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High Methadone Dose Significantly Reduces Cocaine Use in Methadone Maintenance Treatment (MMT) Patients

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ABSTRACT. Aim: To evaluate whether effective methadone treatment affects cocaine use.

Methods: Four hundred twenty-one consecutive patients admitted to a methadone maintenance clinic in Israel (1993-2002) were prospectively studied. Patients' urine samples were analyzed for cocaine during months 1 and 13.

Results: On admission 55(13.1%) of 421 patients had urine positive for cocaine and 366 had negative. Of the 55 cocaine-positive patients, 45(81.8%) stayed in treatment at least one year, as did 267(73%) cocaine-negative. After one year (n = 312) 31 of 45 cocaine users stopped and 25 of 267 started. Methadone dose was highest in 31 patients who stopped cocaine (176.1 ± 42.1 mg/day), followed by 14 who did not stop (161.4 ± 37.5 mg/day), and 25 who started during treatment (122.9 ± 48.7 mg/day), or 242 who never used cocaine (119.5 ± 48.4 mg/day) (ANOVA, $F = 15.6$, $p < 0.0005$).

Conclusions: High methadone dose may reduce cocaine use in patients addicted to both heroin and cocaine.

KEYWORDS. Methadone maintenance treatment, cocaine, heroin, addiction

INTRODUCTION

Methadone maintenance treatment (MMT) is the most effective pharmacotherapy for heroin addiction.[1,2] Good MMT programs include psychosocial as well as medical therapy, and the importance of these to therapeutic success is well established.[3]

In addition to the well-documented heroin abuse reduction during MMT, there are reports describing cocaine abuse reduction in the MMT clinics.[4-9] The reduction in cocaine abuse

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was mostly attributed to the psychosocial services.[4-6,8-9] However, laboratory, as well as human, studies that have been reported recently suggest that methadone itself may have a direct impact on cocaine abuse reduction.[7,10-14]

The current study evaluates whether treatment with methadone (a mu opioid agonist) might have an effect on cocaine use in MMT patients, and whether this effect is dose-dependent.

METHODS

Study Population

We prospectively studied 421 patients meeting criteria similar to U.S. Federal Regulations for entering into methadone treatment (i.e., meeting DSM-IV criteria of dependence plus multiple daily self-administrations of heroin for one year or more) who were admitted to a Methadone Maintenance Treatment Clinic in Tel-Aviv, Israel, between July 1993 and April 2002; of these, 312 (or 74.1%) stayed in treatment for one year or more. The characterization and effectiveness of the clinic have been previously reported.[15]

URINE TOXICOLOGY AND METHADONE

Patients in treatment underwent at least one random observed urine test per week (range 1-11 per month, mean equals 4 samples per month, i.e., 1 sample per week) for the entire length of their treatment (range 1 day-9.6 years), with 312 patients staying for one year or more. All patients' urines were analyzed for the cocaine metabolite benzoylecgonine (as well as opiates, benzodiazepines, THC, amphetamines and methadone) using the EMIT method.[16] Methadone dose was recorded daily, and the doses administered in the beginning of month 13 were recorded for use in data analyses in this study. Admission drug use was defined as "positive" if at least one positive urine for the drug (cocaine) was found in the first month in treatment. At completion of one year of treatment, patients were again defined as "positive" for cocaine use if the patient had at least one positive urine screen for cocaine in month 13.

Statistical Analyses

The changes in number of patients with positive urine toxicology reports on admission and after one year of treatment were evaluated. Proportional differences between groups were analyzed by Chi Square or Fisher's Exact Test. Methadone dose and other continuous variables were analyzed for significant differences using analyses of variance (ANOVA) and analyses of variance with covariance (ANCOVA). Analyses were done using SPSS-11.

RESULTS

Cocaine Use and One Year Retention

The mean age of our patients was 36.6 ± 8 years (range 18-64); 73.4% were male and 26.6% female. Mean years of opiate abuse before admission to MMT was 13.4 ± 7.9 years, range 1-37 (unknown in 17(4%) patients). Mean years of education of our patients was 9.8 ± 2.9 years, range 0-19 (unknown in 37 (8.8%) patients). A total of 275 (65.2%) were born in Israel, and 146 (34.8%) were immigrant, mostly from Russia (n = 85) but also from other parts of Europe (n = 12), Canada (n = 1), South America (n = 1), Asia (n = 15), Africa (n = 17), west bank and Palestinian authority (n = 13) and unknown if Europe or America (n = 2). A total of 268 (63.7%) had one or more children when admitted to MMT. Of our 421 patients, 39 stayed in treatment 3 months or less, and 70 patients stayed more than 3 months but less than one year. Thus the one-year retention in treatment was 74.1% (312 out of 421).

