

A COMPARISON OF LEVOMETHADYL ACETATE, BUPRENORPHINE, AND METHADONE FOR OPIOID DEPENDENCE

ROLLEY E. JOHNSON, PHARM.D., MARY ANN CHUTUAPE, PH.D., ERIC C. STRAIN, M.D., SHARON L. WALSH, PH.D., MAXINE L. STITZER, PH.D., AND GEORGE E. BIGELOW, PH.D.

ABSTRACT

Background Opioid dependence is a chronic, relapsing disorder with important public health implications.

Methods In a 17-week randomized study of 220 patients, we compared levomethadyl acetate (75 to 115 mg), buprenorphine (16 to 32 mg), and high-dose (60 to 100 mg) and low-dose (20 mg) methadone as treatments for opioid dependence. Levomethadyl acetate and buprenorphine were administered three times a week. Methadone was administered daily. Doses were individualized except in the group assigned to low-dose methadone. Patients with poor responses to treatment were switched to methadone.

Results There were 55 patients in each group; 51 percent completed the trial. The mean (\pm SE) number of days that a patient remained in the study was significantly higher for those receiving levomethadyl acetate (89 ± 6), buprenorphine (96 ± 4), and high-dose methadone (105 ± 4) than for those receiving low-dose methadone (70 ± 4 , $P<0.001$). Continued participation in the study was also significantly more frequent among patients receiving high-dose methadone than among those receiving levomethadyl acetate ($P=0.02$). The percentage of patients with 12 or more consecutive opioid-negative urine specimens was 36 percent in the levomethadyl acetate group, 26 percent in the buprenorphine group, 28 percent in the high-dose methadone group, and 8 percent in the low-dose methadone group ($P=0.005$). At the time of their last report, patients reported on a scale of 0 to 100 that their drug problem had a mean severity of 35 with levomethadyl acetate, 34 with buprenorphine, 38 with high-dose methadone, and 53 with low-dose methadone ($P=0.002$).

Conclusions As compared with low-dose methadone, levomethadyl acetate, buprenorphine, and high-dose methadone substantially reduce the use of illicit opioids. (N Engl J Med 2000;343:1290-7.)

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OPIOID dependence is an important national health problem, with an estimated 980,000 long-term users of heroin in the United States.¹ Methadone, introduced in the late 1960s,² and levomethadyl acetate, approved in 1993, are two full μ -opioid agonist substitutes. Buprenorphine, a partial μ -opioid agonist (whose maximal effects are less than that of a full agonist) is under review by the Food and Drug Administration as

a third pharmacotherapy for opioid dependence.^{3,4} Controlled studies of methadone,⁵⁻¹¹ levomethadyl acetate,^{12,13} and buprenorphine^{14,15} have documented their dose-related efficacy in terms of retaining patients in treatment and reducing illicit opioid use.

A clinical advantage of levomethadyl acetate and buprenorphine is the option of less-than-daily doses, which is made possible in the case of levomethadyl acetate by the long half-lives of its two active metabolites, nor-levomethadyl acetate and dinor-levomethadyl acetate. Similarly, clinical pharmacologic studies^{16,17} and controlled trials¹⁸⁻²¹ have supported the feasibility of less-than-daily doses of buprenorphine.

Several controlled trials have compared the efficacy of levomethadyl acetate²²⁻²⁶ or buprenorphine^{11,14,27-29} with that of methadone. We compared levomethadyl acetate, buprenorphine, and methadone as treatments for opioid dependence.

METHODS

Subjects and Randomization

Two hundred twenty patients participated in this single-site, randomized, controlled study with four treatment groups (Fig. 1). The eligibility criteria were an age of 21 to 55 years, a diagnosis of opioid dependence according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),³⁰ evidence of recent opioid use on toxicologic screening, the absence of serious medical or psychiatric illness requiring long-term medication, and negative results on a serum pregnancy test for women during screening. The study was approved by the local institutional review board, and all patients provided written informed consent.

