

# Desipramine in Opioid-Dependent Cocaine Abusers Maintained on Buprenorphine vs Methadone

Alison H. Oliveto, PhD; Alan Feingold, PhD; Richard Schottenfeld, MD; Peter Jatlow, MD; Thomas R. Kosten, MD

**Background:** Cocaine abuse occurs in 40% to 60% of patients entering opioid maintenance treatment, and effective pharmacotherapies are needed for this combined dependence.

**Methods:** This 13-week, randomized, double-blind, placebo-controlled trial evaluated the efficacy of desipramine hydrochloride (0 or 150 mg/d) plus buprenorphine hydrochloride (12 mg/d) or methadone hydrochloride (65 mg/d) in 180 opioid-dependent cocaine abusers (124 men, 56 women). Supervised urine samples were obtained thrice weekly, and self-reported cocaine and heroin use was reported once weekly. Desipramine plasma levels were determined at weeks 4 and 10.

**Results:** In men, opioid abstinence was increased more rapidly over time when treated with methadone than with buprenorphine, whereas cocaine abstinence was increased more with buprenorphine than with methadone. In women, opioid abstinence was increased the least rap-

idly when treated with buprenorphine plus placebo, while cocaine abstinence was increased more rapidly over time when treated with methadone than with buprenorphine. Regardless of sex or opioid medication, desipramine increased opioid and cocaine abstinence more rapidly over time than placebo. Self-reported opioid use confirmed these findings. Desipramine plasma levels were higher in women than in men, particularly those on buprenorphine maintenance. Higher desipramine plasma levels were associated with greater opioid, but not cocaine, abstinence.

**Conclusions:** Desipramine may be a useful adjunctive medication in facilitating opioid and cocaine abstinence in opioid-maintained patients. The efficacy of opioid medications to treat opioid or cocaine dependence may differ by sex. These findings highlight the importance of including sex as a factor when examining treatment outcome in these types of trials.

*Arch Gen Psychiatry.* 1999;56:812-820

From the Departments of Psychiatry (Drs Oliveto, Feingold, Schottenfeld, Jatlow, and Kosten) and Laboratory Medicine (Dr Jatlow), Yale University School of Medicine, West Haven, Conn.

**C**OMBINED OPIOID and cocaine dependence is associated with major health problems, including medical complications, such as infection with the human immunodeficiency virus or hepatitis and endocarditis, and social issues, such as unemployment and illegal activity. Methadone maintenance programs using individual and group counseling have been found to decrease injection opioid use and subsequent risk for complications such as human immunodeficiency virus.<sup>1</sup> However, the rate of cocaine abuse among patients in methadone maintenance programs has increased considerably in the last 10 years.<sup>2-5</sup> For instance, rates of cocaine use among those entering treatment averaged 58% in one recent multisite study,<sup>6</sup> and rates among those in treatment are as high as 40%.<sup>4,5,7,8</sup> Eighty percent of patients using heroin while in a methadone

maintenance program and nearly one fifth (20%) of patients otherwise compliant with program rules reported using cocaine at least once during the week prior to being interviewed.<sup>8</sup> These findings indicate that methadone maintenance alone does not effectively address cocaine abuse.

Various pharmacological agents have been employed to decrease cocaine craving and abuse in methadone-maintained individuals.<sup>9-15</sup> While no pharmacotherapy has demonstrated robust effectiveness for decreasing cocaine abuse, desipramine has attenuated the "desire" for or the "wanting" of more cocaine after cocaine administration<sup>16,17</sup> and has been found to be a useful adjunctive therapy in depressed opioid-dependent cocaine abusers.<sup>18</sup> However, the metabolism of desipramine is inhibited by methadone,<sup>19</sup> which may affect desipramine's efficacy in methadone-maintained patients.

Because the metabolic interaction between desipramine and methadone has not

## SUBJECTS AND METHODS

### SUBJECTS

One hundred twenty-four male and 56 female volunteers (age range, 20-53 years) were recruited from the general greater New Haven, Conn, population after giving written informed consent to participate in a randomized clinical trial approved by the Yale Human Investigations Committee, Yale University, West Haven, Conn. All patients were opioid dependent, having documented prior treatment in a methadone maintenance program (not necessarily within the last year), or having precipitated withdrawal on administration of naloxone hydrochloride (Narcan) (0.8 mg, intramuscularly), and reported regular cocaine use, having test positive for cocaine within a month before study entry. Exclusions included history of a psychosis; current alcohol or sedative dependence, as determined by self-reports, urinalyses, and/or daily breathalyzer tests; current suicidal tendency, as determined by self-reports and clinical assessment by a physician; current use of prescribed psychoactive medications; pregnancy or breastfeeding; notable medical conditions; illiteracy; and prior buprenorphine treatment. Participants were not paid to participate but received treatment at no cost.

### RESEARCH DESIGN

In this 13-week clinical trial, patients were assigned to treatment groups using a simple randomization procedure, whereby for every 8 patients entered, 2 were randomly assigned to 1 of 4 medication groups: (1) buprenorphine hydrochloride (12 mg/d, sublingually) plus desipramine hydrochloride (150 mg/d, orally); (2) buprenorphine hydrochloride (12 mg/d, sublingually) plus placebo; (3) methadone hydrochloride (65 mg/d, orally) plus desipramine hydrochloride (150 mg/d, orally); or (4) methadone hydrochloride (65 mg/d, orally) plus placebo. Staff and subjects were blind to both opioid medication and desipramine dosages. The medication dosages were increased weekly from 4 mg of buprenorphine hydrochloride, 35 mg of methadone hydrochloride, and 50 mg of desipramine hydrochloride to the maintenance dosages—12, 65, and 150 mg,

respectively—over a 3-week period and were maintained at that dosage for 10 weeks. Primary assessments of treatment outcome included treatment retention; illicit drug use, as measured by urine toxicology screening and self-reports; and opiate withdrawal and mood symptoms.

### MEDICATIONS

Methadone (UDL Laboratories, Largo, Fla) was administered orally. Buprenorphine (donated by the National Institute on Drug Abuse, Rockville, Md) was dissolved in 30% alcohol buffer and administered sublingually. Desipramine (Marion Merrell Dow, Kansas City, Mo) and placebo desipramine tablets were placed in size 00 blue opaque capsules and ingested while the patient was being observed by the nurse to increase the probability of compliance. The maintenance dose of methadone was selected because it is similar to the mean dose used in our clinical programs and because doses in this range are effective in reducing opioid use.<sup>38-41</sup> The buprenorphine hydrochloride dose was selected because lower doses (ie, 2 and 6 mg) showed less efficacy than methadone hydrochloride (65 mg) in our previous clinical trial.<sup>22</sup> The desipramine dose was selected to be comparable to the dose of desipramine that produced substantial plasma levels of the drug with minimal side effects in our previous study in methadone-maintained patients.<sup>11</sup>

All medications were administered with nursing supervision once daily using a double-blind, "double-dummy" procedure. All patients received a liquid to swallow and a liquid to hold under the tongue for 2 minutes, one of which contained active opioid maintenance medication, and a set of 3 capsules that may or may not have contained active desipramine. The pharmacist was nonblind. The principal investigator (T.R.K.) kept the medication assignment code in a sealed envelope for access in case of medical emergency.

