Abstract

This study a) compared the effects of buprenorphine versus methadone maintenance on benzodiazepine and alcohol use and b) evaluated the prognostic significance of gender and psychopathology and their interaction with maintenance treatment. Eighty male and 36 female patients were randomly assigned to daily sublingual buprenorphine (4 or 12 mg) or oral methadone (20 or 65 mg). Maintenance medication was not associated with significant differences in alcohol or benzodiazepine use. Rates of abstinence from illicit opioids were significantly higher for females; within the buprenorphine 4-mg group, females also had significantly better retention, lower rates of opioid-positive urine samples, and higher rates of abstinence from illicit opioids. Lifetime sedative dependence was associated with significantly better retention, decreased rates of cocaine-positive urine samples, and increased rates of cocaine abstinence; among buprenorphine-but not methadone-maintained patients, it was also associated with increased rates of abstinence from illicit opioids.

Buprenorphine, a synthetic derivative of thebaine that acts as a high affinity partial mu agonist and potent kappa antagonist, is under development as an alternative to methadone for maintenance treatment of opioid dependence (Blaine, 1992; Cowan, 1995; Fudala and Johnson, 1995). Based on differences in their pharmacological properties, a number of potential advantages of buprenorphine compared with methadone have been suggested. These include a decreased risk of problems associated with accidental overdose (Walsh et al., 1994, 1995b), decreased abuse liability in individuals dependent on opioids (Strain et al., 1995a, 1995b), a potential for less than daily maintenance dosing (Amass et al., 1994; Bigelow, 1995; Fudala et al., 1990; Johnson et al., 1995), and greater ease of withdrawal (Fudala et al., 1990; Lewis and Walter, 1992; Negus and Woods, 1995; San et al., 1992). Results of random assignment, double-blind clinical trials generally support the safety and efficacy of daily sublingual buprenorphine at doses of 8 to 12 mg (Johnson et al., 1992; Kosten et al., 1993; Ling et al., 1996; Schottenfeld et al., 1997; Strain et al., 1994a, 1994b). At these doses, buprenorphine is superior to lower daily doses of oral methadone (20 to 30 mg) or sublingual buprenorphine (2 to 4 mg) and is generally comparable to daily oral methadone doses of 50 to 60 mg for reducing illicit opioid use. In conjunction with previous dose-ranging studies (Bickel et al., 1988; Mello and Mendelson, 1980; Mello et al., 1981; Schottenfeld et al., 1993), these studies document the dose-dependent efficacy of buprenorphine for reducing illicit opioid use and suggest that optimal daily sublingual maintenance doses range minimally from 8 to 16 mg.

Little is known, however, about whether specific subgroups of opioid dependent patients might respond differentially to methadone or buprenorphine. Early studies suggested that buprenorphine might be superior to methadone for maintenance treatment of patients with concurrent opioid and cocaine dependence (Kosten et al., 1989a, 1989b; Mello et al., 1989), but this hypothesis has not been supported in controlled clinical trials (Johnson et al., 1992; Ling et al., 1996; Olivetto et al., 1994; Schottenfeld et al., 1997; Strain et al., 1994a, 1994b). Gender and various measures of psychopathology (especially depression and sociopathy) have been evaluated as important predictors of substance abuse treatment outcome in general (Joe et al., 1995; Kosten TA et al., 1993; McLellan et al., 1983; Rounsaville et al., 1986), but their prognostic significance has not been evaluated systematically in studies comparing buprenorphine and methadone maintenance. Given the critical importance of maintenance dose and the possibility of gender differences in bioavailability, pharmacokinetics, and pharmacodynamics (Harris et al., 1995), exploration of gender effects is particularly important. Depression is also of interest because it is treatable and, untreated, it is a risk factor for escalating cocaine use and continued illicit opioid use after entry into methadone maintenance treatment (Kosten et al., 1987; Ziedonis and Kosten, 1991a, 1991b). Buprenorphine has been used experimentally to treat depression (Bodkin et al., 1995; Nutt et al., 1995), and decreased symptoms of depression have been reported in buprenorphine-maintained patients (Kosten et al., 1990). These findings led to a hypothesis investigated in this study that buprenorphine might be superior to methadone for depressed patients. Because mu opioid agonists are associated with increased alcohol consumption in animal models (Czirr et al., 1987; Reid and Hunter, 1984), and naltrexone, a pure mu antagonist, is effective in the treatment of alcohol dependence (OMalley et al., 1992; Volpicelli et al., 1992), we also hypothesized that maintenance with the partial mu agonist buprenorphine would lead to greater reductions in alcohol and benzodiazepine use compared with methadone maintenance.

