Thrice-Weekly versus Daily Buprenorphine Maintenance

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Background: Buprenorphine is a promising alternative to methadone or levo-acetyl alpha methadol for opioid agonist maintenance treatment, and thrice-weekly dosing would facilitate its use for this purpose.

Methods: After a 3-day induction, opioid-dependent patients (n = 92) were randomly assigned to daily clinic attendance and 12-weeks maintenance treatment with sublingual buprenorphine administered double blind either daily (n = 45; 16 mg/70 kg) or thrice weekly (n = 47; 34 mg/70 kg on Fridays and Sundays and 44 mg/70 kg on Tuesdays). Outcome measures include retention, results of 3×/week urine toxicology tests, and weekly self-reported illicit drug use.

Results: There were no significant differences at baseline in important social, demographic, and drug-use features. Retention was 71% in the daily and 77% in the 3×/week conditions. The proportion of opioid-positive urine tests decreased significantly from baseline in both groups and averaged 57% (daily) and 58% in 3×/week. There were no significant differences between groups in self-reported number of bags of heroin used for any day of the week, including Thursdays (48–72 hours following the last buprenorphine dose for subjects in the 3×/week condition), or in medication compliance (92%, 91%) and counseling attendance (82%, 82%).

Conclusions: At an equivalent weekly dose of 112 mg/70 kg, thrice-weekly and daily sublingual buprenorphine appear comparable in efficacy with regard to retention and reductions in illicit opioid and other drug use. These findings support the potential for utilizing thrice-weekly buprenorphine dosing in novel settings. Biol Psychiatry 2000;47:1072–1079 © 2000 Society of Biological Psychiatry

Key Words: Buprenorphine, clinical trial, heroin dependence treatment, opioid agonist maintenance treatment, opioid dependence, opioid treatment

Introduction

Despite the effectiveness of methadone maintenance treatment (Cooper 1992; Dole 1988, 1989; Newman 1987; Schottenfeld and Kleber, in press), there are critical needs to develop alternatives to methadone for opioid agonist maintenance treatment (Blaine 1992). Problems with methadone maintenance include its limited availability, the need for daily dosing, possible diversion of take-home doses, potential for opioid overdose for patients who use illicit opioids, and difficulty withdrawing from methadone. The need for daily dosing and consequent initial requirement for daily clinic attendance may deter many heroin users from seeking treatment and contribute to the costs and limited reach of treatment. Currently, fewer than one in five heroin users receive treatment for drug dependence (National Institutes of Health 1998).

Levo-acetyl alpha methadol (LAAM) is currently the only other opioid agonist approved by the U.S. Food and Drug Administration (FDA) for maintenance treatment of opioid dependence. One important advantage of LAAM over methadone is its efficacy when administered on a thrice-weekly dosing schedule (Eissenberg et al 1997a), which permits reduced clinic attendance, obviates the need for take-home bottles, and reduces dispensing costs. Like methadone, however, LAAM acts as a pure agonist at the µ receptor, and it shares many of the problems found with methadone, including the potential for overdose and the difficulty of withdrawal from maintenance treatment (Greenstein et al 1992). Buprenorphine, a partial µ agonist and κ antagonist, represents a promising alternative to either methadone or LAAM (Blaine 1992; Lewis and Walter 1992; Johnson et al 1992). Ceiling effects at higher buprenorphine doses result in a lower risk of overdose compared with methadone (Walsh et al 1994, 1995b), and buprenorphine may also have a reduced abuse liability in opiate-dependent individuals (and thus less likelihood of diversion) because its use may precipitate withdrawal symptoms (Strain et al 1995; Walsh et al 1995a, 1995b). Withdrawal symptoms following abrupt discontinuation of buprenorphine are also usually relatively mild (Amass et al 1994; Eissenberg et al 1997b; Fudala et al 1990; Negus
and Woods 1995; San et al 1992). Results of double-blind randomized clinical trials generally support the safety and dose-dependent efficacy of daily sublingual buprenorphine (Johnson et al 1992; Kosten et al 1993; Ling et al 1996; Schottenfeld et al 1997; Strain et al 1994a, 1994b). In conjunction with previous dose-ranging studies (Bickel et al 1988; Mello et al 1980, 1981; Schottenfeld et al 1993), these studies suggest that sublingual buprenorphine doses of 12–16 mg daily lead to the greatest reductions in illicit opioid use. Because of its demonstrated safety and efficacy, a new drug application has been submitted to the FDA for use of buprenorphine sublingual tablets for opioid agonist maintenance treatment.