### EXPERIMENTAL PROCEDURE

Immediately following the screening procedure and the naloxone challenge, if necessary, patients entered treatment and the first dose of medication was administered. Patients attended the clinic daily to receive their medication,

Continued on next page

been noted with buprenorphine,<sup>19</sup> desipramine's efficacy may be enhanced in patients maintained on the partial opioid agonist buprenorphine rather than methadone. Buprenorphine maintenance has retention rates comparable to methadone maintenance,<sup>20-22</sup> and at daily doses of 8 mg or more, it reduces illicit opioid use equivalently to methadone at doses of 60 to 65 mg.<sup>22-27</sup> In addition, buprenorphine reportedly decreases cocaine self-administration in primates<sup>28,29</sup> and cocaine preference in rats.<sup>30</sup> Buprenorphine may also decrease cocaine use<sup>31</sup> compared with methadone maintenance,<sup>32</sup> although double-blind comparisons of buprenorphine with methadone have not confirmed this.<sup>24,26,33,34</sup> Thus, this placebo-controlled clinical trial compared the treatment efficacy of desipramine hydrochloride in buprenorphine hydrochloride- vs methadone hydrochloride-maintained opioid-dependent cocaine abusers. In addition, given reports of sex differences in substance

abuse treatment,<sup>35-37</sup> treatment efficacy was compared within and between sexes.

## RESULTS

### DEMOGRAPHICS

Treatment groups did not differ significantly by age, race, education, income, use of heroin, cocaine, or alcohol, or Structured Clinical Interview for *DSM-III-R* diagnoses (**Table**). The methadone plus placebo group reported less sedative use than the other 3 groups, but no rate of use was clinically important. Similarly, the subsample of patients used in the analyses (n = 164) did not differ on any of these measures except for sedative use (data not shown). Patient characteristics did not significantly differ by sex, except for greater net income for men than women in the past 30 days (mean  $\pm$  SD, \$450  $\pm$  748 vs \$144  $\pm$  406; F = 6.7; P = .01).

weekly to undergo group relapse prevention therapy, and monthly to undergo individual therapy sessions. The content of group sessions was manual guided, consisting of 24 topics presented over the 13-week period; the individual sessions were open ended, focusing on individual patient issues. Over the course of the study, patients completed various self-reports (see the "Assessments" subsection that immediately follows this one) and submitted supervised urine samples to test for illicit drugs. Illicit opioid and cocaine use did not affect a patient's continued participation in the study; however, patient participation was discontinued for benzodiazepine use. Patients could not miss completing weekly assessments or being medicated on more than 2 consecutive occasions; they could not miss group sessions or being medicated on more than 4 occasions within a 4-week period. When patients quit, were dropped from, or successfully completed the study, they were given a referral to participate in a naltrexone or methadone maintenance program. Patients who completed the study were given the option of receiving follow-up on a drug-free basis after detoxification from opioids.

#### ASSESSMENTS

Intake assessments included the Structured Clinical Interview for *DSM-III-R*<sup>42</sup>; Addiction Severity Index, a structured clinical interview used to assess medical, legal, family-social, psychological, drug abuse, and employment problems<sup>43-44</sup>; the Beck Depression Inventory<sup>45</sup>; a weekly drug use inventory assessing amount and frequency of illicit drug use; and a 43-item opioid intoxication and withdrawal symptoms checklist.

The opioid intoxication and withdrawal symptoms checklist and weekly drug use inventory were completed weekly, and the Beck Depression Inventory was completed monthly, prior to being medicated. Urine samples were obtained thrice weekly and tested for illicit opioids, cocaine, and benzodiazepines using Abbott Diagnostics Radioimmunoassay,<sup>46</sup> with cutoffs of more than 300 ng/mL for cocaine or benzodiazepines and more than 200 ng/mL for opiates. Blood samples were drawn at weeks 4 and 10, and desipramine plasma levels were measured using reversed-phase high-pressure liquid chromatography.<sup>47</sup>

#### DATA ANALYSIS

The 4 groups were first compared on baseline characteristics using  $\chi^2$  analyses for categorical demographics (eg, sex, race) and 1-way analyses of variance for continuous data (eg, age, income per month, etc). A survival analysis compared retention across the 4 groups. The initial sample was also dichotomized according to whether subjects completed 13 weeks of treatment, and a  $\chi^2$  test compared the proportion of dropouts across the 4 groups. Sex was added as a between-subjects factor.

Urinalyses and self-report measures were analyzed using hierarchical linear models (HLMs), which examine the linear trend of categorical and continuous data over time and the interaction of temporal trend with treatment factors and subject characteristics.<sup>48</sup> The HLMs allow for inclusion of data from patients who did not complete treatment, varying assessment times, and different numbers of assessments per subject.<sup>49</sup> There are 2 algorithms for HLMs: one for use with categorical and ordinal variables (see MIXOR program<sup>50</sup>), and the other for continuous variables (see MIXREG program<sup>51</sup>). To make urinalyses amenable to ordinal analysis, urinalysis data were first calculated as a weekly mean proportion of urine tests negative for the target drug. Proportions equal to 1.0 were recoded as "0," proportions between 0.67 and 0.75 were recoded as "1," proportions between 0.33 and 0.5 were recoded as "2," and proportions equal to 0.0 were recoded as "3." These analyses yielded z scores that were used to assess the magnitude of the linear increase or decrease in data values over the course of the study as a function of opioid maintenance medication, desipramine condition, and sex. When an interaction with sex occurred, HLM analyses were performed within that sex. All HLM analyses included only subjects ( $n = 164$ ) who completed more than 3 weeks (ie, induction).

The average desipramine plasma level for each subject was entered into a 2-way analysis of variance with opioid medication and sex as factors. This value was also a cofactor with sex and opioid medication in an HLM subanalysis of opioid- and cocaine-free urine samples. In all analyses, statistical significance was inferred from a z score or  $P < .05$ .

#### TREATMENT RETENTION AND ATTENDANCE

Of the 180 patients, 118 (66%) completed the 13-week trial (**Figure 1**). Survival analysis showed no significant differences in dropouts as a function of treatment group (Wilcoxon [Gehan] = 1.7,  $P = .64$ ). A  $2 \times 4$  contingency table comparing dropouts across treatment groups also showed no significant differences ( $\chi^2 = 2.8$ ,  $P = .41$ ). Neither men ( $\chi^2 = 2.6$ ,  $P = .47$ ) nor women ( $\chi^2 = 3.6$ ,  $P = .30$ ) showed differential attrition across treatment groups. Reasons for premature termination of study participation included leaving treatment at the patient's request ( $n = 35$ ), noncompliance with the study protocol ( $n = 12$ ), incarceration ( $n = 8$ ), medical problems ( $n = 5$ ), or death from causes unrelated to the study medications ( $n = 2$ ).