On admission, 13.1% of patients (n = 55) used cocaine, while 366 did not. Forty-five of the 55 cocaine patients stayed in MMT for at least one year (of those who left, 5 left after and 5 before 3 months) (Table 1). Of 366 patients who did not use cocaine on admission, 267 stayed in MMT for at least one year (of those who left, 65 left after and 34 before 3 months) (Table 2).

TABLE 1. Patients with cocaine use on admission: Cocaine in last month of treatment

Time in Treatment	Total n (%)	Yes n (%)	No n (%)	Unknown n (%)
Overall	55 (100)	20 (36.4)	32 (58.2)	3 (5.5)
Left treatment ≤ 3 m	5 (100)	1 (20)	1 (20)	3 (60)
Left treatment > 3 m < 1 y	5 (100)	5 (100)	0	-
Retention ≥ 1 year*	45 (100)	14 (31.1)	31 (68.9)	-

*Cocaine at month 13

TABLE 2. Patients with no cocaine use on admission: Cocaine in last month of treatment

Time in Treatment	Total n (%)	Yes n (%)	No n (%)	Unknown n (%)
Overall	366 (100)	34 (9.3)	303 (82.8)	29 (7.9)
Left treatment ≤ 3 m	34 (100)	1 (2.9)	10 (29.4)	23 (67.6)
Left treatment > 3 m < 1 y	65 (100)	8 (12.3)	51 (78.5)	6 (9.2)
Retention ≥ 1 year*	267 (100)	25 (9.4)	242 (90.6)	-

*Cocaine at month 13

When comparing one-year retention rates of patients who used cocaine in the first month of treatment to those who did not, we found that the one-year retention rate among 55 patients who used cocaine in the first month of treatment was 81.8%, which was not significantly different when compared to the 366 patients who did not use cocaine in the first month of treatment and had a one-year retention rate of 73.0% (267/366) (Fisher's Exact Test p = 0.2) (Table 3).

Of these 45 patients who stayed at least one year, 31 patients (68.9%) stopped abusing cocaine (no cocaine in 13-month urine) (Table 4). Of the 366 non-cocaine patients, 267 stayed in MMT after one year, and 25 of these patients (9.4%) were found to have a cocaine-positive urine toxicology report at month 13.

After one year in treatment, 63.8% (199 of the 312 patients who stayed one year) stopped using opiates as reflected by opiate-free toxicology reports in urine in the 13th month of treatment. We divided the 312 patients who stayed in treatment at least one year into four groups based on their cocaine use. These were

TABLE 3. Age, gender, urine benzodiazepines on admission, and among cocaine abusers/non-abusers on admission

	Admission cocaine abuse N = 55	No admission cocaine abuse N = 366	Fisher's Exact Test	P*
Age (years)	36.5 ± 8.0	37.0 ± 8.1	**F = 0.2	0.7
1 year Retention	81.8%	73.0%		0.2
Sex				0.003
Male	56.4%	76.0%		
Female	43.6%	24.0%		
Benzodiazepines on admission				0.002
Positive	74.5%	52.7%		
Negative	25.5%	47.3%		

*p = two sides significance, **ANOVA

TABLE 4. Proportions of patients who started or stopped cocaine use

Time in Treatment	Started	Stopped
Overall	9.3% (34/366)	58.2% (32/55)
Only subjects with retention ≥ 1 year*	9.4% (25/267)	68.9% (31/45)

*Cocaine at month 13

patients who (a) ceased use while in treatment ("Stopped") (n = 31), (b) continued to use while in treatment ("Always") (n = 14), (c) were cocaine-free in the first month but were positive at month 13 ("Started") (n = 25), or (d) were cocaine-negative at both time points ("Never") (n = 242). Comparisons between groups are presented in Table 5. The groups differed significantly in opiate use rates after one year, with the lowest proportion of illicit opiate abuse in group (a) those who stopped cocaine (19.4%) followed by group (d) those who never used cocaine (33.5%), while those who always used (b) and those who started (c) had the highest proportion of opiate use (64.3% and 68%, respectively) (Chi Square = 19.9, $p < 0.0005$). Patients who stopped cocaine use had the significantly highest proportion of females; 51.6% as compared to 28.6% in the "Always" group, 36% in the "Started" group and 24% in the "Never" group (Chi Square 10.4, $p = 0.02$). Groups also differed significantly in age of admission

