ORIGINAL ARTICLE

Methadone Dose Increase and Abstinence Reinforcement for Treatment of Continued Heroin Use During Methadone Maintenance

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Background: Although methadone maintenance is an effective therapy for heroin dependence, some patients continue to use heroin and may benefit from therapeutic modifications. This study evaluated a behavioral intervention, a pharmacological intervention, and a combination of both interventions.

Methods: Throughout the study all patients received daily methadone hydrochloride maintenance (initially 50 mg/d orally) and weekly counseling. Following baseline treatment patients who continued to use heroin were randomly assigned to 1 of 4 interventions: (1) contingent vouchers for opiate-negative urine specimens (n = 29 patients); (2) methadone hydrochloride dose increase to 70 mg/d (n = 31 patients); (3) combined contingent vouchers and methadone dose increase (n = 32 patients); and (4) neither intervention (comparison standard; n = 28 patients). Methadone dose increases were double blind. Vouchers had monetary value and were exchangeable for goods and services. Groups not receiving contingent vouchers received matching vouchers independent of urine test results. Primary outcome measure was opiate-negative urine specimens (thrice weekly urinalysis).

Results: Contingent vouchers and a methadone dose increase each significantly increased the percentage of opiate-negative urine specimens during intervention. Contingent vouchers, with or without a methadone dose increase, increased the duration of sustained abstinence as assessed by urine screenings. Methadone dose increase, with or without contingent vouchers, reduced self-reported frequency of use and self-reported craving.

Conclusions: In patients enrolled in a methadone-maintainence program who continued to use heroin, abstinence reinforcement and a methadone dose increase were each effective in reducing use. When combined, they did not dramatically enhance each other's effects on any 1 outcome measure, but they did seem to have complementary benefits.

Arch Gen Psychiatry. 2000;57:395-404

HEROIN DEPENDENCE is associated with significant morbidity and mortality.[1-5] Methadone maintenance, particularly when given in conjunction with counseling and other psychosocial services, is an effective treatment of heroin dependence; it reduces illicit drug use, crime, human immunodeficiency virus infection risk, and death, and improves employment and social adjustment.[1,6-11] Nevertheless, some patients continue to use heroin during treatment.[12]

Higher doses of methadone are associated with lower rates of opioid use and improved treatment retention, as shown in randomized clinical trials[13-15] and in retrospective analyses of outcome in clinical populations.[16-18] Furthermore, temporary dose increases can lead to decreases in illicit drug use and improvement in social functioning.[19] Nevertheless, finding effective adjuvant treatments to methadone may have clinical value, since dose increases alone may not always be adequate or acceptable to clinic staff.[10,20,21]

One possible adjuvant treatment is contingency management, a behavioral treatment in which incentives are used to reinforce target behaviors such as drug abstinence. A variety of incentives have been shown to decrease illicit drug use in patients enrolled in methadone-maintenance programs; these include money, goods and services, take-home doses, dose changes, and time of dosing.[22-25] A monetary-based reinforcement schedule developed by Higgins and colleagues[26,27] specifically to encourage sustained drug abstinence has been shown to be an effective treatment of both cocaine and opiate dependence.[28-30] The effectiveness of contingency management may lie in its providing an external control to reinforce patients' capacity for self-control.[31]

Combination of behavioral and pharmacological therapy is a common ap-

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PATIENTS AND METHODS

PATIENTS

Subjects were selected from 285 patients consecutively admitted to a methadone-maintenance program at the Archway Clinic, the treatment research program of the National Institute on Drug Abuse Intramural Research Program in Baltimore, Md. Applicants were first screened by telephone and then in 2 on-site visits that included medical, psychiatric, and drug-use histories, a physical examination, urine and blood laboratory evaluations, and a battery of assessment instruments (Addiction Severity Index[33]; Diagnostic Interview Schedule III, Revised[34]; Beck Depression Inventory[35]; Symptom Check List-90-Revised[36]; and Shipley Institute of Living Scale[37]). Applicants were eligible for the protocol if they were between the ages of 18 and 65 years, qualified for methadone maintenance according to Food and Drug Administration guidelines, and reported histories of drug use by injection. Persons with current major psychiatric illness (as determined by the Diagnostic Interview Schedule III, Revised) and/or unstable serious medical illness and those with current physical dependence on alcohol or benzodiazepines were excluded from this study. Two studies were conducted concurrently, this study focusing on opiate use and the other study focusing on cocaine use. Patients were eligible for enrollment in the opiate use or cocaine use study if at least 3 of 15 urine specimens collected during a 5-week baseline treatment tested positive for heroin or cocaine. Patients who met criteria for opiate use but not cocaine use were assigned to the opiate study. Patients who met criteria for both opiate and cocaine use were randomly assigned to 1 of the studies. This study was approved by the local institutional review board for human research, and all patients gave informed written consent prior to participation. At the time of consent, patients were told that they might receive vouchers and that their methadone dose might increase 1 time during the study after initial stabilization on their maintenance dose.

Standard Treatment

All patients received, without charge, daily oral methadone treatment and weekly individual counseling throughout the 13-week study. Counselors completed a semistructured psychosocial assessment and treatment plan for each patient; reduction of drug use was the primary goal. Counseling sessions were problem focused and included both supportive and motivational techniques. Counselors helped patients develop a functional analysis of their substance use, identify and avoid high-risk situations, avoid drug-using friends and acquaintances, cope with urges to use, and examine short- and long-term consequences of use. At the end of 13 weeks, patients were automatically enrolled in a follow-up study involving a maintenance contingency (to be reported separately).