Patients were enrolled between January 17, 1996, and November 24, 1997. They were stratified according to the following variables: age (under 35 years or at least 35 years old), race (white or other), sex, current cocaine use (yes or no), marital status (currently married or other), and DSM-IV diagnosis of antisocial personality disorder (yes or no). They were randomly assigned to one of four treatment groups comprising 55 patients each: levomethadyl acetate (Orlaam, Roxane), buprenorphine (Reckitt and Colman), and high-dose or low-dose methadone (Methadose, Mallinckrodt). Each stratum was divided into groups of four, and a random-number generator assigned the order of the four conditions in each stratum. To correct imbalances in treatment assignment due to incomplete blocks and to increase the statistical power of the study, randomization of the last 10 patients was constrained to achieve equal numbers of patients for each treatment.³¹

Treatment Groups

Randomization occurred on the day of enrollment. The patients and clinic staff were unaware of treatment assignments and medication doses. The low-dose methadone group (the control

From the Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Dr., Baltimore, MD 21224, where reprint requests should be addressed to Dr. Johnson.

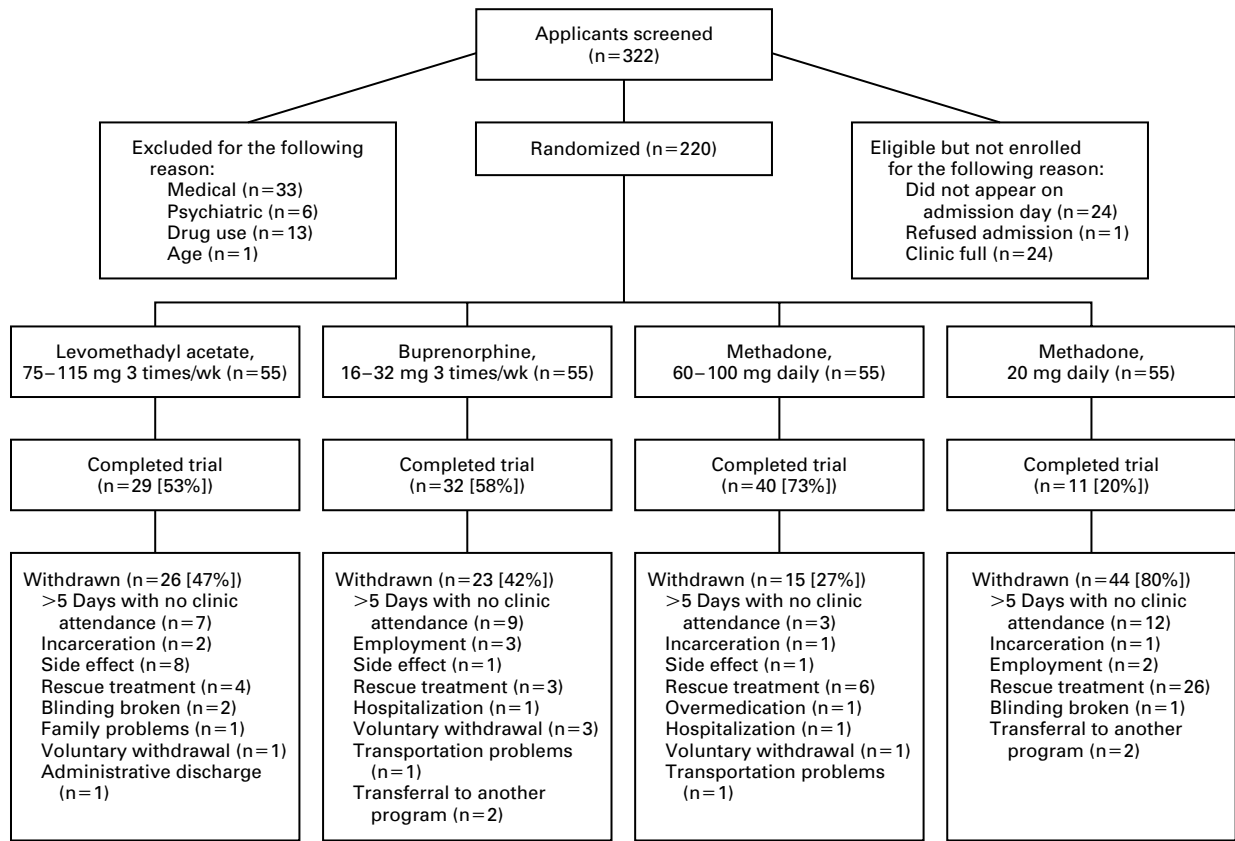


Figure 1. Stages of the Trial. Randomization occurred on the day of entry into the study.

