Heroin Use during Methadone Maintenance Treatment: The Importance of Methadone Dose and Cocaine Use

ABSTRACT

Objectives. The purpose of this study was to examine factors associated with heroin use during methadone maintenance treatment.

Methods. Logistic regression statistical models were used to examine data obtained in a cross-sectional sample of 652 methadone patients.

Results. Heroin use during the 3 months prior to interview was shown to be greatest among (1) patients maintained on methadone dosages of less than 70 mg/day (adjusted odds ratio [OR] = 2.1, 95% confidence interval [CI] = 1.3, 3.4) and (2) patients who used cocaine during treatment (adjusted OR = 5.9, 95% CI = 3.8, 9.1). These results were independent of treatment duration, treatment compliance, alcohol use, and socioeconomic factors. Cocaine users were more likely than nonusers of cocaine to use heroin at all methadone dosage levels.

Conclusions. This study confirms and extends past research showing high-dose methadone maintenance to be important to heroin abstinence. Further investigation of the independent association between heroin use and cocaine use is needed. (*Am J Public Health.* 1995;85:83–88)

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Introduction

There is wide consensus that methadone maintenance treatment reduces drug use and drug injection among opiate addicts.[1–3] While the prescribed dosage level of methadone, an opioid agonist, has long been recognized to be related to reduction of illicit opiate use,[2–7] standards for methadone dosages remain controversial.[8–10] In most treatment settings, the aim of methadone maintenance is to achieve steady opioid receptor coverage so as to prevent abstinence symptoms and reduce opioid craving.[5,6] Opioid blockade (i.e., blocking of the euphoric effects of other opiates[4]) occurs with relatively high dosages of methadone and is the theoretical basis for the 60- to 80-mg/day dosage recommendation of the National Institute on Drug Abuse (NIDA).[1,8] Despite this recommendation, most methadone patients are maintained on dosages well below 60 mg/day.[8,9]

Empirical evidence for high-dose methadone maintenance treatment remains incomplete. Most dosage studies have been short-term clinical trials that have randomized patients to two or three dosage levels only.[7] Observed dose–response data and other information of practical clinical relevance remain scant. Furthermore, few studies have used dosages within the NIDA recommendation. For example, the highest dosage assignment in a recent 13-week trial was 50 mg/day,[11] and more than 50% of subjects in that group had opiate-positive urine samples. This degree of opiate use suggests suboptimal dosage assignment.

Dosage data from clinic-based observational studies have also been incomplete. A large-scale survey of geographically diverse methadone programs[2,12,13] showed heroin use to be lowest among patients on 60 or more mg/day of methadone, but the dose–response analysis did not take into account treatment duration and dosage compliance. An association between high-dose methadone and reduction in heroin use is supported by an Australian observational study[14] conducted over a 2-year period. However, this study may be limited by its small sample size (n = 62).

The use of cocaine and its relationship to opiate use during methadone treatment have not been explored despite the long-standing epidemic of cocaine use among methadone patients.[15] While some investigators show reductions in cocaine use after entry into methadone treatment,[15–17] there are also reports of increases in cocaine use during treatment,[15,17,18] with a strong correlation between heroin and cocaine use.[18] All of these studies have been limited by a failure to examine the level of methadone dose in relation to opiate use for users and nonusers of cocaine. Since methadone is not a pharmacologically specific treatment for cocaine or other stimulant drugs,

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TABLE 1—Subjects' Heroin Use: Its Association with Methadone Dose

Methadone Dose, mg/d	Use of Heroin, % (No.)	Odds Ratio	95% Confidence Interval
<40	32.2 (146)	2.1	1.3, 3.5
40–49	33.0 (115)	2.2	1.3, 3.7
50–59	35.2 (105)	2.4	1.4, 4.1
60–69	30.1 (103)	1.9	1.1, 3.3
70+	18.6 (183)	1.0	Reference

a direct association between methadone dose and cocaine use would not be expected. However, opiate-addicted cocaine users may increase heroin use to counter cocaine dysphoria.[19] While evidence is sparse, it is possible that neurochemical and/or metabolic pathways are involved in the biological attenuation of methadone effects due to cocaine. A recent study reported that cocaine administered during heroin euphoria precipitates the subjective perception of opiate withdrawal symptoms.[20]

In this paper, we examine whether heroin use during methadone maintenance treatment is more likely to occur among (1) patients maintained on methadone dosages under the NIDA recommendation in comparison with those on higher dosages and (2) patients who use cocaine during methadone treatment in comparison with nonusers.