In this study, we analyzed data from a recently completed, random assignment, double-blind clinical trial comparing sublingual buprenorphine (4 or 12 mg) or oral methadone (20 or 65 mg) maintenance (Schottenfeld et al., 1997) to compare the effects of buprenorphine versus methadone maintenance on benzodiazepine and alcohol use, and to evaluate the prognostic significance of gender and psychopathology and their interaction with maintenance treatment.
Methods

Subjects

One hundred sixteen subjects satisfying the study criteria were randomly assigned to one of the four maintenance conditions. Eligibility criteria included meeting FDA criteria for methadone maintenance treatment, fulfilling DSM-III-R criteria for current opioid dependence and cocaine dependence or abuse, and having an opioid-positive urine toxicology test. Exclusion criteria included current psychosis, suicide risk, current dependence on alcohol or sedatives, pregnancy, and the inability to read or understand rating forms and symptom checklists. Women of child-bearing age who agreed to adequate contraception and monthly pregnancy tests were eligible for the study.

The four treatment groups were generally comparable across most important baseline demographic, social, drug abuse, and psychiatric factors. Additional details regarding the recruitment, randomization procedures, and subject characteristics are described in a previous paper (Schottenfeld et al., 1997).

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-III-R (Spitzer et al., 1990) evaluating lifetime and current substance use and mood and antisocial personality disorders. Supervised urine samples for toxicology testing were obtained at baseline, twice weekly during the first 9 months of the study (January to September 1991) and thrice weekly from all subjects after September 1991 until the completion of the study in July 1993. Of the 5288 urine samples scheduled for collection during the time patients remained in the clinical trial, 17.3% (N = 917) were scheduled for collection under the twice weekly schedule. 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 Diagnostics Division of Abbott Laboratories, Abbott Park, IL) was used for toxicology testing, with cutoffs of 200 ng/ml for opioids, 300 ng/ml for cocaine metabolite, and 200 ng/ml for benzodiazepines (Walters, 1987). On a weekly basis, patients reported the number of days they consumed alcohol and the total number of standard drinks they consumed during the preceding week.

Prognostic Factors

The overall sample included 36 women and 80 men. Lifetime rates of major depression or dysthymia, antisocial personality disorder, alcohol dependence, and sedative dependence among the 108 subjects with complete diagnostic data were 24%, 23%, 49%, and 25%, respectively.

Maintenance Treatment

Maintenance medications were dispensed daily under double-blind conditions, with ingestion observed by nursing staff. After induction during the first 2 weeks, subjects were maintained at their full maintenance dose for 22 weeks (weeks 3 through 24). Subjects participated in a 1-hour weekly group counseling session, and subjects were discharged after missing three consecutive days of medication or three consecutive counseling sessions.

Statistical Analyses

Data analyses focused on a) the effects of maintenance treatment (buprenorphine vs. methadone) on self-reports of alcohol and benzodiazepine use during the clinical trial and b) the effects of five potential prognostic factors (gender, lifetime depression, sedative dependence, alcohol dependence, and antisocial personality disorder) and their interaction with maintenance treatment on seven outcome measures (retention in treatment; rates of illicit opioid, cocaine, alcohol, and benzodiazepine use; and rates of abstinence for 3 or more weeks from opiates and from cocaine).

The comparability of the four maintenance treatment groups at baseline with regard to demographic, social, drug abuse, or psychiatric features was evaluated using chi-square and analysis of variance. There were no significant differences found for any of these features (see Schottenfeld et al., 1997). We also used Student’s t-test and chi-square to evaluate baseline gender differences in sociodemographic, drug abuse, and psychiatric variables. As shown in Table 1, compared with male subjects, female subjects were significantly more likely to be married, less likely to be employed full time, and more likely to have a lifetime diagnosis of sedative dependence; they also reported drinking to intoxication on average for fewer years and on average weighed significantly less. To evaluate whether these gender differences were distributed comparably across the four maintenance groups, we used chi-square and an analysis of variance in an eight-level classification (crossing maintenance treatment and gender). As shown in Table 2, the groups were generally comparable at baseline, and there were no significant baseline differences for any of the variables.