group) received a fixed dose of 20 mg of methadone. However, the doses of levomethadyl acetate, buprenorphine, and high-dose methadone were adjusted within prespecified ranges to ensure that comparisons between drugs were based on individually optimized doses.

Levomethadyl Acetate

Levomethadyl acetate was administered at a dose of 75 to 115 mg on Mondays and Wednesdays (to approximate a dose of methadone of 60 to 100 mg daily); the Friday doses were 40 percent higher (to a maximal dose of 105 to 161 mg) to compensate for the longer interval before the next dose.³²

Buprenorphine

Buprenorphine was administered at a dose of 16 to 32 mg on Mondays and Wednesdays (to approximate a dose of methadone of 60 to 100 mg daily)¹¹; the Friday doses were 50 percent higher (24 to 48 mg).³³

High-Dose and Low-Dose Methadone Groups

The doses for patients in the high-dose methadone group were in the upper range of doses generally used in clinical practice (60 to 100 mg). The dose in the low-dose control group (20 mg) was the minimally effective dose, according to the results of previous controlled trials.^{6,11}

Procedures

The study had three phases: dose induction (weeks 1 and 2), maintenance (weeks 3 to 17), and disposition (weeks 18 to 28).

On days of clinic attendance, all the patients received three solutions, only one of which contained active medication. Levomethadyl acetate and methadone were dispensed as oral solutions of different colors, and buprenorphine was dispensed sublingually as a 40 percent aqueous alcohol solution. Missed doses were treated according to preestablished blinded protocols developed by the investigators. Patients were discharged from the study if they were absent for five consecutive calendar days.

Dose Induction

Patients attended the clinic daily and received gradually increasing doses of medication. Patients assigned to levomethadyl acetate received 25 mg on day 1 and then began alternating between placebo and levomethadyl acetate, with 10-mg increases until the dose reached 75 mg. Buprenorphine was administered daily until day 7, starting at 4 mg on day 1 and increasing to 8 mg on days 2 through 7. On day 8, patients began alternating between placebo and 16-mg doses of buprenorphine. Patients assigned to high-dose methadone started with 20 mg, with 10-mg increases daily until the dose reached 60 mg. Patients assigned to low-dose methadone continued to receive 20 mg daily throughout the study.

Maintenance

Starting in week 3, patients attended the clinic three times a week, on Monday, Wednesday, and Friday. All patients received bottles of medication to take home for the other four days of the week.

Dose Increases

Patients receiving levomethadyl acetate, buprenorphine, or high-dose methadone could receive blinded increases in the dose starting in week 3 if they met preestablished criteria. Four dose increases were allowed, with one increase every two weeks. Doses were increased in 10-mg increments for levomethadyl acetate (on Monday and Wednesday, from 75 to 115 mg) and high-dose methadone (daily, from 60 to 100 mg), and in 4-mg increments for buprenorphine (on Monday and Wednesday, from 16 to 32 mg). Patients were evaluated weekly, and their doses were increased if they met two criteria: more than 83 percent attendance, with no Friday absences, and more than 33 percent of urine specimens opioid-positive during the previous week. The attendance criterion ensured that the patient received each intended dose before receiving further dose increases. The intent was to achieve individually optimized doses and to avoid confounding comparisons between drugs by potential differences in the adequacy of the dose.

