RESEARCH REPORT

Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial

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Abstract

Aims. To evaluate the safety and efficacy of an 8 mg/day sublingual dose of buprenorphine in the maintenance treatment of heroin addicts by comparison with a 1 mg/day dose over a 16-week treatment period. As a secondary objective, outcomes were determined concurrently for patients treated with two other dose levels. Design. Patients were randomized to four dosage groups and treated double-blind. Setting. Twelve outpatient opiate maintenance treatment centers throughout the United States. Participants. Two hundred and thirty-nine women and 497 men who met the DSM-III-R criteria for opioid dependence and were seeking treatment. Intervention. Patients received either 1, 4, 8 or 16 mg/day of buprenorphine and were treated in the usual clinical context, including a 1-hour weekly clinical counseling session. Measurement. Retention in treatment, illicit opioid use as determined by urine toxicology, opioid craving and global ratings by patient and staff. Safety outcome measures were provided by clinical monitoring and by analysis of the reported adverse events. Findings. Outcomes in the 8 mg group were significantly better than in the 1 mg group in all four efficacy domains. No deaths occurred in either group. The 8 mg group did not show an increase in the frequency of adverse events. Most reported adverse effects were those commonly seen in patients treated with opioids. Conclusions. The findings support the safety and efficacy of buprenorphine and suggest that an adequate dose of buprenorphine will be a useful addition to pharmacotherapy.

Introduction

Buprenorphine, a potent partial opiate agonist that has been undergoing extensive clinical testing for treatment of opiate addiction, is likely to become the next medication added to the armamentarium of opiate dependence pharmacother-
Pharmacologically, buprenorphine is a partial agonist at the mu receptor and a weak antagonist at the kappa receptor. Because it binds tightly to, and dissociates slowly from, these receptors buprenorphine exhibits an agonist "ceiling effect", most noticeably in its respiratory depression effect, which accords the medication a high degree of clinical safety. Its tight binding with slow dissociation from receptors also provides blockade for the effects of subsequently administered agonists, precipitates withdrawal in patients maintained on a sufficient dose of full agonist, and provides prolonged duration of action with poor reversibility by naloxyne. Buprenorphine's weak antagonist effect at the kappa receptor renders it devoid of psychotomimetic effects.

Buprenorphine is poorly absorbed after oral administration and exhibits a large first pass effect. It is, however, well absorbed after sublingual administration, reaching 60–70% of the plasma concentration achieved by parenteral routes. Buprenorphine is widely distributed throughout the body with a peak plasma concentration of approximately 90 minutes and a terminal half-life of 4–5 hours. It is highly bound to plasma protein and is metabolized by conjugation and N-dealkylation. Most buprenorphine metabolites are excreted by the fecal route.

Buprenorphine has been under intensive study for the treatment of opioid dependence since the late 1970s when Jaskinski and colleagues showed that it could substitute for morphine, preventing the opioid withdrawal syndrome while producing rather modest withdrawal of its own. Extensive research by Mello & Mendelson demonstrated buprenorphine's limited level of reinforcing efficacy in comparison to opioids and established its ability to suppress heroin self-administration in opioid-dependent primates and humans.

Over the past decade a series of controlled clinical trials, using such outcome measures as illicit opiate use, retention in treatment, craving and global rating of improvement, have substantiated buprenorphine's clinical safety and efficacy. More than a half-dozen well controlled clinical trials involving more than 1000 patients have been reported. Pivotal studies compared one or more doses of buprenorphine to one or more doses of methadone in an attempt to position buprenorphine on the methadone dosage spectrum and to determine its ability to substitute sufficiently for both heroin and methadone. The first such study involved 45 heroin addicts assigned, in double-blind manner, to either 2 mg/day sublingual buprenorphine or 30 mg/day methadone. Results indicated that, at these doses, buprenorphine was less effective than methadone in its ability to block the physiological and subjective effects of 6 mg hydromorphone but treatment retention, reduction of illicit opioid use and self-report of symptoms were comparable. Extending upon these findings, the same group conducted a cross-over, dose–response study comparing the effects of 6 and 12 mg hydromorphone in subjects maintained on 2, 4, 8 or 16 mg buprenorphine. Study results indicated that 8 mg sublingual buprenorphine effectively blocks subject-reported "high" and "drug effect".