TABLE 5. One year retention year patients only: Differences between groups of cocaine users after one year

	Cocaine use continued from admission (b)	Stopped using cocaine (a)	Cocaine use started during treatment (c)	Never used cocaine (d)	Chi Square	*p
	N = 14	N = 31	N = 25	N = 242		
Age (y)	39.9 ± 5.0	36.2 ± 8.9	33.1 ± 7.7	37.4 ± 7.9	**F = 3	0.03
Opiate abuse (y)	19.5 ± 6	13.8 ± 8	11.3 ± 9.2	13.4 ± 8	**F = 3	0.03
Sex					10.4	0.02
Male	71.4%	48.4%	64.0%	76.0%		
Female	28.6%	51.6%	36.0%	24.0%		
Illicit opiates used during 13th month					19.9	< 0.0005
Positive	64.3%	19.4%	68.0%	33.5%		
Negative	35.7%	80.6%	32.0%	66.5%		
Illicit benzodiazepines used during 13th month					6.4	0.09
Positive	56.4%	74.5%	56.4%	52.7%		
Negative	43.6%	25.5%	43.6%	47.3%		
One year						
Methadone dose (mg/day)	161.4 ± 37.5	176.1 ± 42.1	122.9 ± 48.7	119.5 ± 48.4	**F = 15.6	< 0.0005

*p = two sides significance, **ANOVA

(ANOVA F = 3, $p = 0.03$) and in duration of continued illicit opiate abuse since admission to MMT (ANOVA F = 3, $p = 0.03$) (see Table 5).

In the "good outcome" group, those who stopped plus those who never used cocaine (n = 273) as compared to the "bad outcome" group, those who continued abusing cocaine plus those who started abusing cocaine (n = 39), we found that the proportion of patients who used benzodiazepines during month 13 was significantly lower in the "good outcome" group (46.1%) as compared to 64.1% in the "bad outcome" group (Fisher's exact test, $p = 0.04$). Also, in the "good outcome" group, the proportion of patients who were positive for illicit opiate abuse during month 13 was significantly lower (31.9%) as compared to 66.7% in the "bad outcome" group (Fisher's exact test, $p < 0.0005$). The groups did not differ in gender proportion (27.1% female and 72.9% male in the "good outcome" group and 33.3% female and 66.7% male in the "bad outcome" group, Fisher's Exact test, $p = 0.4$), in admission age (37.2 ± 8 y in the "good outcome" group, and 35.5 ± 7.5 y in the "bad outcome" group, ANOVA F = 1.3, $p = 0.3$), or in methadone dose after one year (125.9 ± 50.9 mg/day in the "good outcome" group vs. 136.7 ± 48.3 mg/day in the "bad outcome" group, ANOVA F = 2.7, p = 0.1). A total of 205 out of 421 (48.7%) stayed in treatment for 2 years or more. Retention did not differ significantly between cocaine users 22(40%) and "non cocaine" users 183(50%) on admission (Fisher's Exact Test = 0.2). With respect to treatment retention, of the 312 patients who had stayed at least one year, the 2-year retention differed significantly between groups; it was 70.2% in the "never used cocaine" group while the "continued," "stopped," and "started" cocaine groups had 50%, 48.4%, and 52% 2-year retention, respectively (Chi Square 9.6, p = 0.02).

Cocaine Use and One Year Methadone Dose

In order to evaluate the possible effect of methadone dose on cocaine use, we evaluated

the methadone dose after one year in treatment (dose in the beginning of month 13). Comparison between the groups of patients who used cocaine on admission and patients with no admission cocaine use showed that cocaine use patients had a significantly higher methadone dose at one year (171.6 ± 40.9 mg/day (n = 45) vs. 119.8 ± 48.3 mg/day (n = 267), respectively) (ANOVA, F = 46, $p < 0.0005$).

When comparing the methadone dose between patients who "Stopped," "Started," "Always," or "Never" used cocaine after one year, it can be seen that methadone doses after one year were highest in (a) patients who stopped using cocaine (N = 31) (176.1 ± 42.1 mg/day), followed by (b) those who continued to use (N = 14) (161.4 ± 37.5 mg/day), to (c) those who started using during treatment (n = 25) (122.9 ± 48.7 mg/day), while the lowest dose of methadone was in d) patients who had never used cocaine (n = 242) (119.5 ± 48.4 mg/day) (ANOVA, F = 15.6, $p < 0.0005$) (Table 5).

