A Controlled Trial Comparing Buprenorphine and Methadone Maintenance in Opioid Dependence
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Abstract

Background: Buprenorphine is a partial agonist at the micro-opioid receptor that has been proposed as an alternative to traditional full agonist maintenance therapy for the treatment of opioid addiction. We report on a clinical trial in which the relative safety and efficacy of long-term fixed-dose buprenorphine maintenance was examined in comparison to low- and high-dose methadone maintenance.

Methods: Two hundred twenty-five treatment-seeking opioid addicts (46 women, 179 men) were randomly assigned to receive, in a double-blind manner, either 8 mg/d of buprenorphine, 30 mg/d of methadone, or 80 mg/d of methadone maintenance over a 1-year period. Objective and subjective measures of efficacy (urine toxicology, retention, craving, and withdrawal symptoms) were examined at the study midpoint and at termination, and safety data were tabulated over the entire 52-week study period.

Results: Patients assigned to high-dose methadone maintenance performed significantly better on measures of retention, opioid use, and opioid craving than either the low-dose methadone or the buprenorphine group at both 26-week and 52-week time points. Performance on these measures was virtually identical
between the latter two groups. No serious adverse health effects attributable to buprenorphine were noted.

Conclusions: Buprenorphine maintenance at 8 mg/d appears to be less than optimally efficacious under the conditions of the present study. Continued research is needed to reconcile these findings with the more positive results reported by other investigative groups. There are no apparent health risks associated with long-term buprenorphine maintenance at this dosage.

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Opioid maintenance therapy remains the primary pharmacological approach for the treatment of opioid dependence. The benefits of maintenance therapy, including significant reductions in illicit opioid use, increases in treatment retention, and improved psychosocial functioning, have been clearly demonstrated within the methadone maintenance model. [1-7] Further, methadone maintenance therapy for opioid addiction has been shown to decrease the mortality and morbidity associated with illicit drug use, [1,8,9] dramatically diminish the transfer of the human immunodeficiency virus, [10-12] profoundly reduce criminal activity, [13-15] and normalize disruptions in immune and neuroendocrine function caused by heroin use. [16]

In spite of these benefits, methadone treatment is considered undesirable pharmacotherapy by a significant number of addicts and communities. Provision of an alternative opioid maintenance agent may help attract some of the over 500 000 untreated opioid addicts in the United States to maintenance pharmacotherapy. Levo-alpha-acetyl-methadol, [17] recently approved by the Food and Drug Administration (FDA), is one such alternative. The extensive evaluation of buprenorphine further illustrates the desire of the research and treatment community to find effective alternatives to methadone.

Buprenorphine, a partial opioid agonist at the micro receptor, is a potent analgesic that is available for clinical use as a sublingual tablet in many parts of the world and as an injectable form in the United States. The potential utility of buprenorphine for the treatment of opioid addiction was apparent in the definitive work of Jasinski et al, [18] who demonstrated that daily dosages of 8 mg sublingually blocked the effects of subsequently administered morphine and did not appear to induce significant physical dependence. Mello and Mendelson's [19-21] extensive work in the animal and the clinical laboratory demonstrated that buprenorphine suppresses heroin self-administration by opioid-dependent primates and humans.
Buprenorphine appears to have many clinical advantages. It is acceptable to some heroin users who do not want or qualify for methadone maintenance. [22] Buprenorphine has a more favorable safety profile than methadone. Although buprenorphine is used intravenously by heroin addicts in countries where the sublingual tablet is available as an analgesic, [23] its abuse potential appears substantially lower than that for full agonists such as methadone or heroin. Buprenorphine may be less likely than other partial opioid agonists to precipitate opioid withdrawal, if given to patients already maintained on an opioid agonist such as methadone. [24]

Buprenorphine produces physical dependence of the opioid type. Because of buprenorphine's tight binding to the micro receptor, the onset of withdrawal symptoms after maintenance treatment is generally delayed for 24 hours or more and symptom intensity may not peak for 5 or more days. The overall intensity of withdrawal symptoms appears less intense than with methadone.

Several controlled clinical trials comparing the effectiveness of buprenorphine and methadone in maintenance treatment have been published [25,26] or are currently in some stage of completion. Since a variety of doses of each drug is represented in these studies, the aggregate results should provide a better understanding of the relative effectiveness of the two drugs. The purpose of the present study was to compare a dose of buprenorphine that was considered to be clinically optimal with two doses of methadone, one of which most would agree represents a relatively low dose (30 mg/d) and the other a relatively high dose (80 mg/d). Such a design also permitted another comparison of low- vs high-dose methadone, an issue that continues to be of some interest to clinicians.