Methods

The sample comprised patients enrolled in the Montefiore Methadone Maintenance Treatment Program, located in the Bronx, New York City. Of 1560 patients enrolled in the program between June 1985 and January 1989, 700 agreed to participate in a human immunodeficiency virus (HIV) seroprevalence and risk factor study.[21] Data were obtained (1) in interviews regarding the use of heroin and cocaine, other psychoactive drug use including alcohol, drug treatment history, and sociodemographic information and (2) through clinic records of prescribed methadone dosages and results of urine toxicology testing. The interviewers were not part of the clinic staff; they were trained to carefully explain the confidentiality of HIV study data. For this analysis, a minimum of 3 months in treatment was required. Both interview drug use data and urine toxicology data were used to classify drug use over the 3 months prior to the interview. Forty-eight people were excluded as a result of either insufficient time in treatment or insufficient drug use data.

Sample Characteristics

Among the 652 methadone patients included in this analysis, 51% had been in treatment 5 or more years, and 44% had been maintained at or above the NIDA minimum recommended dose of 60 or more mg/day. The sample contained nearly equal numbers of male and female patients (47% female). The median age at time of interview was 34 years. Twenty-four percent of patients described themselves as African American; 25%, as White; and 51%, as Hispanic. The population was one of low socioeconomic status: 68% had an income under $10 000, 53% did not have a high school diploma, 62% were unemployed, and 18% were homeless during the year prior to the interview. Seventy-eight percent were married (including common-law marriages), and 58% had dependents living in the same home.

We compared the sociodemographic and drug treatment characteristics of the sample with the remainder of the clinic patients present at the time of study enrollment (n = 1560). In comparison with the rest of the clinic patients, the study sample had a statistically significant ($P < .05$) higher average dose of methadone (64 mg/day vs 59 mg/day) and a greater proportion enrolling in treatment before 1982 (36% vs 31%). No other variables, including age, race, gender, education, income, and drug use, differed between the two groups.

Methadone Dose and Urine Toxicology Data

Methadone dose was calculated as a time-weighted average of dosages after initial stabilization. Typically, dosages were prescribed in 5- to 10-mg increments over a 6- to 8-week period until maintenance levels were achieved. In this sample, average dosages ranged from 20 mg/day to 100 mg/day. The dosage distribution was relatively uniform (no group involving less than 15% of the sample), except for the highest dosages (13% at 70 to 79, 8% at 80 to 89, and 6% at 90 to 100 mg/day). Change in dosage once maintenance levels were achieved was minimal.

Patients were required to submit urine samples on randomly selected days. The primary metabolites of heroin (morphine) and cocaine (benzoylecgonine) were tested by thin layer chromatography and by the enzyme-multiplied immunoassay technique. Urine test results were restricted to the five most recent tests prior to interview. In addition, results of urine toxicology tests for the presence of methadone in urine were available as an indicator of methadone compliance.

Statistical Methods

For all categorical data analyses, odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated; statistical significance was based on two-tailed Mantel-Haenszel chi-square tests. Maximum likelihood logistic regression analyses[22] were used to assess the associations between methadone dose, cocaine use, and heroin use during treatment. Analyses adjusted for all variables associated with heroin use at $P < .10$ based on maximum likelihood statistics (Wald tests) as a criterion for variable retention. Variables used in the analyses are listed in the Appendix.