A 25-week, double-blind, parallel group study involving 162 subjects compared the effectiveness of 8 mg/day sublingual buprenorphine to 20 mg/day and 60 mg/day methadone for short-term maintenance and detoxification. The 8 mg/day buprenorphine dose was comparable to 60 mg/day methadone and superior to 20 mg/day methadone with respect to treatment retention and illicit opioid use. All groups provided a high rate of positive urine samples throughout the study, however, indicating that buprenorphine above 8 mg/day would be needed to control illicit opioid use. When Kosten and colleagues compared 2 mg/day and 6 mg/day sublingual buprenorphine to 35 mg/day and 65 mg/day methadone, the higher buprenorphine dose was superior to the lower dose on all measures, although neither was as effective as the two methadone doses. In a 26-week, variable dose comparison study, Strain and colleagues allowed "clinically guided" dose changes over a 14-week period, resulting in a mean buprenorphine dose of 8.9 mg/day compared to a mean methadone dose of 54 mg/day. Patients in both groups had comparable rates of illicit opioid use.

In a long-term double-blind fixed dose study involving 225 opioid addicts who were randomized to either 8 mg/day sublingual buprenorphine, 30 mg/day or 80 mg/day methadone,
subjects on the high methadone dose performed significantly better on all measures than those on either the low methadone dose or buprenorphine, but nearly identical results were obtained from the latter two groups. The investigators concluded that 8 mg/day buprenorphine was comparable to 30 mg/day methadone, but that neither of these doses was optimal for opioid maintenance treatment.

Two additional studies\(^4\)\(^{,}\)\(^{21}\) that compared multiple doses (up to 32 mg) of buprenorphine and methadone confirmed the earlier findings that buprenorphine produces both an opiate agonist effect similar to methadone but with more rapid onset and longer duration of action and an agonist ceiling effect at doses in the 8 to 32 mg/day range. When 12 mg/day sublingual buprenorphine and 65 mg/day methadone were compared to 4 mg/day buprenorphine and 20 mg/day methadone\(^{22}\) in 30 subjects dually addicted to opioids and cocaine, the high doses of buprenorphine and methadone were found superior to both low doses. Buprenorphine was found to deter illicit opioid, but not cocaine use. In the adjustable dose study by Strain\(^{19}\) an optimal response was achieved at mean doses of 11.2 mg/day buprenorphine and 67 mg/day methadone.\(^{19}\)

From these studies, it appeared that 8 mg of buprenorphine was as effective as low to moderate doses of methadone in reducing illicit opioid use and improving treatment retention. Sublingual buprenorphine in the range of 6–12 mg/day compared favorably with 30–60 mg/day methadone and, when equipotent doses were used, buprenorphine appeared to be as effective as methadone in suppressing opioid withdrawal symptoms.\(^{15}\)\(^{,}\)\(^{17}\)

The Medication Development Division of the US National Institute on Drug Abuse (NIDA) and the drug sponsor (Reckitt and Colman) have initiated efforts to seek approval from the US Food and Drug Administration (FDA) for the clinical use of buprenorphine in opioid dependence.\(^{23}\) The present multicenter trial was intended to provide pivotal information for the anticipated New Drug Application (NDA) in the United States. The primary objective was to establish the efficacy of an 8 mg/day sublingual dose of buprenorphine by comparison with a 1 mg/day dose, which was adopted to serve essentially as a placebo. Since it was expected that outcomes associated with other doses might be useful or even necessary in the NDA process, data were also collected on a 4 mg/day and a 16 mg/day dose, stipulating in advance that all analyses involving these two dosage groups would be considered secondary outcomes. This decision was based upon statistical considerations, specifically, control of Type I error rate and sample size requirements for adequate power.

**Methods**

**Subjects**

Opioid addicts seeking treatment were recruited at 12 clinics in the United States. The goals at each site were to enroll 60 patients, of whom 25% were to be women. There was also an attempt to achieve racial diversity. The final sample consisted of 736 patients. Actual enrollment ranged from 53 to 70 patients at the various sites and, overall, about a third of the patients were women. The racial distribution was 48.8% Caucasian, 21.9% Afro-American and 28.1% Hispanic. The average was 36 years. The majority of patients reported completion of high school (32%) or some college (31%). Nearly 10% were college graduates and the remainder had less than 12 years of schooling. Only 26% were currently married; divorce/separation accounted for 30% and 40% had never married. Almost a third reported that they had been unemployed for the past 3 years. Half had been on methadone maintenance some time in the past. The four dosage groups were not significantly different on any of these characteristics.