The mean proportion of counseling sessions attended ranged from 0.73 to 0.76 across treatment groups,

a difference that was nonsignificant ( $F_{(3,173)} = -0.1$ ,  $P = .95$ ). Higher attendance was associated with greater retention (Pearson  $r = 0.38$ ,  $P < .001$ ), but did not interact with treatment group on treatment retention (Wilcoxon [Gehan] = 1.9,  $P = .59$ ).

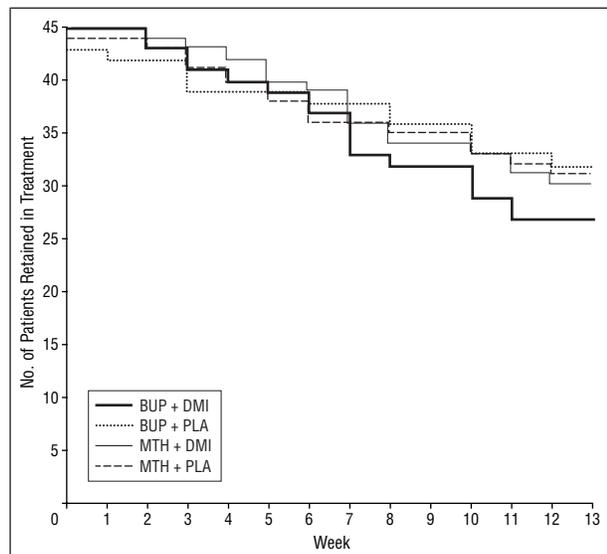
#### ILLICIT DRUG ABSTINENCE AND SELF-REPORTS

A sex  $\times$  time  $\times$  opioid medication  $\times$  desipramine condition interaction was observed for illicit opioid abstinence ( $z = -1.97$ ,  $P < .05$ ; **Figure 2**). Among men (Figure 2, A and C), opioid abstinence was increased more rapidly by methadone than by buprenorphine ( $z = 3.7$ ,  $P = .0002$ ), and by desipramine than by placebo ( $z = -3.3$ ,  $P = .001$ ). Among women (Figure 2, B and D), opioid abstinence was also increased more rapidly by desipramine than by placebo ( $z = -5.05$ ,  $P < .001$ ). Moreover, a time  $\times$  opioid medication  $\times$  desipramine condition in-

## Research Subject Characteristics at Admission to Study\*

Measure	Treatment Groups				F	P	$\chi^2$	P
	BUP + DMI (n = 45)	BUP + PLA (n = 45)	MTH + DMI (n = 45)	MTH + PLA (n = 45)				
Age, y	34.5 (5.7)	34.3 (7.7)	32.7 (5.8)	33.9 (7.0)	0.6	.58	...	...
Sex, No. of M/F	35/10	34/11	24/21	31/14	...	...	7.7	.05
Race							3.8	.7
White	30	28	35	32	...	...	...	...
African American	9	12	7	10	...	...	...	...
Hispanic	6	5	3	3	...	...	...	...
Education, y	11.6 (1.2)	12.1 (1.8)	11.7 (1.8)	11.9 (1.7)	0.8	.49	...	...
Net income, \$/mo	341 (651)	514 (887)	331 (535)	228 (555)	1.4	.25	...	...
Heroin use, No. of days per month	29.0 (4.6)	28.7 (4.9)	28.5 (5.5)	29.5 (2.4)	0.4	.74	...	...
Heroin route, No. of patients using IV/IN	26/18	25/19	23/21	29/15	...	...	1.8	.62
Cocaine use, No. of days per month	12.8 (11.9)	11.8 (9.9)	12.2 (11.6)	12.9 (11.0)	0.1	.96	...	...
Cocaine route, No. of patients using IV/IN/smoke	20/9/12	15/13/14	13/9/20	22/8/11	...	...	7.9	.24
Sedative use, No. of days per month	0.6 (1.2)	0.4 (0.9)	0.8 (1.7)	0.05 (0.2)	3.7	.01	...	...
Alcohol use, No. of days per month	5.3 (8.2)	5.4 (9.4)	2.9 (5.9)	4.5 (8.0)	0.9	.44	...	...
Beck Depression Inventory score	12.7 (6.4)	10.5 (7.8)	10.0 (5.6)	9.4 (6.9)	2.1	.1	...	...
SCID diagnoses, No. of patients meeting criterion								
Depression	6	10	8	7	...	...	1.4	.71
Dysthymia	1	2	2	1	...	...	0.7	.88
Alcohol	9	9	4	9	...	...	2.6	.46
Global Functioning score	58.6 (5.4)	58.6 (6.1)	58.9 (5.5)	59.5 (6.4)	0.2	.88	...	...

\*Data are given as mean (SD) unless otherwise indicated. BUP indicates buprenorphine hydrochloride; DMI, desipramine hydrochloride; PLA, placebo; MTH, methadone hydrochloride; IV, intravenous; IN, intranasal; SCID, Structured Clinical Interview for DSM-III-R; and ellipses, not applicable.



**Figure 1.** The number of patients retained in this 13-week study is plotted as a function of the week number for each medication group. BUP indicates buprenorphine hydrochloride; DMI, desipramine hydrochloride; PLA, placebo; and MTH, methadone hydrochloride.

interaction occurred ( $z = -2.05$ ,  $P = .04$ ), such that opioid abstinence increased the least rapidly in the buprenorphine plus placebo group.

A sex  $\times$  time  $\times$  opioid medication interaction was observed for cocaine abstinence ( $z = 2.3$ ,  $P = .02$ ), with buprenorphine-maintained men showing greater cocaine abstinence over time than buprenorphine-maintained women relative to methadone-maintained men and women (**Figure 3**). Among men (Figure 3, A and C), cocaine abstinence was increased more rapidly by bu-