Urine and Breath Toxicology Studies

Each Monday, Wednesday, and Friday, urine specimens were collected under observation of trained staff. Qualitative testing was conducted using an enzyme multiplied immunoassay technique (EMIT; Syva Corp, Palo Alto, Calif) system for cocaine (benzoylecgonine), opiates (morphine), benzodiazepines (oxazepam), phencyclidine, barbiturates, amphetamines, and marijuana. Cutoffs for positive specimens were 300 ng/mL for cocaine, opiates, and benzodiazepines; 25 ng/mL for phencyclidine; 1000 ng/mL for amphetamines; and 50 ng/mL for marijuana. Breath alcohol levels were determined on the same days using a breath-testing device (Alco-Sensor III; Intoximeters Inc, St Louis, Mo).

Self-report Questionnaires

Self-reports of drug use were collected immediately after each urine collection. Patients were asked the amount and number of times they had used an illicit drug, and the dollars spent on alcohol and other drugs on each day since their last visit. (On the rare occasions when patients reported use of morphine, codeine, oxycodone, or propoxyphene, these were converted to heroin dose equivalents.[38]) On Wednesdays, patients completed a craving questionnaire and the Lifestyle Changes Questionnaire.[39] On the craving questionnaire, patients rated how much they had wanted cocaine and heroin during the past week on a scale from 0 (not at all) to 4 (extremely). On the Lifestyle Changes Questionnaire, patients indicated whether they had engaged in any of 9 activities to stop, reduce, or avoid cocaine/heroin use during the past week and whether they had committed crimes.

Study Timeline and Groups

The study consisted of a 5-week baseline treatment and an 8-week intervention. Baseline treatment began on study enrollment and continued until the patient had provided 15 urine specimens, typically 5 weeks. At the end of baseline treatment, participants assigned to the opiate study were randomized to 1 of the following 4 groups: (1) contingent vouchers (vouchers given for opiate-negative urine samples) (2) dose increase (methadone hydrochloride dose increase to 70 mg/d and noncontingent vouchers), (3) combined treatment (contingent vouchers plus methadone dose increase); and (4) comparison standard (noncontingent vouchers and no methadone dose increase).

proach to medical and psychiatric problems such as hypertension, diabetes mellitus, and depression. It is also likely to be useful in the treatment of drug dependence. For example, methadone treatment plus intensive counseling and other services is more effective than methadone alone.[11] We hypothesized that contingency management and methadone dose increase, 2 effective treatments acting through different mechanisms, would be more effective in combination than either alone. This study evaluates that hypothesis. The following 4 conditions were compared: methadone dose increase, voucher reinforcement of opiate-negative urine specimens, a combination of the 2, and a comparison standard condition (as described in the "Standard Treatment" subsection of the "Patients and Methods" section). We chose a baseline dose of 50-mg methadone as it had been reported to be customary in more than half of the programs surveyed in 1988.[32] We reasoned that some methadone clinic staff may be more inclined to adopt new behavioral strategies than to provide higher methadone doses.

For patients who qualified for both the cocaine and opiate studies, randomization to a study was by coin flip. This was followed by assignment to contingent or noncontingent vouchers. The first 10 patients were assigned to contingent vouchers to allow for yoking of noncontingent patients. Thereafter, patients were assigned to a voucher condition by coin flip. Dose randomization was then conducted (separately for the contingent and noncontingent groups) by the study pharmacist, using a random-number table.

METHADONE INTERVENTION

Methadone hydrochloride (Mallinckrodt Inc, St Louis, Mo) was administered daily in a constant volume (35 mL) of cherry-flavored solution. Dose was stabilized at 50 mg within the first week of treatment and held constant through the 5-week baseline treatment. The dose increase was given as 60 mg on days 1 through 3 and 70 mg on day 4 of the intervention. Dose assignment was blinded to patients and treatment and research staff. Patients initially seen with signs of opioid side effects were evaluated by a physician (A.U.), and dose adjustments were made as indicated.

VOUCHER INTERVENTION

Contingent Groups

Patients in these 2 groups earned vouchers based on the results of the 3 times weekly urine tests. The value of the vouchers began at $2.50 and increased by $1.50 for each consecutive opiate-negative urine specimen, and for every 3 consecutive opiate-negative urine specimens patients earned an additional $10 voucher.[40] A patient who met voucher criteria for 8 consecutive weeks could earn a total of $554 (average $9.89/d). If the patient provided an opiate-positive urine specimen or failed to provide a specimen, the patient did not receive a voucher, and the value of the next earned voucher was reset to $2.50. Earned vouchers were given the day after urine collection. Vouchers were exchangeable for goods and services (eg, movie passes, bus passes, or exercise equipment) that would support a drug-free lifestyle. When the patient accumulated enough vouchers for a purchase, a staff member determined whether the purchase was consistent with treatment goals. Items were purchased by staff and given to patients in the clinic; no money was given directly to patients.

Noncontingent Groups

Patients in these 2 groups received vouchers independent of their urine test results. Each patient was randomly linked to a patient in a contingent group, independent of methadone dose and blind to the patient. For each clinic visit numbered from 1 to 24 (3 visits per week for 8 weeks) that the contingent patient earned a voucher for testing opiate negative, the noncontingent patient received a voucher for providing a urine specimen. If the noncontingent patient did not provide a urine specimen or did not attend clinic, the voucher was forfeited; patients were not told when this occurred.

