

Moderate- vs High-Dose Methadone in the Treatment of Opioid Dependence

A Randomized Trial

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METHADONE HYDROCHLORIDE is a μ -agonist opioid used for opioid dependence treatment. It has good oral bioavailability, can be dosed once per day, suppresses opioid withdrawal, and provides cross-tolerance to the effects of other opioids. Outpatient treatment combining daily methadone plus counseling has been available for more than 30 years.¹ More than 110 000 patients receive methadone treatment in the United States,² and expansion of methadone treatment has been identified as an important means for decreasing drug use as well as transmission of human immunodeficiency virus infection.³ Expansion of methadone treatment in the United States has been difficult, due to community opposition and misperceptions regarding its efficacy, but there has been marked growth in other countries.⁴

Despite methadone treatment's extensive history, controversy regarding optimal dosing persists. Early clinical trials assessing the dose-related efficacy of methadone produced conflicting results,⁵⁻⁸ and by the late 1980s surveys of dosing practices found some methadone clinics having average daily maintenance doses of less than 30 mg, and other clinics using average daily doses of greater than 60 mg.⁹ While reports and

Context Methadone hydrochloride treatment is the most common pharmacological intervention for opioid dependence, and recent interest has focused on expanding methadone treatment availability beyond traditional specially licensed clinics. However, despite recommendations regarding effective dosing of methadone, controlled clinical trials of higher-dose methadone have not been conducted.

Objective To compare the relative clinical efficacy of moderate- vs high-dose methadone in the treatment of opioid dependence.

Design A 40-week randomized, double-blind clinical trial starting in June 1992 and ending in October 1995.

Setting Outpatient substance abuse treatment research clinic at the Johns Hopkins University Bayview Campus, Baltimore, Md.

Participants One hundred ninety-two eligible clinic patients.

Intervention Daily oral methadone hydrochloride in the dose range of 40 to 50 mg (n = 97) or 80 to 100 mg (n = 95), with concurrent substance abuse counseling.

Main Outcome Measures Opioid-positive urinalysis results and retention in treatment.

Results By intent-to-treat analysis, through week 30 patients in the high-dose group had significantly lower rates of opioid-positive urine samples compared with patients in the moderate-dose group (53.0% [95% confidence interval {CI}, 46.9%-59.2%] vs 61.9% [95% CI, 55.9%-68.0%]; $P = .047$). These differences persisted during withdrawal from methadone. Through day 210 no significant difference was evident between dose groups in treatment retention (high-dose group mean retention, 159 days; moderate-dose group mean retention, 157 days). Nineteen (33%) of 57 patients in the high-dose group and 11 (20%) of 54 patients in the moderate-dose group completed detoxification.

Conclusions Both moderate- and high-dose methadone treatment resulted in decreased illicit opioid use during methadone maintenance and detoxification. The high-dose group had significantly greater decreases in illicit opioid use.

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manuals describing methadone treatment recommend using at least 50 to 60 mg/d,¹⁰⁻¹³ recent clinical trials examining methadone dose have continued to produce conflicting results.¹⁴⁻¹⁹ In general, it appears that low daily doses of methadone (eg, 20-35 mg) are less effective than moderate doses (50-80 mg). However, no contemporary studies have examined doses greater than 80 mg/d.

The purpose of the present study was to compare moderate- with high-daily dose methadone in a contemporary

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population of opioid-dependent patients. In a previous clinical trial conducted at the same clinic, a comparison of low- to moderate-daily dose methadone showed dose-related differences in treatment retention and rates of illicit opioid use.^{13,14} The question of optimal methadone dose is particularly pertinent since physician, office-based methadone treatment for opioid dependence is being actively considered.³

METHODS

Protocol

Patients seeking opioid dependence treatment were enrolled in the study. Eligibility criteria for participation were age 18 years or older, current intravenous opioid dependence (including documentation of at least 2 previous methadone detoxification attempts or a prior episode of methadone maintenance treatment, a urine sample positive for opioids, and physical examination consistent with acute and chronic needle use), no chronic medical illnesses, absence of major mental illness, negative pregnancy test result for women, and at least 1 month since the patient's last treatment at this clinic. The study was approved by the institutional review board, and written informed consent was obtained.