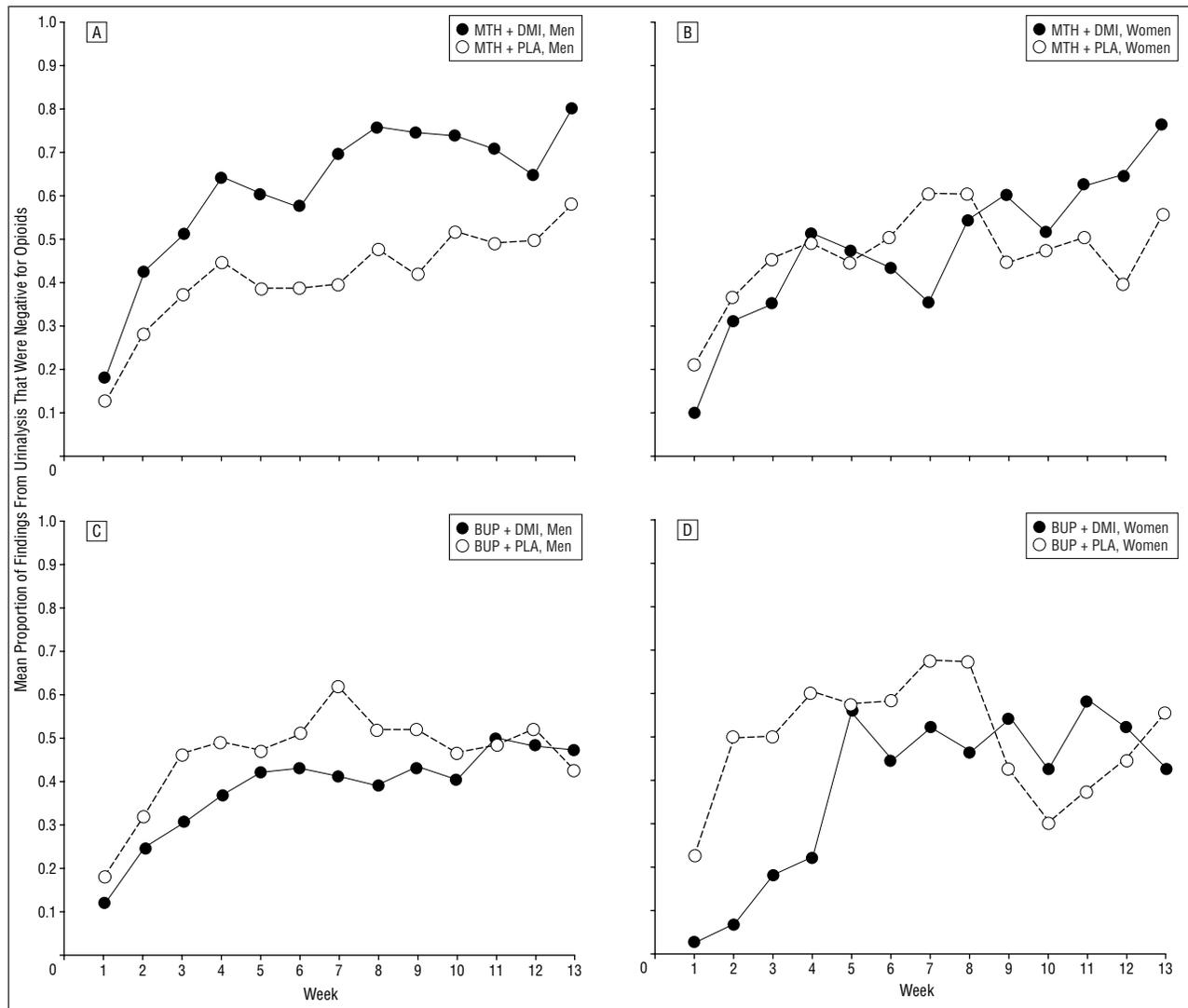
renorphine than by methadone ( $z = -2.2$ ,  $P = .03$ ), and by desipramine than by placebo ( $z = -4.4$ ,  $P = .001$ ). Among women (Figure 3, B and D), cocaine abstinence was increased more rapidly by methadone than by buprenorphine ( $z = 2.2$ ,  $P = .03$ ), and by desipramine than by placebo ( $z = -2.6$ ,  $P = .009$ ).

Patients receiving desipramine appeared to report fewer days of opioid use over time than those receiving placebo ( $z = 1.95$ ,  $P = .05$ ; **Figure 4**), but self-reported cocaine use showed no significant differences by opioid medication ( $z = -0.18$ ,  $P = .85$ ) or desipramine condition ( $z = -1.44$ ,  $P = .15$ ) (Figure 4). Other self-reported measures of cocaine (eg, number of dimes used per week) or heroin use (ie, dollar value used per week) also showed no significant differences. No measure differed by sex across treatment regimens.

Neither depressive symptoms on the Beck Depression Inventory nor opioid withdrawal symptoms differed over time by opioid medication or desipramine.

### DESIPRAMINE PLASMA LEVELS AND SIDE EFFECTS

Desipramine plasma levels were marginally lower in patients treated with buprenorphine (mean  $\pm$  SD,  $413 \pm 332$  nmol/L; range, 56-1448 nmol/L) than in patients treated with methadone ( $551 \pm 261$  nmol/L; range, 0-1140 nmol/L; 2-tailed unpaired  $t_{63} = -1.85$ ,  $P = .07$ ). Desipramine plasma levels were significantly higher in women ( $646 \pm 342$  nmol/L) than in men ( $411 \pm 250$  nmol/L), regardless of the opioid maintenance agent ( $F_{(1,64)} = 11.2$ ,  $P = .001$ ). In addition, the difference in desipramine plasma levels between women and men was significantly greater during the buprenorphine ( $792 \pm 524$  nmol/L vs  $337 \pm 226$  nmol/L) than the methadone maintenance period ( $600 \pm 272$  nmol/L



**Figure 2.** Findings from urinalysis testing for opioids in methadone hydrochloride (MTH)-maintained men (A) and women (B) as well as buprenorphine hydrochloride (BUP)-maintained men (C) and women (D) during the 13-week trial. The mean proportion of urine samples testing negative for opioids are plotted as a function of week for patients in the different medication groups. DMI indicates desipramine hydrochloride; PLA, placebo. The typical sample size for each weekly mean is equal to that retained in treatment, as shown in Figure 1.

vs  $509 \pm 252$  nmol/L;  $F_{(1,64)} = 5.0$ ,  $P = .03$ ). Desipramine plasma levels were higher for those men treated with methadone than those treated with buprenorphine (2-tailed unpaired  $t_{42} = -2.35$ ,  $P = .02$ ), but not higher in women treated with methadone (unpaired  $t_{19} = 1.1$ ,  $P = .29$ ).

Opioid abstinence increased more rapidly in patients with higher desipramine plasma levels, regardless of opioid medication or sex ( $z = -2.11$ ,  $P = .03$ ; **Figure 5**). Desipramine plasma levels did not affect cocaine abstinence.

