Thrice-weekly supervised dosing with the combination buprenorphine-naloxone tablet is preferred to daily supervised dosing by opioid-dependent humans

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Abstract

A sublingual tablet formulation of buprenorphine combining 8 mg of buprenorphine with 2 mg of naloxone is being targeted for use in settings where less than daily dosing strategies and/or prescription-based dispensing will likely be employed. This study determined patient preferences for, and clinical outcomes during, daily and 3-day per week supervised dosing schedules using the combination tablet. Twenty-four opioid-dependent subjects completing a 16-day baseline entered an outpatient triple crossover trial. Twenty-one days of daily dosing were compared to two different 21-day periods of 3-day per week supervised dosing: a 3-day per week clinic schedule and a 3-day per week take-home schedule in which tablets were provided to subjects to take at home on days between clinic visits. Thirteen patients completed the study. Significantly more doses were ingested under the 3-day per week schedules. Illicit drug use did not differ across conditions and 45% of urine samples tested positive for illicit opioids. Subjects ‘liked’ both 3-day per week schedules more than the daily schedule, and ratings of feeling ‘good’ were higher for the 3-day take-home as opposed to 3-day clinic condition. Almost all subjects (91%) rated 3-day take-home as the most preferred schedule. Overall, reducing clinic attendance improved medication compliance and increased client satisfaction without impacting illicit drug use. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Buprenorphine; Buprenorphine-naloxone; Dosing regimen; Abuse; Pharmacotherapy

1. Introduction

Buprenorphine is a high affinity, partial μ-opioid agonist pending FDA approval as a pharmacotherapy for opioid dependence treatment (cf., Bickel and Amass, 1995). Buprenorphine is a safe and effective alternative to methadone (Bickel et al., 1988; Johnson et al., 1992; Strain et al., 1994; Ling et al., 1996) and levomethadyl acetate hydrochloride (LAAM; Chutuape et al., 1999) that produces significant and substantial improvements over time in psychosocial functioning (Strain et al., 1996). Buprenorphine also has unique features that permit novel uses which may alter current strategies for maintenance and detoxification treatment (cf. Bickel and Amass, 1995; Amass et al., 2000).

An important feature of buprenorphine is that, unlike methadone and like LAAM, it can be used safely on an alternate-day or thrice-weekly basis without the use of take-home medication. However, like methadone and unlike LAAM, buprenorphine can also be administered safely on a daily basis. This feature may promote the use of buprenorphine in diverse settings, including primary care facilities and office-based practices. Alternate-day buprenorphine dosing regimens have been examined in several placebo-controlled studies with liquid (Fudala et al., 1990; Amass et al., 1994, 1998; Johnson et al., 1995; Bickel et al., 1999) and tablet (Amass et al., 2000) formulations and consistently have been found to be as effective as daily dosing. Importantly, using multiples of the daily dose when dosing every other day yields slightly better treatment outcomes and is intrinsi-
cally safe (Amass et al., 1994, 1998, 2000). Buprenorphine’s partial agonist nature results in a ceiling on agonist activity such that high dose buprenorphine treatment does not interfere with patient management (Amass et al., 1993; Walsh et al., 1994, 1995). Despite this ceiling effect, higher doses continue to produce extended action since plasma buprenorphine concentrations increase proportionately as a function of dose (Walsh et al., 1994). Finally, alternate-day dosing regimens are preferred to daily dosing by buprenorphine-maintained outpatients (Amass et al., 1998), suggesting this regimen could be used to reinforce behavior change such as opioid abstinence.

Laboratory-based evaluations have shown that the liquid formulation of buprenorphine is well tolerated at 72-hour dose intervals (Eisenberg et al., 1997; Bickel et al., 1999), leading to the development of successful 3-day per week dosing regimens using the liquid formulation in multiple treatment settings, including primary care clinics (O’Connor et al., 1996, 1998; Schottenfeld et al., 1999). These 3-day per week regimens do not require the use of take-home doses and seem to have comparable efficacy to daily maintenance when an equivalent weekly dose is used (Schottenfeld et al., 1999).