Eighty percent of the patients in the levomethadyl acetate group, 96 percent of those in the buprenorphine group, and 91 percent of those in the high-dose methadone group met the criteria for dose increases. The mean maximal Monday and Wednesday doses were 100 mg of levomethadyl acetate, 27 mg of buprenorphine, 90 mg of high-dose methadone, and 20 mg of low-dose methadone. The average number of days required to achieve the maximal dose was 69 for levomethadyl acetate, 72 for buprenorphine, 68 for high-dose methadone, and 1 for low-dose methadone.

Rescue Treatment

A double-blind rescue procedure was implemented for patients with a poor response to treatment. Patients received rescue treatment if they attended more than 83 percent of clinic days, if they missed no Fridays, and if at least 66 percent of their urine specimens during the previous two weeks were opioid-positive. The patients also had either to request a dose increase or to report use of illicit opioids at more than 50 percent of the pretreatment level. The earliest they could receive rescue treatment was week 6 (for the low-dose methadone group) or week 13 (for all other groups). For rescue treatment, the patients were switched to an equivalent dose of methadone and followed clinically; they remained blinded to the treatment procedures, and data collection was continued, but data obtained after rescue treatment were excluded from analysis.

Take-Home Recall Procedure

To discourage methadone diversion and ensure compliance with medication, take-home bottles were randomly recalled. All take-home bottles scheduled for recall contained placebo. In a recall, patients were contacted by telephone and required to return their take-home bottles to the clinic; recalled bottles were replaced with a bottle containing placebo in the levomethadyl acetate and buprenorphine groups or with a bottle containing methadone (the scheduled dose) in the methadone groups.

Outcome Measures

The three primary outcome measures for assessing the efficacy of the medications were continued participation in the study (retention); opioid use, measured by the percentage of positive urine specimens, the degree of continuous abstinence from opioid use (defined by at least 12 consecutive opioid-free urine specimens), and the patients' own reports of frequency of use; and the patients' global ratings of the severity of their drug problem. Additional prespecified outcome measures were the percentage of cocaine-positive urine specimens, the duration of continuous abstinence from cocaine use, breath alcohol readings, side effects, and sex-related differences.

Statistical Analysis

Patient retention was calculated from the day of admission (first dose) to the day of study completion (119 days), the breaking of

the dose code, the last administration of medication, or rescue. Kaplan–Meier estimates³⁴ of mean retention times were compared among the groups by the Mantel–Cox log-rank test.³⁵

Urine specimens were collected under observation on Monday, Wednesday, and Friday and analyzed on site for opioid and cocaine metabolites by the enzyme-multiplied immunoassay technique (Dade Behring Diagnostics, San Jose, Calif.). Findings of opioid or cocaine metabolites at a level of 300 ng or more per milliliter were considered positive results. Missed urine specimens were collected the following day (except Sundays). The percentage of missing samples was similar in all four groups (4.2 percent in the levomethadyl acetate group, 5.1 percent in the buprenorphine group, 3.0 percent in the high-dose methadone group, and 5.8 percent in the low-dose methadone group); these samples were considered positive for purposes of analysis. Breath alcohol levels (in grams per deciliter) were determined randomly on clinic days with a breath alcohol sensor (Alco-Sensor III, AlcoPro, Knoxville, Tenn.). The doses of medication were adjusted according to preestablished blinded protocols when the breath alcohol level was 0.05 g per deciliter or higher (26 doses were adjusted for this reason).

For each patient, we analyzed the weekly percentages of positive urine specimens separately for opioids and cocaine by multilevel analysis with an autoregression covariance structure³⁶ for the week factor, using SAS Proc Mixed software (SAS Institute, Cary, N.C.). The restricted maximum-likelihood methods used in multilevel modeling have the flexibility to handle repeated-measures data sets with missing observations.³⁷ We compensated for the potential effect of informative missing data by using study retention and the percentage of missed clinic visits as covariates.³⁸ The percentages of patients who submitted at least 12 consecutive negative urine specimens were compared separately for opioids and cocaine by Fisher's exact test.³⁹

The patients reported the frequency of opioid use each week, starting with the week before admission. Of 2993 scheduled reports, 196 were excluded from analysis because they were missing or were at least 3 SD from the mean: 6.8 percent of all scheduled reports for the levomethadyl acetate group, 7.4 percent for the buprenorphine group, 6.9 percent for the high-dose methadone group, and 8.5 percent for the low-dose methadone group. The data were analyzed according to the week with the multilevel analysis described above.