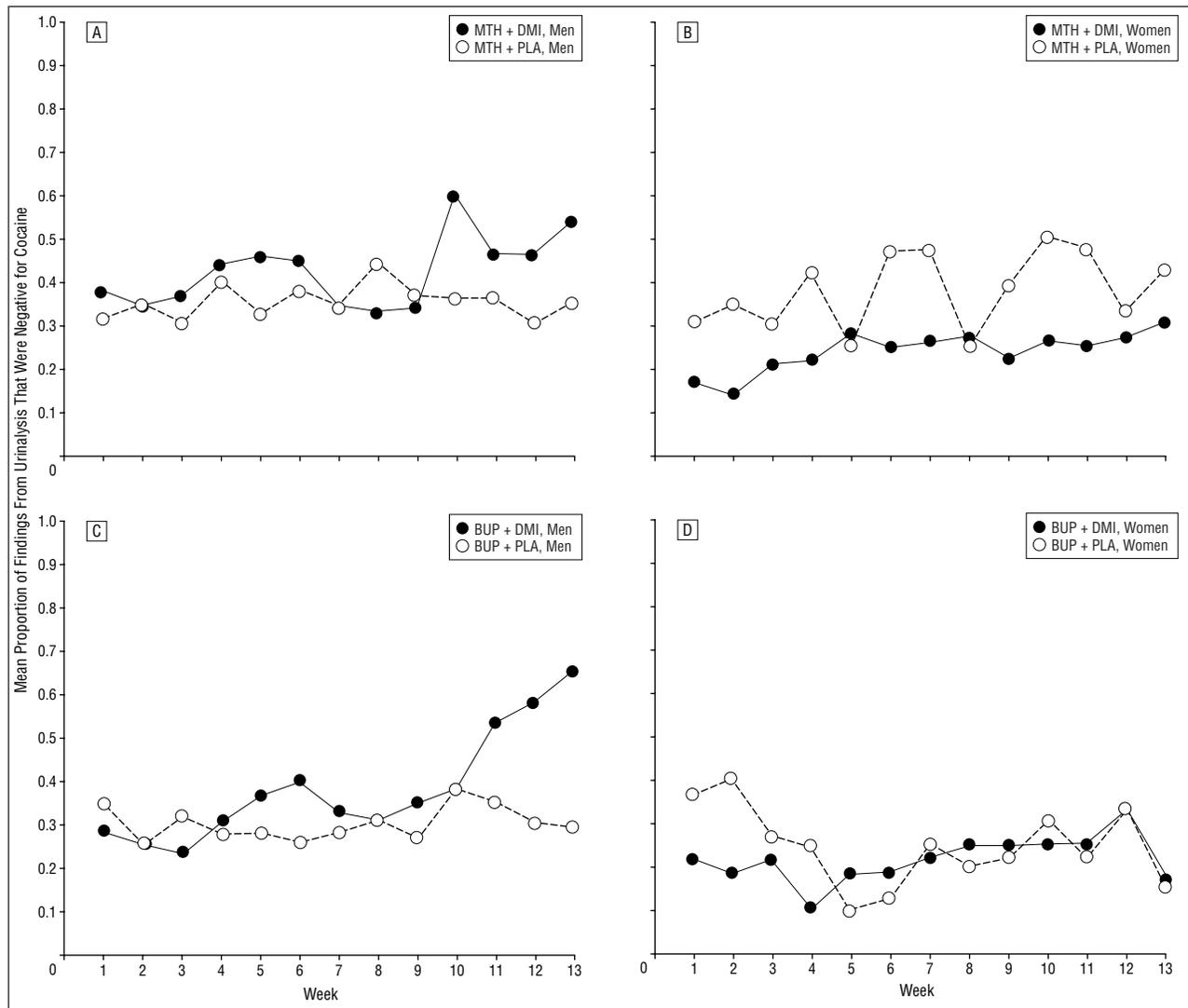
Side effects reported that were possibly owing to desipramine included sweating ( $n = 6$ ), nausea ( $n = 5$ ), dry mouth ( $n = 5$ ), muscle spasm ( $n = 4$ ), and orthostatic hypotension. The desipramine dosage was decreased in 5 individuals owing to desipramine side effects, but 4 still discontinued treatment.

#### COMMENT

This study found sex differences in the facilitation of opioid and cocaine abstinence. Although desipramine

facilitated opioid and cocaine abstinence in men and women to a greater extent than placebo, methadone facilitated opioid abstinence in men to a greater extent than buprenorphine, while buprenorphine plus placebo was the least efficacious in women. Cocaine abstinence was facilitated more by buprenorphine in men but by methadone in women. These differences in urinalysis results owing to desipramine condition mirrored self-reports of heroin use but not of cocaine use. These results did not appear owing to simple attrition or differential counseling attendance, since neither significantly differed among the 4 treatment groups. Desipramine plasma levels were higher in women than in men and also higher in men treated with methadone than with buprenorphine, but not in women. Higher desipramine plasma levels facilitated greater opioid but not cocaine abstinence.

That methadone facilitated greater opioid abstinence than buprenorphine in men and that buprenorphine plus placebo was least efficacious in women is consistent with previous reports that buprenorphine is



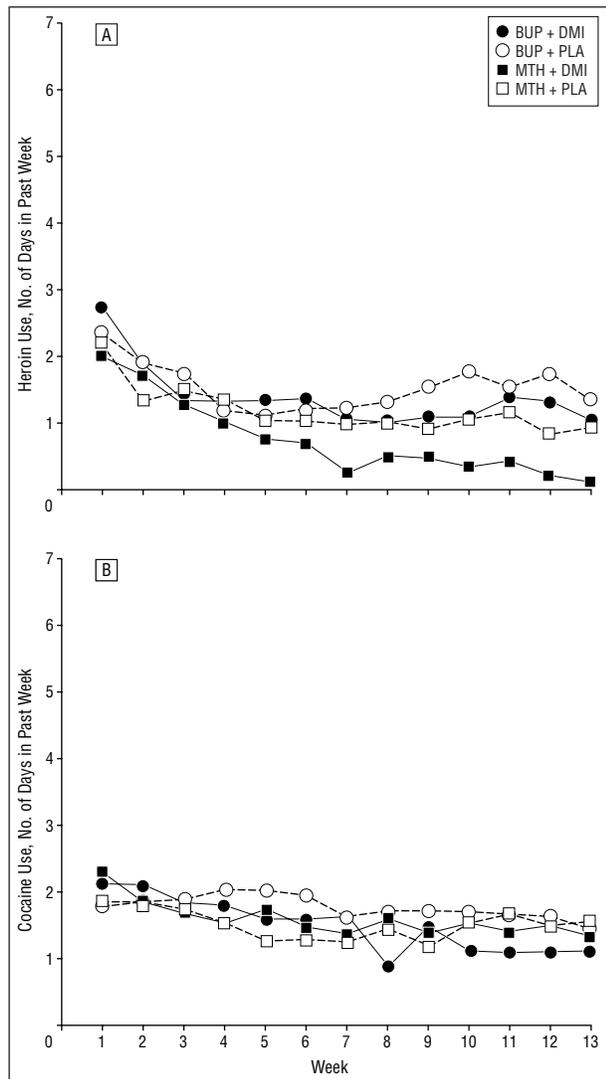
**Figure 3.** Findings from urinalysis testing for cocaine in methadone hydrochloride (MTH)-maintained men (A) and women (B) as well as buprenorphine hydrochloride (BUP)-maintained men (C) and women (D) during the 13-week trial. The mean proportion of urine samples testing negative for cocaine are plotted as a function of week for patients in the different medication groups. DMI indicates desipramine hydrochloride; PLA, placebo. The typical sample size for each weekly mean is equal to that retained in treatment, as shown in Figure 1.

not more effective than methadone in reducing opioid use.<sup>22,24,25,27</sup> Moreover, the findings from women support a previous observation that women showed greater rates of opioid abstinence than men when treated with 4 mg of buprenorphine hydrochloride, but not 12 mg,<sup>37</sup> suggesting that lower buprenorphine doses may be necessary to improve opioid abstinence in women.