A number of recent studies suggest that buprenorphine, like LAAM, may be suitable for thrice-weekly administration during maintenance treatment. Buprenorphine has a high binding affinity and dissociates very slowly from the μ receptor (Boas and Villiger 1985, Kajiwara et al 1986), leading to dose-dependent and long duration of attenuation of both opioid withdrawal and opioid self-administration (Bickel et al 1988; Fudala et al 1990; Schottenfeld et al 1993). In general, patients experience no problems with withdrawal symptoms or increased agonist effects during alternate-day or every third, fourth, or fifth day administration of buprenorphine at sublingual doses of 8–40 mg (Amass et al 1994; Bickel et al 1995, 1996, 1997; Eissenberg et al 1997b; Fudala et al 1990; Johnson et al 1995). Patients also generally report a preference for alternate-day or even less frequent dosing (Bickel et al 1995, 1997). Results of several studies suggest that higher doses of buprenorphine (12–24 mg SL) are needed to attenuate or block hydromorphone effects for 48–72 hours (Amass et al 1996; Bickel 1988; Rosen 1994; Walsh 1995b). Johnson et al (1995) compared daily and alternate-day dosing with 8 mg SL buprenorphine under double-blind conditions and found no significant differences (but a trend favoring daily dosing) in the primary outcome measures of retention in treatment or rates of opioid-positive urine samples.

This randomized, double-blind, 12-week clinical trial compared daily and thrice-weekly administration of buprenorphine for the maintenance treatment of opioid dependence. The study specifically evaluated the clinical efficacy of thrice-weekly versus daily buprenorphine dosing, while controlling for clinic attendance across both conditions. Doses were chosen to provide an optimal daily dose (16 mg/70 kg) and a thrice-weekly dose providing an equivalent weekly buprenorphine dose (112 mg/70 kg, administered as 34 mg/70 kg on Sunday and Friday and 44 mg/70 kg administered on Tuesday). Pilot studies conducted before beginning the clinical trial found that the thrice-weekly dose schedule was well tolerated by patients, and buprenorphine plasma levels 48 hours following the 34 mg/70 kg dose and 72 hours following the 44 mg/70 kg dose were comparable to plasma levels 24 hours following a daily dose of 16 mg/70 kg (Chawarski et al 1999).

Methods and Materials

Subjects

Subjects were recruited from individuals seeking opioid agonist maintenance treatment at the APT Foundation’s Legion Avenue Program or from respondents to word-of-mouth advertisements about the availability of an experimental agonist maintenance program. Subjects were eligible for the study if they met FDA criteria for methadone maintenance, had a urine toxicology test positive for opioids, and met DSM-IV criteria for opioid dependence. Signs of opiate withdrawal (pupil or blood pressure elevations, piloerection, lacrimation, rhinorhea, vomiting, yawning, pupil dilation) following intramuscular injection of naloxone 0.8 mg were used to verify current physiologic opioid dependence in subjects with no prior history of methadone maintenance (n = 40 or 43.5%). One patient out of 41 tested failed to demonstrate evidence of opioid withdrawal and was not admitted to the study. Exclusion criteria included current psychosis or major depression, suicide risk, current dependence on cocaine, alcohol, or sedatives, pregnancy, and the inability to read or understand rating forms. Women of childbearing age who agreed to adequate contraception and monthly pregnancy tests were eligible for the study. The study protocol was approved by the Human Investigations Committee of Yale University School of Medicine.