Eligible applicants were admitted to a 40-week methadone treatment program and randomly assigned to 1 of 2 methadone dose schedules. Group assignment and methadone dosing were double-blind for patients and staff who had patient contact. During the first week of treatment all participants received 30 mg of methadone daily. Over the subsequent 5 weeks patients in the high-dose condition had dose increases of 10 mg each week, while patients in the moderate-dose condition had dose increases of 2 mg each week. Thus, beginning in week 6, high-dose patients achieved a stabilization dosage of 80 mg/d, and moderate-dose patients achieved a stabilization dosage of 40 mg/d.

During weeks 8 to 30, participants were eligible to receive double-blind dose increases and decreases. Dose increases were made in increments of 10 mg and 5 mg for the high- and moderate-dose

conditions, respectively. The maximum number of dose increases was 2 (ie, to maximums of 100 mg and 50 mg of methadone for the high- and moderate-dose conditions, respectively). Increases were at least 3 weeks apart and were based on continued illicit opioid use as evidenced by at least 2 of the patient's last 4 urine samples testing opioid positive. Dose decreases were ordered if the patient requested such, and appeared to be overmedicated or had 6 consecutive opioid-negative urine samples. Subjects and staff were not given details regarding the criteria for dose changes but were told dose changes were possible during the study.

During weeks 31 to 40 of treatment, dose was tapered at a rate of 10% per week. Participation at the treatment and research clinic was time-limited, and enrollees were informed of this and encouraged to engage in long-term, community-based treatment after study participation. Subjects and staff were unaware of the phases or details of the dosing schedule, and were simply instructed that all patients would be detoxified by the end of the 40 weeks. Patients interested in applying to transfer to community-based methadone treatment were assisted by clinic staff. Patients who missed 3 consecutive days of medication were discharged from treatment.

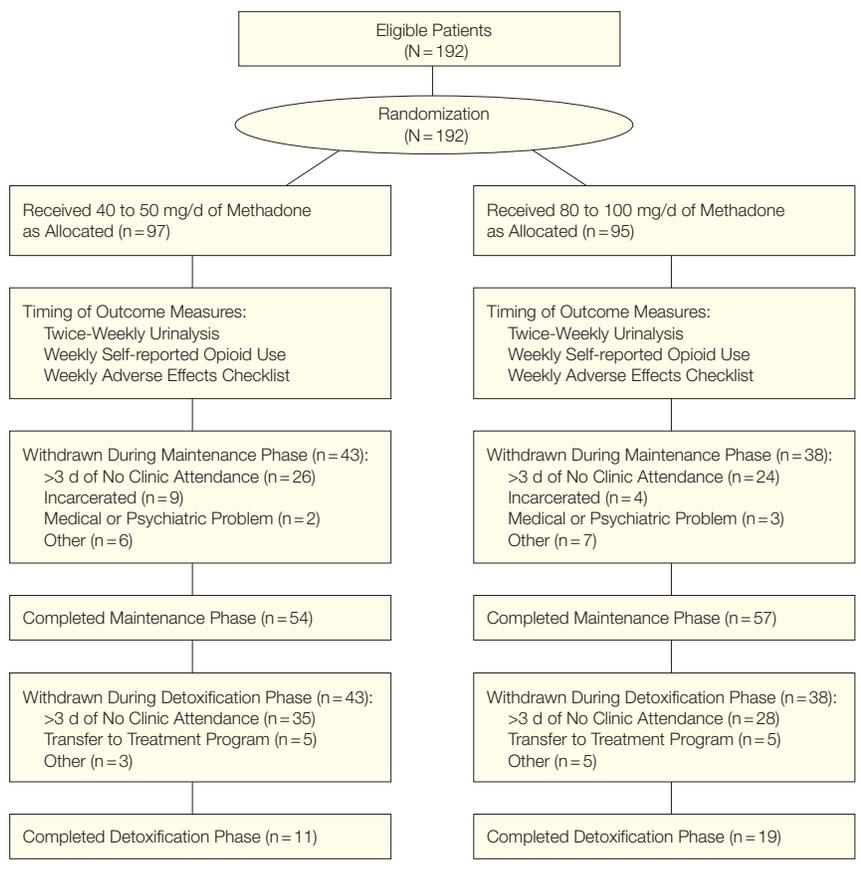
Patients were assigned a counselor who set treatment goals and developed an individualized treatment plan, and received weekly individual and group therapy focusing on relapse prevention. On-site medical services were provided by a full-time internist. Take-home medication was provided only on major holidays and for extenuating circumstances.