Treatment with buprenorphine in the United States will employ a sublingual combination tablet containing buprenorphine and naloxone in a 4:1 ratio (Chiang and Hawks, 1994; Chiang et al., 1996a, b). This combination tablet was developed to help mitigate potential diversion and abuse of buprenorphine once it becomes available for widespread clinical use. The combination tablet is expected to be particularly useful sublingually because of the different parenteral to sublingual potencies of buprenorphine and naloxone. While buprenorphine has an \( \approx 2:1 \) 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 and allow the combination tablet to behave like buprenorphine alone, while precipitating withdrawal if administered parenterally by opioid-dependent individuals. This combination tablet can be administered safely and effectively on an alternate-day basis (Amass et al., 2000).

Three-day dosing strategies have not been evaluated using the buprenorphine-naloxone combination tablet and at least three issues are unclear: (a) whether 3-day per week buprenorphine dosing at the clinic offers any therapeutic advantages over a schedule in which take-home medication is provided on intervening dose days, (b) whether a reduced attendance schedule compromises early treatment outcome, or (c) whether a 24 mg combination tablet dose would be well tolerated during a 72 h inter-dose-interval given that this represents use of increasing doses of sublingual naloxone. The purpose of the present study was to establish the preference for daily and 3-day per week supervised dosing schedules using the combination tablet and investigate clinical outcomes using these schedules. Daily combination tablet administration was compared to two different 3-day per week dosing schedules. Under one 3-day per week schedule (3-day clinic), subjects ingested all of their medication at each clinic visit. On the other 3-day per week schedule (3-day take-home), subjects received one dose at each clinic visit and doses to take at home on days between clinic visits.

2. Methods

2.1. Subjects

Forty-six opioid-dependent subjects (30 male, 16 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 comprehensive intake interview conducted in a 2–3 h session prior to admission.

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. Subjects 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 45.5 years (range 22–62). Subjects reported using opioids regularly for an average of 15.9 years (range 1–35) and spending $487 (range $25–$3150) per week on opioids. Thirty-nine subjects reported primarily intravenous, five reported primarily intramuscular, 1 reported primarily intranasal and one reported primarily oral opioid use. Forty-one subjects reported having received methadone treatment previously. Seven subjects transferred from a methadone maintenance program directly into this study. These subjects were being maintained on an average of 41 mg of methadone (range 20–60) at the time of transfer. One subject had previously received buprenorphine for 6 days in a prior study (Amass et al., 2000). Weekly pregnancy tests (urine hCG, Abbott Laboratories) for the 16 female subjects were negative throughout the study.

2.2. Buprenorphine induction and stabilization

A 2-day, rapid, buprenorphine-alone induction procedure was used for all patients (Amass et al., 2000), including those transferred from a methadone maintenance treatment program. On the first day of participation, subjects received 1 ml of a sublingual solution containing 2 mg of buprenorphine1. On the second day, subjects received one sublingual tablet containing 8 mg of buprenorphine.

Following buprenorphine induction, subjects received 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 to (a) stabilize patients on a 24-h dosing schedule of the buprenorphine-naloxone tablet and (b) allow a period during which early treatment dropouts could be identified and culled from the final study sample.

2.3. Medication administration

Buprenorphine sublingual solution, and buprenorphine-alone and buprenorphine combination sublingual tablets were manufactured by Reckitt and Colman Products (Hull, UK) and supplied through the National Institute on Drug Abuse and Research Triangle Institute. The buprenorphine solution contained 2 mg/ml of buprenorphine in a 30% ethyl alcohol vehicle. Dosing conditions were double-blind for dose magnitude (i.e. patients and nurses knew they were receiving or dispensing buprenorphine on one of the three dosing schedules, but were blind to the dose of buprenorphine). The dispensing nurse placed the buprenorphine solution under the subject’s tongue and instructed the subject to hold the liquid under their tongue for 5 min. 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 their tongue until dissolved.