PATIENTS AND METHODS

PATIENTS

The sample consisted of 225 patients who met DSM-III-R criteria for opioid dependence and who were seeking treatment at the Pizarro Treatment Clinic, an outpatient treatment facility located about 1 mile from downtown Los Angeles in California. The Pizarro Treatment Clinic serves an approximately 60% male patient population with an ethnic mix that is predominantly Hispanic (about 55%) but with moderate representation of African Americans (30%) and whites (15%).

Screening procedures were conducted at baseline by intake counselors. Volunteers aged 18 to 65, who were mentally competent to give informed consent, were accepted if they were in good general health and met the DSM-III-R diagnosis of opioid dependence and the FDA criteria for methadone maintenance treatment, [27] but were not currently enrolled in a methadone
maintenance program. Patients were excluded if they had acute hepatitis or other acute medical conditions that seemed to contraindicate participation; if they met the DSM-III-R diagnosis of dependence on alcohol, sedative-hypnotics (including benzodiazepines), cocaine, or amphetamines; if they were currently using anticonvulsants, disulfiram, or neuroleptics daily; or if for some reason they could not reasonably be expected to remain available to attend clinic for the duration of the trial. Women of childbearing age were required to be practicing birth control, and those already pregnant or still nursing a child were excluded.

Patients were not paid for their participation, but medication and counseling services were provided free of charge. The informed consent documents and the study protocol were approved by the Institutional Review Board of Friends Medical Science Research, Inc. Patient enrollment began October 16, 1990, and was completed on schedule in September 1992.

METHODS
Drug Assignment

After screening for eligibility and baseline observations, including laboratory studies, patients were assigned to one of three fixed-dose treatment schedules in blocks of 15, using a computer-generated random numbers list. The treatments were methadone, 30 mg/d (M30); methadone, 80 mg/d (M80); and buprenorphine, 8 mg/d. In order to conduct the study in a double-blind fashion, each patient received both an oral and a sublingual form of medication, only one of which was active. Unit doses were prepared weekly by a contract research pharmacist who was the only individual locally who had knowledge of drug assignment.

Each dose of methadone was made to a volume of 40 mL and administered in a vehicle consisting of 0.2 mg denatonium benzoate per 1000 mL in a cherry syrup concentrate. Buprenorphine was initially obtained in powder form from the National Institute on Drug Abuse (NIDA) and put into solution by dissolving in 30% alcohol to form a buprenorphine concentration of 8 mg/mL. The 1-mL doses of buprenorphine were dispensed in 1.5-mL pediatric oral syringes. Placebo buprenorphine consisted of the 30% alcohol without added buprenorphine, and the methadone placebo consisted of the denatonium benzoate vehicle without methadone. During the last year of the study, unit doses of buprenorphine (also in 30% alcohol) and buprenorphine placebo were supplied by NIDA.

A preliminary evaluation of the effectiveness of the double-blind selection conducted early in the study revealed a general tendency (82%) for patients to assume that they were receiving buprenorphine (41 of 50). All 13 patients assigned to buprenorphine guessed correctly. Only one of the 17 high-dose
methadone patients guessed correctly and two of this group guessed incorrectly that they were receiving low-dose methadone. Among the 20 patients on low-dose methadone, four guessed correctly, one guessed placebo, and another guessed 40 mg of methadone plus buprenorphine.

All doses of study medication were administered by the dispensing nurse. The oral dose was administered first, followed by the sublingual dose. Patients were instructed to delay swallowing the sublingual dose for up to 5 minutes to assure absorption and were observed by clinic staff for compliance.

To avoid possible withdrawal symptoms precipitated by the antagonistic action of buprenorphine during induction, the study drugs were not administered while the patient was under the acute influence of opioids. Before the first dose of medication, each patient completed a subjective checklist of opioid withdrawal symptoms and was examined by a staff physician for eligibility to begin treatment. The first dose of precoded medication consisted of either 2 mg of buprenorphine (and a methadone placebo) or 30 mg of methadone (and a buprenorphine placebo). Patients were observed for 2 hours after the initial dose. Buprenorphine was increased to 4 mg on day 2 and 8 mg on day 3. For patients assigned to the M80 group, the methadone dose was increased by 5 mg daily until the 80-mg dose was reached.