Since the study sought to determine the relative efficacy of moderate- vs high-dose methadone, the primary period of study interest was the first 30 weeks. Three primary outcome measures were reported: self-reported illicit opioid use, urinalysis toxicology, and treatment retention. Self-reported opioid use was assessed weekly for the first 12 weeks of the study, and then once every other week thereafter with the drug use ques-

tionnaire. The drug use questionnaire asked the number of times drugs, such as illicit opioids, were used in the past week. Results for patients who remained in treatment to the end of the stable dosing phase (the retained sample) were used to examine possible time-course effects. A total of 111 subjects were included in this analysis; all in-treatment self-reported drug use data for 1 subject, who was assigned to the high-dose condition and remained in treatment to the end of the stable dosing phase, were lost. Patients provided observed urine samples twice weekly (Mondays and Thursdays). Samples were tested on-site using enzyme-multiplied immunoassay technique for the presence of opioids, cocaine, and benzodiazepines, with cutoff calibration concentrations of 300 µg/mL for each test (morphine, benzoylecgonine, oxazepam). The specificity of the enzyme-multiplied immunoassay technique system ranges between 96% and 100% (Syva Corp, Palo Alto, Calif).

Two approaches were used to summarize urine results. First, the overall percentages of positive test results for opioids, cocaine, and benzodiazepines were calculated for each patient through the end of the stable dosing period (intent-to-treat analysis). Second, patients who remained in treatment to the end of the stable dosing phase (the retained sample) had their urine data summarized in 3-week blocks by calculating the percentage of urine samples positive for opioids in each block; these results were used to examine possible time-course effects. Finally, treatment retention was calculated as the total number of days from admission to discharge, or to the last day of the stable dosing period (day 210) if the patient remained longer. An adverse effects checklist, as a secondary outcome measure, was reported based on data from the first 30 weeks. Patients rated symptoms for severity on a 5-point scale with a zero equaling not at all to a 4 equaling very severe. Forms were completed weekly for the first 12 weeks, then every other week for the remaining period. Results for constipation and sleepiness or grogginess are reported.

Figure 1. Progress of Patients From Randomization to Detoxification



Randomization occurred on the day of admission to the study.

Secondary outcomes for patients who entered the dose-tapering period (weeks 31-40) are presented here to characterize the relative efficacy of methadone detoxification. The percentages of positive urine test results for opioids, cocaine, and benzodiazepines were calculated for each patient during the detoxification period, and treatment retention during this phase was also determined.

Statistical Analysis

Power analyses based on effects detected in an earlier clinical trial of methadone treatment¹³ indicated that 96 patients in each group would be needed to detect a medium effect size (0.20) with 80% power in an intent-to-treat analysis.

Multilevel analyses were conducted for the drug use questionnaire, urine time course data, and the adverse effects checklist using SAS PROC MIXED statistical software (SAS Institute Inc, Cary, NC) with a heterogeneous autoregressive covariance structure for the repeated measurements.²⁰ This statistical technique allows for correlations among observations within an individual subject, for the presence of missing data, for subjects measured at different time-points, and for covariates that change over time. The response of individual

Table. Demographic Characteristics and Baseline Drug Use*

Characteristic	Total Sample (N = 192)	Dose Comparison		Retention Comparison	
		Moderate (n = 97)	High (n = 95)	Retained (n = 111)	Dropout (n = 81)
Age, mean (SD), y	37.6 (5.5)	38.0 (5.5)	37.2 (5.5)	37.4 (5.8)	37.9 (5.1)
White	49.0	47.4	50.5	50.5	46.9
Men	64.6	67.0	62.1	65.8	63.0
Married	18.8	16.5	21.1	21.6	14.8
Employed	25.0	28.9	21.1	27.0	22.2
Legally free†	71.9	66.0	77.9	73.9	69.1
Education, mean (SD), y	11.2 (1.7)	11.1 (1.7)	11.3 (1.7)	11.1 (1.7)	11.3 (1.8)
Prior drug treatments, mean (SD), No.	4.1 (2.5)	4.0 (2.6)	4.2 (2.5)	4.1 (2.3)	4.1 (2.8)
Baseline drug use, mean (SD), No.‡					
Opioids§	25.3 (12.5)	25.8 (12.1)	24.7 (12.9)	23.8 (11.6)	27.1 (13.5)
Cocaine§	5.6 (9.5)	4.5 (8.0)	6.6 (10.9)	5.1 (9.5)	6.2 (9.7)
Benzodiazepines	0.2 (0.6)	0.2 (0.7)	0.2 (0.6)	0.2 (0.7)	0.2 (0.6)