After giving written informed consent, 97 subjects began buprenorphine; 92 subjects completed three days of buprenorphine induction (4 mg, 8 mg, and 12 mg sublingual liquid) and were randomly assigned to one of the two maintenance groups. An urn randomization procedure, which uses a computer-calculated algorithm to modify ongoing randomization probabilities based on prior composition of treatment groups (Project Match Research Group 1993; Crits-Christoph et al 1997), was used to balance groups by gender, employment status, and history of alcohol dependence.

Maintenance Medications

Maintenance medications were dispensed daily, and ingestion observed by nursing staff. To maintain double-blind conditions, subjects receiving thrice-weekly buprenorphine received identical-appearing placebo doses on Mondays, Wednesdays, Thursdays, and Saturdays. The highest dose of buprenorphine in the thrice-weekly schedule was administered on Tuesdays to avoid the possibility of confounding the effects of placebo administration for 2 consecutive days and differences between weekend and weekday drug use. A research pharmacist prepared all medications and was the only person with knowledge of drug assignment. Buprenorphine solutions were prepared in 30% ethanol (vol/vol), and doses were weight adjusted (16 mg/70 kg), with a maximum weekly dose equivalent to 21.3 mg daily and the maximum dose administered on any day in the thrice-weekly schedule limited to 64 mg. The 30% ethanol solution used as the
vehicle for dissolving buprenorphine served as the placebo. All patients received identical volumes of buprenorphine solution on all study days and were instructed to hold the liquid under their tongue for 5 minutes. Average weight-adjusted weekly doses were 17.9 mg daily in the daily schedule and 36.4 mg (on Sundays and Fridays) and 47.1 mg (on Tuesdays) in the thrice-weekly group.

Beginning Day 4, subjects assigned to daily dosing continued to receive 12 mg daily until the first Monday following Day 4, at which time the dose was increased to 16 mg daily. Subjects assigned to thrice-weekly received 16 mg, 22 mg, and 28 mg on Days 4, 5, and 6 before beginning the regular thrice-weekly schedule. After completing 12 weeks of maintenance treatment with either daily or thrice-weekly buprenorphine, buprenorphine doses were tapered during a 2-week period prior to discharge or transferring subjects to methadone maintenance or another treatment program. During the tapering period, all subjects received buprenorphine daily, and buprenorphine doses were reduced in increments of 4 mg from 16 mg/day to 4 mg/day at 2-day intervals; subjects were then maintained on 4 mg/day for 9 days prior to discontinuing buprenorphine.

All subjects were required to participate in a one-hour weekly manual-guided group counseling session to enhance motivation for abstinence from illicit drugs and to develop coping skills and behavioral techniques to prevent relapse. Subjects were not discharged from the study for continued illicit drug use. They were discharged from the study for medical reasons, for missing three consecutive days of medication or three consecutive counseling sessions, and for physical or verbal abuse at the clinic.

**Assessments**

At baseline, trained research interviewers assessed subjects using a structured drug use interview, the Addiction Severity Index (McLellan et al 1992), and sections of the Structured Clinical Interview for DSM-IV (First et al 1996) evaluating lifetime and current substance use and affective disorders. Supervised urine samples for toxicology testing were obtained at baseline, and thrice weekly on Mondays, Wednesdays, and Fridays. All urine samples were tested for opioids and the cocaine metabolite, and one sample per week from each subject was also tested for benzodiazepines. The Abbott Tdx system (Abbott Laboratories, Abbott Park, IL) was used for toxicology testing, with cutoffs of 200 ng/mL for opioids and benzodiazepines and 300 ng/mL for cocaine metabolite.