Since off-site administration of medication was not allowed, patients had to attend the clinic daily. If patients missed more than four consecutive clinic visits, they received half of their full dose on their first day back, three fourths on their second day back, and a full dose on their third day back. In general, patients who missed seven consecutive clinic visits were dropped from the study, but there were a few patients who were openly treated with 40 mg of methadone daily during a brief inpatient stay for concurrent illness. It was not necessary to break the double-blind code for any patient before the conclusion of the trial.

In terms of what was known of the safety of buprenorphine, it was not expected that there would be a problem in administering the drug for a full year. However, to ensure the safety of the participants, there was close medical monitoring throughout. Baseline observations included a complete physical examination and laboratory workup (complete blood cell count, urinalysis, serum chemistry, and electrocardiogram). The electrocardiogram was repeated every 3 months and the other laboratory tests were conducted monthly. The pregnancy status of the female patients was determined at baseline and monthly. One patient became pregnant during the trial and, according to the protocol, was dropped from the study without breaking the blind and was treated openly with methadone. It was later determined that she had been assigned to the M30 group.

OUTCOME MEASURES
Determining the relative efficacy of the three maintenance schedules in a study lasting a full year required some a priori decisions about the criteria that would be used to evaluate efficacy, as well as the time points at which efficacy would be assessed. On the basis of past experience, it was thought to be quite possible that a treatment advantage apparent in the short term would be completely obscured at the end of a year. Accordingly, it was decided to base our efficacy evaluation on the first 26 weeks and to consider safety issues over the entire year. It was also our intention to analyze the experience over the first 17 weeks for direct comparison with the results of the study by Johnson et al, [25] which had recently been completed. Hereafter, their study will be referred to as the ARC study.

The protocol identified four efficacy measures: days of retention in treatment, urinalysis for drugs of abuse, a patient measure of craving, and a checklist of opioid withdrawal symptoms. In calculating days of retention in treatment, patients were considered to be active participants until the day of their last study dose.

Urine specimens were collected in the morning three times weekly (Monday, Wednesday, and Friday) under direct observation or with the use of an FDA-approved, tamper-proof collecting system (Franklin Diagnostics, Cedar Knolls, NJ). For a few weeks at the beginning of the study, if a patient missed a scheduled collection, a specimen was collected the following day, but this procedure was soon abandoned in favor of the Monday/Wednesday/Friday collection only. Samples were analyzed for opioids in the form of morphine by fluorescence polarization immunoassay (FPI), using the Abbott Diagnostics TDX system (Irving, Tex). This method, which employs an antibody specific to morphine, is linked with mechanized fluorescence polarization. Controls and a fixed percentage of FPI-positive results were cross-confirmed by gas-liquid chromatography (GLC) or high-pressure liquid chromatography (HPLC). Assay morphine sensitivity for FPI was 30 ng/mL, and 0.1 to 1 ng/mL for GLC and HPLC. The first specimen obtained each week (usually on Monday) was also tested for the presence of other drugs of abuse (cocaine, amphetamines, benzodiazepines). The results of these urinalyses were not made known to anyone locally, but were transmitted electronically to a remote location (Maryland) for monitoring purposes. As a supplement to the urinalyses, patients provided a self-report of drug use weekly to a research technician.

To assess craving, patients were asked each week to estimate the maximum amount of opioid craving at any time during the past 7 days by making a mark on a 100-mm line designated as no craving at one end and maximum craving ever experienced at the other. Patient's summary scores were computed by counting the frequency of ratings below a cut point of 50 on the craving scale and were used for comparison.
Each week, patients were also asked to what extent they experienced opioid withdrawal symptoms or possible medication side effects during the previous week. This information was recorded on a symptom-sign checklist that had been used in several earlier multicenter clinical trials of levo-alpha-acetyl-methadol. Specific symptom-signs were not enumerated, but when their presence was elicited by general questioning, there were additional probes to enable a judgment as to their severity, such as mild, moderate, or severe.

In addition to these measures directly relevant to safety and/or efficacy, data collection at baseline included the Addiction Severity Index and a drug-use history. If patients were terminated from the study early, attempts were always made to repeat the laboratory studies and to determine the reason for termination.