Patients were screened for study participation by trained research assistants and were examined by physicians to establish eligibility and discuss the informed consent. Patients had to meet DSM-III criteria\(^{24}\) for opioid dependence and, in some instances, federal or state criteria for methadone maintenance. Daily use of opioids during the previous 6 months was a requirement but patients were excluded if in a methadone maintenance program during the previous 30 days. They were also excluded from the study if they had a diagnosis of alcohol dependence or a medical condition (such as active tuberculosis, unstable cardiovascular or liver disease, unstable diabetes or AIDS) that would have made participation in the study medically hazardous. Patients using neuroleptics, anticonvulsants or disulfiram were also excluded. Women of childbearing
potential had to agree to practice birth control and were informed that they would be removed from the study if they became pregnant. Three women did become pregnant during the study.

All patients included in the study signed an informed consent as approved by local and/or central Institutional Review Boards. They were not paid for participation, but medication and counseling services were provided without charge. It was explained that records would be assigned a code number and that specific patient identifiers would not be kept in research records. A federal Certificate of Confidentiality was obtained for the study. Acceptable patients who signed the consent form became study subjects when they received their first dose of buprenorphine.

**Treatment procedures**

Study medication was supplied by NIDA in unlabeled triangular-shaped plastic vials with break-off tops that contained 1, 4, 8 or 16 mg of buprenorphine dissolved in 30% ethyl alcohol. These supplies were packaged into individual pre-coded patient kits and distributed by the Central Research Pharmacy (CRP) of the US Department of Veteran’s Affairs in Albuquerque, New Mexico. Randomization to treatment was achieved by assigning patients to the medication that had been labeled in a blinded fashion by the research pharmacy using a random numbers table. Patients were inducted onto 1, 4, 8 or 16 mg/day of buprenorphine over 1–5 days depending on their assigned dose. Patients assigned to 1 mg/day received 1 mg/day throughout. Those assigned to 4, 8 or 16 mg/day received 2 mg on day 1, 4 mg on day 2 and a 4 mg/day increment for each succeeding day where needed to reach their assigned level. Patients who missed 4–6 consecutive days of dosing were re-inducted on buprenorphine using the same schedule as initial induction, but if they required more than three re-inductions or missed seven or more consecutive doses they were removed from the study. Patients who were hospitalized for treatment of intercurrent medical conditions were switched to methadone or other suitable medication and retained in the study if the break in buprenorphine dosing was less than 7 days.

Daily sublingual buprenorphine doses were administered under observation at the clinic; no take-home doses were allowed. Patients were instructed to hold the liquid under their tongue for 5 minutes. Patients and staff at the study sites were blind to medication dose, but the study code could be broken by the CRP in a medical emergency. Patients were treated for up to 16 weeks, but those who so desired were allowed to enter a separate 36-week extension protocol that continued the double-blind dosing. The extension permitted dose modification by doubling or halving, to a maximum of 32 mg/day, the patient’s assigned dose, depending on the clinical needs. The results of this experience will be reported separately. Patients not wishing to participate could elect to taper off buprenorphine or seek other available treatment.

In addition to their pharmacotherapy and daily contact with dispensing nurses and research staff, patients were offered a 1-hour weekly counseling session on problems of daily living, drug abuse-related issues and education about HIV infection.

**Efficacy measures**

Following general FDA guidelines, an a priori decision was made to evaluate efficacy using four outcome domains: retention in treatment, evidence from urine tests of illicit opioid drug use, craving, and global ratings by patients and staff.

Retention in treatment was defined as the number of days from first to last dose. Some patients were terminated from the study at their own request (n = 42) but others simply failed to appear and, after seven consecutively missed visits, were administratively terminated (n = 261). Only 375 patients completed the full 16 weeks of treatment. As a group, the completers were more likely to be male, less likely to have been using i.v. or smoking as their primary mode of abuse, and more likely to be older.