Research staff collected weekly self-report ratings of drug and alcohol use and opiate withdrawal symptoms, using the Weekly Drug Use Inventory and the Opiate Withdrawal Symptom Checklist. (Copies of all instruments are available from the authors on request.) In the Weekly Drug Use Inventory, subjects are asked to report drug use each day of the week, the routes of administration used for each drug, and the average amount used each day in grams or dollar value. The Opiate Withdrawal Symptom Checklist is a 20-item questionnaire rating withdrawal symptoms experienced in the past 24 hours (e.g., “My nose has been runny”) on a scale from 1 (“not at all”) to 4 (“very much”). Ratings of withdrawal symptoms were collected before medication dosing on Monday mornings. Data were collected from subjects during the time they participated in the study.

### Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Daily (n = 45)</th>
<th>Thrice-weekly (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Male</td>
<td>71.1</td>
<td>74.5</td>
</tr>
<tr>
<td>% White</td>
<td>75.5</td>
<td>74.5</td>
</tr>
<tr>
<td>Mean (SD) years age</td>
<td>36.2 (7.2)</td>
<td>37.6 (7.9)</td>
</tr>
<tr>
<td>% Married</td>
<td>13.6</td>
<td>17.8</td>
</tr>
<tr>
<td>Mean (SD) years education</td>
<td>11.9 (1.6)</td>
<td>11.6 (2.6)</td>
</tr>
<tr>
<td>% Employed</td>
<td>42.9</td>
<td>36.2</td>
</tr>
<tr>
<td>% Current IV users</td>
<td>43.9</td>
<td>56.1</td>
</tr>
<tr>
<td>% Cocaine positive urtox</td>
<td>24.4</td>
<td>23.4</td>
</tr>
<tr>
<td>% No cocaine use last 30 days</td>
<td>71.1</td>
<td>74.5</td>
</tr>
<tr>
<td>Mean (SD) years heroin use</td>
<td>10.1 (8.8)</td>
<td>9.9 (7.4)</td>
</tr>
</tbody>
</table>

### Statistical Analysis

Chi-square and t tests were utilized to compare groups on baseline characteristics. Differences in retention were analyzed using the Kaplan-Meier product limit method and the generalized Wilcoxon test (Allison 1995; Selvin 1991). Chi-square was used to analyze treatment group effects on the proportion of subjects achieving 3 or more consecutive weeks of abstinence in each condition. Random regression models (RRM) were used to examine the effects of treatment group on repeated urine toxicology results and self-report data regarding daily drug use and opioid withdrawal symptoms (Gibbons et al 1993; Hedeker and Mermelstein 1996; Littell et al 1996). RRM provide p values for the Wald statistics, expressed as $\chi^2$. To develop a continuous outcome measure with regard to urine toxicology results, the results of urine toxicology testing during the 12 weeks of maintenance were aggregated into four successive 3-week periods. The proportion of tests positive for illicit opioids or cocaine during induction and each successive 3-week period were then calculated for each subject and used in the RRM. During the time subjects remained in the study, 2.3% (72/3092) of scheduled urine toxicology samples were not obtained and were coded as positive. Leaving missing values as missing or imputing them to the average value for the subject over the preceding weeks did not affect the significance of the major findings. Urine toxicology data were available for 412 aggregated measurements, or 89.6% of the total 460 expected 3-week aggregates, had all 92 subjects remained in treatment for the 12 maintenance weeks and 1 induction week. A total of 1009 weekly assessments were collected during treatment, out of a total possible 1196 assessments (84.4%), had all 92 subjects provided information for 13 weeks.