Every four weeks, the patients rated the severity of their drug problem from 0 (no drug problem) to 100 (worst ever). The data from the last assessment before completion of the study or discharge were analyzed by one-way analysis of variance.¹⁵ Fourteen patients dropped out before completing any severity assessment, and 14 of 206 patients missed their final assessment and were excluded from analysis (1.0 percent were missed in the levomethadyl acetate group, 1.5 percent in the buprenorphine group, 2.0 percent in the high-dose methadone group, and 2.4 percent in the low-dose methadone group).

All reported P values are two-tailed.

RESULTS

Demographic Characteristics

There were no significant differences between groups in demographic characteristics or stratification variables (Table 1).

Study Retention

Patients were enrolled between January 17, 1996, and November 24, 1997. There were significant differences in study retention among the four groups. Pairwise comparisons showed significantly greater mean retention among patients receiving levomethadyl acetate (89 ± 6 days), buprenorphine (96 ± 4 days),

TABLE 1. CHARACTERISTICS OF THE 220 STUDY PARTICIPANTS.*

CHARACTERISTIC	LEVOMETHADYL ACETATE (N=55)	BUPRENORPHINE (N=55)	HIGH-DOSE METHADONE (N=55)	LOW-DOSE METHADONE (N=55)
Age (yr)	37±1	36±1	36±1	36±1
Female sex (%)	40	34	36	27
Nonwhite race (%)	56	66	54	66
Education (yr)	11±0.3	11±0.2	11±0.2	11±0.2
Married (%)	13	16	26	20
Employed (%)	20	31	36	31
Legal problems (%)†	14	34	27	34
Antisocial personality (%)‡	26	36	29	29
Use of other drugs in previous 30 days (no. of days)				
Alcohol	2.3±0.5	3.8±1.0	2.7±0.7	2.9±0.8
Cocaine	10.5±1.6	7.8±1.4	8.3±1.5	7.5±1.4
Heroin	29.8±0.1	29.6±0.2	29.3±0.3	29.7±0.2
Opiate use in previous week (no. of times)§	28.8±3.0	21.7±2.0	25.3±2.1	30.9±3.0
DSM-IV–defined current abuse or dependence (%)				
Alcohol	9¶	6	7	13
Cocaine	47	46	47	42
Opiates	100	100	100	100
Other drugs	0.0¶	1.8	5.5	0.0
No. of previous treatments	2.5±0.4	2.0±0.3	2.4±0.3	1.6±0.3

*Plus–minus values are means ±SE. DSM-IV denotes *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition.

†Legal problems were defined as a pending trial, parole, or probation.

‡Antisocial personality was defined according to the DSM-IV.

§The patient reported the total number of times he or she used illicit opiates during the week before study admission.

¶The percentage is based on 53 patients.

||The percentage is based on 54 patients.

or high-dose methadone (105±4 days) than among those receiving low-dose methadone (70±4 days, P<0.001) (Fig. 2A). The difference between patients taking high-dose methadone and those taking levomethadyl acetate was also significant (P=0.02), but not that between high-dose methadone and buprenorphine.

Overall, 51 percent of the patients completed the 17-week trial (53 percent of the levomethadyl acetate group, 58 percent of the buprenorphine group, 73 percent of the high-dose methadone group, and 20 percent of the low-dose methadone group). When patients who received rescue treatment were included, the rates of retention were 60 percent, 64 percent, 84 percent, and 58 percent, respectively.