Urine samples were collected each Monday, Wednesday and Friday, either under direct observation or in an FDA-approved urine collection device with a built-in temperature strip. Samples were shipped to the Center for Human Toxicology at the University of Utah where they were analyzed for the presence of opioids and cocaine using an immunoassay technique with cut-off at 300 mg/ml for opiates and benzoylcegonine. All Monday samples were also tested for amphetamines and benzodiazepines. Clinical sites were not informed of the results of urine testing.

Evidence of illicit opioid drug use based upon
urine test results can be summarized in a number of ways. All are highly inter-correlated and all are influenced by retention. We chose to report percentage negative for opioids, excluding missing specimens from both numerator and denominator of each patient. This method has the apparent advantage of avoiding imputation of missing data as either negative or positive, but at the cost of discarding potentially meaningful information. We also report the percentage of patients who contributed 13 consecutive urine specimens, all of which tested negative for opioids regardless of when this occurred during their tenure in the study. To be considered a success this index demands a period of sustained abstinence but all urine test results before and after the achievement of this criterion of success are ignored. Finally, we used the number of negative urines contributed by each patient as another dependent variable. This number can vary from 0 to 48 in this 16-week study that calls for a thrice weekly urine collection. To obtain a perfect score a patient must attend clinic faithfully, provide all scheduled urine specimens, all of which test negative for opioids, and stay in treatment for the full course. Because of this, the score provides an excellent way to rank patients along a continuum of success–failure using only urine test results as data. This is our preferred approach and, in discussing the advantage of this index, we have termed it the Treatment Effectiveness Score (TES) to emphasize these points.26

Retention affects each of these indices in different ways. A patient who provides three opioid-free urines in the first week of the study and then drops out will have the same percentage negative score (100%) as the patient who stays the full course without a single urine positive for opioids. Clearly, these are two clinically discriminable outcomes. To be considered a success by the criterion of 13 consecutive negative urines, a patient must remain in the study for at least a month, but could then drop from the study and resume illicit drug use and still be considered a success. There are no methods that adequately capture clinically meaningful patterns of illicit drug use. Reporting results using study completers only does not solve these problems even though it does hold length of treatment constant. The treatment groups can no longer be considered random samples, there is the potential bias introduced by differential attrition, and much clinically meaningful information is lost by excluding patients with varying but incomplete participation from the analysis. However, some data are reported in this manner to supplement the primary analyses.

Craving for heroin was measured weekly on a 10 cm visual analog scale labeled zero at one end (no craving for heroin) and 100 at the other end (the most intense craving ever experienced for heroin). Patients were asked to indicate their peak craving for opioids at any time during the past week. Craving for cocaine and for alcohol were also measured but occurred at such low levels and so infrequently that these ratings were of no interest.

At 4-week intervals patients were asked to rate the global severity of all aspects of their current drug problem on a scale of 0 (no problem) to 100 (very severe). The research team with direct patient contact also rated each patient at regular staff meetings and recorded their consensus using the same scale format. In addition, at the time of termination from the study (either early or after 16 weeks) each patient was rated as much better, a little better, no change, slightly worse or much worse since entering the study.

Safety monitoring
Study site physicians were responsible for the day to day clinical management of the patients and could withhold a buprenorphine dose if significant signs of opioid toxicity were observed or if otherwise deemed medically necessary. In practice this rarely occurred. Each week patients were questioned in general terms, without the use of a questionnaire, regarding their general state of health. Specific symptoms or complaints were recorded on an adverse event report form and submitted to the study sponsor and to the Study Chairman. At one time during the trial the adverse events were reviewed by the study’s Data Monitoring Board, whose members were blind to patients’ dosage groups. Patient complaints were assigned by a computer program to a specific coding symbol for adverse events.27

Data management and analysis
Case report forms were completed at the study sites and reviewed for completeness and consistency by study monitors from an outside contractor. Verified data forms were sent to the Cooperative Studies Program Coordinating
Center at the US Department of Veteran's Affairs Medical Center in Perry Point, Maryland where the data were key-entered, key-verified, computer edited, and all interim and final analyses were performed.

The study design provided for detection of clinically important differences in outcome measures between the 1 mg and 8 mg groups with statistical power of at least 0.80. The 4 mg and 16 mg groups were included to provide information on additional doses of buprenorphine and the sample sizes for these groups were chosen to match the sample sizes of the 1 mg and 8 mg groups. Since the primary comparison was between the 1 mg and 8 mg group, statistical significance for this comparison was set at the 0.05 level. The other five pair-wise comparisons of dosage groups were considered a priori to be of secondary interest and these comparisons were adjusted using a Bonferroni correction, so that a significant level of 0.01 was considered to be statistically significant.