All study patients received the same psychosocial and other treatment services. Each patient was assigned a primary counselor who coordinated psychosocial counseling services. All counselors had a college education and had received specialized training in drug and alcohol abuse counseling. In addition to regular contact with research staff, patients were encouraged to attend weekly individual counseling sessions that focused on crisis intervention and case management; few patients took advantage of the offer. However, since the study focused on pharmacological efficacy, no patients were discharged for nonattendance of counseling sessions. There was no difference between groups in the proportion of the number of sessions attended (P = .95). On average, patients attended 48% of possible sessions, each averaging 13.8 minutes.

There was concern during the planning of this study about randomizing patients to a fixed-dose maintenance schedule for a full year when past experience had shown that there would be patients in all three groups who would remain in the study without significant diminution of heroin use. Considering the dangers of human immunodeficiency virus infection associated with intravenous drug use, some of these patients clearly would need more aggressive treatment than would be provided by the fixed-dose design. The compromise adopted was to monitor urine results remotely to avoid breaking the blind but to inform the treatment physician whenever a patient obtained 12 consecutive urine samples positive for heroin (a missing urine sample was considered positive). The patient was then considered to be an early terminator. For purposes of computing retention, the last study day was the day the 12th positive urine sample was obtained. The study code was not broken for these patients. They, in effect, entered a new protocol that permitted escalating the dose of their assigned drug while still maintaining the double-blind selection.

DATA ANALYSIS
Retention rates were estimated by the Kaplan-Meier product limit method, and survival curves of the three groups were compared using the Wilcoxon rank sum test. Differences among groups in number of completers at various time points were evaluated by chi squared analysis. Urine samples were considered to be opioid-free if the test reading was less than 300 mg/mL. Percent opioid-free urine samples were calculated for each patient by dividing the number of opioid-free urine samples by the number of urine samples scheduled for collection while that patient was still an active study participant (missing urine samples were also counted for inclusion in the denominator). A second dependent variable to evaluate opioid use, the treatment effectiveness score (TES), [29] consisted of the number of opioid-free urine samples obtained during the time frame being evaluated. The Kruskal-Wallis test was used to compare groups using these two urine-based outcome variables and the craving scale data. Statistical tests were considered to be significant at P<.05.

RESULTS
SAMPLE CHARACTERISTICS

Three hundred ten patients were screened in order to achieve the target sample of 75 patients per group. There were three main reasons for exclusion. Twenty-two patients simply did not return to the clinic after the preliminary screening contact, another 21 had a medical condition that made them ineligible, and 21 had evidence of significant polydrug dependence (crack cocaine, four patients; benzodiazepines, one patient; and alcohol, 16 patients). The (Table 1) shows the demographics of the study patients. There were no baseline differences between groups except for race. Cox regression of all randomized patients using demographic and drug-use characteristics as covariates showed higher retention to be associated with increasing age (chi squared=6.08, df=1, P=.01). Nonsignificant associations were observed with gender (chi squared=0.01, df=1, P=.93), race (chi squared=4.58, df =2, P=.10), and duration of addiction (chi squared=3.83, df=1, P=.05).
Efficacy results

The percentage of patients still active in the study over time is shown in the (Figure 1) for the full year. Applying the Wilcoxon rank sum test to the survival curves showed that over the first 26 weeks the M80 group had significantly better retention than both the M30 group (P=.04) and the buprenorphine group (P=.009). Over the entire year, the M80 group had better retention than the M30 (P=.02) and buprenorphine groups (P=.009). The differences between the M30 and buprenorphine groups failed to achieve significance at either 26 weeks (P=.33) or 1 year (P=.44).

Figure 1. Patients in each group still in treatment at the end of each study week.
To evaluate retention in a different manner, the percentage of patients who completed 26 weeks of treatment was 52%, 40%, and 35% for the M80, M30, and buprenorphine groups, respectively. The overall comparison was not significant (chi squared=4.846, df=2, P=.09). Similarly, 31%, 19%, and 20% in each of the three groups, respectively, completed 52 weeks of treatment. These outcomes were not significantly different (chi squared=3.652, df=2, P=.16).

At one time or another during the projected 52-week period of maintenance treatment, 60 patients were terminated because they failed to give a single sample negative for opioids in any series of 12 consecutive scheduled urine samples: 29 in the M30 group, 16 in the M80 group, and 15 in the buprenorphine group. The three groups are significantly different in this respect (chi squared=8.319, df=2, P=.02), with the M30 group worse than both the M80 (chi squared=4.571, df=1, P=.03) and buprenorphine groups (chi squared=5.435, df=1, P=.02). Nearly all of these patients continued to receive their assigned study drug in a double-blind fashion for a longer period with varying amounts of dose escalation before their tenure in the study was terminated for a variety of other reasons. If these patients are considered to be members of the study until they finally terminated for other reasons, the retention figures at week 26 increase to 58%, 58%, and 44% for the M80, M30, and buprenorphine groups, respectively, and to 35%, 22%, and 23% at week 52. However, the overall comparison of the three groups at these two time points is still not significant.