DATA ANALYSIS

To ensure comparability among groups, intake measures were analyzed by analysis of variance (ANOVA) (for continuous variables), Pearson χ^2 (for categorical variables), or the Fisher exact test (for categorical variables with expected cell sizes <5). Retention rates were compared across groups with survival analysis, using a log-rank test of time until the provision of the final urine sample; patients who left before the final week of intervention were coded as dropouts. Patients with 3 or more sporadically missing urine specimens (ie, not due to dropout) during the intervention were coded as poor attenders; this was compared across groups using the Fisher exact test. These analyses used a cell-means model (treating group as a between-patients factor with 4 levels); subsequent outcome analyses used a 2×2 (contingency $\times$ dose) factorial model.

Urine/breath data on drug use were collapsed into "mean baseline percent negative" and "mean intervention percent negative" for each subject, then analyzed with repeated-measures ANOVAs with 1 within-subject factor (phase) and 2 between-patient factors (contingency and dose). The time course of opiate and cocaine use during intervention was further analyzed with generalized linear mixed models fit with the SAS macro GLIMMIX.[41] GLIMMIX analyzes dichotomous repeated measures with missing data points by invoking the SAS procedure MIXED[42] with a logit link, and gives adjusted proportions. A first-order autoregressive error structure was used. Good model fits were not obtainable for alcohol and other drugs, probably owing in part to underdispersion (lack of variation) both within and across groups. Continuous measures taken at repeated timepoints during intervention (eg, craving, self-reported use, and lifestyle changes) were analyzed with mixed regressions (SAS MIXED procedure). Each model contained 1 within-patient factor (time) and 5 between-patient factors—contingency, dose, baseline percent negative (or mean), poor attendance, and dropout.[43]

Longest duration of opiate abstinence was calculated for each patient as the longest run of consecutive opiate-negative urine specimens during intervention; this was compared across groups with an ANOVA with 2 between-patient factors (contingency and dose), and was also analyzed with each patient's baseline percent negative as a covariate.

All analyses were 2 tailed; α level was set at .05.

RESULTS

PATIENT CHARACTERISTICS

Of the 285 patients who enrolled, 253 completed the 5-week baseline treatment. Of these, 29 met the criteria for opiate use only, 22 for cocaine use only, and 190 for both. Twelve patients did not meet criteria for either drug; they received standard treatment for the duration of the study. A total of 120 patients who met criteria for opiate use were randomized to 1 of the groups in our study. Among the 43 demographic variables compared (**Table 1**), significant differences across groups were found for 2; regression analyses showed that neither predicted treatment response.

One patient randomized to the combined treatments group did not tolerate the dose increase. His dose was decreased to 50 mg/d, and he completed the study. His data were included in the combined treatments group for analysis.

†Table 1. Patient Characteristics at Intake

Characteristic*	Group			
	Comparison Standard (n = 28)	Contingent Vouchers (n = 29)	Dose Increase (n = 31)	Combined Treatments (n = 32)
Mean ± SD age, y	37.4 ± 6.9	37.4 ± 7.0	38.8 ± 6.1	37.0 ± 7.4
Male, %	57.1	65.5	77.4	68.8
Race, %				
African American	46.4	44.8	35.5	40.6
White	53.6	55.2	64.5	59.4
Marital status, %				
Married	14.3	27.6	6.5	18.8
Divorced/widowed	25.0	17.2	19.4	28.1
Never married	46.4	27.6	41.9	50.0
Separated	14.3	26.7	32.3	3.1
Mean ± SD education, y	10.8 ± 0.5	11.5 ± 0.3	11.4 ± 0.3	11.2 ± 0.4
Employment, %				
Full-time	25.9	31.0	38.7	18.8
Part-time	18.5	6.9	16.1	15.6
Unemployed	55.6	62.1	45.2	65.6
Mean ± SD income last 30 d, $				
Total	1755 ± 1386	1539 ± 1072	1749 ± 2695	1568 ± 1278
Illegal	738 ± 894	692 ± 1007	961 ± 2684	991 ± 1358
Mean ± SD self-reported drug use—life years				
Heroin	13.3 ± 7.4	12.6 ± 9.2	13.3 ± 8.4	11.8 ± 6.8
Cocaine	5.8 ± 7.4	7.4 ± 7.0	3.9 ± 6.7	4.8 ± 5.7
Alcohol	4.0 ± 6.3	3.8 ± 6.5	4.5 ± 7.2	3.2 ± 5.7
Sedatives/tranquilizers	0.7 ± 2.2	0.04 ± 0.2	0.06 ± 0.2	0.3 ± 1.1
Marijuana*	3.5 ± 5.3	6.1 ± 7.5	4.7 ± 8.4	1.4 ± 3.4
Mean ± SD self-reported drug use—past 30 d				
Heroin	25.9 ± 9.0	28.8 ± 5.4	26.4 ± 8.4	26.9 ± 7.9
Cocaine	10.4 ± 11.1	13.4 ± 12.4	7.3 ± 10.0	11.3 ± 12.4
Alcohol	7.8 ± 7.9	3.7 ± 7.0	4.8 ± 6.1	3.7 ± 7.4
Sedatives/tranquilizers	0.6 ± 1.6	1.0 ± 3.2	1.4 ± 3.3	0.2 ± 0.6
Marijuana	1.2 ± 2.6	2.1 ± 5.9	2.1 ± 3.3	1.2 ± 5.1
Current diagnosis (% from *DIS-III-R*)				
Generalized anxiety disorder	3.6	0	3.2	0
Phobia	14.3	13.8	3.2	3.2
Antisocial personality	10.7	24.1	16.1	16.1
Alcohol dependence	3.6	6.9	6.4	12.9
Sedative dependence	3.6	10.3	3.2	9.7
Cocaine dependence†	32.1	44.8	12.9	41.9
Heroin/opioid dependence	100	100	100	100
Phencyclidine	3.6	0	0	0
Gambling	0	6.9	0	3.2
Mean ± SD BDI score	16.6 ± 9.0	20.5 ± 11.8	15.9 ± 10.0	15.9 ± 9.1
Mean ± SD SCL-90-R				
Global Severity Index				
Positive Symptom	64.5 ± 12.2	63.1 ± 9.2	59.5 ± 9.5	60.9 ± 9.6
Distress index	58.4 ± 10.6	58.0 ± 7.5	54.2 ± 8.4	56.7 ± 9.1
Mean ± SD Shipley Institute of Living Scale				
Vocabulary	41.9 ± 6.9	37.7 ± 12.9	38.6 ± 11.7	38.7 ± 12.4
Abstract thinking	50.4 ± 6.3	48.1 ± 13.5	48.1 ± 9.5	48.6 ± 11.3

