPsych Consulting, Denver, CO). Subjects completed an adjective rating scale (Bickel et al., 1988a,b), six visual analog scales (VAS), the Addiction Research Center Inventory (ARCI) short form (Martin et al., 1971; Jasinski, 1977) and a dose identification questionnaire (Amass et al., 1994a, 1998). Subjects were instructed to respond to these questions according to their experience over the past 24 h. The adjective rating scale was comprised of 16 signs and symptoms of opioid withdrawal and 16 typical opioid agonist effects. Subjects rated themselves on a scale ranging from 0 (none) to 9 (severe) (maximum cumulative score = 144). The items in the opioid withdrawal scale were muscle cramps, depressed or sad, painful joints, excessive yawning, hot or cold flashes, trouble getting to sleep, sick to stomach, irritable, runny nose, poor appetite, weak knees, excessive sneezing, tense and jittery, watery eyes, abdominal cramps and fitful sleep. The items in the opioid agonist effects scale were drug effect, loaded or high, rush, flushing, excessive sweating, nodding, dry mouth, turning of stomach, itchy skin, relaxed, coasting or spaced out, talkative, pleasant sickness, drive, nervousness and drunken. The VAS items were: “How HIGH have you been?”, “Have you felt any DRUG EFFECT at all?”, “Have you felt any GOOD drug effects?”, “Have you felt any BAD drug effects?”, “Have you felt any WITHDRAWAL SICKNESS?” and “How much did you LIKE the drug effect?” Subjects positioned a cursor on the computer screen and clicked along a 100-unit line, anchored at each end by ‘Not at all’ and ‘Extremely’. The ARCI short form consisted of 49 true/false items and contained five major subscales: MBG, PCAG, LSD, and BG and A, an index in opioid-abusing subjects of euphoria, sedation, dysphoria and stimulation, respectively. For the dose identification questionnaire, subjects responded to the question, “What do you think you received for your medication yesterday?” by choosing “Placebo (no dose)”, “Single dose of buprenorphine” or “Double dose of buprenorphine”.

Nursing staff blind to the treatment conditions completed an observer rating inventory on which they rated...
the subjects on a scale of 0 (not at all) to 9 (severe) on seven signs of opioid withdrawal (tearing eyes, runny nose, perspiration, gooseflesh, yawning, restlessness, tremor; maximum cumulative score = 63) and five signs of opioid effects (skin itching, vomiting, sedation, nodding, soap-boxing and rapping; maximum cumulative score = 45). This observer-rating scale, based on Addiction Research Center agonist and withdrawal scales (Himmelsbach, 1939; Jasinski et al., 1978), has been used previously in similar studies of alternate-day dosing (Amass et al., 1994a, 1998; Bickel et al., 1999).

2.8. Pupil measurements

Pupil diameter was determined daily before medication administration. Photographs were taken of one of the subject's eyes with a Polaroid close-up camera at 2 × magnification at 1 foot-candle of ambient illumination (Amass et al., 1994a; Bickel et al., 1999).

2.9. Data analysis

The study sample was classified into three groups for the purposes of data analyses: ‘dropouts’ (n = 21) were defined as those subjects who left treatment sometime during the 16-day baseline period; ‘non-completers’ (n = 12) were defined as those subjects who completed the baseline period but left the study at some point during exposure to the three 21-day treatment conditions; and ‘completers’ (n = 14) were defined as those subjects who completed the entire study.

Analyses of variance (ANOVAs) were used to compare dropouts, non-completers and completers on selected intake measures (e.g. ASI composite scores, number of DSM-IV Substance Dependence or Abuse diagnoses, age and years of regular opioid use) to determine if any of these characteristics distinguished these groups from one another. Similarly, repeated measures ANOVAs were used to compare non-completers and completers on average baseline measures of subject- and observer-rated effects to determine if baseline responding could predict early treatment termination. Wilcoxon rank sum tests, appropriate for comparing two groups with non-normally distributed data, compared differences in the mean number of drug-positive urines obtained during baseline for the non-completer and completer groups.