Results

Of the 652 study participants, 140 (21.5%) reported heroin use during the 3 months prior to the interview. Forty-six of the 512 patients (9%) reporting no heroin use had at least one positive urine test. In total, 186 of 652 methadone patients (28.5%) were classified as heroin users during the observation period of this study. Of the 652 study participants, 294 (45.1%) reported cocaine use during the 3 months prior to interview. Forty-three of the 358 (12%) reporting no cocaine use had cocaine-positive urines. In total, 337 of 652 (51.7%) individuals were classified as cocaine users.

The expected association between heroin use during treatment and methadone dose was confirmed in these data; that is, the odds of heroin use for patients maintained on lower dosages of methadone were higher. In our data, patients on

dosages under 70 mg/day had higher levels of heroin use than did those on dosages of 70 mg/day or above (Table 1). In comparison with methadone dosages of 70 or more mg/day, odds ratios for lower dosages were on the order of 2.0, with little variation for each dosage level.

While heroin use was lowest for patients with the greatest durations of time in treatment, the association between methadone dose and heroin use was independent of time in treatment. Heroin was used by 51.6% (83/161) of patients in treatment for less than 1 year. For those in treatment from 1 to 2 years, the overall percentage using heroin was 41.7% (25/60). In contrast, only 17.9% (77/431) of patients in treatment for more than 2 years used heroin. The association between heroin use and methadone dose was examined separately for those in treatment 2 years or less and for those in treatment more than 2 years. Higher odds of heroin use for methadone dosages under 70 mg/day relative to higher dosages (Table 2) were found (odds ratios of 2.3 and 1.9, respectively).

TABLE 2—Heroin Use and Methadone Dose Stratified by Time in Treatment

Treatment Time and Methadone Dose, mg/d	Use of Heroin, % (No.)	Odds Ratio[a]	95% Confidence Interval
≤2 years in treatment			
<70	51.4 (179)	2.3	1.1, 4.6
≥70	38.1 (42)	1.0	Reference
>2 years in treatment			
<70	20.7 (290)	1.9	1.1, 3.5
≥70	12.1 (141)	1.0	Reference

[a]The common odds ratio (Mantel-Haenszel) was 2.1 (95% CI = 1.3, 3.2).

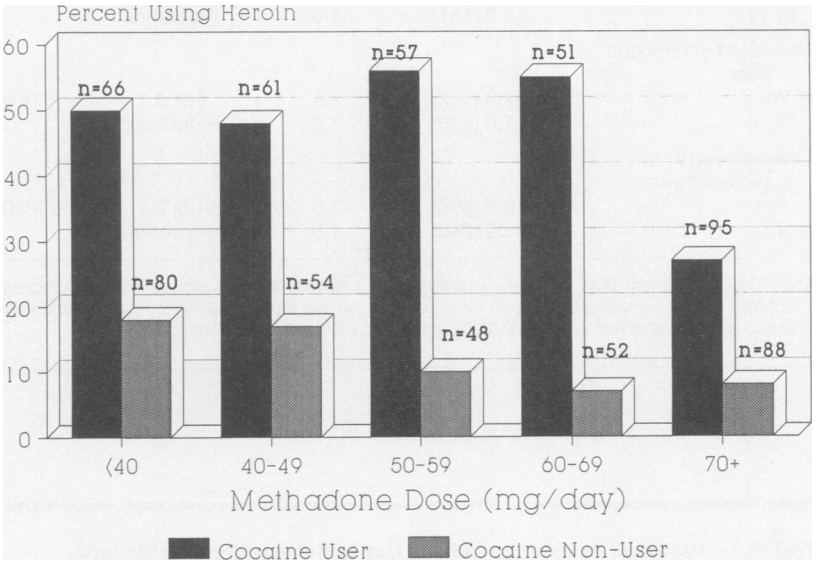

FIGURE 1—Heroin use among cocaine users and nonusers, by methadone dose.