Chi-square analyses were used to test for differences in dosage groups for discrete variables, while analysis of variance techniques were used to test for differences in continuous variables. Because normality assumptions could not be assumed in analyzing the TES, the Kruskal–Wallis analysis of variance tests were used. Time to an event was analyzed using the Kaplan–Meier product limit estimator for estimating the survival time curves and the log rank test was used for testing statistical significance.

Results

Retention

Overall, 51% of the patients completed the 16-week study. Completion rates by dosage group were 40% for the 1 mg group, 51% for the 4 mg group, 52% for the 8 mg group and 61% for the 16 mg group. The 1 mg group had significantly poorer retention than both the 8 mg group ($p = 0.019$) and the 16 mg group ($p < 0.001$). None of the other comparisons was significant.

Figure 1 shows the proportion of subjects remaining in treatment at each week of the study by group. The log rank tests for the Kaplan–Meier estimates of the time to dropout curves show the same results as the overall completion analyses, i.e. statistically significant differences between the 1 mg and 8 mg groups ($p = 0.019$) and between the 1 mg and 16 mg groups ($p = 0.0003$), but no other significant pair-wise differences. The reasons that patients were terminated from the study are shown in Table 1.

Urine opiate toxicology

The three efficacy outcome measures based upon urine testing are summarized in Table 2. Results are generally consistent. The 8 mg group did significantly better than the 1 mg group on all three measures. The 1 mg group did significantly worse than the other three dosage groups on percentage negative for opioids and on the Treatment Effectiveness Score. Other pairwise comparisons were non-significant on these two variables. The 16 mg group had significantly more patients with 13 consecutive negative urines than both the 1 mg group ($p < 0.001$) and the 4 mg group ($p < 0.006$).

Craving

Using the score on the heroin craving scale at screening as the covariate, analyses of covariance were performed for the 4, 8, 12 and 16-week ratings, using all patients remaining in treatment on those occasions. Significantly higher craving scores were observed for the 1 mg group compared to the 8 mg group at weeks 4 ($p < 0.01$), 8 ($p < 0.01$) and 12 ($p = 0.04$), but not at week 16 ($p = 0.15$). The sample sizes in these comparisons ranged from 123 patients in the 1 mg group and 142 in the 8 mg at week 4 to 72 patients in the 1 mg group and 98 patients in the 8 mg group at week 16. The 1 mg group also had significantly higher craving scores than the 4 mg group at 4 weeks and the 16 mg group at weeks 4 and 8. In contrast, Fig. 2 shows the craving scores by week based only on those subjects who completed the full 16 weeks of treatment. The only statistically significant results of the covariance analyses based upon the completer sample occurred at 8 weeks between the 1 mg and 8 mg group and between the 1 mg and 16 mg group.

Global ratings

In comparisons of the staff ratings of the severity of patients’ drug problems, the 8 mg group had significantly better (lower) scores than the 1 mg group at each of the 4, 8, 12 and 16-week rating periods based on analysis of covariance using
Figure 1. Proportion of patients in each dosage group still in treatment by week.

Table 1. Reasons for patient terminations

<table>
<thead>
<tr>
<th>Reason for termination</th>
<th>1 mg</th>
<th>4 mg</th>
<th>8 mg</th>
<th>16 mg</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Completed 16-wk protocol</td>
<td>74</td>
<td>40.0</td>
<td>93</td>
<td>51.1</td>
<td>98</td>
</tr>
<tr>
<td>Missed 7 consecutive days</td>
<td>85</td>
<td>45.9</td>
<td>62</td>
<td>34.1</td>
<td>66</td>
</tr>
<tr>
<td>Subject’s request</td>
<td>18</td>
<td>9.7</td>
<td>8</td>
<td>4.4</td>
<td>9</td>
</tr>
<tr>
<td>Buprenorphine toxicity</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Unrelated medical event</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
<td>1.1</td>
<td>2</td>
</tr>
<tr>
<td>Required 4th re-induction</td>
<td>2</td>
<td>1.1</td>
<td>3</td>
<td>1.6</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>2.2</td>
<td>13</td>
<td>7.1</td>
<td>7</td>
</tr>
<tr>
<td>Totals</td>
<td>185</td>
<td>100</td>
<td>182</td>
<td>100</td>
<td>188</td>
</tr>
</tbody>
</table>

screening global ratings as the covariate. For the patient self-ratings, the 8 mg group had significantly better scores than the 1 mg group at weeks 4, 8 and 12, but not 16. There were no significant differences between the 1 mg and 4 mg group. The 16 mg group had better staff
Table 2. Efficacy results based on urine opioid toxicology

