Retention, HIV Risk, and Illicit Drug Use during Treatment: Methadone Dose and Visit Frequency

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ABSTRACT

Objectives. This study examined two major methadone treatment factors, visit frequency and methadone dose, posited to be important in reducing intravenous drug use and human immunodeficiency virus (HIV) transmission.

Methods. One hundred fifty opiate-dependent subjects randomly assigned to four groups received 50 or 80 mg of methadone and attended a clinic 2 or 5 days per week.

Results. Survival analysis indicated higher dropout rates for groups having five vs two visits per week (χ^2 [1] = 7.76). Higher proportions of opiate-positive results on urine screens were associated with lower methadone doses (F [1,91] = 4.74).

Conclusions. Receiving take-home doses early in treatment enhanced treatment retention. The 50-mg dose combined with five visits per week produced the worst outcome. Fewer visits enhanced retention at 50 mg, but opiate use rates were higher at this dose than they were for either 80-mg group. The HIV infection rate at entry was 9%. No subjects seroconverted during the study. Risk behaviors for acquired immunodeficiency syndrome declined over time regardless of group/dose assignment. These results have important implications for modification of regulatory and clinic policy changes. (*Am J Public Health*. 1998;88:34–39)

Introduction

Despite regulatory constraints, methadone has proven uniquely effective as a treatment for opiate dependence.[1–3] A constellation of conditions permits patients to return to activities unrelated to drug abuse or to seek previously inaccessible opportunities. Methadone exemplifies the pharmacological substitution strategy for treating drug dependency while contributing to the reduction of human immunodeficiency virus (HIV) transmission. Yet this strategy continues to meet resistance. It is not permitted in several states, and in others there are calls for its elimination. Notably, regulations governing methadone administration have been focused primarily on precluding "diversion," not on treatment efficacy[4–6]; in fact, current regulations effectively reduce treatment availability and effectiveness. A reexamination of policy, practice, costs, and implications for availability of services is needed.

Methadone has been used for 3 decades, but optimal dosing and visit conditions are ill defined.[5] Recent data from studies of cocaine dependency treatment indicate that reduced visit frequency requirements enhance retention.[7] In a demonstration research project with methadone, Senay et al.[8] found no diversion by long-term patients receiving many methadone take-home doses.

The issues regarding treatment with methadone have been critically reviewed.[9–13] Dole and Nyswander[1] originally emphasized higher doses over longer periods on the basis of assumptions regarding the modified neurochemistry of the user. However, other strategies have been favored, including "detoxification," which entails brief stabilization at the lowest sufficient dose followed quickly by dose reduction. In practice, this has not produced impressive

results. Patients may even return to other opiate use while the methadone dose is decreasing.[14]

Illicit opiate use during methadone treatment should be dose dependent, with higher doses of methadone providing more effective substitution than lower doses. Yet the trend in the late 1970s and 1980s was toward lower doses. Recognition of needle sharing as a vector for HIV transmission may have stayed this trend, but problems still exist.

The study described here systematically addressed pragmatic issues influencing cost, effectiveness of treatment, and HIV spread. The main independent variables were methadone dose and visit frequency.

Subjects and Methods

Subjects

Ninety men and 33 women (n = 123), aged 18 to 50 years (mean = 38.3, SD = 5.98), completed the consent process. Of 107 subjects completing a 2-week dosing stabilization period, there were 76 men and 31 women (mean = 38.2 years, SD = 5.95). Subjects were recruited through advertisements and referrals. All met criteria of the *Diagnostic and Statistical Manual*

of Mental Disorders, 3rd edition, revised (DSM-III-R), for opiate dependence, and all were in good physical and psychiatric health. Exclusion criteria included medical disorders precluding methadone administration, other Axis I diagnoses, positive results on a tuberculosis test, probation or parole, enrollment of a significant other in the study, the inability to read English, and an inability or unwillingness to comply with study requirements. The study was approved by the Committee for the Protection of Human Subjects, University of Texas–Houston, Health Science Center.

Treatment Setting

The Treatment Research Clinic is a university medical center–based facility[15] whose staff includes master's degree–level therapists, nurses, clinical psychiatrists, clinical and research psychologists, research assistants, and medical technicians. Medication was prepared in the clinic pharmacy. Drug screens were conducted in the department's Analytical Neurochemistry Section.

Study Design

Subjects were randomly assigned to 50 or 80 mg of methadone and to two or five visits per week, Monday and Thursday or Monday through Friday, respectively. Take-home doses were given for non-visit days. Study phases were (1) intake, (2) stabilization/dose run-up, and (3) 24-week treatment. Daily clinic visits during stabilization permitted the monitoring of medication, emergent psychiatric or medical conditions, and compliance. Use of the carefully monitored stabilization period resulted in approval from the Drug Enforcement Administration for dispensing methadone take-home doses at the start of treatment, 3 months earlier than permitted by federal regulation.