*Values are percentages unless otherwise indicated. There were no significant differences between the moderate- and high-dose groups, or for the retained vs dropout groups, for any of the listed demographic variables.
 †Indicates not incarcerated, on parole, probation, or with an impending trial.
 ‡Based on use in the week prior to admission.
 §Value is number of times used. Data are from the drug use questionnaire obtained on the day of admission to the study.
 ||Value is number of days used. Data are based on the past week drug use form obtained on the day of admission to the study.

subjects was first modeled, and then the estimates for each individual were combined in a group analysis.²¹⁻²³

Treatment retention curves were compared using a Cox regression model. The percentages of positive urine samples for the intent-to-treat group during the maintenance phase, and for patients who entered the detoxification phase, were analyzed using analysis of covariance. Covariates used for multilevel analyses, analyses of covariance, and survival analyses are described below. The Tukey test was used for pairwise comparisons among means.

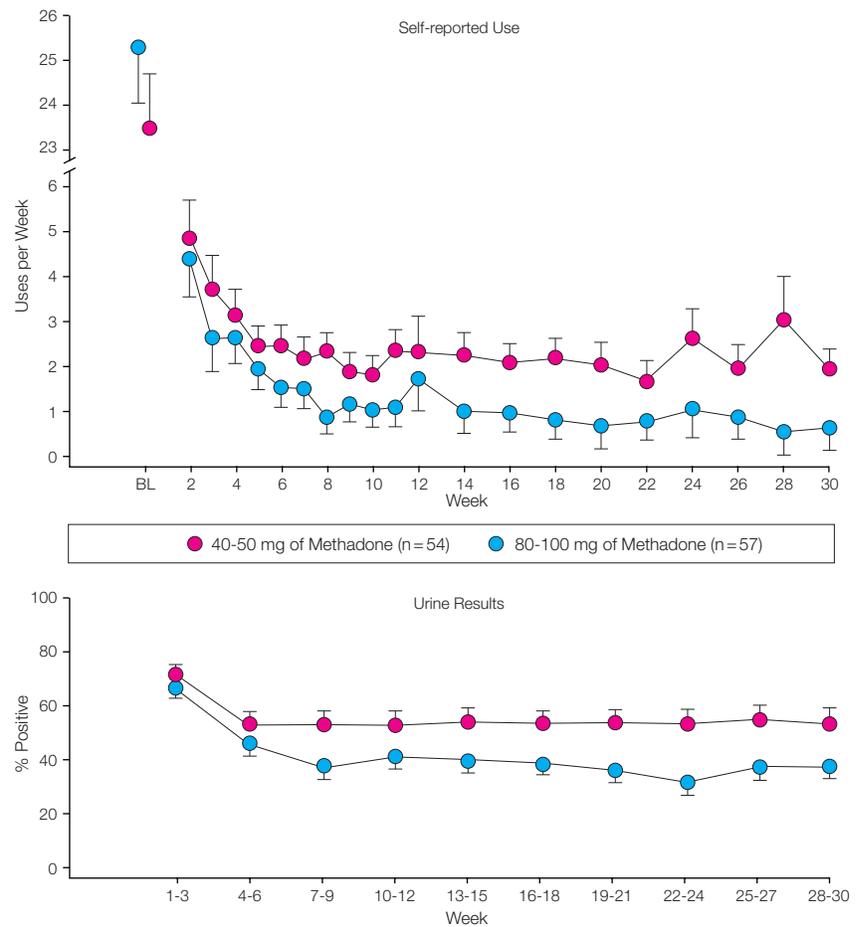
The following descriptive statistics are reported for each group: the average dose of methadone from the beginning of week 8 (when dose increases could occur) to the end of the stable dosing period, the number of patients receiving dose increases, and the number of patients receiving dose decreases.