**DIS-III-R indicates Diagnostic Interview Schedule III, Revised; BDI, Beck Depression Inventory; and SCR-90-R, Symptom Checklist-90-Revised.*
†None of the comparisons across groups was significant except years of marijuana use ($F_{3,116} = 2.86$, P = .04) and current cocaine dependence ($\chi^2_3 = 8.40$, P = .04).

RETENTION, MISSING URINE SPECIMENS, AND VOUCHER EARNINGS

Overall, 112 (93.3%) of 120 patients completed the 8-week intervention (**Table 2**). Discharges were due to failure to meet attendance requirements (eg, missing 3 consecutive medication days; n = 7) or voluntary transfer to another program (n = 1). No significant between-group differences were noted in retention. However, a trend toward poorer attendance (missed visits) was noted in the comparison standard group (Table 2); this was controlled for in subsequent analyses.

OPIATE URINE RESULTS

Percentage of Opiate-Negative Urine Specimens

All 4 treatment groups improved during the intervention, as indicated by an increase in the percentage of opiate-negative urine specimens from baseline to intervention and

Table 2. Retention, Missing Urine Specimens, and Voucher Earnings

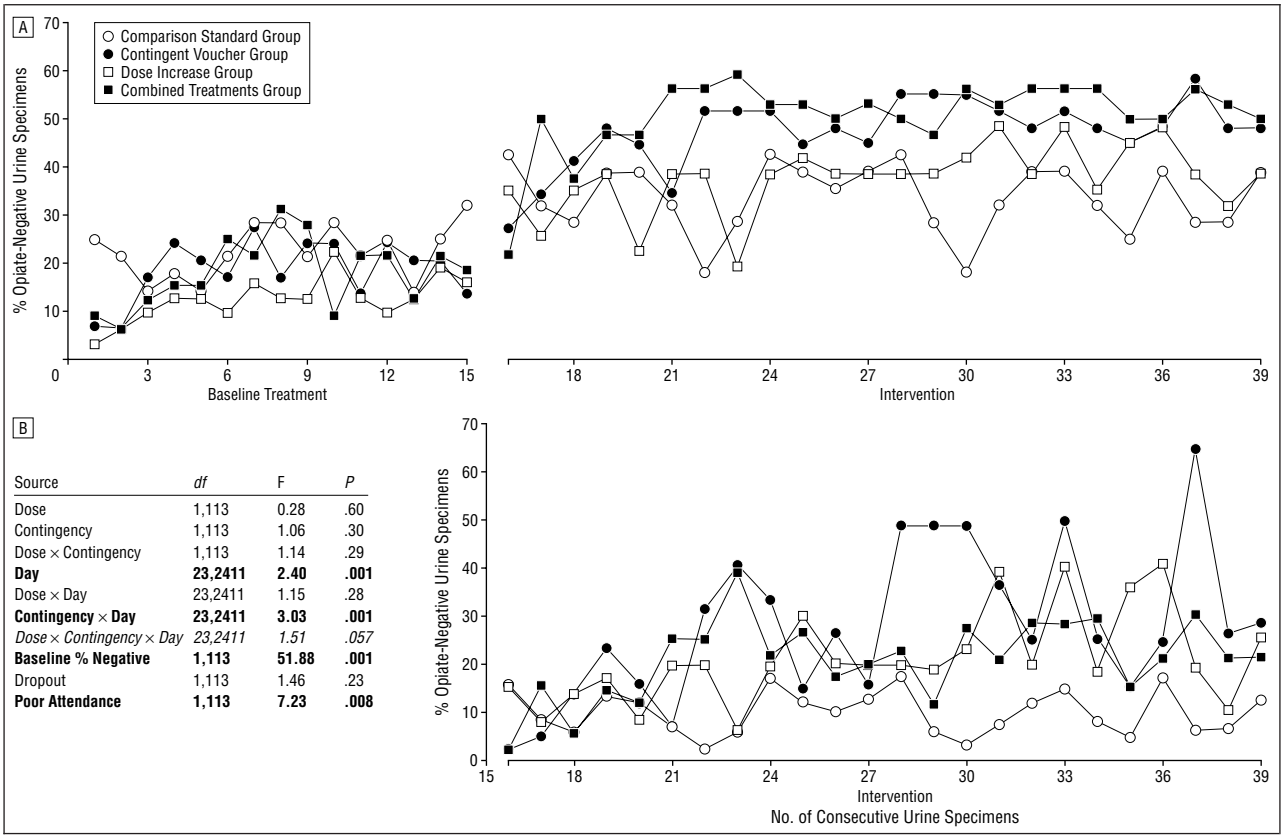
Variable	Group: Comparison Standard (n = 28)	Contingent Vouchers (n = 29)	Dose Increase (n = 31)	Combined Treatment (n = 32)	Analysis
Retention					
No. (%) of patients completing 8-wk intervention	27 (96.4)	27 (93.1)	27 (87.1)	31 (96.9)	Survival analysis: log-rank $\chi^2_3 = 3.59$, $P = .31$
No. of weeks in treatment, including baseline					
Mean ± SD	12.9 ± 0.3	12.9 ± 0.5	12.6 ± 1.3	12.8 ± 0.9	$F_{3,116} = 0.90$, $P = .44$
Range	11.4-13	10.9-13	7.1-13	7.9-13	
Sporadically missing urine specimens during intervention					
Mean ± SD	1.9 ± 1.9	1.0 ± 1.1	1.1 ± 1.2	1.0 ± 1.6	$F_{3,116} = 2.33$, $P = .08$
Range	0-6	0-3	0-4	0-7	
% Poor attenders (missing ≥3 visits)	10 (35.7)	5 (17.2)	4 (12.9)	3 (9.4)	Fisher exact, $P = .06$
Mean ± SD voucher earnings, $	205.57 ± 206.49	190.14 ± 220.90	161.68 ± 213.41	180.20 ± 193.81	$F_{3,116} = 0.23$, $P = .88$