Opioid Use

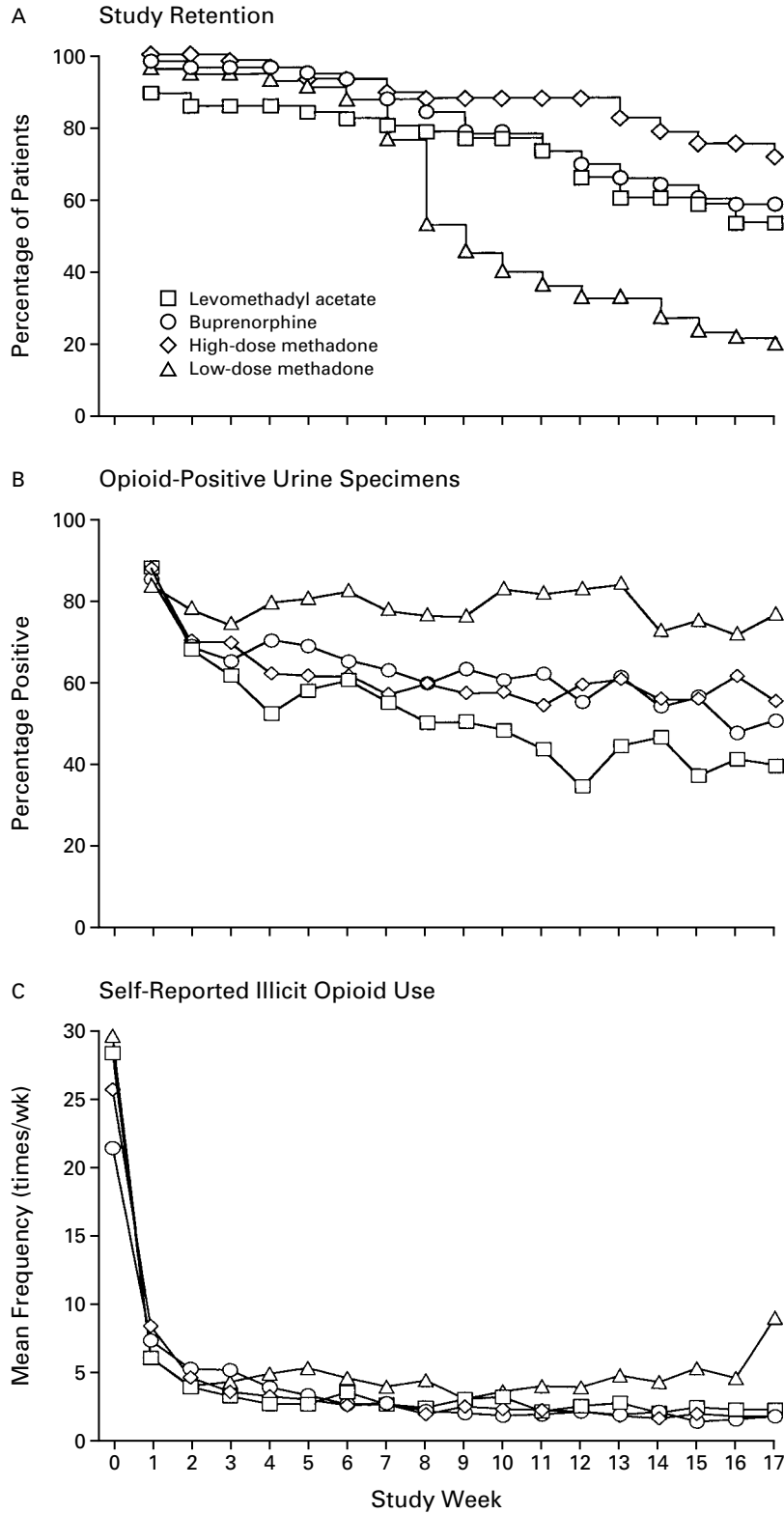
Overall, patients receiving levomethadyl acetate, buprenorphine, and high-dose methadone submitted fewer opioid-positive urine specimens than did patients receiving low-dose methadone (Fig. 2B and Table 2). The percentage of patients with at least 12 consecutive opioid-negative urine specimens differed

significantly among groups (P=0.005), ranging from 36 percent in the levomethadyl acetate group to 8 percent in the low-dose methadone group (Table 2). There were no significant differences between groups in self-reported use of illicit opioids; however, each group did report a significant reduction in use over time (Fig. 2C and Table 2). On a scale of 0 to 100, patients in the low-dose methadone group gave their drug problems the highest severity rating (mean, 53); the lowest rating was in the buprenorphine group (mean, 34) (Table 2).