The results were similar and still significant after adjustment (stratified) for patients with positive or negative urine benzodiazepines (ANOVA, corrected model F = 8, $p < 0.0005$). The former adjustments were performed because patients who had positive urine benzodiazepines in month 13 had significantly higher methadone dose compared to those with negative urine benzodiazepines (145.2 ± 49.1 mg/day [n = 151] vs. 110.5 ± 46.2 mg/day [n = 161] F = 41.4, $p < 0.0005$).

Since patients were admitted to the clinic over a long period of time (between 1993 and 2002), we examined the relationship between methadone dose and year of admission. We found that methadone doses significantly increased by the patients' years of admission (from 88.1 ± 37.9 mg/d in 1993 to 169.4 ± 69.7 mg/d in 2002, ANOVA F = 10.2, $p < 0.0005$). We also found an increase in the proportion of patients who used cocaine on admission from 1993 through 2002 (from 0 in 1993 to 30.4% in 2002, Chi Square = 36.2, $p < 0.0005$). We then compared the methadone dose in the negative and positive admission cocaine groups adjusted by year of admission, and found that patients with positive urine samples for cocaine still had significantly higher methadone doses compared to patients who had negative urine toxicology reports for cocaine on admission in any admission year group (ANCOVA corrected model F = 6.7, $p < 0.0005$, cocaine group F = 10.8, $p = 0.001$, admission year; F = 3.8, $p < 0.0005$).

DISCUSSION

The current study included 421 MMT patients who were admitted to the clinic throughout almost 10 (9.8) years. A net reduction in cocaine use was observed after one year of treatment. Cocaine and non-cocaine-abusing patients had a similar one-year retention rate, while among those who stayed in treatment at least one year, the cocaine-abusing patients were receiving significantly higher methadone doses, as compared to non-cocaine-abusing patients at 13 months of treatment. Moreover, the level of illicit opiate abuse was significantly lower in patients who used cocaine on admission and stopped their cocaine use, as compared to those who started, those who did not stop, and those who never used cocaine.

The high methadone dose in the patients who stopped cocaine use after one year was independent of the patient's year of admission. This fact is very important, as over this 10-year period changes have occurred not only in the broader treatment world, but also in Israel and in our clinic. With respect to MMT, there was an increase in the acceptable methadone dose level from 80 to 120 mg recommended from 1964 (published in 1966)[1] to 150 mg in 1996.[17,18] Also, since the clinic opened in June, 1993, there has been an increase in cocaine abuse in Israel.[19] The census of our MMT clinic almost doubled in numbers of patients between the end of 1997 (n = 150) and the end of 2002 (n = 290). Also, in the later period (late 2000 to 2002), a greater number of the patients came directly from the hospital, following a very fruitful collaboration with the Tel-Aviv Medical Center, as compared to those who came mainly from the street.

The reduction in cocaine use in patients in MMT observed in this study supported the idea that MMT may have had an effect on cocaine use on a biological level.

It has been shown that cocaine significantly disrupts the endogenous opioid system, includ-

ing mu and kappa opioid receptor density.[14,20-22] In an animal model of "binge"-pattern cocaine administration, mu opioid receptor density was significantly increased after 14 days of binge-pattern cocaine administration, specifically in those brain regions that contain abundant terminals of the mesolimbic-mesocortical dopaminergic system, including the nucleus accumbens, amygdala, and anterior cingulate, and also the nigrostriatal system, including the caudate putamen.[20-22] Prodynorphin and kappa opioid receptors have also been shown to be activated in response to chronic and binge administration of cocaine in animal models[21-24] and dynorphin peptides acting at the kappa opiate receptor have been shown to counter-modulate the effect of cocaine by lowering dopaminergic tone.[14,25]

Research in humans, using positron emission tomography (PET) in abstinent chronic cocaine addicts, as compared to nonaddicted controls, revealed significantly higher levels of binding to mu receptors in brain regions similar to those found in animal studies. The severity of self-reported craving correlated positively with the level of mu receptor binding.[26]

Opioid receptor antagonists have been found to attenuate the rewarding effect of cocaine in several different animal models.[27,28] It has also recently been shown that the rewarding effect of cocaine, as measured by conditioned place preference, is reduced in mu opioid receptor knockout mice.[29]

Our cocaine use reduction finding alone does not clarify whether the effect is directly due to the methadone, to a behavioral or medical intervention, or a combination of these factors.