Table 3. Baseline vs Intervention Drug Use, Percentage of Negative Urine Specimens

	Group: Comparison Standard (n = 28)	Contingent Vouchers (n = 29)	Dose Increase (n = 31)	Combined Treatments (n = 32)	ANOVA*-Arcsin-Transformed Percentages: $F_{1,116}$; P: Phase	Dose × Phase	Contingency × Phase	Contingency × Dose × Phase
% Opiate-negative[a,b]								
Baseline mean (SEM)	22.6 (4.8)	18.6 (4.4)	12.7 (3.0)	18.1 (3.5)				
Intervention mean (SEM)	33.8 (5.5)	47.4 (7.9)	37.8 (5.8)	50.8 (7.0)	**72.96; .001**	1.49; .22	**8.15; .005**	1.12; .29
Intervention, adjusted[c]	9.0	24.4	19.6	19.2				
% Cocaine-negative[a,d]								
Baseline mean (SEM)	38.8 (6.7)	25.3 (5.5)	40.1 (7.3)	37.1 (6.7)				
Intervention mean (SEM)	34.8 (5.9)	35.4 (7.4)	39.7 (7.7)	38.5 (7.0)	0.10; .75	0.28; .60	**6.11; .01**	2.46; .12
Intervention, adjusted[c]	9.6	20.0	12.1	16.5				
% Cannabis-negative[a,d]								
Baseline mean (SEM)	77.1 (6.3)	81.8 (6.2)	78.4 (5.8)	85.4 (5.4)				
Intervention mean (SEM)	78.9 (6.3)	79.6 (6.5)	80.8 (5.6)	83.7 (5.7)	0.06; .81	0.00; .98	2.07; .15	0.03; .87
% Benzodiazepine-negative[a,d]								
Baseline mean (SEM)	89.0 (4.7)	96.1 (1.5)	87.1 (4.7)	91.9 (2.9)				
Intervention mean (SEM)	87.9 (5.4)	94.2 (2.0)	87.0 (4.6)	89.5 (3.3)	0.95; .33	0.31; .58	0.62; .43	0.08; .78
% Alcohol-negative[d,e]								
Baseline mean (SEM)	99.0 (0.4)	99.8 (0.2)	99.6 (0.3)	99.3 (0.5)				
Intervention mean (SEM)	99.7 (0.2)	99.7 (0.2)	98.0 (1.6)	98.9 (0.8)	0.39; .53	2.38; .13	0.28; .60	0.91; .34

**ANOVA indicates analysis of variance. Bold text indicates* $P < .05$.
[a] *Urine specimens.*
[b] *All missing urine specimens (including those due to dropout) were considered positive for opiates.*
[c] *Adjusted percentages are from GLIMMIX[41] (generalized linear mixed model; SAS Publications, Cary, NC) analyses of intervention data, controlling for baseline percent negative, dropout, and poor attendance. Missing urine specimens were coded as missing. For statistical analyses, see Figure 1, B.*
[d] *Mean percent negative of all nonmissing urine specimens.*
[e] *Breath specimens.*

significant main effect of phase (**Table 3**). Baseline opiate use tended to be higher in patients assigned to the dose increase and combined treatment groups (Table 3); the baseline difference was not significant (data not shown), but should be borne in mind so that the true magnitude of the experimental-intervention effects can be appreciated. For example, the raw data (**Figure 1**, A) suggest that the dose increase group performed little better than the comparison standard group through most of the intervention. However, when baseline opiate use is controlled for (Figure 1, B), a clearer dissociation emerges between the 2 groups. The significant interaction of contingency × day (Figure 1, B) reflects increasing abstinence over time in the 2 groups receiving contingent vouchers. The near-significant interaction of dose × contingency × day reflects the fact that the methadone dose increase became effective by itself over time, but did not increase the effectiveness of contingent vouchers. The tendency for all groups to look worse in the GLIMMIX estimates (Figure 1, B) than in the raw data (Figure 1, A) is the result of controlling for dropout. The adjusted percentage of opiate-negative urine specimens was significantly lower for poor attenders (n = 22) than for good attenders (n = 98)—7.8% vs 33.7%, respectively.