Patients' rates of in-treatment drug use may be related to rates of pretreatment drug use²⁴⁻²⁶; therefore, these correlations were examined. Pretreatment opioid and cocaine use was assessed using the drug use questionnaire, and pretreatment benzodiazepine use was assessed using the past week drug use form, a questionnaire assessing the number of days during the previous week that drugs such as benzodiazepines were used. Results from these questionnaires represent rates of use in the week prior to admission. In-treatment drug use was calculated as the overall percentage of positive urine samples for each drug category during maintenance treatment. Pretreatment rates of opioid, cocaine, and benzodiazepine use significantly correlated with in-treatment drug use, so these measures of baseline drug use were included as covariates in all analyses.

Assignment

Participants were randomized individually after being stratified on 2 baseline variables: presence vs absence of pretreatment cocaine use (defined as either a cocaine-positive urine sample at the time of application or any self-reported cocaine use in the 30 days prior to admission); and a low vs high level of pre-

Figure 2. Illicit Opioid Use



Top, Self-reported illicit opioid use across time as assessed by the drug use questionnaire. Results shown are for the retained sample and represent the number of times illicit opioids were used in each prior week. Values for the baseline period (BL) represent the week prior to admission and are unadjusted means. All other values represent adjusted means. Bottom, Percentage of opioid-positive urine samples across time for the same sample. Urine specimens were collected twice per week, and results were summarized in 3-week blocks. Results shown are adjusted means.

treatment illicit opioid use (defined as pretreatment self-reported illicit opioid use averaging no more than once per day vs more than once per day). The order of condition assignments within each stratum was random, and assignments were sealed in numbered envelopes within larger envelopes corresponding to each stratum. On the day of admission, a research assistant with no patient contact determined the patient's stratification, drew the next sequential envelope from that stratum, and assigned the patient the dose condition contained in the envelope. Dose codes were entered into a database accessible only to pharmacy

staff and selected research assistants with no patient contact. Sealed dose codes were maintained at the dispensary in case of emergency. No breaking of dose codes was required.

Masking

Commercial oral methadone hydrochloride solution (10 mg/mL; Mallinckrodt, St Louis, Mo) was used to prepare each methadone dose. All patients received identically appearing, individually prepared doses in a volume of 60 mL, labeled with the patient's name and date. Doses were masked with cherry-flavored liquid concentrate (Mallinck-

rod). Patients ingested each dose under direct nursing observation and immediately rinsed their bottle with water that they then drank.

RESULTS

Participant Flow

FIGURE 1 shows stages of the trial. There were no significant differences between the moderate- vs high-dose groups for variables listed in the TABLE, and there were no significant differences between the retained vs dropout groups for any of these variables.

Maintenance Phase Self-reported Drug Use

The retained group reported using opioids an average of 24 times in the week prior to admission (Table). Rates of opioid use decreased dramatically (about 90%) for both groups when compared with this pretreatment rate of use (FIGURE 2). During the latter half of the stabilization phase, the high-dose group reported using illicit opioids an average of 1 or fewer times per week, while the moderate-dose group was reporting use of illicit opioids an average of 2 to 3 times per week. There was a significant difference between groups ($P = .01$), and a significant difference across time ($P = .001$) in self-reported illicit opioid use, but no significant group \times time effect.

Maintenance Phase Urine Results

All patients enrolled in the study (the intent-to-treat population) were included in these analyses, thus providing an overall measure of drug use through week 30 for each participant. High-dose condition patients ($n = 95$) had a significantly lower rate of opioid-positive urine samples (53.0%; 95% confidence interval [CI], 46.9%-59.2%) compared with moderate-dose condition patients ($n = 97$) (61.9%; 95% CI, 55.9%-68.0%; $P < .001$). High-dose condition patients also had lower but not significant differences in rates of cocaine use (61.5%; 95% CI, 54.7%-68.4% vs 66.9%; 95% CI, 60.2%-73.7%) and benzodiazepine use (17.4%; 95% CI, 12.7%-22.0% vs 17.8%; 95% CI, 13.2%-22.4%).

Analysis of urine results for time-course effects showed a significant difference between dose groups ($P = .003$), and a significant change over time ($P < .001$), but no significant group \times time effect (Figure 2). Both the moderate- and high-dose groups showed a decline in opioid-positive urine results from weeks 1 to 3 through weeks 4 to 6 of treatment. However, the high-dose group continued to show a decline in the rate of opioid-positive test results in weeks 7 to 9, while the moderate-dose group did not. Both groups had relatively stable rates of opioid-positive urine samples after weeks 7 to 9 of treatment.