That opioid medication had opposite effects on cocaine abstinence in men and women suggests that previous negative findings with buprenorphine on cocaine abstinence may have been obscured by sex differences in treatment response.<sup>24,26,33,34</sup> Although women had higher desipramine plasma levels than men, desipramine plasma levels were not related to cocaine abstinence. Why women had higher desipramine plasma levels than men is unclear, but may be owing to differential metabolism of desipramine or differential compliance with taking desipramine. That methadone-maintained men had higher desipramine plasma levels than buprenorphine-maintained men is consistent with a previous report that

the metabolism of desipramine may be inhibited by methadone.<sup>19</sup> These same complicating factors of sex differences may also have obscured previous results in which desipramine was used in methadone-treated patients.<sup>11</sup> Moreover, the success of desipramine in facilitating greater opioid and cocaine abstinence may be due to the use of more sophisticated analyses examining trends over time in the current study, as opposed to more traditional statistical techniques used in previous studies reporting negative findings.<sup>11,13</sup> In particular, our major differences appear to be delayed until late in the trial when examining the raw urinalysis results (Figures 2 and 3).

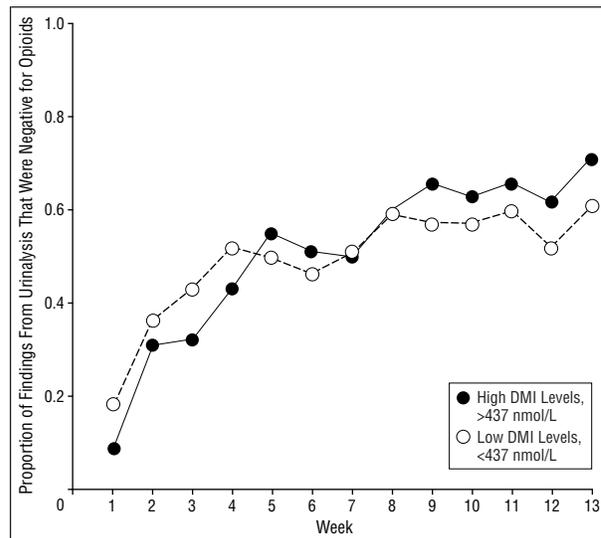
Although desipramine had similar effects on opioid-free urine samples and self-reported heroin use, cocaine toxicology results and self-reported drug use generally did not show similar findings. Both good agreement<sup>52-55</sup> between and poor validity or reliability<sup>56-59</sup> of these assessments have been reported previously. Factors affecting the correlation between urinalyses and self-reports may include treatment status,<sup>60</sup> the type of self-report



**Figure 4.** Self-reported heroin (A) and cocaine (B) use during the 13-week trial. The mean number of days that patients used heroin or cocaine during the previous week of the study are plotted as a function of week for patients in the different medication groups. BUP indicates buprenorphine hydrochloride; DMI, desipramine hydrochloride; PLA, placebo; and MTH, methadone hydrochloride. The typical sample size for each weekly mean is equal to that retained in treatment, as shown in Figure 1.

methods used,<sup>53,61</sup> the population of respondents,<sup>62</sup> the type of urinalyses used,<sup>54,55</sup> and the drug targeted.<sup>54,59</sup> The poor agreement between cocaine urinalyses and self-reports in this study may be owing to the fact that the self-reporting instrument did not assess drug use with a time line. The instrument was completed by the patients themselves immediately prior to receiving medication, when they may have been more focused on receiving the medication. Finally, given that cocaine use was often grounds for treatment dismissal in area clinics, patients may have been predisposed to underreport their use.

The findings that retention and counseling attendance did not differ across treatment groups indicate that methadone and buprenorphine, with or without desipramine, were equally acceptable to patients. These findings are consistent with previous comparisons of metha-



**Figure 5.** Findings from urinalysis testing for opioids in patients treated with desipramine hydrochloride (DMI) during the 13-week trial. The mean proportion of urine samples negative for opioids are collapsed across opioid maintenance medication and plotted as a function of week for patients with high and low desipramine plasma levels.

done and buprenorphine without adjunctive therapy,<sup>27,63</sup> and suggest that adjunctive treatments such as desipramine may generally be tolerated in opioid-maintained patients. Furthermore, only 5% of patients treated with desipramine complained of side effects severe enough to warrant dose reduction, although most of these discontinued desipramine treatment. In addition, although human laboratory findings suggest that cocaine's cardiovascular effects may be enhanced by desipramine,<sup>16,17</sup> no adverse reactions from cocaine use were reported during the study. Thus, desipramine's side effects profile and possible interactions with cocaine minimally limit its acceptance and safety, but close monitoring of patients treated with this agent would be prudent for optimal therapeutic efficacy.

Because at least 20% to 50% of the urine samples still contained opioids or cocaine, more flexible dosing of the opioid medication may assist in optimizing opioid abstinence, as has been demonstrated elsewhere.<sup>27,64,65</sup> Other treatment modalities in addition to pharmacotherapy may also improve efficacy for combined opioid and cocaine dependence, including employing a higher level of counseling intervention<sup>66-68</sup> or applying contingency management procedures whereby incentives are given based on demonstrated drug abstinence.<sup>69-73</sup>

In conclusion, these findings suggest that desipramine plus methadone may optimally facilitate opioid abstinence, while desipramine plus buprenorphine may facilitate cocaine abstinence in men; whereas desipramine plus methadone optimally facilitates both opioid and cocaine abstinence in women. These findings highlight the importance of examining sex differences in these types of trials and suggest that adjunctive medications such as desipramine may enhance treatment outcome. Further research is necessary to determine the reliability of these findings.

Accepted for publication May 25, 1999.

This work was supported in part by US Public Health grants DA05626, K02-DA00112, and P50-DA04060 from the National Institute on Drug Abuse, Rockville, Md.

A preliminary report of this entire work (N = 180) was presented at the 1997 Annual Meeting of the College on Problems of Drug Dependence, Nashville, Tenn, June 14-19, 1997. An interim analysis of this work (n = 141) was published previously. (NIDA Res Monogr. 1996;162:179.)

The authors thank Donald Hedeker, PhD, for his expert statistical advice and Stephanie Heck and Donna Cofrancesco for their assistance with manuscript preparation.

Reprints: Alison Oliveto, PhD, Department of Psychiatry, VA Connecticut Healthcare System, 116A-4, Bldg 36, 950 Campbell Ave, West Haven, CT 06516 (e-mail: [oliveto.alison\\_h@west-haven.va.gov](mailto:oliveto.alison_h@west-haven.va.gov)).