Source	*df*	F	*P*
Dose	1,113	0.28	.60
Contingency	1,113	1.06	.30
Dose × Contingency	1,113	1.14	.29
Day	**23,2411**	**2.40**	**.001**
Dose × Day	23,2411	1.15	.28
Contingency × Day	**23,2411**	**3.03**	**.001**
Dose × Contingency × Day	*23,2411*	*1.51*	*.057*
Baseline % Negative	**1,113**	**51.88**	**.001**
Dropout	1,113	1.46	.23
Poor Attendance	**1,113**	**7.23**	**.008**

Figure 1. *A, Percentage of patients abstinent on 39 successive urine test days during the 5-week baseline treatment (15 specimens) and 8-week intervention (24 specimens) in the 4 treatment groups: comparison standard group (no dose increase and noncontingent vouchers; n = 28); contingent voucher group (n = 29); dose increase group (n = 31); and combined treatments group (n = 32). Missing specimens (including those due to dropout) were assumed to be opiate positive. B, GLIMMIX[41] (generalized linear mixed model, SAS Publications, Cary, NC) estimates of percentage of patients abstinent on 24 successive urine test days during the intervention, controlling for dropout, poor attendance, and each patient's baseline percent negative. Treatment groups and numbers were the same as mentioned in Figure 1, A. Results of statistical analysis are shown at the bottom of the figure. Times sign indicates interaction, bold text,* P<.05, *and italics,* P.05<P≤.10.

Longest Duration of Abstinence

The number of consecutive opiate–negative urine specimens was selectively and significantly increased by contingent vouchers (**Figure 2**). An ANOVA of data from the intervention showed a significant effect of contingency ($F_{1,116} = 10.02$, $P = .002$) and no effect of dose ($F_{1,116} = 0.11$, $P = .75$) or dose × contingency interaction ($F_{1,116} = 0.27$, $P = .60$). Similar results were obtained in an analysis of covariance controlling for baseline percent negative, with a significant effect of the covariate baseline percent negative ($F_{1,115} = 23.35$, $P<.001$), a significant effect of contingency ($F_{1,115} = 11.35$, $P = .001$), and no effect of dose ($F_{1,115} = 0.88$, $P = .35$) or dose × contingency interaction ($F_{1,115} = 1.22$, $P = .27$).

SELF-REPORTED OPIATE USE

In repeated-measures ANOVAs of baseline vs intervention means (not reported here), self-reported use decreased significantly across phases in all groups. Analyses of intervention data alone (controlling for baseline means, dropout, and poor attendance) showed that the dose change significantly reduced self-reported frequency of use, and tended to reduce the amount of money spent on opiates (**Table 4**). The reduction in frequency became especially pronounced in the dose increase group toward the end of intervention (reflected in a near-significant interaction of dose × contingency × time).

SELF-REPORTED OPIATE CRAVING

A mixed regression on intervention data showed that the dose increase, with or without contingent vouchers, significantly reduced opiate craving (Table 4). Visual inspection of the time course of unadjusted means (data not shown) suggests a transient increase in opiate craving in the contingent vouchers group coinciding with its initial reduction in use during intervention that was not apparent in the combined treatments group.

POSITIVE LIFESTYLE CHANGES AND CRIMINAL ACTIVITY

Mixed regressions on intervention data showed that the comparison standard group reported a markedly small number of changes relative to the other 3 groups (reflected in the trend toward a dose × contingency interaction). Self-reported crime decreased throughout intervention for the combined treatments group (which started highest and ended lowest) while remaining relatively constant for the other 3 groups.

USE OF COCAINE AND OTHER DRUGS

Comparison of baseline vs intervention cocaine use showed a significant contingency × phase interaction, but this primarily reflected baseline differences (Table 3). GLIMMIX analysis of intervention data alone, controlling for baseline, showed significant interactions of time × dose ($F_{23,2411} = 1.97$, $P = .004$), time × contingency ($F_{23,2411} = 1.78$, $P = .01$), and time × dose × contingency ($F_{23,2411} = 1.90$, $P = .006$). Visual inspection of the raw and adjusted proportions (not shown) suggested that these interactions represented temporal fluctuations of doubtful clinical significance. Still, cocaine-negative urine specimens during intervention were slightly more frequent in the contingent voucher and combined treatment groups than in the other groups.

Positive results for other drugs were comparatively rare and did not differ systematically by group or across phases (Table 3). Throughout the study, only 6.7% of patients ever tested positive for phencyclidine, 2.5% for barbiturates, and 1.7% for amphetamines.

COMMENT

The findings from our study support 3 major conclusions: (1) that abstinence reinforcement with contingent vouchers was effective in decreasing opiate use and increasing sustained abstinence, with or without a methadone dose increase; (2) that a 1-time methadone dose increase of 20 mg/d had beneficial therapeutic effects, including reduced self-reported frequency of use and craving; and (3) that the combination did not significantly enhance overall decreased opiate use but retained the individual benefits of both treatments. These treatment effects were observed when administered as adjunct treatments to an active (though modest) dose of a pharmacotherapy (methadone) and weekly individual counseling. Overall, patients improved over time, with large and significant main effects of study phase on almost every outcome measure and a large and significant main effect of day during the intervention phase. Retention was high, with 93.3% of the patients completing the study.

The contingency intervention produced greater decreases in opiate use and had significant effects on more outcome measures than the methadone dose increase. The GLIMMIX estimates (Figure 1, B) suggest that the contingency intervention produced especially robust effects even in the absence of a dose increase. In addition, the contingency intervention, but not the dose increase, increased longest duration of abstinence. Thus, the contingency intervention encouraged continuous rather than sporadic abstinence. Self-reported positive lifestyle changes were associated with the contingency intervention. Lifestyle changes had been seen in patients receiving contingency management treatment for their cocaine use.[39] There was only marginal evidence for decreased use of other drugs, as had occurred in our earlier study.[39] However, use of drugs other than cocaine and heroin was rare in this study, and the small variations in rates of urine specimens postive for other drugs probably were not clinically significant.