Heroin and Cocaine Use during Treatment

Heroin use during treatment was associated with cocaine use. Of the 337 individuals who used cocaine during the observation period, 148 (43.9%) also used heroin. In contrast, only 38 of 315 (11.8%) nonusers of cocaine used heroin during treatment (OR = 6.1, 95% CI = 4.1, 9.1). This association was independent of methadone dose. Odds ratios for the associations between cocaine use and continued heroin use were 5.1 and 4.4 in the low methadone dose and high methadone dose groups, respectively. The dose-adjusted overall odds ratio (Mantel-Haenszel) was 4.9 (95% CI = 3.4, 7.2); there was no evidence of odds ratio heterogeneity (Breslow-Day test, $P = .09$). In comparison with nonusers of cocaine, cocaine users had a consistently higher degree of heroin use at each dosage level (Figure 1).

Variables Associated with Cocaine Use

Drug use, drug treatment, and sociodemographic variables that could have explained or modified the above associations between methadone dose, cocaine use, and heroin use were examined in logistic regression models. Cocaine use within 3 months of the interview was examined as an endpoint in intermediate analyses before variables associated with heroin use were modeled. Variables independently associated with cocaine use included years in methadone treatment, age at first cocaine or heroin use, race/ethnicity, educational level, homelessness in the previous year, and unemployment in the previous year (Table 3). As expected, methadone dose was not statistically associated with cocaine use. Daily alcohol use, reported by 20% of patients, was not statistically associated with cocaine use either in single variable analysis or in logistic regression. Alcohol use is of theoretical importance since cocaine users are known to use alcohol to counter cocaine dysphoria; alcohol and alcohol-associated liver conditions are known to affect methadone metabolism.[23,24]

Variables Associated with Heroin Use

Logistic regression was used to estimate independent associations of heroin use with methadone dose, duration of treatment, and cocaine use during treatment (Table 4). Methadone dose (<70 mg/day) remained independently associated with heroin use during treatment (adjusted OR = 2.1, 95% CI = 1.3, 3.4) after adjustment for time in treatment and other variables. The adjusted odds ratio for the association between heroin use and cocaine use was 5.9 (95% CI = 3.8, 9.1). The interaction between methadone dose and cocaine use was tested in the model but was not statistically significant ($P = .28$). Other variables independently associated with heroin use during methadone treatment included years in treatment, any prior history of methadone treatment dropout, and methadone noncompliance (indexed by lack of methadone in urine). No sociodemographic variables were retained except for home-

TABLE 3—Variables Associated with the Use of Cocaine during Methadone Treatment

	Use of Cocaine, % (No.)	Odds Ratio	95% Confidence Interval	P
Time in treatment, y				
≤2	60.1 (221)	2.1	1.5, 3.0	.000
>2	43.4 (431)	1.0	Reference	
Age at first injection, y				
≤15	64.7 (116)	2.1	1.3, 3.2	.001
>15	47.6 (536)	1.0	Reference	
Race/ethnicity				
African American	60.4 (159)	2.9	1.8, 4.7	.000
Latino	53.8 (325)	1.9	1.3, 2.9	.002
White	35.2 (168)	1.0	Reference	
Education, y				
≤12	53.7 (521)	1.6	1.0, 2.4	.035
>12	38.2 (131)	1.0	Reference	
Homeless in previous year				
Yes	67.9 (112)	2.1	1.2, 3.1	.004
No	47.0 (540)	1.0	Reference	
Unemployed in previous year				
Yes	56.2 (396)	1.5	1.0, 2.1	.030
No	41.5 (246)	1.0	Reference	

Note. Odds ratios and 95% confidence intervals were derived from maximum likelihood logistic regression and were adjusted for all other variables in the table. Classification of the endpoint based on the model was as follows: 68.3% concordant, 28.1% discordant (c = .70).