Several studies have reported a decrease in cocaine use among MMT patients. Ball and Ross[4] reported that in patients who had been in treatment for more than 4.5 years, the use of cocaine was only 16%, as compared to 47% use among patients who were treated for less than 6 months. However, they did not have initial cocaine use data and the availability of cocaine varied greatly with time of admission. Initial cocaine use was reported by Borg et al.,[7] who analyzed all patients in one MMT by dividing study subjects into three groups: patients in treatment (a) less than six months, (b) 6-53 months, and (c) 54 or more months, and compared the cocaine use in the last month of treatment to initial use. They found a decrease in cocaine use in all three groups (net reduction of 59%). Magura et al.[6] analyzed heroin and cocaine urines in a sample of 1038 patients who were admitted between 1989 and 1990 to 15 MMT clinics in New York City, and found that about 50% of patients decreased or stopped cocaine use. Some studies which compared the effectiveness of diverse psychosocial treatments in the MMT patients reported decreases in cocaine use, but attributed the reduction to the psychosocial treatments only.[5,8-9]

As was reported, heroin-addicted patients who are treated with the opiate-agonist methadone demonstrate less benefit and less improvement if the methadone is not accompanied by psychosocial interventions.[3] Undoubtedly, cocaine-abusing patients, for whom the methadone may have only a partial contribution, should benefit and improve in treatment through diverse psychosocial treatment. Thus, the above finding is not in contrast to the possible direct contribution of the methadone.

In contrast, one study did not find cocaine reduction after 17 weeks in MMT, but found reduction among patients who received additional specific psychosocial approach.[30] However, the results of this study are limited, as they were based on patients' self-reports and not on urine toxicology tests. None of the studies above has shown any relation between methadone dose and cocaine use. Thus, looking at the study by Magura et al.[6] it should be noted that the methadone dose was quite low (mean methadone dose for 80% of the patients was less than 58 mg/day, and only 20% had an 84 mg/day mean methadone dose). Also, the above study ignored time in treatment, which could explain some of the results.

In the current study, the additional finding that the methadone dose was highest in those who succeeded in eliminating cocaine use as well as opiate use indicates a possible role for the methadone itself in cocaine use reduction. These results were still significant after adjustment for other variables found to be associated with methadone dose, such as positive urine benzodiazepine toxicology reports on admission[31] (as significantly higher methadone doses were found in patients with positive benzodiazepine reports on admission compared to those

with negative urine toxicology for benzodiazepine) and, as was mentioned, year of admission since there were increases in the mean doses of methadone given each year.

The fact that the one-year retention rate of patients who used cocaine on admission (81.8%) was not significantly different from the retention rate of patients that did not use cocaine on admission (73.0%) also suggests that methadone treatment contributes to the cessation of cocaine use as well. However, the direct contribution cannot be evaluated, as no data is available on patients with only cocaine addiction (and not heroin addiction) receiving methadone.

Results showed that testing positive for cocaine use on admission does not relate to (or predict) retention in treatment after 2 years. However, of those patients who stayed one year, 70.2% of patients who "never" used cocaine (none on admission, or after one year in MMT) stayed 2 years in treatment compared with only around half (50%, 48%, 52%), respectively, in the 3 cocaine groups (continued, stopped, or started use cocaine after one year respectively).

We emphasize that the current study was not a randomized trial, and the methadone dose of each patient was determined by his or her physician.

The possibility that staff attitudes may influence dose changes cannot be excluded. Thus it could be that the physician's awareness of the patient's cocaine use may underlie his or her decision to increase the dose rather than reports of physiological needs or discomfort. On the other hand, the clinic staff's understanding was that methadone treats narcotic addiction and not cocaine dependence. The clinic staff determined the adequate methadone dose based on clinical observation, urine results, and patient reports, rather than with any objective measure or marker.

Chaisson et al.[32] reported that 24% of patients start cocaine use while in methadone maintenance treatment (a higher proportion than our clinic showed), while Borg et al.,[7] in a finding that was similar to ours, found that 10% started to use it. However, this proportion is quite low as compared to other clinics in the USA. The proportion of patients abusing cocaine in methadone programs in the Bronx, New York City, before 1978 was 18%, while in 1982 it had increased dramatically to 59%, reflecting the crack epidemic in the USA.[33] Thus proportional differences in cocaine use between clinics or time periods can be biased due to changing drug use patterns as well as differences in the urine detection method used and the frequency with which the samples were taken.

In respect to the biological finding of cocaine's effect on the endogenous opioid system, our results are very striking. However, further investigation on a larger number of patients, with evaluations of methadone plasma levels, should be done with adjustments for other possible confounders.

In summary, the current study reinforces the previously-found decrease of cocaine use in long-term MMT patients. It also adds additional support to the importance of the methadone dose in mediating that effect.

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