Finally, data from the 14 completers were used to compare the efficacy of the three 21-day treatment conditions. Each dependent variable was reduced to an average (e.g. self-reports, pupil diameter) or sum (e.g. positive/missed urines, medication compliance) across each treatment condition. Repeated measures ANOVA were then performed with the subject effect treated as random. Similar analyses were conducted to evaluate day-to-day fluctuations in the dependent variables within each treatment condition. These latter analyses were done to elucidate any potential differences between active drug and placebo days during alternate-day dosing (or between odd and even days during daily dosing).

Analyses were conducted using SAS (SAS Institute Inc., 1996) statistical software. All tests were two-tailed and statistical significance was specified at α = 0.05.

3. Results

3.1. Buprenorphine induction

Seven (24%) of the 29 subjects inducted with combination products complained of withdrawal symptoms sufficient to warrant notation by medical staff on the second day of participation. The symptoms consisted of prototypic signs of opioid withdrawal including sweating, runny nose, chills and vomiting. By comparison, only two (11%) of the 18 subjects inducted with buprenorphine alone products complained of withdrawal symptoms on the second day of treatment.

Of the 29 subjects inducted with combination tablets, six subjects (21%) had transferred into the study from methadone-maintenance programs. The average methadone dose at the time of transfer onto buprenorphine was 50 mg (range 35–60). Of the seven subjects who had reactions following combination tablet induction, four (57%) were methadone-maintenance transfers receiving an average methadone maintenance dose of 48 mg (range 35–60) at the time of buprenorphine induction.

Of the 18 subjects inducted with buprenorphine alone tablets, three subjects (17%) had transferred into the study from methadone-maintenance programs. The average methadone dose at the time of transfer onto buprenorphine was 39 mg (range 30–44). The two subjects who had reactions following induction with buprenorphine alone products were both illicit users of heroin and did not transfer into the study from a methadone-maintenance program.

3.2. Treatment retention and post-study status

Forty-five percent of the subjects (21/47) dropped out during the treatment baseline. Six of these subjects dropped out following the first or second day, six did so following the fourth, sixth or seventh day and the remainder dropped out after 8–13 days. Eight of these subjects dropped out abruptly and did not provide a reason for leaving; two subjects left due to difficulty adjusting to the medication; two subjects left because their friend discontinued the study; one subject left due to administrative problems at the clinic; and two subjects left due to inability to commute to the clinic each
day. Four of these subjects later returned to participate in an efficacy evaluation of buprenorphine–naloxone and methadone (Amass et al., 2000a); one transferred to methadone maintenance treatment at another facility; and one who had been in the present study for only a few days later returned to participate in another laboratory study at the center (Amass et al., 2000b).

Fifty-five percent of the subjects (26/47) initiated at least one of the three treatment conditions. Of these 26 subjects, 54% (14/26) completed the study. Of the 12 subjects who did not complete the three treatment conditions (i.e. non-completers), five dropped out during the 8 mg/24 h condition, five dropped out during the 8 mg/48 h condition and two dropped out during the 16 mg/48 h condition. The condition under which the non-completer subjects left the study did not vary as a function of the order to which they were exposed to the treatment conditions.

Of the 12 non-completers, four left treatment abruptly and did not provide a reason for leaving, seven later returned to participate in an efficacy evaluation of buprenorphine–naloxone and methadone (Amass et al., 2000a), and one transferred to methadone maintenance treatment at another facility.

Of the 14 completers, 12 subjects transferred directly into another efficacy evaluation of buprenorphine–naloxone and methadone (Amass et al., 2000a) and two requested detoxification with buprenorphine–naloxone. One of these two subjects completed detoxification and continued on naltrexone; the other subject left treatment during the detoxification without providing a reason.

3.3. Intake differences amongst dropouts, completers and non-completers

Subjects who dropped out of the study during the baseline condition had significantly higher Addiction Severity Index (ASI) Drug Problem composite scores than those who completed the study (t = 2.53, P = 0.01; data not shown). Dropout’s ASI scores did not differ from those obtained from non-completers. No other significant differences were observed on intake variables among these three groups of subjects.