The extent of opioid use by the three groups was analyzed using two outcome measures. Each patient had 1% more opioid-free scores reflecting opioid use after varying lengths of time during his or her tenure in the study. Over the first 26 weeks the means+/−SDs of these scores were 61.9+/−31.6 for the M80 group, 44.6+/−33.5 for the buprenorphine group, and 44.5+/−36.0 for the M30 group. The median scores were 72, 47, and 46, respectively. The comparison of the three groups by the Kruskal-Wallis test was significant (H=12.635, df=2, P=.002), with the M80 group better than both the M30 (H=8.882, df=1, P=.003) and buprenorphine (H=9.999, df=1, P=.002) groups. Over the entire 52 weeks, the means, standard deviations, and medians were virtually the same as after the first 26 weeks. Over 52 weeks, the groups were significantly different (H=11.131, df=2, P=.004), with the M80 group better than both the M30 (H=7.930, df=1, P=.005) and buprenorphine (H=8.698, df=1, P=.003) groups.

The use of the TES yielded essentially the same results. Take values between zero and 78 for any patient (three samples per week for 26 weeks). A score of 78 could only be achieved by a patient who stayed in the study for 26 weeks and gave the full complement of 78 urine samples, all of which were negative. There were three such patients in this study, one in each of the study groups. The means+/−SDs of the TES were 41.3+/−27.3 for the M80 group, 26.5+/−26.3 for
the buprenorphine group, and 26.5+/−26.7 for the M30 group. The median scores for the three groups were 49, 16, and 24, respectively. The overall Kruskal-Wallis test was significant (H=14.366, df=2, P=.001) with the M80 groups superior to both the M30 (H=10.772, df=1, P=.001) and buprenorphine (H=10.654, df=1, P=.001) groups. Again, the results after 52 weeks were very similar to the 26-weeks results. The maximum score could be achieved by a patient who completed the study and gave 156 opioid-free urine samples. A single patient from the M80 group achieved this goal. The mean+/−SDs were 64.9+/−52.5 for the M80 group, 41.9+/−49.8 for the buprenorphine group, and 40.1+/−46.6 for the M30 group. The median scores were 59, 16, and 24, respectively. The groups differed significantly (H=12.159, df=2, P=.002), with the M80 group better than both the M30 (H=9.709, df=1, P=.002) and buprenorphine (H=8.358, df=1, P=.004) groups.

The same pattern of results was observed in the craving symptom data over 26 weeks (H=8.446, df=2, P=.02), with the M80 group showing less craving than either the M30 (H=4.794, df=1, P=.03) or buprenorphine (H=7.492, df=1, P=.006) groups and over 52 weeks (H=10.213, df=2, P=.006).

The expectation was that the extent to which patients experienced symptoms of opioid withdrawal would correspond roughly to the other efficacy data. As one way of testing this, we tallied the number of patients who were rated as experiencing moderate or severe discomfort at least once during their tenure in the study for each of 11 withdrawal symptoms, and evaluated these frequencies by a 2X3 chi squared test. The three groups differed only on the symptom of nausea (chi squared=8.382, df=2, P=.02), with patients in the M30 group reporting this more frequently (29 of 75) than those in either the M80 (17 of 75) or buprenorphine (14 of 74) groups.

ADVERSE EVENTS

Numerous and diverse adverse events were recorded for each of the three groups. Many of these represented chronic conditions such as anemia, asthma, and controlled diabetes mellitus, or preexisting aches and pains, dental problems, and the like, which may or may not have prompted a visit to a health care provider. Another large set of events were the results of accidents (broken bones, burns, lacerations) that seemed to reflect a chaotic lifestyle (stab wounds, swollen and infected jaw due to assault, alcohol withdrawal) or, in other instances, the ordinary diseases of everyday life (ear infection). These minor problems were perhaps more frequent or intense because of the compromised health status of these patients.

Fourteen patients were hospitalized at one time or another, usually for brief periods. Two of these patients died. One male patient in the M30 group died of
multiple stab wounds to the abdomen during an altercation that occurred after 43 days in the study, and the other died of cancer at his brother's home after a brief hospitalization. Overall, adverse events were about equally represented in all three groups, and no clustering of type of event was apparent.