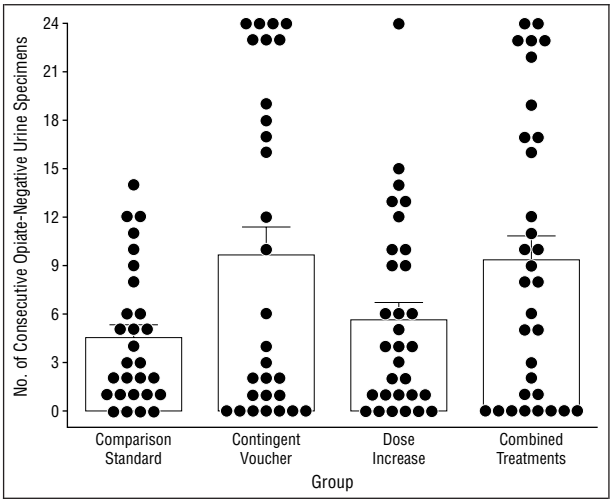


Figure 2. *Longest duration of sustained abstinence from illicit opiates during the 8-week intervention: comparison standard group (no dose increase and noncontingent vouchers (n = 28); contingent voucher group (n = 29); dose increase group (n = 31); and combined treatments group (n = 32). Each point represents maximum number of consecutive opiate-negative urine specimens for an individual patient; the bars and brackets represent means and SEM of each treatment group.*

Our results are consistent with findings in other clinics showing contingency management to be a powerful tool for the treatment of illicit drug abuse.[44] In particular, this study replicates and expands the findings of a pilot study conducted in a similar population in our clinic.[29] Using an ABA design, we applied the escalating-reinforcement schedule to 13 patients who were continuing to use heroin during methadone maintenance (50-80 mg/d). Opiate-positive urine specimens decreased from 78% before to 24% during the 12-week voucher intervention and increased to 41% thereafter. Bickel et al[30] have shown that a similar intervention improved outcome in a 26-week outpatient detoxification program. Patients receiving contingent vouchers for opioid-negative urine specimens had significantly greater completion rates and longer durations of abstinence than seen in a standard treatment with counseling.

A 1-time methadone dose increase from 50 to 70 mg/d produced increases in opiate abstinence, decreases in self-reported frequency and cost of use, and decreases in craving. Larger changes were seen in self-reported use than in urine test results. The decreases in self-reported frequency of (and money spent on) opiate use in the dose increase group may reflect quantitative changes not detected by our qualitative urinalyses. The decreases in craving likely reflect pharmacological actions of the 20-mg increase. Even so, the modest size of the effects raises the issue of whether the dose change was too small. The 50-mg/d dose was originally chosen because it was in the range of doses commonly prescribed in community methadone-maintainence programs in the United States when this study was initiated.[32,45] We chose a 20-mg dose increase to 70 mg because we wanted a dose that nearly all patients could tolerate (in fact, only 1 patient required a dose decrease). Because our primary interest was in the interaction between the pharmacological and behavioral treatments, we also wanted to avoid choosing a methadone dose so ef-

Table 4. Self-reported Opiate Use, Craving, Positive Lifestyle Changes, and Criminal Activity

	Group Means (SEMs)				Mixed Regression: F; *P*						
	Comparison Standard (n = 28)	Contingent Vouchers (n = 29)	Dose Increase (n = 31)	Combined Treatments (n = 32)	Dose	Contingency	Dose × Contingency	Time	Time × Dose	Time × Contingency	Time × Dose × Contingency
Self-reported opiate use[a]											
Mean frequency per day											
Baseline	0.43 (0.06)	0.43 (0.06)	0.66 (0.10)	0.49 (0.06)							
Intervention	0.39 (0.09)	0.26 (0.08)	0.28 (0.05)	0.22 (0.05)							
Intervention (adjusted)*	0.58 (0.08)	0.46 (0.08)	0.31 (0.08)	0.41 (0.08)	**7.27; .008**	0.03; .85	3.42; .07	1.05; .40	1.13; .30	1.12; .31	1.51; .055
Mean amount per day, mg											
Baseline	0.62 (0.13)	0.74 (0.13)	0.88 (0.13)	0.82 (0.13)							
Intervention	0.49 (0.12)	0.39 (0.17)	0.34 (0.07)	0.39 (0.10)							
Intervention (adjusted)	0.89 (0.14)	0.74 (0.14)	0.58 (0.14)	0.75 (0.15)	2.18; .14	0.02; .99	2.64; .11	1.18; .26	1.29; .16	0.85; .66	1.22; .22
Mean dollars spent per day											
Baseline	4.15 (1.17)	4.69 (1.09)	5.37 (1.00)	5.29 (1.01)							
Intervention	3.01 (1.00)	2.17 (1.27)	1.90 (0.56)	1.60 (0.55)							
Intervention (adjusted)	4.98 (1.01)	3.92 (1.02)	2.98 (0.97)	3.20 (1.06)	*3.10; .08*	0.30; .58	0.71; .40	1.10; .33	1.06; .39	0.98; .48	1.09; .35
Craving†											
Baseline	1.77 (0.12)	1.91 (0.19)	2.10 (0.16)	1.62 (0.18)							
Intervention	1.34 (0.18)	1.49 (0.16)	1.36 (0.18)	1.05 (0.18)							
Intervention (adjusted)	1.61 (0.19)	1.65 (0.19)	1.30 (0.18)	1.40 (0.20)	**4.40; .04**	0.29; .59	0.06; .81	1.05; .39	1.68; .11	1.19; .31	0.85; .546
Positive lifestyle changes‡											
Baseline	4.28 (0.30)	3.42 (0.34)	3.25 (0.39)	3.56 (0.37)							
Intervention	3.82 (0.48)	4.09 (0.50)	3.72 (0.45)	4.04 (0.42)							
Intervention (adjusted)	2.83 (0.44)	4.00 (0.43)	3.79 (0.41)	3.81 (0.45)	1.55; .22	3.80; .054	3.42; .07	0.89; .51	0.60; .76	0.63; .73	0.11; .99
Criminal activities‡											
Baseline	0.06 (0.03)	0.17 (0.05)	0.06 (0.04)	0.14 (0.06)							
Intervention	0.00 (0.00)	0.04 (0.03)	0.03 (0.03)	0.04 (0.02)							
Intervention (adjusted)	0.03 (0.03)	0.04 (0.03)	0.08 (0.03)	0.06 (0.03)	2.36; .13	0.03; .87	0.62; .43	0.94; .48	**2.06; .046**	0.96; .457	*1.97; .06*