Maintenance Phase Retention

There was no significant difference between dose groups for treatment retention. Through the end of the stable dosing phase (day 210), patients assigned to the high-dose condition remained an average of 159 days, while patients assigned to the moderate-dose condition remained an average of 157 days.

Maintenance Phase Adverse Effects

There were no significant differences between dose groups on self-reports of constipation or sleepiness or grogginess. For both measures, the most common rating was not at all. Ratings of sleepiness or grogginess as moderate, severe, or very severe were 3.3%, 0.5%, and 0.1%, respectively, for the moderate-dose group, and 2.9%, 1.2%, and 0.3%, respectively, for the high-dose group.

Detoxification Phase Urine Results and Retention

Patients in the high-dose group continued to have significantly lower rates of opioid-positive urine samples (46.4%; 95% CI, 37.3%-55.5%) compared with the moderate-dose group (66.9%; 95% CI, 57.9%-75.9%; $P = .002$) during the detoxification phase. There was no significant difference between groups in rates of cocaine- or benzodiazepine-positive urine samples during this period. In addition, there were no significant differences between dose conditions for treatment retention (Figure 1).

Dose Increases, Decreases, and Average Dose

The average stable daily dose of methadone hydrochloride for patients who remained in treatment until at least week 8 was 45.8 mg for the moderate-dose condition ($n = 87$) and 89.5 mg for the high-dose condition ($n = 80$). In the high-dose condition there were 119 dose increases and 13 dose decreases. There were 89 requests for dose increases (6 by patients who had already achieved the maximum dosage possible of 100 mg/d), and 15 requests for dose decreases. In the moderate-dose condition there were 140 dose increases and 4 dose decreases. There were 169 requests for dose increases (27 by patients who had already achieved the maximum dosage possible of 50 mg/d), and 3 requests for dose decreases.

COMMENT

This clinical trial examined moderate- vs high-dose methadone in the outpatient treatment of opioid dependence. Results show that both doses of methadone were effective in maintaining patients in treatment and substantially decreasing rates of illicit opioid use. The high-dose group had significantly greater decreases in opioid use compared with the moderate-dose group. When compared with the pretreatment period, both groups had substantial decreases in illicit opioid use that were clinically significant.

Patients reported an average of 1 to 3 illicit opioid uses per week during treatment, while urine results showed 40% to 55% of samples were opioid positive (Figure 2). These self-report and urine sample results are consistent with each other. Urinalysis testing has great sensitivity for detecting occurrence of any drug use, but little sensitivity for detecting declines in frequent drug use. Single instances of drug use result in positive urinalysis results for 2 to 4 days. Thus, 1 to 3 uses per week may correspond to this proportion of opioid-positive urinalysis test results.

An earlier clinical trial at this same site found clear and significant dose-related differences between low- (20 mg) and moderate-daily dose methadone hydro-

chloride (50 mg) and found both to be superior to nonmaintenance detoxification treatment, as assessed by treatment retention, rates of illicit opioid use from self-reports and urine testing, and other measures related to drug abuse.^{13,14} The present study addressed the question of whether methadone's therapeutic efficacy continued to be dose-related at higher doses. While dose-related differences were found for opioid use in the present study, unlike the earlier study there was no significant difference between dose groups for treatment retention. While cross-study comparisons should be viewed with caution, the results from these 2 studies suggest that improvements in treatment retention can occur as dose is increased up to a moderate-dosage range (around 50 mg/d), but further improvements in retention may not be achieved with higher doses of methadone.

Results from this study were analyzed to examine possible sex differences in dose response, and no significant sex effects were found for any of the primary outcome measures reported here. Similarly,

results were analyzed to determine if methadone dose influenced cocaine use, and no such effect was found.

There were no significant differences between the 2 dose groups in self-reported adverse effects. The frequency and severity of adverse effects were low for both groups. For example, fewer than 5% of ratings for sleepiness or grogginess attained even moderate intensity.

The relatively moderate differences between dose conditions in the present study are not inconsistent with earlier clinical trials with methadone hydrochloride that reported little difference in outcome at daily doses above 40 to 50 mg,⁶⁻⁸ although more recent studies have generally found significant differences between lower and higher methadone doses.^{15,17,18} This study differs from these others by using a higher dose of methadone, which might be expected to produce even greater dose differences. Because urine testing is a relatively insensitive means for detecting substantial changes in drug use, the differences between doses found for urine results

from this study can reflect substantial changes in drug use, especially when compared with pretreatment levels.