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Buprenorphine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean percentage negative for opioids¹</td>
<td>18.5 29.2 32.9 38.3</td>
</tr>
<tr>
<td>Percentage of patients with 13 consecutive negative urines²</td>
<td>8.6 14.3 17.6 26.8</td>
</tr>
<tr>
<td>Mean number of negative urines (TES)³</td>
<td>5.6 9.6 10.3 13.9</td>
</tr>
<tr>
<td>Total patients⁴</td>
<td>185 182 188 181</td>
</tr>
</tbody>
</table>

¹ Eight mg vs. 1 mg: F = 17.57, df 1/362, p < 0.0001. ² Eight mg vs. 1 mg: Chi-square = 6.48, 1 df, p = 0.017. ³ Eight mg vs. 1 mg: ANOVA F = 17.62, df 1/371, p < 0.0001. ⁴ For percentage negative, n = 182, 175, 182, 179.

Figure 2. Mean heroin craving scores for each dosage group by week based upon patients completing full study. ●, 1 mg, n = 72; □, 4 mg, n = 93; ▲, 8 mg, n = 98; ▼, 16 mg, n = 110.

global scores than the 1 mg group on all four rating periods (p < 0.01) but the patient self-rating was significant only at week 4. The ratings of patient progress at early termination or completion are shown in Table 3. There were 21% of the 1 mg group rated as “much better” at termination compared to 38% of the 8 mg group.

Adverse events
No deaths occurred during the study. There
were 51 serious medical events reported (12 in the 1 mg dose group, 13 in the 4 mg group, 14 in the 8 mg group, and 12 in the 16 mg group). These ranged from items such as depression through cardiovascular events to accidents. Elevated liver function tests accounted for 14 of these and were observed in patients from all groups (four in the 1 mg group, three in the 4 mg group, five in the 8 mg group, and two in the 16 mg group). None of the serious medical events were dose related. A host of minor complaints/adverse events was reported. Many of these were those frequently seen in patients treated with methadone or other opioids. Other complaints were those commonly associated with the opioid withdrawal syndrome. Thirty-one percent of patients complained of headache at one time or another, but there was no difference among dosage groups. Other frequently voiced complaints included insomnia (25.8%), pain (25.1%), opiate withdrawal (23.9%) and infections (21.5%). Possible dose-related events were constipation, which occurred more frequently in the 8 mg group than in the 1 mg group ($p = 0.043$), and diarrhea, which was a more frequent complaint in the 1 mg group than the 8 mg group ($p = 0.041$). Considering the number of complaint categories and the number of pair-wise comparisons, the yield of statistically significant differences was remarkably low. Two deaths were reported in the extension study mentioned earlier, but neither case was judged to be related to the study drug.

**Conclusions**

Using conventional standards, the results of this study are supportive of the efficacy of the 8 mg/day sublingual dose of buprenorphine. There was clear superiority of this dose compared to the 1 mg control in each of the four efficacy outcome domains.

Examination of the data from other perspectives provides a better understanding of patient responses to buprenorphine. About half the patients remained in treatment for 16 weeks. This is roughly comparable to retention figures of 42% and 44% reported for the 8 mg dose in two other studies over a 17-week treatment period. Higher retention figures might be achieved in regular clinic practice where more flexible criteria for treatment retention are possible, and especially if there is vigorous and individualized psychosocial treatment addressed towards this problem. However, retention does not tell the whole story. Our completers did not necessarily attend clinic faithfully: the median percentage of clinics attended by the 375 patients who remained in treatment was 89% and 18% (63/375) attended clinics less than 70% of the time. These missed clinic visits also translate into missing urine specimens, which reached 18% among completers. Moreover, clinic attendance without reduction in the use of opioids cannot be considered an unqualified therapeutic success for buprenorphine.