2.4. Study design

Beginning on day 17, subjects received each of three, 21-day dosing conditions: ‘Daily’, ‘3-Day At Clinic’ and ‘3-Day with Take-homes’ using multiples of combination tablets which each contained 8 mg of buprenorphine and 2 mg of naloxone. During the ‘Daily’ dosing condition, subjects received one combination tablet every 24 h and were told ‘This is your maintenance dose’. During both 3-Day conditions, subjects only attended the clinic on Mondays, Wednesdays and Fridays and they could not receive medication on intervening days if they missed a scheduled clinic visit. During the ‘3-Day At Clinic’ dosing condition, subjects ingested two combination tablets on Mondays and Wednesdays and were told ‘This is a double dose’. On Fridays, subjects ingested three combination tablets and were told ‘This is a triple dose’. During the ‘3-Day with Take-homes’ condition, subjects ingested one combination tablet at the clinic on Mondays, Wednesdays and Fridays, received combination tablets to take at home for the intervening days and were told ‘This is a maintenance dose; here’s one take-home for tomorrow’ or ‘This is a maintenance dose; here’s two take-homes for Saturday and Sunday’. 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

Urine samples were collected thrice weekly under observation (Mondays, Wednesdays and Fridays) before medication administration and analyzed for the presence of opioids using the Enzyme Multiplied Immunoassay Technique (Behring Corporation, San Jose, CA). Samples also were analyzed for the presence of cocaine metabolites, amphetamines, benzodiazepines, barbiturates, and cannabinoids on one randomly chosen day per week. Cutoff calibration concentrations of

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1 The original protocol was designed to deliver two tablets on day 1, each containing 2 mg of buprenorphine, for a total tablet dose of 4 mg. However, due to low availability of 2 mg tablet supplies, NIDA substituted the sublingual solution for use on day 1 in this study. NIDA estimated that 1 ml of this sublingual solution was roughly equivalent to providing a 4 mg tablet dose of buprenorphine on day 1.
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.

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.

2.6. Counseling

Subjects received individual, manualized behavioral counseling sessions (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-rated measures

Subject-rated measurements were collected before medication administration on the last day of attendance scheduled for each dosing condition. Measures were collected using a Macintosh Powerbook 520 computer (Apple Computer, Cupertino, CA) running custom-designed data acquisition software (BioPsych Consulting, Sherman Oaks, CA). Subjects completed four visual analog scales (VAS), and answered a dosing schedule question. Subjects were instructed to respond to these questions according to how they had been feeling during the past 3 weeks. The VAS items were: ‘How much have you LIKED this dosing schedule?’; ‘How GOOD have you felt during the last 3 weeks?’; ‘How BAD have you felt during the past 3 weeks?’, and ‘How much WITHDRAWAL SICKNESS have you felt during the past 3 weeks?’.

Subjects answered a dosing schedule question asked subjects to respond true or false to the statement, ‘You’ve experienced three dosing schedules: ‘Daily’, ‘3-Day’, and ‘3-Day with Take-Homes’. Please tell us how you liked them by answering the following three questions: Which dosing schedule did you like the BEST?, Which dosing schedule did you like SECOND best?, Which dosing schedule did you like the LEAST?’ For each of the three questions, subjects could respond ‘Daily’, ‘3-Day’ or ‘3-Day with Take-homes’.

2.8. Data analysis

Subjects were classified into three groups for the purposes of data analyses: ‘Dropouts’ (n = 22) were defined as subjects who left treatment during the 16-day baseline period; ‘Non-completers’ (n = 11) were defined as 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 = 13) were defined as subjects who completed the entire study.