**Adjusted means are from mixed regressions on Intervention data, controlling for baseline means, dropout, and poor attendance. Bold text indicates* P<*.05; italics,* P*.05*<P≤*.10.*

†*Heroin craving was rated on a scale of 0 (not at all) to 4 (extremely).*

‡*Lifestyle changes and criminal activities are the mean of the total reported per week.*

[a]*Data were available for 120 subjects. "Time" refers to each of 24 self-reported days during Intervention;* df *are (1, 114) for dose and contingency and (23, 2516) for time and its interactions.*

[b]*Data were available for 113 of the 120 subjects. "Time" refers to each of 8 weeks during Intervention;* df *are (1, 104) for dose and contingency and (7, 653) for time and its interactions.*

[c]*Data were available for 115 of the 120 subjects. "Time" refers to each of 8 weeks during Intervention;* df *are (1, 106) for dose and contingency and (7, 694) for time and its interactions.*

fective that no enhancement of effects by the combination would be possible. Previous clinical trials have found significant differences between 20 and 50 mg of methadone,[15] 40 and 80 mg,[13] and 20 and 65 mg.[14] Retrospective analyses of outcome in clinical populations have generally used ranges of methadone doses.[16-18] We found only 1 other study that evaluated the effects of a change in methadone dose[19]; that study demonstrated a positive effect of dose change, though the exact doses were not reported.

As noted earlier, combination therapies are widely used in medicine, often resulting in better outcome. Stitzer and Walsh[46] have proposed that the most effective treatments of psychostimulant abuse will be combinations of behavioral and pharmacological therapy. A secondary goal of this study was to test the concept of increasing the effect of a modestly effective pharmacotherapy with a behavioral treatment. Because no effective pharmacotherapies have been identified for cocaine dependence, we attempted to test the hypothesis in opioid abusers, for whom effective pharmacological agents are available. In this study, a 40% increase in methadone dose served as the model pharmacotherapy and abstinence reinforcement served as the behavioral treatment. There was little evidence of a clinically significant interaction between the 2 in decreasing opiate use per se. Thus, the concept of enhancing a pharmacological therapy with a behavioral therapy was not confirmed. One reason may have been that, while we chose a methadone dose increase that was modestly effective,

the behavioral intervention may have been so powerful that it produced a ceiling effect above which the medication was unable to add to the outcome. Nevertheless, patients in the combination group showed the positive effects of both treatments (eg, lower craving from the methadone dose increase and sustained abstinence from the contingency management) which patients receiving either treatment alone did not, suggesting added benefit from combining treatments.

Our study had several limitations. As noted earlier, the methadone doses were modest and were not individualized. This aspect of the study design may have contributed to the high overall rates of opiate use seen in both the baseline treatment and intervention. In addition, the methadone dose intervention was blinded, while the behavioral intervention was not, perhaps biasing against our finding a larger effect of dose increase. However, a double-blind study in a similar geographical context found similar rates of opiate-positive urine specimens, even at high (80- to 100-mg) methadone doses.[47] A second limitation was that there were baseline differences in opiate use among the groups. Although we were able to control for these differences, they might have reduced our ability to detect between-group treatment effects. Finally, our intervention phase was brief, and thus our results may be primarily relevant to induction into long-term maintenance.

Overall, in patients enrolled in a methadone-maintainence program who continued to use heroin, abstinence reinforcement and a methadone dose increase were each effective in reducing use. Abstinence reinforcement, with or without a dose increase, had the valuable therapeutic benefit of producing sustained abstinence; this was not seen with a dose increase alone. The dose increase, however, had greater effects on self-reported use and craving. When combined, the 2 treatments did not dramatically enhance each other's effects on any 1 outcome measure, but they did seem to have complementary benefits. Although a methadone dose increase is an effective and practical "first-line" treatment for many patients who continue to use heroin, there may be some situations in which dose increases alone are ineffective or impossible for regulatory or philosophical reasons.[10,12,20,21] In these cases, abstinence reinforcement should be considered.

Accepted for publication January 11, 2000.

This study was supported in part by the National Institute on Drug Abuse Intramural Research Program, Baltimore, Md.

Presented in part at the annual scientific meeting of the College on Problems of Drug Dependence, Phoenix, Ariz, June 15, 1998.

We are grateful to Robert Brooner, PhD; the Archway Clinic treatment staff and technicians; Ken Silverman, PhD, Charles R. Schuster, PhD, and Conrad Wong, who helped design the clinical trial; and to Anna DeJesus, who assisted in the implementation of this study.

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