COMMENT

This study has extended the safety evaluation of the 8-mg dose of buprenorphine to a full year, provided additional methadone benchmarks with which to evaluate the efficacy of buprenorphine, and increased the size and diversity of the experience base with buprenorphine.

There was confidence in the safety profile of buprenorphine before the study was undertaken. There was no expectation of serious adverse effects and none were found. At the clinical level, we believe buprenorphine to be a safe drug.

The evidence in this study supporting the efficacy of the 8-mg daily dosage of buprenorphine as a maintenance drug is, at best, indirect. The observed fact is that the outcomes of the buprenorphine group are almost identical to those of the M30 group. In the past we have argued that while 30 mg of methadone is a reasonable starting dose for most street addicts entering either detoxification or maintenance, it is a marginally effective maintenance dose for most. Schuster [30] has cautioned, for instance, that for many patients doses below 60 mg may not be adequate to prevent withdrawal symptoms or to provide blockade of intravenous heroin during the 24 hours between methadone doses.

What the study demonstrates with some certainty is that, as a group, patients can be expected to do better on 80 mg of methadone daily than they will on 30 mg of methadone or 8 mg of buprenorphine. They can be expected to stay in treatment longer, use less opioids, and have less craving. However, many individuals remained in treatment and reduced their heroin use to a clinically significant extent in all three groups.

At this stage in the development of buprenorphine as a maintenance treatment, the research interest is shifting from whether or not buprenorphine is effective to a search for the daily dosage that will be considered optimal for most patients. The tactic of this search to date has been to compare one or more doses of buprenorphine with one or more doses of methadone in an attempt to position buprenorphine on the methadone dosage spectrum. Work in progress continues this tactic, but also makes direct comparisons among several buprenorphine doses.

One issue that needs to be resolved is how the results of the ARC study. [25] That study evaluated outcomes in 162 patients during 17 weeks of maintenance treatment and concluded that 8 mg/d of buprenorphine was as effective as 60
mg/d of methadone, and that both were superior to 20 mg/d of methadone in reducing illicit opioid use and retaining patients in treatment. In the first 17 weeks of our study, there was essentially no difference in outcome between the M30 and buprenorphine groups, and the M80 group was unequivocally superior to both groups in retention and in measures of opioid use.

The difference in observed outcome of the buprenorphine groups in the two studies is not the issue. In fact, these outcomes are remarkably similar; retention was 42% in the ARC study and 44% in the current study. The percent of opioid-free urine samples was 58% in the ARC study and 58% in the current study.

There were four methadone doses represented in the two studies. The expectation was that the ARC 20-mg methadone dose group would have the worst outcomes and that our M80 group would have the best; those expectations are borne out. The ARC 20-mg methadone dose group had 20% retention and 29% opioid-free urine samples after 17 weeks, while our M80 group had 64% retention and 72% opioid-free urine samples. Where expectation failed was that the ARC 60-mg methadone dose group did so poorly (32% retention and 44% opioid-free urine samples) compared with our M30 group, which had 44% retention and 57% opioid-free urine samples.

The ARC study was meticulously designed, scrupulously conducted, and thoughtfully analyzed. The puzzling observation of the essential equivalence of the buprenorphine groups in the two studies and the apparent reversal in effectiveness of the 30- and 60-mg methadone groups very likely reflects chance variation. There are, of course, some implications for the conclusions of the ARC study concerning the adequacy of the 8-mg dose of buprenorphine. First, the observed differences between their 20-mg and 60-mg groups are not robust. In all of their comparisons of these two groups, only the difference in the percentage of opioid-free urine samples was significant (P<.04). Second, the fact that their 60-mg methadone and buprenorphine groups do not differ significantly does not support the inference that these two doses are equipotent. They may be roughly comparable. Discussion in terms of statistical power and confidence intervals might have helped put these results in better perspective.

It is our confident belief on the basis of this and other studies, as well as our clinical experience, that buprenorphine will, in due course, be declared a safe and effective drug for maintenance treatment of heroin addicts. However, it is our impression that 8 mg/d of buprenorphine is not an optimal dosage. Because of the excellent safety profile, there is no reason to believe a higher dose will not be well tolerated, and this might move the effectiveness of this promising drug into a more advantageous position in relation to standard methadone practice.

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