Analyses of variance (ANOVA) were used to compare dropouts, non-completers and completers on selected intake measures (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 13 completers were used to compare treatment outcomes during the three 21-day treatment conditions. Repeated measures ANOVA were performed on the average of each dependent variable (e.g. VAS and dosing schedule question) or the sum score for the dependent variable across each treatment condition (e.g. positive/missed urines, medication compliance) with the subject effect treated as random. For medication compliance, a total of seven doses could have been ingested each week, regardless of dosing condition. During each 3-day condition, if the patient received their medication at the clinic visit, the number of doses ingested was calculated as being ‘two’ if the visit was on a Monday or a Wednesday, and as ‘three’ if the visit was on a Friday. For the preference questionnaire, chi-square goodness of fit tests were compared against the null hypothesis that one-third of subjects would be expected to prefer each condition if that condition had no differential effect.
Analyses were conducted using SAS (SAS Institute Inc., 1996) statistical software. All tests were two-tailed and statistical significance was specified at \( \alpha = 0.05 \).

3. Results

3.1. Treatment retention and post-study status

Forty-eight percent of the subjects (22/46) dropped out during the treatment baseline. Four of these subjects dropped out following the first or second day, nine did so following 3–7 days and the remaining nine dropped out after 8–16 days. Fourteen of these subjects dropped out abruptly and did not provide a reason for leaving; three subjects left due to conflicts with work or family. Five of these subjects later returned to participate in another efficacy evaluation of buprenorphine-naloxone and methadone (Amass et al., in press).

Fifty-two percent of the subjects (24/46) initiated at least one of the three treatment conditions. Of these 24 patients, 54% (13/24) completed the study. Of the 11 subjects who did not complete the three treatment conditions (i.e., non-completers), five dropped out during the daily dosing condition, three dropped out during the 3-Day Clinic condition and three dropped out during the 3-Day Take-Home. 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 11 non-completers, seven left treatment abruptly and did not provide a reason for leaving. Four subjects later returned to participate in another efficacy evaluation of buprenorphine-naloxone and methadone (Amass et al., in press).

Of the 13 completers, one left treatment abruptly after completing the study and did not provide a reason for leaving. Ten subjects transferred directly into another efficacy evaluation of buprenorphine-naloxone and methadone (Amass et al., in press). Two subjects 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.

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

There were no significant differences observed on intake variables among these three groups of subjects.

3.3. Baseline differences amongst completers and non-completers

Completers differed significantly from non-completers only on the amount of illicit cocaine use during baseline. Completers submitted significantly fewer cocaine-positive urine samples (mean = 0.23, SEM = 0.25) than non-completers (mean = 1.55, SEM = 0.27) during the baseline (\( z = 2.891, P = 0.004 \); data not shown).

3.4. Condition effects: treatment completer sample

3.4.1. Medication compliance

Significantly more doses were taken under the 3-Day Clinic and 3-Day Take-Home conditions relative to daily dosing (\( F_{(3,24)} = 6.02; P = 0.007 \); Fig. 1). An average of 19.6, 19.9 and 17.1 doses were taken during the 3-Day Clinic, 3-Day Take-Home and daily dosing conditions, respectively.

3.4.2. 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.

3.4.3. Subject-rated measures

Average VAS ratings obtained at the end of exposure to each dosing condition are illustrated in Fig. 2. Sig-

![Fig. 1. Mean number of doses taken during each of the three dosing conditions for the completer (n = 13) patient sample. The maximum possible number of doses available during each condition is shown on the y-axis. Vertical bars indicate \( \pm 1 \) SEM. Asterisk denotes significant difference from daily dosing condition.](image)

Table 1

<table>
<thead>
<tr>
<th>Drug screened</th>
<th>Daily dosing</th>
<th>3-Day Clinic</th>
<th>3-Day Take-Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>38</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>Cocaine</td>
<td>21</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>12</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>37</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>24</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>12</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