It is possible that dosages in excess of 100 mg/d may be required for optimal benefit in some patients. However, current federal regulations in the United States discourage methadone dosages greater than 100 mg/d. Well-conducted clinical trials testing such high doses would likely be needed to support revision of those regulations. In the meantime, the results from the current study provide evidence that significantly improved outcomes can be achieved with daily methadone doses greater than 40 to 50 mg. The most important aspect from therapeutic and public health perspectives is that methadone treatment over a broad range of doses is associated with large and significant clinical improvements.

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REFERENCES

- Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction: a clinical trial with methadone hydrochloride. *JAMA*. 1965;193:80-84.
- Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *National Drug and Alcoholism Treatment Unit Survey (NDATUS): Data for 1994 and 1980-1994*. Rockville, Md: US Dept of Health and Human Services, Public Health Service; 1996.
- National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addiction. *JAMA*. 1998;280:1936-1943.
- Farrell M. *A Review of the Legislation, Regulation and Delivery of Methadone in 12 Member States of the European Union: Final Report*. Luxembourg, Belgium: Office for Official Publications of the European Communities; 1996.
- Ling W, Charuvastra C, Kaim SC, Klett J. Methadyl acetate and methadone as maintenance treatments for heroin addicts. *Arch Gen Psychiatry*. 1976; 33:709-720.
- Goldstein A. Dosage, duration, side effects: blind controlled dosage comparisons with methadone in 200 patients. In: Proceedings of the Third National Conference on Methadone Treatment; New York, NY; November 14-16, 1970:31-37.
- Garbutt GD, Goldstein A. Blind comparison of three methadone maintenance dosages in 180 patients. In: Proceedings of the Fourth National Conference on Methadone Treatment; San Francisco, Calif; January 8-10, 1972:411-414.
- Goldstein A, Judson BA. Efficacy and side effects of three widely different methadone doses. In: Proceedings of the Fifth National Conference on Methadone Treatment; Washington, DC; March 17-19, 1973: 21-44.
- US General Accounting Office. *Methadone Maintenance: Some Treatment Programs Are Not Effective; Greater Federal Oversight Needed*. Washington, DC: US General Accounting Office; 1990.
- Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment*. New York, NY: Springer-Verlag NY Inc; 1991.
- Parrino MW. *State Methadone Treatment Guidelines; Treatment Improvement Protocol (TIP) Series 1*. Rockville, Md: US Dept of Health and Human Services, Center for Substance Abuse Treatment; 1993.
- Rettig RA, Yarmolinsky A, eds. *Federal Regulation of Methadone Treatment*. Washington, DC: National Academy Press; 1995.
- Strain EC, Stitzer ML, eds. *Methadone Treatment for Opioid Dependence*. Baltimore, Md: Johns Hopkins University Press; 1999.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Dose-response effects of methadone in the treatment of opioid dependence. *Ann Intern Med*. 1993; 119:23-27.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Methadone dose and treatment outcome. *Drug Alcohol Depend*. 1993;33:105-117.
- Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA*. 1992;267:2750-2755.
- Kosten TR, Schottenfeld R, Ziedonis D, Falconi J. Buprenorphine versus methadone maintenance for opioid dependence. *J Nerv Ment Dis*. 1993;181:358-364.
- Ling W, Wesson DR, Charuvastra C, Klett J. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry*. 1996;53:401-407.
- Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry*. 1997;54:713-720.
- Singer JD. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. *J Educ Behav Stat*. In press.
- Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. *Arch Gen Psychiatry*. 1993;50: 739-750.
- Kreft I, De Leeuw J. *Introducing Multilevel Modeling*. London, England: Sage Publications Ltd; 1998.
- Diggle PJ, Liang K, Zeger SL. *Analysis of Longitudinal Data*. New York, NY: Oxford University Press Inc; 1996.
- Iguchi MY, Stitzer ML. Predictors of opiate drug abuse during a 90-day methadone detoxification. *Am J Drug Alcohol Abuse*. 1991;17:279-294.
- Farley TA, Cartter ML, Wassell JT, Hadler JL. Predictors of outcome in methadone programs: effect of HIV counseling and testing. *AIDS*. 1992;6:115-121.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Useful predictors of outcome in methadone-treated patients: results from a controlled clinical trial with three doses of methadone. *J Maintenance Addict*. 1998;1:15-28.