3.4. Baseline differences amongst completers and non-completers

Completers differed significantly from non-completers on several baseline measures of self-reported drug effects as well as on the degree of illicit opioid use during baseline. Mean baseline subject-reported opioid withdrawal effect ratings (F = 7.87, P = 0.01), opioid agonist effect ratings (F = 7.84, P = 0.01), and visual analog scale ratings of ‘bad drug effects’ (F = 6.90, P = 0.01), ‘withdrawal sickness’ (F = 7.90, P = 0.01) and ‘drug effect’ (F = 4.57, P = 0.04) were significantly lower in completers compared to non-completers (Fig. 1). Moreover, completers submitted significantly fewer opioid-positive urine samples than non-completers during the baseline (z = 2.22, P = 0.03; Fig. 2).

3.5. Condition effects: treatment completer sample

3.5.1. Medication compliance

There were no differences in compliance across the three dosing conditions. Subjects were medicated on 86%, 84% and 88% of days during the 8 mg daily, 8 mg and 16 mg alternate-day conditions, respectively.

3.5.2. Illicit drug use

The percentages of drug-positive urine samples obtained from subjects who completed the study are shown in Table 1. There were no significant differences in the number of drug-positive samples obtained across conditions.

3.5.3. Subject- and observer-rated measures

Subject- and observer-rated measures did not differ across the three treatment conditions. There were also no significant day-to-day fluctuations (i.e. odd versus even day differences) within each treatment condition on any of these measures.

3.5.4. Pupil diameter

Average pupil diameter differed significantly across each 21-day treatment condition (F = 4.02, P = 0.03; Fig. 3). Mean pupil diameter was significantly larger during the 8 mg/24 h condition (4.1 ± 0.25) than it was during the 16 mg/48 h condition (3.8 ± 0.25; t = −2.79, P = 0.01) and there was a trend toward larger pupil diameter during the 8 mg/48 h condition as compared to the 8 mg/24 h condition (3.9 ± 0.25; t = −1.82, P = 0.08). There were no significant day-to-day fluctuations within each treatment condition in pupil diameter.

3.5.5. Dose identifications

There were no significant differences across conditions in the percentage of time subjects identified the medication as a ‘Single dose’, a ‘Double dose’ or a ‘Placebo dose’ (data not shown). When data were collapsed across all three conditions, subjects identified their dose as a ‘Single dose’ on 54% of occasions, as a ‘Double dose’ on 10% of occasions and as a ‘Placebo dose’ on 36% of occasions. The distribution of dose identifications within each treatment condition and across days (i.e. odd versus even) within each condition were similar.
4. Discussion

The combination buprenorphine–naloxone tablet was as acceptable and effective when administered on alternate days as when administered every day. There were no reports of any significant opioid agonist or withdrawal effects by subjects or staff during the study, and rates of medication compliance and drug abstinence were roughly equivalent across daily and alternate-day conditions. These results compliment other placebo-controlled studies comparing daily versus alternate-day dosing using the 8 mg buprenorphine-only solution formulation (Fudala et al., 1990; Amass et al., 1994a, 1998; Johnson et al., 1995) and extend these earlier studies by establishing efficacy of alternate-day dosing with the combination buprenorphine–naloxone tablet. Further, increasing the daily dose of buprenorphine may not be essential for use with alternate-day combination tablet dosing, although doing so may retain more patients in treatment when dosing every other day since fewer subjects dropped out during the present study’s 16-mg (double-dose) alternate-day condition. Overall, alternate-day dosing studies support the notion that slightly better outcomes with alternate-day dosing are likely when higher doses are used (Fudala et al., 1990; Amass et al., 1994a, 1998; Johnson et al., 1995). The current study’s results raise five important points.

First, procedures for transitioning patients onto the combination tablet should be given careful consideration. Twice as many subjects inducted with the combi-
Table 1
Percentage of urine samples positive for drugs of abuse a

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<tr>
<td>Barbiturates</td>
<td>7</td>
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a N = 14, treatment completers.

Fig. 3. Mean pupillary diameter (mm) obtained during each 21-day exposure to the three dosing conditions from the 14 patients who completed the study. Vertical bars indicate ±1 S.E.M. Asterisk denotes significant difference from 8 mg/24 h and 16 mg/48 h conditions.