### Results

**Randomization and Retention in Treatment**

Characteristics of study sample are shown in Table 1. The two treatment groups were comparable across baseline demographic, social, drug abuse, and psychiatric factors. The percentage of subjects completing 12 weeks of maintenance treatment did not differ between the two treatment groups (76.6% vs. 71.1%), and the average number of weeks (SD) in treatment was 11.0 (4.0) in 3
×/week and 11.2 (3.7) in daily (Wilcoxon \( \chi^2 = 0.102, \text{df} = 1, p = .64 \)). Reasons for premature termination included missing medications 3 days in a row (12 in daily and 6 in thrice weekly); missing 3 consecutive groups (\( n = 1 \)), exacerbation of pre-existing medical problems (\( n = 2 \)), depression requiring medication treatment (\( n = 1 \)), and abusive behavior (\( n = 1 \)). No patients reported adverse medication effects. Of the 67 patients who completed the maintenance phase of the study, 10 elected medical detoxification, 12 transferred to methadone maintenance, and 45 elected transfer to another buprenorphine research protocol.

Effects on Illicit Opioid Use

As shown in Figure 1, the proportion of opioid-positive urine tests declined substantially over time (Wald \( \chi^2 = 76.7, \text{df} = 4, p < .001 \)) but did not differ between treatment groups (57% vs. 58% in daily and 3×/week, respectively; Wald \( \chi^2 = 0.04, \text{df} = 1, p = .84 \)), and there was no significant interaction between treatment group and time (Wald \( \chi^2 = 5.4, \text{df} = 4, p = 0.25 \)). Three or more consecutive weeks of abstinence from illicit opioids, as documented by urine toxicology testing, was attained by 42.6% in the thrice-weekly group and 37.8% in the daily group (\( \chi^2 = 0.22, \text{df} = 1, p = .64 \)). There were also no significant differences in the mean length of longest period of continuous opioid abstinence (if abstinent) among subjects medicated 3×/week (7.8 ± 3.0) compared to the daily group (6.5 ± 3.1, \( t = 1.25, \text{df} = 35, p = 0.22 \)). Analyses based on self-report measures of illicit opiate use were consistent with analyses of urine toxicology data. As shown in Figure 2, there were significant reductions in self-reported days per week using heroin over time for both treatment groups (Wald \( \chi^2 = 1187.3, \text{df} = 12, p < .001 \)) but no differences between the two treatment group (1.3 ± 0.23 vs. 1.7 ± 0.22; Wald \( \chi^2 = 1.2, \text{df} = 1, p = .27 \)), and no significant interactions between treatment group and time (Wald \( \chi^2 = 19.4, \text{df} = 2, p = .08 \)). Bags of heroin used on any day of the week, including Thursdays (48–72 hours following the highest medication dose in the thrice-weekly group) also did not differ between groups. Withdrawal scores decreased significantly over time in both groups (Wald \( \chi^2 = 112, \text{df} = 12, p < .001 \)), but opioid withdrawal ratings collected 48 hours following buprenorphine dosing in patients in the thrice-weekly group also showed no difference (Wald \( \chi^2 = 0.54, \text{df} = 1, p = .46 \)).

Effects on Cocaine Use

Although cocaine dependence was an exclusion criterion, almost half of the subjects (46.7%) were unable to abstain from cocaine for at least 3 weeks. As shown in Figure 3, cocaine use increased over time in both groups (Wald \( \chi^2 = 13.4, \text{df} = 4, p < .001 \)). The proportion of subjects achieving 3 or more consecutive weeks of abstinence from cocaine was 51.1% and 55.3% in the daily and thrice-weekly groups, respectively (\( \chi^2 = 0.16, \text{df} = 1, p = .69 \)). There were no significant effects of dosing condition on the proportion of cocaine-positive urine samples (Wald \( \chi^2 = 1.2, \text{df} = 1, p = .26 \)) and averaged 38.1% and 31.2%.
Three consecutive weeks abstinence from cocaine during the trial was significantly associated with greater reductions in opioid-positive urine samples (Wald $\chi^2 = 6.26$, df = 1, $p < .012$), with rates of opioid-positive samples averaging 49% and 66%, respectively, among subjects who were or were not cocaine abstinent (Wald $\chi^2 = 8.8$, df = 1, $p = .003$).