\( * n = 13, \) treatment completers.
sific condition effects were obtained on two of the four VAS measures. Subjects ‘liked’ both 3-day per week schedules significantly more than the daily schedule \((F_{(2,20)} = 8.70; \ P = 0.002)\), with average scores being 1.5–2 times greater during 3-day as opposed to daily dosing conditions. Ratings of ‘good’ were also significantly higher for the 3-Day Take-Home (mean = 71.2, \(\text{SEM} = 6.04\)) as opposed to 3-Day Clinic (mean = 54.4, \(\text{SEM} = 6.04\)) condition \((F_{(2,20)} = 3.92; \ P = 0.04)\). There were no significant differences across the three dosing conditions on subject’s responses to the dosing schedule question ‘I’d continue with the same dosing schedule if I could’. A total of 85, 77 and 67% of subjects reported they would continue on the 3-Day Take-Home, 3-Day Clinic and daily dosing schedules if they could, respectively (data not shown). Significantly more subjects (91%) rated the 3-Day Take-Home as the best schedule (Fig. 3; chi-square estimate = 16.545, \(df = 2, \ P = 0.0003\)) while significantly more subjects (82%) rated daily dosing as the least preferred schedule (data not shown; chi-square estimate = 12.182, \(df = 2, \ P = 0.002\)).

4. Discussion

This study demonstrated that outcomes with 3-day per week dosing with buprenorphine-naloxone using multiples of the daily dose is acceptable and preferred to daily dosing by patients, improves medication compliance, and seems comparable to daily dosing. This laboratory’s findings with alternate-day (Amass et al., 2000) and 3-day per week dosing schedules with the buprenorphine-naloxone tablet replicate earlier findings with the liquid buprenorphine formulation (Amass et al., 1994, 1998; Bickel et al., 1999) and continue to support using larger doses when dosing less frequently. The current study also suggests that using contingent 3-day per week schedules with or without take-homes for reinforcing opioid abstinence might be effective, and has shown that up to 6 mg of sublingual naloxone is tolerated during 3-day buprenorphine-naloxone dosing without incident. The current study’s results raise five important points.

First, 3-day per week supervised dosing schedules were liked significantly more than daily schedules and a 3-day per week dosing schedule that included take-home buprenorphine-naloxone for intervening days was almost exclusively preferred by patients to a 3-day per week dosing schedule that did not include take-home doses. These results, along with those of another report demonstrating patient preference for alternate-day dosing (Amass et al., 1998) suggest that these schedules might be able to be used as positive reinforcers for enhancing opioid treatment outcomes. Although a direct evaluation of this idea remains to be accomplished, preliminary results from an efficacy evaluation of buprenorphine-naloxone and methadone lend some support to this contention. Seven patients maintained on either 8 or 16 mg of the buprenorphine-naloxone tablet for 8 months showed significant reductions in opioid use when weekly opioid abstinence was reinforced with access to a 3-Day Take-Home dosing schedule (Kamien et al., in press).

Second, reducing clinic attendance requirements in the present study improved medication compliance without compromising other aspects of treatment outcome such as drug use and retention. Rates of medication compliance and illicit opioid use were also similar across the two different 3-day per week dosing schedules. Although tracers or tablet recall procedures did not monitor ingestion of take-home medication in the present study, the fact that illicit opioid use and self-reports of feeling ‘bad’ and ‘withdrawal’ did not increase during the take-home condition suggests that these doses were indeed ingested and not sold to purchase illicit opioids. Thus, absent any other behavioral contingencies, the therapeutic advantage of using a 3-Day Clinic over a 3-Day Take-Home schedule is not obvious. Reducing visit frequency requirements during
methadone treatment enhances early treatment retention, and together with the present results suggests that regulatory and clinic policy changes might be warranted (Rhoades et al., 1998). Although illicit drug use continued during this study, the rates of opioid use were consistent with or lower than those observed in similar controlled studies (Johnson et al., 1995; Schottenfeld et al., 1999; Amass et al., 2000) and are also consistent with the pattern of drug use reported in controlled comparisons of buprenorphine to methadone (Strain et al., 1994; Ling et al., 1996). Certainly, titrating doses to meet individual patient needs and/or adding a contingency management strategy would likely further reduce rates of illicit drug use.