Alcohol and Cocaine Use and Side Effects of Treatment

Alcohol use was low at base line and throughout the study (only 3 percent of all breath samples had alcohol levels ≥0.01 g per deciliter). Only one participant regularly tested positive for alcohol; all others showed sporadic use, if any. Patients receiving low-dose methadone were the least likely to abstain from cocaine use (Table 2).

Side effects were assessed every four weeks by an open-ended questionnaire and coded to the Coding Symbols for Thesaurus of Adverse Reaction Terms



No. AT RISK	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Levomethadyl acetate	55	49	47	46	44	42	40	33	32	29								
Buprenorphine	55	54	53	52	48	43	40	36	33	31								
High-dose methadone	55	55	54	51	49	48	48	45	41	39								
Low-dose methadone	55	53	52	50	42	25	20	18	13	11								

Figure 2 (facing page). Results over the Course of the Trial. Panel A shows the percentage of patients in each group remaining in the study at the end of each week. There was a significant difference among the groups ($P<0.001$). In pairwise post hoc comparisons the results for levomethadyl acetate, buprenorphine, and high-dose methadone were significantly different from those for low-dose methadone (all $P<0.001$), and the results for high-dose methadone were significantly different from those for levomethadyl acetate ($P=0.02$). Panel B shows the adjusted mean percentage of opioid-positive urine specimens each week for the intention-to-treat sample. Means were calculated by maximum-likelihood estimation, with study retention and percentage of clinic visits missed as covariates. There was a significant difference among groups ($P<0.001$). Pairwise post hoc comparisons showed that the results for levomethadyl acetate, buprenorphine, and high-dose methadone were significantly different from those for low-dose methadone ($P<0.05$ for all comparisons). Panel C shows the patients' self-reported frequency of illicit opioid use during each week for the intention-to-treat sample. Means were calculated by maximum-likelihood estimation, with study retention and percentage of clinic visits missed as covariates. There was a significant difference among the groups over time ($P=0.002$).

(COSTART) system.⁴⁰ The percentage of patients reporting side effects was similar among groups. At least one side effect was reported by 55 percent of the patients receiving levomethadyl acetate, 49 percent of those receiving buprenorphine, 45 percent of those receiving high-dose methadone, and 40 percent of those receiving low-dose methadone. The most

common was constipation (21 percent of all reports), followed by nausea (8 percent) and dry mouth (6 percent). No toxic interactions associated with illicit-drug use were observed in any of the groups. There were no significant effects of sex on any outcome measure.

DISCUSSION

Levomethadyl acetate, buprenorphine, and high-dose methadone were all effective in treating opioid dependence and were superior on multiple measures to low-dose methadone. The percentage of patients retained at 17 weeks compared favorably with rates reported elsewhere for these medications.^{11,14,23,24,27-29} The proportion of opiate-positive urine specimens and self-reported opioid use decreased over time.

As compared with patients taking low-dose methadone, those taking levomethadyl acetate had a significantly higher rate of continuous abstinence from opioids, and those taking high-dose methadone and buprenorphine had a trend toward a higher rate of continuous abstinence. The greater effectiveness of levomethadyl acetate during maintenance therapy may reflect more stable blood levels with less variation in trough-to-peak concentrations.⁴¹ Levomethadyl acetate, however, was less effective than high-dose methadone in terms of patient retention, particularly during the dose-induction period. The high dropout rate among patients taking levomethadyl acetate may be explained, in part, by the longer period re-

TABLE 2. SELECTED OUTCOME MEASURES.