TABLE 4—Variables Associated with the Use of Heroin during Methadone Treatment

	Use of Heroin, % (No.)	Odds Ratio	95% Confidence Interval	P
Methadone dose, mg/d				
<70	32.6 (469)	2.1	1.3, 3.4	.002
≥70	18.0 (183)	1.0	Reference	
Methadone in urine				
Not detected	50.0 (24)	4.6	1.7, 12.0	.002
Detected	27.7 (628)	1.0	Reference	
Time in treatment, y				
≤ 2	48.9 (221)	3.2	2.2, 4.9	.000
>2	18.1 (431)	1.0	Reference	
History of prior treatment dropout				
Yes	38.3 (214)	1.7	1.1, 1.9	.013
No	23.7 (438)	1.0	Reference	
Cocaine use 3 mo prior to interview				
Yes	44.8 (330)	5.9	3.8, 9.1	.000
No	11.8 (322)	1.0	Reference	
Homeless in previous year				
Yes	44.6 (112)	1.6	1.0, 2.6	.052
No	25.2 (540)	1.0	Reference	

Note. Odds ratios and 95% confidence intervals were derived from maximum likelihood logistic regression and were adjusted for all other variables in the table. Classification of the endpoint based on the model was as follows: 79.5% concordant, 20.1% discordant (c = .80).

lessness in the previous year, which showed borderline statistical significance ($P = .05$). The model was not modified when cocaine users were classified as predominantly speedball (heroin–cocaine admixture) users vs other types of cocaine users.

Discussion

In our study, patients maintained on methadone dosages of less than 70 mg/day had a 2.1 odds of using heroin during methadone maintenance treatment in comparison with patients maintained on 70 or more mg/day after adjustment for duration of treatment, treatment compliance, and other factors. The magnitude of this association is consistent with that of a recent small-scale study of methadone dose and heroin use.[14] A high degree of occupation of opioid receptors by methadone is known to block the euphoric effects of opiates and is probably a central mechanism in reduction of illicit opiate use.[6] On the basis of early methadone studies,[4–6] the 70-mg/day dose threshold observed in our data is consistent with the occurrence of opioid blockade in most patients, although a few patients may require much higher dosages to achieve blockade.[25] It is important to note the overall low level of heroin use in our clinic sample (28.5%), with only 18% heroin use among patients on 70 or more mg/day. The overall success of this clinic probably stems from the use of methadone dosages that are relatively high in comparison with those of many other clinics.[8,9]

Given the likelihood of opioid blockade among most high-dose patients in this study, the finding of a strong association between cocaine and heroin use even at high dosages is difficult to explain. For low-dose patients, the use of heroin as an antidote to acute dysphoria after cocaine use has been discontinued is plausible. However, this explanation should not hold for patients maintained on blockade dosages, since there would be no expected psychoactive effect of heroin. Greater accessibility to heroin among cocaine users relative to nonusers of cocaine is an unlikely explanation for the findings in high-dose patients. Simple behavioral explanations are difficult to accept since the economic, social, and medical (addiction-related) conditions of an opiate addict's life mitigate against use of a costly, illicit substance that has little psychoactive effect.

It is possible that cocaine-using high-dose methadone patients do not experi-

ence opioid craving and blockade in the same manner as nonusers of cocaine. Although speculative, there are three primary areas of action that may account for the high level of heroin use among cocaine users despite maintenance on high-dose methadone: (1) cocaine use may exacerbate opioid abstinence symptoms and/or craving and alter opioid blockade threshold through neurochemical mechanisms; (2) cocaine use may induce stress-mimetic changes that alter adrenal–pituitary control of the opioid receptor–ligand system; and (3) cocaine use may be associated with a high rate of hepatic metabolism of methadone.

The most direct evidence of stimulant–opioid interaction comes from a recent study showing that administration of cocaine during opioid euphoria precipitates early withdrawal symptoms among heroin addicts.[20] This finding is consistent with the claim of methadone patients that cocaine counters methadone effects.[26] Although the primary euphorigenic effects of stimulants such as cocaine and of opiates such as heroin are neurochemically distinct, there are common links in dopaminergic, serotoninergic, and α-2-adrenergic reward pathways.[27,28] One site of action may be the locus ceruleus related to panic and anxiety reactions. Another possible pathway for which there is some evidence is that of cocaine-induced depletion of serotonin. In both animal and human studies, attenuation of the effects of exogenous opioids has been associated with depletion of serotonin (e.g., because of lesions of the raphe nuclei).[29] It is also possible that cocaine exerts an influence on the opioid receptor system itself. Although the mechanism of action is not well established, a recent animal study showed an increase in opioid receptors due to chronic administration of cocaine.[30] Hypothetically, a greater supply of ligand would be required for receptor coverage after cocaine administration.