<table>
<thead>
<tr>
<th>TABLE 1 Baseline Comparability of Treatment Groups</th>
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<tr>
<th></th>
<th>Methadone (47 reg.)</th>
<th>Buprenorphine (12 reg.)</th>
<th>Methadone (35 mg)</th>
<th>Buprenorphine (4 mg)</th>
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</tr>
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</table>

TABLE 1 Baseline Comparability of Treatment Groups
The effects of maintenance treatment on rates of alcohol and benzodiazepine use were evaluated using random regression models, which were specifically designed for unbalanced repeated measures with missing data (Gibbons et al., 1993). This approach allows for intrasubject serial correlation and unequal variance and covariance structures across time. Random regression models provide p-values for the main effects of maintenance treatment, time, and the interaction between maintenance treatment and time. Random regression models estimate missing values by incorporating available trend data for each individual with information on the behavior of the group from which the subject is drawn.

The effects on retention of each of the five prognostic variables (gender, lifetime depression, alcohol dependence, sedative dependence, and antisocial personality disorder) and the effects of an interaction between maintenance treatment and the prognostic variable were analyzed using the Kaplan-Meier product limit method and the generalized Wilcoxon test (Selvin, 1991). Random regression models were utilized to examine the effects of each of the five prognostic variables and their interactions with maintenance treatment on rates of illicit opioid- and cocaine-positive urine toxicology samples during the maintenance phase. The results of urine toxicology testing were aggregated into eight successive 3-week periods, to develop a continuous outcome measure. The baseline value and proportion of tests positive for illicit opioids or cocaine during each successive period were calculated for each subject and used in the random regression model. When significant interactions were found between maintenance treatment and a prognostic variable, stratified analyses were used to assess the significance of the prognostic factor within each maintenance treatment group. Contingency tables and chi-square analyses were used to evaluate the effects of each of the prognostic variables on the two main categorical outcomes, the proportion of subjects achieving 3 or more consecutive weeks of documented abstinence from illicit opioids and the proportion achieving 3 or more weeks of abstinence from cocaine.

Because we found significant effects of gender and significant interactions between gender and maintenance treatment on several outcome measures, we also evaluated the possibility that the effects of gender might be related to gender differences in weight and weight-adjusted maintenance dose. On average, male subjects weighed significantly more than female subjects, and consequently they received on average lower maintenance doses, calculated on a mg/kg basis. Multiple regression was used to disentangle the effects of weight and gender on rates of opioid-positive urine samples. All significance levels were set at p < .05.

Results

Maintenance Treatment Effects on Alcohol and Benzodiazepine Use

There were no significant effects of maintenance treatment on either reported days using alcohol (Wald [chi]² = 2.74, df = 3, p = .43) or rates of benzodiazepine-positive urine samples (Wald[chi]² = 5.72, df = 3, p = .13), and the effects of time and the interaction between time and maintenance treatment were also not significant for alcohol or benzodiazepine use.

Gender Differences in Treatment Retention

Gender did not significantly affect retention across all maintenance treatments (Wilcoxon [chi]² = 2.4, df = 1, p = .12), but there was a significant interaction between gender and maintenance treatment (Wilcoxon [chi]² = 16.04, df = 7, p < .025). Stratifying by maintenance group, gender effects were significant only in the buprenorphine 4-mg group (Fig. 1), where women had better retention than men (Wilcoxon [chi]² = 4.94, df = 1, p < .03).
Gender Differences in Illicit Opioid and Cocaine Use

Rates of opioid-positive urine samples were significantly related both to maintenance treatment (Wald $[\chi^2] = 29.4$, $df = 3$, $p < .001$), with lower rates found at higher maintenance doses, and to time (Wald $[\chi^2] = 340.06$, $df = 8$, $p < .001$), with rates generally decreasing over time. Female patients had nonsignificantly lower rates of opioid-positive urine tests compared with males (56.3% vs. 67.2%; Wald $[\chi^2] = 3.2$, $df = 1$, $p = .074$). There were significant interactions between maintenance treatment and gender (Wald $[\chi^2] = 8.49$, $df = 3$, $p < .05$) and between maintenance treatment and time (Wald $[\chi^2] = 66.58$, $df = 24$, $p < .001$).