Adherence to Medication Dosing and Counseling and Maintenance of the Double Blind

Medication compliance (92%, 91%) and attendance at counseling sessions (82%, 81%) were comparable between patients in the thrice-weekly and daily dosing conditions. Medication compliance on placebo medication

Figure 2. Reported days of heroin use per week at baseline, during induction, and during the 12 weeks of maintenance treatment in the daily (diamonds) and thrice weekly (squares) groups. Error bars represent standard errors.

Figure 3. The proportion of cocaine-positive toxicology tests at baseline, during induction, and during the four successive 3-week periods of maintenance treatment in the daily (diamonds) and thrice weekly (squares) groups. Error bars represent standard errors.
days (Mondays, Wednesdays, Thursdays, and Saturdays) averaged 90% and 89%, respectively, in the daily and thrice-weekly groups. Self-report data available from the last 53 subjects enrolled in the study also suggest that subjects did not reliably identify whether they were receiving thrice-weekly or daily dosing: At Week 4, 44% of subjects receiving thrice-weekly buprenorphine and 54% of subjects receiving daily dosing reported thinking that they were receiving daily dosing.

**Discussion**

This study provides strong support for the efficacy of thrice-weekly compared to daily buprenorphine dosing, when patients in both conditions receive relatively high and equivalent total weekly buprenorphine doses. Illicit opioid use declined substantially and comparably in both groups during maintenance treatment and are comparable to those of patients treated with methadone 65 mg daily in a previous study (Schottenfeld et al 1997). The comparable efficacy of daily and thrice-weekly buprenorphine dosing is also consistent with recently reported results supporting the comparable efficacy of thrice-weekly buprenorphine and LAAM (Chutuape et al, in press). The lack of differences in self-reported daily illicit opioid use for any day of the week suggest that subjects did not detect or respond adversely to placebo medication days in the thrice-weekly condition. The two groups were also comparable in medication compliance (92%, 91%) and counseling attendance (82%, 82%), and patients were as likely to attend the clinic and ingest the daily dose whether receiving a thrice-weekly buprenorphine, daily buprenorphine, or placebo dose. Thus, patients receiving thrice-weekly buprenorphine did not detect or respond differently to placebo buprenorphine dosing. The comparable efficacy of thrice-weekly and daily buprenorphine dosing for reducing illicit opioid use extends previous findings that patients tolerate and prefer less than daily buprenorphine dosing (Amass et al 1998; Bickel et al 1995, 1997).

Relatively high buprenorphine doses (total weekly dose of 112 mg/70 kg) were used in this study in both the daily and thrice-weekly groups. Although preventing withdrawal symptoms is an important criterion for evaluating the efficacy of opioid agonist maintenance treatment, the “gold standard” for assessing efficacy remains the elimination or reduction of illicit opiate use. Relatively low daily doses of methadone (20–35 mg) are generally sufficient to prevent withdrawal, but higher doses are more effective in reducing illicit opioid use. Thus, the pharmacologic targets of opioid agonist maintenance treatment include attenuating the reinforcing effects of illicit opioid use and reducing craving, in addition to preventing withdrawal (Amass et al 1996; Chutuape et al, in press). In order to block opioid effects for 48–72 hours, buprenorphine doses of 12–24 mg are needed. Thus, we used higher doses to effect reductions in illicit opioid. Previous studies have established the dose-dependent efficacy of buprenorphine during daily administration, with optimal daily doses appearing to range from 8–16 mg using a sublingual liquid preparation. In an earlier study, we found that plasma buprenorphine concentrations 72 hours following a 44-mg dose and 48 hours following a 34-mg dose during thrice-weekly dosing at a schedule providing a total weekly dose of 112 mg were comparable to concentrations 24 hours following daily administration of a 16 mg-dose (Chawarski et al 1999). Plasma concentrations 24 hours following the 16-mg daily dose were considerably higher than concentrations 72 hours following a 32-mg dose and 48 hours following a 16 mg dose during thrice-weekly dosing with a total weekly buprenorphine dose of 64 mg. Although these findings support the use of relatively high buprenorphine doses for thrice-weekly dosing, the efficacy of lower thrice-weekly doses has not been systematically evaluated. Despite the substantial reductions in illicit opioid use found with the buprenorphine doses used in the current study, 52% of urine samples tested positive for illicit opioids during maintenance treatment. A longer period of treatment and additional pharmacologic and behavioral interventions may be needed to reduce use even more.