Second, a number of subjects in this study dropped out during the first 2 weeks of treatment or failed to complete the entire study. One possibility is that the fixed dose protocol led to some candidates not receiving an optimal clinical dose of the combination tablet. This theory is consistent with our observation of increased self-reports of adverse effects and greater illicit opioid use in the non-completer sample. Further, the bioavailability of tablet preparations of buprenorphine may be about 50–60% of the corresponding sublingual solution dose (Mendelson et al., 1996; Schuh and Johanson, 1999) and higher doses of the combination tablet may have reduced the number of drop outs in this study.

Third, the results of the present alternate-day dosing evaluation differ from an earlier report with regard to obtained differences in self-report measures across daily and alternate-day dosing where sample sizes and study settings were similar. Pupil diameter was the only dependent measure that distinguished the three dosing conditions in the present study, whereas earlier work (Amass et al. 1998) revealed small but significant differences between daily and alternate-day dosing on several subject-rated measures of opioid effects as well as discriminations of active from inactive medication during alternate-day dosing. Similarly, our results differ from those reported in another placebo-controlled study in which subjects receiving 8 mg of the solution formulation of buprenorphine every other day on a residential research ward reported increased withdrawal scores relative to subjects receiving 8 mg every day (Fudala et al., 1990). However, a significant methodological difference between the present study and these earlier studies was the absence of mandated abstinence and compliance procedures. Those procedures were eliminated in the current study to permit comparison of the efficacy of the dosing schedules on standard measures such as drug use and treatment retention. Although compliance rates were good in the present study, over 50% of urine samples were positive for opiates across the dosing conditions. This supplemental opioid use likely obscured any potential differences in subject ratings across conditions that might have otherwise been observed. Although this rate of supplemental opioid use is not optimal, it is consistent with the pattern of drug use reported in other controlled trials of alternate-day buprenorphine treatment (Johnson et al., 1995), as well as controlled comparisons of buprenorphine to methadone (Strain et al., 1994; Ling et al., 1996).

Fourth, the present study attests to the safety of using a combination product for alternate-day dosing when multiples of the daily maintenance dose are administered. Up to 4 mg of sublingual naloxone was administered every other day during the 16 mg/48 h dosing condition. No adverse reactions were observed in response to doubling a subject’s maintenance dose in any of the subjects studied. This latter finding is consistent with laboratory studies of sublingual naloxone in opioid dependent subjects (Preston et al., 1990). Even higher levels of sublingual naloxone (i.e. up to 6 mg) are well tolerated with the combination tablet as suggested by studies with 3-day combination tablet dosing (Amass et al., 2000b).
Fifth, this study’s limitations reduce the generality of the findings to most clinical settings. For example, a relatively small number of subjects were studied, the duration of treatment was short, a fixed dose protocol was used, and patients with active psychiatric comorbidity were excluded from participation. Certainly, the fixed dose protocol may have led to some candidates not receiving an optimal clinical dose of the combination tablet and may have affected early subject attrition. The high rate of study drop outs may have also reduced power to detect differences across treatments, although the crossover, counterbalanced design allowed each subject to serve as their own control. Studies that address these limitations are needed.

Buprenorphine’s use as both a daily and alternate-day treatment has practical and therapeutic value. Alternate-day buprenorphine treatment is a clinically viable alternative to daily dosing that does not increase the risk of medication diversion typically associated with take-home agonist therapy (Goldman and Thistel, 1978; Kirn, 1988). Although the combination tablet was developed to allow take-home dosing while mitigating diversion, the abuse liability of the combination tablet awaits further study. There may still be occasions when patient instability may warrant withholding take-home medication for protective reasons. The combination tablet can also be used on a 3-day dosing schedule (e.g. Monday–Wednesday–Friday) and, like alternate-day dosing (Amass et al., 1998), this thrice-weekly dosing schedule is preferred by subjects to daily dosing (Amass et al., 2000b). When the use of take-home medication is not warranted, alternate-day dosing may also augment patient outcomes during buprenorphine therapy since reducing dosing frequency early in treatment increases retention in opioid dependent individuals (Rhoades et al., 1998). Finally, alternate-day (and thrice-weekly) dosing is a feature of buprenorphine that may promote its use in multiple settings, including primary care and office-based practices. Such use may facilitate expanding models of opioid maintenance therapy and help better address the ever growing problem of heroin addiction.

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