## REFERENCES

- Zweben JE, Payte JT. Methadone maintenance in the treatment of opioid dependence: a current perspective. *West J Med.* 1990;152:588-599.
- Hubbard RL, Allison M, Bray RM, Craddock SG, Rachal JV, Ginzburg, HM. An overview of client characteristics, treatment services, and treatment outcomes for outpatient methadone clinics in the treatment outcome prospective study (TOPS). In: Cooper JR, Altman F, Brown BS, Czechowicz D, eds. *Research on the Treatment of Narcotic Addiction—State of the Art.* Rockville, Md: National Institute on Drug Abuse; 1983:714-747.
- Kaul B, Davidow B. Drug abuse patterns of patients on methadone maintenance treatment in New York City. *Am J Drug Alcohol Abuse.* 1981;8:17-25.
- Kosten TR, Gawin FH, Rounsaville BJ, Kleber H. Cocaine abuse among opioid addicts: demographic and diagnostic factors in treatment. *Am J Drug Alcohol Abuse.* 1986;12:1-16.
- Kosten TR, Rounsaville BJ, Kleber HD. A 2.5-year follow-up of cocaine use among treated opioid addicts. *Arch Gen Psychiatry.* 1987;44:281-284.
- Ball J, Corty E, Bond H, Myers C, Tommasello A. The reduction of intravenous heroin use, non-opiate abuse and crime during methadone maintenance treatment: further findings. *NIDA Res Monogr.* 1988;81:224-230.
- Ball JC, Ross A, Jaffe JH. Cocaine and heroin use by methadone maintenance patients. *NIDA Res Monogr.* 1989;95:328.
- Strug DL, Hunt DE, Goldsmith DS, Lipton DS, Spunt B. Patterns of cocaine use among methadone clients. *Int J Addict.* 1985;20:1163-1175.
- Gawin FH, Ellinwood EH. Cocaine and other stimulants: actions, abuse and treatment. *N Engl J Med.* 1988;318:1173-1182.
- Handelsman L, Chordia PL, Escovar IM, Quesada TP. Amantadine for the treatment of cocaine dependence in methadone-maintained patients [letter]. *Am J Psychiatry.* 1988;145:533.
- Kosten TR, Morgan CM, Falcioni J, Schottenfeld RS. Pharmacotherapy for cocaine-abusing methadone-maintained patients using amantadine or desipramine. *Arch Gen Psychiatry.* 1992;49:894-898.
- Margolin A, Kosten TR, Petrakis I, Avants SK, Kosten TA. Bupropion reduces cocaine abuse in methadone maintained patients [letter]. *Arch Gen Psychiatry.* 1991;48:87.
- Arndt IO, Dorozynsky L, Woody GE, McLellan AT, O'Brien CP. Desipramine treatment of cocaine dependence in methadone-maintained patients. *Arch Gen Psychiatry.* 1992;49:888-893.
- Kosten TR, Steinberg M, Diakogiannis IA. Crossover trial of mazindol for cocaine dependence. *Am J Addict.* 1993;2:161-164.
- Margolin A, Avants SK, Kosten TR, Nickou C. A double-blind study of mazindol for the treatment of cocaine abuse in newly abstinent cocaine abusing methadone-maintained patients: a preliminary report [abstract]. *NIDA Res Monogr.* 1994; 141:446.
- Kosten TR, Gawin FH, Silverman DG, Fleming J, Compton M, Jatlow P, Byck R. Intravenous cocaine challenges during desipramine maintenance. *Neuropsychopharmacology.* 1992;7:169-176.
- Fischman MW, Foltin RW, Nestadt G, Pearlson GD. Effects of desipramine maintenance on cocaine self-administration by humans. *J Pharmacol Exp Ther.* 1990; 253:760-770.
- Ziedonis DM, Kosten TR. Depression as a prognostic factor for pharmacological treatment of cocaine dependence. *Psychopharmacol Bull.* 1991;27:337-343.
- Kosten TR, Gawin FH, Morgan CH, Nelson JC, Jatlow PI. Evidence for altered desipramine disposition in methadone maintained patients treated for cocaine abuse. *Am J Drug Alcohol Abuse.* 1990;16:329-336.
- Resnick RB, Resnick E, Galanter M. Buprenorphine responders: a diagnostic subgroup of heroin addicts? *Prog Neuropsychopharmacol Biol Psychiatry.* 1991; 15:531-538.
- Resnick RB, Galanter M, Pycha C, Cohen A, Grandison P, Flood N. Buprenorphine: an alternative to methadone for heroin dependence treatment. *Psychopharmacol Bull.* 1992;28:109-113.
- Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. *J Nerv Ment Dis.* 1993;181:358-364.
- Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA.* 1992;267:2750-2755.
- 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.
- Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry.* 1996;53:401-407.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Buprenorphine vs methadone in the treatment of opioid-dependent cocaine abusers. *Psychopharmacology.* 1994; 116:401-406.
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Comparison of buprenorphine to methadone in the treatment of opioid dependence. *Am J Psychiatry.* 1994;151: 1025-1030.
- Mello NK, Mendelson JH, Bree MP, Lukas SE. Buprenorphine suppresses cocaine self-administration by rhesus monkeys. *Science.* 1989;245:859-862.
- Mello NK, Lukas SE, Kamien JB, Mendelson JH, Drieze J, Cone EJ. The effects of chronic buprenorphine treatment on cocaine and food self-administration by rhesus monkeys. *J Pharmacol Exp Ther.* 1992;260:1185-1193.
- Kosten TA, Marby DW, Nestler EJ. Cocaine-conditioned place preference is attenuated by chronic buprenorphine treatment. *Life Sci.* 1991;49:201-206.
- Schottenfeld RS, Pakes J, Ziedonis D, Kosten TR. Buprenorphine: dose-related effects on cocaine and opioid use in cocaine-abusing opioid-dependent humans. *Biol Psychiatry.* 1993;34:66-74.
- Kosten TR, Kleber HD, Morgan C. Treatment of cocaine abuse with buprenorphine. *Biol Psychiatry.* 1989;26:637-639.
- Fudala PJ, Jaffe JH, Dax EM, Johnson RE. Use of buprenorphine in the treatment of opioid addiction, II: physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clin Pharmacol Ther.* 1990; 47:525-534.
- Oliveto AH, Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Cocaine use in buprenorphine- vs methadone-maintained cocaine users. *Am J Addict.* 1994;3: 43-48.
- Kosten TA, Gawin FH, Kosten TR, Rounsaville BJ. Gender differences in cocaine use and treatment response. *J Subst Abuse Treat.* 1993;10:63-66.
- Camacho LM, Bartholomew NG, Joe GW, Cloud MA, Simpson DD. Gender, cocaine and treatment HIV risk reduction among injection opioid users in methadone maintenance. *Drug Alcohol Depend.* 1996;41:1-7.
- Schottenfeld RS, Pakes JR, Kosten TR. Prognostic factors in buprenorphine- vs methadone-maintained patients. *J Nerv Ment Dis.* 1998;186:35-43.
- McGlothlin WH, Anglin MD. Long-term follow-up of clients with high- and low-dose methadone programs. *Arch Gen Psychiatry.* 1981;38:1055-1063.
- Hargreaves WA. Methadone dose and duration of treatment. Research on the Treatment of Narcotic Addiction-State of the Art. NIDA, Alcohol, Drug Abuse, and Mental Health Services, Rockville, Md, 1983.
- Dole VP. Methadone treatment and the acquired immunodeficiency syndrome epidemic. *JAMA.* 1989;262:1681-1682.
- Hatziaudreu EJ, Sisk JE, Hughes R. *The Effectiveness of Drug Abuse Treatment: Implications for Controlling AIDS/HIV Infection.* Office of Technology Assessment; September 1990. Series on AIDS-related Issues.
- Spitzer RL, Williams JBW, Gibbons M, First MB. *Structural Clinical Interview for DSM-III-R.* Washington, DC: American Psychiatric Association Press; 1990.
- McLellan AT, Luborsky L, Woody GE, O'Brien CP. An improved diagnostic instrument for substance abuse subjects: the addiction severity index. *J Nerv Ment Dis.* 1980;168:26-33.
- Kosten TR, Rounsaville BJ, Kleber HD. Concurrent validity of the addiction severity index. *J Nerv Ment Dis.* 1983;171:606-610.
- Beck AT, Ward CH, Mendelson M. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;3:461-471.
- Walters, R. *An Abused Drug Assay System.* Reprinted from *American Clinical Products Review*; March 1987.
- Proelss HF, Logman HJ, Miles DG. High performance liquid chromatographic analysis for simultaneous determination of commonly used antidepressants. *Clin Chem.* 1978;24:1948-1953.