MEASURE*	LEVOMETHADYL ACETATE (N=55)	BUPRENORPHINE (N=55)	HIGH-DOSE METHADONE (N=55)	LOW-DOSE METHADONE (N=55)	P VALUE
Primary outcomes					
Study retention (days)					<0.001
Mean ±SE	89±6	96±4	105±4	70±4	
95% CI	78–100	88–105	98–112	62–79	
Opioid-positive urinalysis (% positive results/wk)					0.005
Mean ±SE†	52±4	62±4	62±4	79±5	
95% CI	44–60	55–70	54–69	70–88	
Self-reported opioid use (no. of times/wk)					0.002
Mean ±SE†	4±1	4±1	4±1	6±1	
95% CI	3–6	3–5	3–6	4–8	
≥12 Consecutive opioid-negative urinalyses (% of patients)	36	26	28	8	<0.005
Patient's rating of severity of drug problem					0.002
Mean ±SE‡	35±4	34±4	38±4	53±4	
95% CI	28–43	27–42	30–45	45–60	
Secondary outcome					
≥12 Consecutive cocaine-negative urinalyses (% of patients)	36	30	38	14	0.02

*CI denotes confidence interval.

†Estimated least-square means and P values for differences among the groups over time are given.

‡The patient's ratings of the global severity of his or her drug problem were assessed every four weeks (range, 1 [no drug problem] to 100 [worst ever]). Data presented are from the last interview before discontinuation of the study drug or discharge from the study.

quired to achieve the targeted maintenance dose (nine days, as compared with five for methadone)⁴² and the greater reinforcement provided by daily treatment with a full agonist (methadone). Our difficulty in retaining patients during the induction of levomethadyl acetate treatment corroborates earlier findings.^{25,43-45}

The low level of retention in the low-dose methadone group at 17 weeks (20 percent) reflects primarily the substantial proportion of patients receiving rescue treatment; the sharp decline in retention observed after week 6 in this group coincided with the earliest time that patients could receive rescue treatment. The fact that a large proportion of patients receiving low-dose methadone continued to use illicit opioids while they were receiving maintenance therapy at a dose of 20 mg of methadone is consistent with other reports that low doses of methadone are less effective in retaining patients in treatment programs and reducing illicit opioid use.^{6,11,14,28} Nevertheless, the rescue procedure was successful, since 81 percent of such patients in the low-dose methadone group completed 17 weeks of treatment.

Most of the development and evaluation research on buprenorphine has been based on daily doses. Our study used thrice-weekly doses and found that outcomes were approximately equivalent to those with either daily methadone or thrice-weekly levomethadyl acetate. Thus, thrice-weekly buprenorphine may also offer greater convenience to patients and clinic staff.

Urinalysis and self-reporting are surrogate measures of drug-taking behavior that differ in their sensitivity in detecting abstinence. Urinalysis may overestimate drug use; opioid use can decline by 75 percent (for example, from four times to once daily) and still yield 100 percent opioid-positive urine specimens, and frequent testing can allow carryover between consecutive tests. Self-reported drug use is open to either over- or underreporting. However, even though quantitative methods for more accurate detection of new drug use are currently being developed,⁴⁵ both urinalysis and self-reports are accepted surrogate measures of drug use.^{46,47}

The strengths of our study include the use of doses based on clinical criteria, ensuring that comparisons between drugs were based on individually optimized doses for three of the randomly assigned treatment groups. The use of a fixed-dose control group allowed us to demonstrate differences in outcome measures and to analyze a heterogeneous population of heroin users. The rescue procedure allowed us to retain 87 percent of all patients who received rescue treatment and allowed 66 percent of the total population to remain in treatment. Our rescue procedure also addressed potential ethical concerns.⁴⁸

In summary, levomethadyl acetate, buprenorphine, and high-dose methadone were more effective than low-dose methadone in reducing the use of illicit opi-

oids. As compared with low-dose methadone, levomethadyl acetate produced the longest duration of continuous abstinence; buprenorphine administered three times weekly was similar to levomethadyl acetate in terms of study retention and was similar to high-dose methadone in terms of abstinence.

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