Buprenorphine was well tolerated by patients in this study. There were no reports of serious adverse effects of buprenorphine among patients in either treatment group. No patient requested dose adjustments or medication discontinuation due to medication side effects, and no patient needed to be withdrawn from the study protocol because of medical complications associated with buprenorphine. Given that there are reports of dose-related hepatotoxicity associated with some opioid agonists and antagonists (Mitchell et al 1987; Pfohl et al 1986), it is also of note that despite the relatively high buprenorphine doses used in the thrice-weekly condition, there was no evidence of liver toxicity associated with thrice-weekly dosing. Five of the 92 patients developed elevations of liver function enzymes that did not necessitate discontinuation from the study. Three of these patients had hepatitis C (1 in daily dosing and 2 in thrice weekly). For the other two patients, serum γ-glutamyltransferase (γ-GTP) increased from 14 at baseline to 144 at study completion (normal range < 37) for a thrice-weekly patient, and γ-GTP increased from 29 at baseline to 73 and serum glutamate pyruvate transaminase increased from 43 to 144 (normal < 50) for a daily patient.

Although dosing condition did not differentially affect cocaine use, the cocaine use of patients in this study is particularly notable, because cocaine dependence was an
exclusion criterion for study participation, and 70 of the 92 patients tested negative for cocaine at baseline. The proportion of cocaine-positive urine samples increased over time in both groups; and less than half of the patients abstained from cocaine for 3 or more consecutive weeks during the 12-week trial. The high prevalence of cocaine use in the study sample suggests that using diagnostic criteria for cocaine dependence, based on patient self-report only, will need to be augmented by repeated urine toxicology results negative for cocaine in future studies directed at opioid-dependent patients without heavy cocaine use. Additionally, the higher rates of illicit opioid use among patients with cocaine abuse points to the importance of evaluating potential differential effects of treatments on patients with and without cocaine abuse or dependence.

A limitation of this study is the relatively limited power to prove comparability of the two doses and exclude the possibility of a Type II error. The findings of nearly identical proportions of opioid-positive urine tests and self-reported heroin use in the two groups makes it highly unlikely that significant differences would have resulted from a larger sample size. The effect size (Cohen’s d = 0.037) calculated from the observed data regarding opioid-positive urine tests is extremely low, and a sample size of 19,000 would be needed to have a power of 0.80 to detect a significant difference between treatments with p < .05 (Cohen 1988). In this study, buprenorphine doses were calculated on a mg/70-kg basis in an attempt to optimize buprenorphine doses at the outset of treatment, because the protocol did not permit dose adjustments during the maintenance period. In clinical practice, mg/kg dosing may not be necessary, because doses can be adjusted according to the response of the individual patient. Additionally, subjects in this study attended the clinic daily to ingest active medication or placebo under double-blind conditions. The results of thrice-weekly dosing may differ if patients attend the clinic less frequently or are aware of the days they do not receive buprenorphine. Nevertheless, the results of this study support the clinical efficacy of thrice-weekly dosing and use of this dosing schedule. Thrice-weekly dosing reduces the costs to clinics and the inconvenience to patients, and the efficacy of thrice-weekly dosing will also facilitate use of buprenorphine outside of traditional narcotic maintenance treatment programs, such as in primary care clinics and physician offices.

References


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Thrice-Weekly vs. Daily Buprenorphine