Overall, a significantly higher proportion of female compared with male patients became abstinent from illicit opioids (50.0% vs. 27.5%; $[\chi^2] = 5.6$, $df = 1$, $p < .02$). Stratified by maintenance treatment, gender differences were significant only in the buprenorphine 4-mg group (Table 3), where females had lower rates of opioid-positive toxicology tests compared with males (63.7% vs. 83.6%; Wald $[\chi^2] = 11.92$, $df = 1$, $p < .001$) and higher rates of abstinence from illicit opioids (50% vs. 0%; $[\chi^2] = 12.2$, $df = 1$, $p < .001$).

Stratifying by maintenance treatment, gender differences were significant in the buprenorphine 12-mg and methadone 20-mg groups, with female patients having higher rates of cocaine-positive samples than male patients in the buprenorphine 4-mg group (81.7% vs. 53.8%; Wald $[\chi^2] = 5.7$, $df = 1$, $p < .02$) and lower rates than male subjects in the methadone 20-mg group (38.2% vs. 62.5%; Wald $[\chi^2] = 4.03$, $df = 1$, $p < .05$). Although a higher proportion of female compared with male patients achieved 3 or more consecutive weeks of documented abstinence from cocaine (47.2% vs. 31.3%), the difference was not significant ($[\chi^2] = 2.7$, $df = 1$, $p < .04$).
Gender Differences, Controlling for Weight

Because patients received fixed maintenance doses that were not calculated on a mg per kg basis and, on average, males weighed more than females, we considered the possibility that the effects of gender on illicit opioid use were a result of gender differences in the weight-adjusted maintenance dose. Consistent with this possibility, across all four maintenance conditions, the mean (SD) weight was significantly lower among patients who achieved 3 or more consecutive weeks of abstinence from opioids, 148.5 (28.3) lbs, compared with those who did not become abstinent, 162.5 (34.7) lbs (t = 2.18, p = .04). To disentangle the effects of gender and weight, we used regression models to evaluate the effects of weight alone and then weight and gender on rates of opioid-positive urine samples within each of the four maintenance groups. Weight alone explained relatively little of the variance in rates of opioid-positive tests within each of the four maintenance groups (adjusted r squares ranged from .003 to .07) and was not significant in any of the models. The model for weight and gender was significant only in the buprenorphine 4-mg group (F = 4.5, p = .021), where the effects of gender remained significant even after controlling for weight. The adjusted r square for weight and gender was .20, whereas the adjusted r square for weight alone in the buprenorphine 4-mg group was .07 (F = 3.09, p = .089).

Effects of Lifetime Psychiatric and Other Substance-Use Disorders

A lifetime diagnosis of sedative dependence was significantly associated with higher retention (Wilcoxon [chi]² = 8.4, df = 1, p < .005), lower rates of cocaine-positive urine tests (52% vs. 65%; Wald [chi]² = 5.3, df = 1, p < .02), and increased rates of abstinence from cocaine (35.6% vs. 30.9%; [chi]² = 5.3, df = 1, p < .025). There were significant interactions between lifetime history of sedative dependence and maintenance treatment regarding retention (Wilcoxon [chi]² = 20.9, df = 7, p < .005) and rates of abstinence from both illicit opioids ([chi]² 21.3, df = 7, p < .005) and cocaine ([chi]² = 16.1, df = 7, p < .025). Patients with a history of sedative dependence had lower attrition from treatment and higher rates of abstinence from cocaine in the buprenorphine 4-mg and 12-mg and methadone 20-mg groups but not in the methadone 65-mg group. Patients with a history of sedative dependence had higher rates of achievement of opioid abstinence than patients without sedative dependence in the buprenorphine 4-mg and 12-mg groups (42.9% vs. 5.3% and 66.7% vs. 36.8%), whereas in the methadone 20-mg and 65-mg groups, the rates were slightly lower for patients with a history of sedative dependence compared with those without sedative dependence (20.0% vs. 24.0% and 55.6% vs. 66.7%; [chi]² = 21.3, df = 7, p < .003). Overall, a lifetime history of sedative dependence did not significantly affect rates of opioid-positive urine tests (Wald [chi]² = 1.95, df = 1, p = .16) or benzodiazepine-positive urine tests (Wald [chi]² = 2.67, df = 1, p = .10), nor were there interactions between maintenance treatment and sedative dependence regarding rates of opiate-positive urine tests (Wald [chi]² = 2.53, df = 3, p = .47) or benzodiazepine-positive tests (Wald [chi]² = 2.36, df = 3, p = .50).