Shifting to the Treatment Effectiveness Score (TES) for another perspective, 42% (306/736) failed to contribute a single urine negative for opioids: 55% (102/185) of the 1 mg group, 40% (74/182) of the 4 mg group, 36% (68/188) of the 8 mg group and 34% (62/181) of the 16 mg group. Sixty-eight patients completed 16 weeks of treatment without producing a single urine negative for opioids (21 from the 1 mg group, 16 from 4 mg, 13 from 8 mg and 18 from the 16 mg dose groups).
group). Not a single patient contributed the full complement of negative urines (i.e. a TES of 48) and only 18% (132/736) provided more than 24 negative urines (i.e. 50% of the maximum TES). Acceptance of the efficacy of buprenorphine as a maintenance treatment has to be tempered by the reality that the drug use status of many patients will not be altered by buprenorphine.

Several questions remain. Is the 8 mg dose optimal? Could drug use status be improved by a higher dose? This study was not designed as a dose–response study but there is an apparent monotonic relationship between dosage and outcome measures that is difficult to ignore. The 4 mg dose was significantly better than the control on some outcome variables but the effect was generally not as robust as that of the 8 mg dose. The 16 mg group did better generally than the 8 mg group in this study but the differences did not reach an acceptable level of statistical significance.

How does buprenorphine at 8 mg or at any other dose compare with alternative pharmacotherapies? There has been no direct comparison of buprenorphine with LAAM but there are several with methadone. One study\(^\text{17}\) concluded that buprenorphine at 8 mg daily was superior to methadone at 20 mg daily and “equivalent” to methadone at 60 mg daily. Another study\(^\text{18}\) concluded that 6 mg of buprenorphine was superior to 2 mg of buprenorphine in some ways, but that patients who received methadone at either 35 mg or 65 mg did significantly better than either buprenorphine dose. A study using a flexible dosing procedure\(^\text{19}\) demonstrated that an average dose of 8.9 mg of buprenorphine was roughly equivalent to an average dose of 54 mg/day of methadone. A fourth study (20) concluded that 8 mg of buprenorphine was significantly less effective than 80 mg of methadone and essentially indistinguishable from 30 mg of methadone. A consensus seems to be developing that the 8 mg dose is equivalent to a relatively modest dose of methadone. If this consensus hardens, it will not necessarily imply that buprenorphine has limited clinical utility. It will still be important to have a range of clinical therapeutic choices.

Does buprenorphine have clinically meaningful advantages? There are some characteristics that make this compound particularly attractive. As noted earlier, Jaskinski et al.\(^\text{11}\) observed that withdrawal symptoms associated with buprenorphine were modest. Two studies have presented data on duration of blockade which suggested the potential of less than daily dosing.\(^\text{30,31}\) Walsh et al.\(^\text{4}\) reported that “single doses of buprenorphine up to 70 times the recommended analgesic dose are well tolerated by nondependent humans”. Ongoing research with a combination of buprenorphine–naloxone tablets appears likely to result in a take-home product with characteristics of low-abuse liability, low-diversion potential and diminished risk of overdose in non-tolerant individuals. The high safety profile, long duration of action and patient acceptance, as evidenced by the ease of patient accrual in this study, make buprenorphine an attractive alternative to methadone or LAAM for the treatment of opioid dependence, and the buprenorphine/naloxone combination product offers the potential first opportunity in three decades to treat opioid addicts in the private physician’s office away from the traditional methadone clinic setting. A sequential pharmacological treatment strategy beginning with buprenorphine might be advantageous because it offers patients and clinicians the widest subsequent treatment options. Because of its high safety profile, patients can be treated more vigorously with buprenorphine. Patients who respond well to buprenorphine can opt to continue, at perhaps less than daily dosing, or to work towards abstinence through detoxification, with or without a subsequent period of naltrexone treatment. Patients whose level of physical dependence can not be adequately addressed by buprenorphine, a partial agonist, can be offered the full agonists, LAAM and methadone. One can conclude that, for the maintenance treatment of opioid dependence, buprenorphine will be a useful and welcome addition to methadone, LAAM and naltrexone which, together, in the United States have attracted less than 20% of heroin addicts into treatment.\(^\text{32}\) Eventually, the place of buprenorphine in the overall strategy of opioid maintenance pharmacotherapy will have to be determined in the context of wider clinical practice.

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