Another potential mechanism for use of heroin among opioid-dependent cocaine users may be rooted in the common complaint of patients that "methadone does not hold" in response to acute stressors.[31] The heaviest cocaine users are known to have an erratic and extremely stress-filled life-style characterized by periods of sleep deprivation during cocaine binges that may last several days followed by periods of deep depression.[19,32] Changes in pituitary–adrenal metabolism appear to induce an acute dysphoric reaction similar to opioid abstinence syndrome among opioid-dependent individuals.[31] While there is no evidence of impaired adrenal function due to methadone itself,[33,34] it is possible that stress reactions alter the thresholds at which opiate abstinence symptoms, craving, and blockade occur. In this study, several markers of social disadvantage and, by inference, greater exposure to stressors were found to be related to cocaine use: low income (< $10 000 per year), low educational attainment, homelessness, unemployment, and self-identification with a racial or ethnic minority group. Of these, homelessness was independently associated with continued heroin use during treatment; however, our study design was inadequate to address the interrelationship of cocaine use, stress, and methadone metabolism.

A third possible explanation may be that differences in methadone metabolism and, thus, opioid receptor coverage exist between cocaine users and nonusers. There is no evidence of a direct effect of cocaine on methadone metabolism; however, without direct measurement of methadone clearance, one cannot rule out differences in metabolism between users and nonusers.[35] Agents known or strongly suspected to accelerate hepatic metabolism and thus decrease the bioavailability of methadone include rifampin and phenytoin.[23] Alcohol use has been associated with both increased and decreased plasma methadone levels.[23,24] These agents have the potential to confound the association between cocaine and heroin use. There was no indication of the use of either rifampin or phenytoin among patients in the sample at the time of study. In our analysis, heavy alcohol intake was not associated with cocaine use or with heroin use.

In addition to the analyses described above, we conducted a methodological substudy of the impact of treatment dropout patterns on the sample chosen for study. This substudy (reported elsewhere[36]) found that while there was a faster rate of dropout for patients on low-dose methadone, selection due to dropout was not sufficient to seriously bias the findings of the study. The estimated odds ratio for the association between methadone dose and heroin use without differential dropout was 2.7, in comparison with the observed odds ratio of 2.1. Examination of sampling factors related to cocaine use and heroin use showed negligible bias in this effect measure.

Conclusions

These data strongly support the use of high-dose methadone maintenance treatment to control illicit opioid (heroin) use whether or not patients also use cocaine. As in other studies,[4,7,11,12,14] high-dose methadone appears to be a critical factor in cessation of heroin use. The strong, independent association between cocaine use and continued use of heroin during methadone treatment has not been reported previously and requires further study. The full distribution of dose-associated opioid withdrawal, craving, and blockade phenomena and modifying factors should be examined prospectively in conjunction with methadone plasma levels.[35] Patients in methadone treatment have long maintained that cocaine "eats up the methadone"[26]; whether this is simply a perception without neurological, metabolic, or other meaningful biologic mechanisms, however, remains to be determined. □

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APPENDIX—Candidate Variables for Statistical Models

Drug use and treatment variables
- Year of first treatment entry
- Years in treatment (cumulative)
- Age at first use of heroin
- Age at first use of cocaine
- No methadone in urine
- History of dropout from treatment (hiatus of 1 or more months)
- Daily alcohol use
- Counselor assignment

Sociodemographic variables
- Homeless 1 or more months in prior year
- Unemployed 1 or more months in prior year
- Years of education
- Income ($0–$10 000, $10 000–$20 000, > $20 000)
- Race/ethnicity (Black, Hispanic, White)
- Gender
- Age