Lifetime diagnoses of depression, antisocial personality disorder, and alcohol dependence were not significantly associated with retention, rates of opioid- or cocaine-positive urine tests, or abstinence from cocaine, and there were no significant interactions between any of these disorders and maintenance treatment regarding retention or rates of opioid- or cocaine-positive urine samples. Rates of abstinence from illicit opioids were significantly higher for patients with a history of depression or dysthymia (64.3%) compared with patients without a depressive disorder (31.9%; [chi]² = 5.53, df = 1, p < .02), but there were no other significant effects of depression or dysthymia on rates of abstinence from illicit opioids. Gender differences in weight-adjusted maintenance doses account for some of the gender differences in outcome, especially in the low-dose buprenorphine maintenance group, but gender differences in rates of opioid-positive urine tests in the buprenorphine 4-mg group persist even after controlling for weight. Marital status, work status, and years using alcohol to intoxication were not significantly associated with rates of opioid-positive urine samples or rates of abstinence from illicit opioids, suggesting that baseline gender differences in these factors do not account for the findings of gender differences in outcome. Because lifetime sedative dependence was significantly associated with abstinence from illicit opioids, and female subjects were more likely than males to have a history of sedative dependence, it is not possible in this study to disentangle fully the effects of gender and sedative dependence. The findings in this study of gender differences in response to maintenance on buprenorphine 4 mg sublingual are consistent with the possibility that there are gender differences in central opioid neuronal pathways, as suggested by recent PET findings of increased mu receptor density in women (Zubieta et al., 1996) and findings of greater analgesic response to kappa opioids in women compared with men (Gear et al., 1996). Increased mu receptor density may account for the finding that female patients had a better response than male patients to lower doses of the partial agonist buprenorphine.

The results of this study are consistent with the hypothesis that buprenorphine might be superior to methadone for the treatment of patients with a history of sedative dependence but do not support its superiority for the treatment of patients with depression, alcohol dependence, or antisocial personality disorder. A lifetime history of sedative dependence was associated with an overall improved prognosis, and rates of abstinence from illicit opioids were higher among patients with, compared to those without, a history of sedative dependence in both buprenorphine-maintained groups but not in either methadone group. The small number of patients with lifetime sedative dependence treated in each of the conditions should be taken into consideration in evaluating these findings. Rates of alcohol and benzodiazepine use, however, were not significantly lower for patients maintained on buprenorphine compared with methadone, and there was no other indication that patients with a history of alcohol or sedative dependence responded differentially to buprenorphine compared with methadone maintenance. A lifetime diagnosis of depression or dysthymia was associated with significantly increased rates of abstinence from illicit opioids, but there were no other significant effects of lifetime depression on treatment outcomes and no indications of any differential effects of maintenance on buprenorphine versus methadone for patients with or without lifetime depression. Although antisocial personality disorder has often been considered to confer a poor prognosis (Leal et al., 1994; Rounsaville and Kleber, 1986), the findings of this study that outcomes are not significantly associated with antisocial personality disorder are consistent with more recent studies and reviews (Cacciola et al., 1995, 1996; Gerstley et al., 1990).

Several limitations of the current study should be noted. First, the relatively small numbers of female patients and patients with comorbid psychiatric disorders included in each maintenance group limits the power of the study to exclude the possibility that significant differences associated with these factors were not
missed (type II error). Second, patients with current suicide risk or dependence on alcohol or sedatives were excluded from the study, and it is possible that patients with current depression or alcohol dependence might respond differentially to maintenance on buprenorphine versus methadone. A relatively restricted range of alcohol and benzodiazepine use at baseline may have also constrained detection of differential effects of maintenance treatment on use of these substances during the study. Finally, the large number of analyses conducted increases the possibility that some of the significant differences found in this study could have resulted by chance. Given the exploratory nature of this study and the importance of minimizing the likelihood of a type II error, however, we did not adjust the significance level to correct for the problem of multiple comparisons. Consideration should be given to using weight-adjusted maintenance doses in future studies of buprenorphine and methadone. Additional studies are needed to evaluate prospectively the effects of gender and current psychiatric comorbidity on response to maintenance treatment with buprenorphine compared with methadone.

References


Ovid: Prognostic Factors in Buprenorphine- versus Methadone-Maintain...