Medication and Therapy Sessions

On visit days, subjects ingested medication under observation and received take-home doses for intervening days. Dosing was single blind. Social, employment, drug use, living arrangement, and long-term goals were discussed in weekly one-hour structured therapy sessions. Subjects were instructed to use common behavioral strategies to avoid drug use.

Visits, Reimbursement, and Data Collection

First contact was typically by telephone screening interview, at which time an appointment was scheduled. Following the consent, the Structured Clinical Interview for DSM-III-R, Addiction Severity Index, Hamilton-Depression, Hamilton-Anxiety, Beck Depression Inventory, Profile of Mood States, and Medication Side Effects Questionnaire were completed (the latter two on a weekly basis), as were a drug history, Desire To Use Drugs Inventory, and a complete physical examination. The Desire to Use Drugs Inventory presents a 9-point scale on which subjects rated "desire to use opiates" (0 = none, 8 = very strong) in 14 high-risk situations; a total score was the average across all situations. Pre- and posttest HIV counseling were also provided. The primary dependent measures were length of time in study and urinalysis drug screen results.

Dispensary visits were 30 minutes while therapy sessions were 60 minutes. Visit procedures were monitored for consistency, and subjects provided two observed urine samples per week. Subjects received about $14.00 per week for research elements as well as bus or parking tokens.

Urine samples were split, with half retained for retesting in our certified on-site laboratory. Qualitative testing was by Syva EMIT System (Palo Alto, California) and the Toxi-Lab thin-layer chromatographic system (Irvine, California). The EMIT procedures use the Syva ETS instrumentation testing for drugs/metabolites (e.g., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine). The Toxi-Lab system tests for approximately 200 drugs and metabolites. Gas chromatography and nitrogen phosphorous detection were used to clarify results of the two screening procedures.

Data Analysis

An a priori power analysis indicated that a sample of 26 subjects per cell (total sample = 104) was necessary to detect the expected group differences when setting alpha equal to .01 and one minus beta (power) equal to .80. In anticipation of subjects dropping out before the study phase began, 142 subjects were enrolled. The final sample size entering the 24-week treatment phase was 107.

Data analyses were conducted on the basis of all subjects who began the stabilization period (i.e., "intent to treat" analysis, n = 123) and of those subjects who began the 24-week treatment phase when the differences in visit frequency were initiated (n = 107). The stabilization period ensured an adequate sample of those who tolerated the assigned medication dose notwithstanding the exclusion of emergent dual-diagnosis patients. Baseline differences between those who entered the study and those who dropped out during stabilization were evaluated to assess randomization bias.

Subjects were required to complete 75% of the data collection requirements each month to preclude discharge. In practice, no subjects were directly discharged because of intermittent data collection; rather, this percentage served as a definitive end point for subjects who were dropouts. Triplicate data check procedures were used. SAS, BMDP, and SPSS software were used to compute statistical analyses. Group differences in retention were analyzed as survival data (completers were coded as right-censored) with the use of the SAS module, LIFREG, which allows for discrete and continuous predictor variables. The proportion of urine screens that tested positive for opiates was calculated for weeks 1 to 4, 5 to 8, 9 to 12, 13 to 16, 17 to 20, and 21 to 24, and were analyzed with the use of a maximum likelihood approach to repeated measures analysis of covariance for "unbalanced" data[16,17] (BMDP program 5V), which uses all available observations but does not impute data.

Resulting chi-square values were corrected for sample size and reported as F-test equivalents.[18] Other measures were similarly evaluated for change.

Results

Dropouts in Stabilization

All subjects who were offered the opportunity to participate accepted; however, 16 of the 123 randomized subjects (13%) did not complete the stabilization period. There were no significant demographic differences across the four experimental groups. Sample characteristics were age (mean = 38.3, SD = 5.98), sex (29% female), race (52% White, 19% Black, 29% Hispanic), marital status (21% married, 19% separated, 33% divorced), education (mean = 11.8 years, SD = 2.1), and employment (25% full time, 15% part time, 5% homemaker, 1% student, 54% unemployed).

At intake there were no significant differences across groups on the Beck Depression Inventory (mean = 12.9, SD = 8.7) or on individual or total scores of the Profile of Mood States (total score mean = 74.5; SD = 37.4). Statistically significant but not clinically relevant differences in intake scores did, however, exist between the 50-mg and 80-mg groups ($P < .05$), with Hamilton-Depression scores of x10.4

(SD = 5.9) vs x7.5 (SD = 5.91) and Hamilton-Anxiety scores of x7.3 (SD = 5.3) vs x5.16 (SD = 4.9), respectively. Composite scores on the Addiction Severity Index did not differ across the groups at intake.