Third, consistent with findings with alternate-day combination tablet dosing (Amass et al., 2000), the present study supports the safety of using a combination product for 3-Day Clinic dosing when multiples of the daily maintenance dose are administered. Sublingual naloxone doses up to 6 mg were well tolerated by all subjects exposed to multiple doses of the combination tablet and no adverse reactions were observed in response to tripling a subject’s maintenance doses. This finding is consistent with laboratory studies of sublingual naloxone in opioid dependent patients (Preston et al., 1990) as well as findings with buprenorphine solution formulations (Bickel et al., 1999; Petry et al., 1999; Schottenfeld et al., 1999).

Fourth, 3-day per week combination tablet dosing seemed as effective as daily dosing. These results extend other findings with alternate-day combination tablet dosing (Amass et al., 2000) and are also consistent with controlled studies examining 72-h inter-dosing-intervals (Eissenberg et al., 1997; Bickel et al., 1999) and 3-day per week dosing (Schottenfeld et al., 1999) using the liquid formulation of buprenorphine. While a 3-day per week dosing regimen may be very convenient to use in drug treatment settings, open label evaluations of thrice-weekly dosing with liquid buprenorphine formulations indicate such regimens are also safe, adaptable to, and practical for use in primary care settings (O’Connor et al., 1996, 1998). Thus, 3-day per week buprenorphine dosing may address unmet demands for expanding effective, efficient, and accessible drug treatment services for opioid addiction. Creating such services is supported by clinicians, policy makers, federal and state agencies (McLellan et al., 1993; Dennis et al., 1994; Wenger and Rosenbaum, 1994; National Institutes of Health, 1997) and is consistent with the desires of active heroin users who want more flexible types of treatment programming that include maintenance models which reduce demands on patients (Koester et al., 1999).

Fifth, this study’s limitations reduce the generality of the findings to most clinical settings. For example, a small number of subjects were studied and many subjects dropped out and were not exposed to all three dosing schedules, limiting conclusions regarding the relative efficacy of the dosing schedules. Regardless of the small number of subjects studied, however, the counterbalanced, within-subject design that exposed completing subjects to each dosing schedule allowed the subjects to serve as their own controls, strengthening the preference data. Other limitations include the short duration of treatment, the fixed dose protocol, and the exclusion of patients with active psychiatric comorbidity. 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 bioavailability of tablet preparations of buprenorphine may be as little as 50% of the sublingual solution (Nath et al., 1999; Schuh and Johanson, 1999) and higher doses of the combination tablet may have reduced the number of drop outs in this study. Interestingly, patients in the non-completer sample provided significantly more cocaine-positive urine samples during the first 2 weeks of treatment than those patients in the completer sample. Cocaine use may have played a role in these patients early treatment termination given the negative impact of cocaine use on treatment outcomes of methadone-maintenance patients (Kidord and Stitzer, 1993; Hartel et al., 1995). Additional studies to address these limitations are needed.

As clinical experience with buprenorphine builds, buprenorphine-naloxone may come to be considered a first-line treatment option for opioid dependence, due to its safety, limited agonist activity, ability to be administered on a less-than-daily basis and its diminished potential for abuse. Overall, the findings with 3-day per week buprenorphine dosing have obvious practical and clinical importance. Thrice-weekly dosing schedules (with or without take-homes) are equally effective and may improve program cost-effectiveness by reducing patient visits and allow clinics to treat more patients each week. Three-day per week schedules without take-homes can also help programs reduce the risk of buprenorphine abuse or diversion, which may still be possible with a combination tablet among some populations of opioid abusers (e.g. buprenorphine-maintained patients; Strain et al., 1997). Thrice-weekly dosing may also augment patient outcomes during buprenorphine therapy, may improve retention when daily clinic attendance is a barrier to treatment, and those that do not involve take-home medication are consistent with treatment aims of decreasing drug ingestion as a daily behavior. As noted above, these dosing schedules show promise as positive reinforcers for enhancing opioid treatment outcomes. Lastly, buprenorphine’s ability to be dispensed in a multitude of ways may promote its use in multiple settings, including primary care and office-based practice. This flexibility should facilitate using buprenorphine to fur-
ther expand models for delivery of opioid maintenance treatment and help us better address the dangerous and ever-growing problem of heroin addiction.

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