48. Bryk AS, Raudenbush SW. Application of hierarchical linear models to assessing change. *Psychopharmacol Bull.* 1987;101:147-158.
49. Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, Shea MT, Imber SD, Sotsky SM, Watkins JT. Some conceptual and statistical issues in analyses of longitudinal psychiatric data. *Arch Gen Psychiatry.* 1993; 50:739-750.
50. Hedeker D, Gibbons RD. MIXOR: a computer program for mixed-effects ordinal probit and logistic regression analysis. *Comput Methods Programs Biomed.* 1996; 49:157-176.
51. Hedeker D, Gibbons RD. A random-effect ordinal regression model for multi-level analysis. *Biometrics.* 1994;50:933-934.
52. Ben-Yehuda N. Are addicts' self-reports to be trusted? *Int J Addict.* 1980;15: 1265-1270.
53. Ehrman RN, Robbins SJ. Reliability and validity of 6-month timeline reports of cocaine and heroin use in a methadone population. *J Consult Clin Psychol.* 1994; 62:843-850.
54. Magura S, Goldsmith D, Casriel C, Goldstein PJ, Lipton DS. The validity of methadone clients' self-reported drug use. *Int J Addict.* 1987;22:727-749.
55. Preston KL, Silverman K, Schuster CR, Cone EJ. Comparison of self-reported drug use with quantitative and qualitative urinalysis for assessment of drug use in treatment studies. *NIDA Res Monogr.* 1997;167:130-145.
56. Lindsay MK, Carmichael S, Peterson H, Risby J, Williams H, Klein L. Correlation between self-reported cocaine use and urine toxicology in an inner-city prenatal population. *J Natl Med Assoc.* 1997;89:57-60.
57. Mieczkowski T, Newel R, Wraight B. Using hair analysis, urinalysis, and self-reports to estimate drug use in a sample of detained juveniles. *Subst Use Misuse.* 1998;33:1547-1567.
58. San L, Torrens M, Tato J, Castillo C, de la Torre R, Arranz B. Monitoring patterns of substance abuse in drug-dependent patients. *J Subst Abuse Treat.* 1998;15: 425-430.
59. Wish ED, Hoffman JA, Nemes S. The validity of self-reports of drug use at treatment admission and at follow-up: comparisons with urinalysis and hair assays. *NIDA Res Monogr.* 1997;167:200-226.
60. Sherman MF, Bigelow GE. Validity of patients' self-reported drug use as a function of treatment status. *Drug Alcohol Depend.* 1992;30:1-11.
61. Ehrman RN, Robbins SJ, Cornish JW. Comparing self-reported cocaine use with repeated urine tests in outpatient cocaine abusers. *Exp Clin Psychopharmacol.* 1997;5:150-156.
62. Magura S, Kang SY. The validity of self-reported cocaine use in two high-risk populations. *NIDA Res Monogr.* 1997;167:227-246.
63. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Buprenorphine versus methadone in the treatment of opioid dependence: self-reports, urinalysis, and addiction severity index. *J Clin Psychopharmacol.* 1996;16:58-67.
64. Bertschy G. Methadone maintenance treatment: an update. *Eur Arch Psychiatry Clin Neurosci.* 1995;245:114-124.
65. Hartel DM, Schoenbaum EE, Selwyn PA, Kline J, Davenny K, Klein RS, Friedland GH. Heroin use during methadone maintenance treatment: the importance of methadone dose and cocaine use. *Am J Public Health.* 1995;85:83-88.
66. McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. *JAMA.* 1993;269:1953-1959.
67. Woody GE, Luborsky L, McLellan AT, O'Brien CP, Beck AT, Blaine J, Herman I, Hole A. Psychotherapy for opiate addicts: does it help? *Arch Gen Psychiatry.* 1983; 40:639-645.
68. Woody GE, McLellan AT, Luborsky L, O'Brien CP. Psychotherapy in community methadone programs: a validation study. *Am J Psychiatry.* 1995;152: 1302-1308.
69. Higgins ST, Budney AJ, Bickel WK. Applying behavioral concepts and principles to the treatment of cocaine dependence. *Drug Alcohol Depend.* 1994;34:87-97.
70. Higgins ST, Budney AJ, Bickel WK, Foerg F, Donham R, Badger G. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Arch Gen Psychiatry.* 1994;51:568-576.
71. Iguchi MY, Stitzer ML, Bigelow GE, Liebson IA. Contingency management in methadone maintenance: effects of reinforcing and aversive consequences on illicit polydrug use. *Drug Alcohol Depend.* 1988;22:1-7.
72. Magura S, Casriel C, Goldsmith DS, Strug DL, Lipton DS. Contingency contracting with polydrug-abusing methadone patients. *Addict Behav.* 1988;13: 113-118.
73. Stitzer M, Iguchi MY, Felch LJ. Contingency take-home incentive: effects on drug use of methadone maintenance patients. *J Consult Clin Psychol.* 1992;60: 927-934.