There were no sociodemographic differences between those who did and did not begin the 24-week treatment period. However, early dropouts differed somewhat on three self-report measures and one urine screen measure. Greater Addiction Severity Index therapist-rated drug use severity on the Addiction Severity Index was noted (x = 7.94 vs 7.10; $t(38) = 3.55$; $P = .001$), although the(behavior-based) composite drug use scores on the index were not different. In the month prior to treatment, dropouts self-reported more opiate use (100% vs 82%; $\chi^2 (1) = 5.79$; $P = .016$) than non-dropouts and no methadone use (0% vs 48%; $\chi^2 [1] = 18.7$; $P < .001$). Of the early dropouts' intake urine screens, 100% had positive results for at least one drug vs 85% for those who continued ($\chi^2 [1] = 4.523$; $P = .0334$); however, the groups did not differ in their intake urine screens for opiate use. While the early dropouts, as a group, present as more severely dependent than those who continued in study, many of those who continued were equally severe.

AIDS Risk

At intake, 9% of subjects tested were HIV positive. There were no differences across groups and no increase in the seropositive rate by study end. A 10-item scale of risk behaviors (e.g., injection drug use, sexual relationship with injection drug user, etc.) was gathered at intake, at 3 months, and at 6 months. Analysis of the acquired immune deficiency syndrome (AIDS) risk score across the three time periods as a function of dose and visit frequency indicated a decreased average risk score ($F(2,122) = 5.48$; $P = .005$). There were no differences by methadone dose level or visit frequency.

Retention

Of the 107 subjects who completed stabilization and entered treatment, 71 (66%) remained to complete the 24-week study. Figure 1 presents retention curves by dose and visit frequency. A survival analysis found length of retention to vary as a function of visit frequency ($\chi^2 [1] = 7.76$; $P = .0053$) and age ($\chi^2 [4] = 11.06$; $P = .0259$). Additionally, there were strong trends for the dose-by-visit frequency interaction ($\chi^2 [1] = 3.38$; $P = .066$) and for reports of methadone use in the month

before subjects began the study ($\chi^2 [1] = 3.51$; $P = .061$). Subjects who were required to visit the clinic less frequently were less likely to drop out. Subjects on 80 mg of methadone were well sustained in treatment independent of visit frequency. Of subjects receiving 50 mg, only those who were required to visit the clinic less often remained in the study at a rate paralleling the higher-dose patients. Younger subjects dropped out earlier than older subjects, as did those subjects who reported no methadone use in the month before beginning the study. Retention was the only outcome variable for which the results differed between the "intent to treat" and "study treatment period" analyses. In the former, age was not a predictor of retention and the dose-by-visit frequency interaction effect was larger ($\chi^2 [1] = 4.96$; $P = .0257$).

Drug Screens and Drug Use

Subjects' urine screens were examined for differences in the proportion of those testing positive for opiate (non-methadone) and cocaine use as a function of methadone dose, visit frequency, and intake urine screen status. In a related study,[7] we reported that subjects having cocaine-positive results on urine screens at intake differed in treatment outcome from those with negative results. This same method of grouping subjects by intake urine screen status was used for the following analyses.

The proportion of opiate-positive results on urine screens per month (16 screens maximum) was calculated for each subject. Data were considered missing for those with fewer than four screens. Proportions of those with opiate-positive results are presented in Figure 2 by methadone dose, visit frequency, and month of study. BMDP-5V was used to calculate an unbalanced repeated measures analysis of all observed data to assess effects of dose, visit frequency, and intake status across the 6 months.

The proportion of those with opiate-positive results on urine screens was found to vary as a function of dose ($F(1,91) = 4.74$; $P = .0321$); intake status ($F(1,91) = 19.70$; $P < .0001$); and the interaction of dose, intake status, and month ($F(5,355) = 2.697$; $P = .0208$). The mean percentage of opiate-positive results on urine screens was approximately 20% in the 80-mg/day group, compared with 45% in the 50-mg/day group. This confirmed our major hypothesis concerning effectiveness of higher compared with lower doses of methadone. Subjects presenting with opiate positive urine screens at intake were consistently more

likely to have opiate-positive results throughout the study. However, subjects who were administered 80 mg methadone evidenced fewer opiate-positive results on urine screens regardless of intake status. The disparity between intake status groups became larger as the study progressed.

Cocaine-positive results on urine screens were analyzed as described for opiate screens and again grouped by intake status. As presented in Figure 2, cocaine-positive results varied as a function of intake status ($F(1,91) = 112.92$; $P < .0001$), the interaction of dose by month ($F(5,355) = 2.428$; $P = .0350$), and intake status by month ($F(5,355) = 2.264$; $P = .0473$). Cocaine-positive results on urine screens for the subjects who tested positive for cocaine at intake remained at approximately 80% throughout the study while cocaine-positive results for those who tested negative at intake approximated 20%. Subjects receiving higher doses of methadone were more likely to have cocaine-positive results on urine screens, and the difference increased in the final study months.[19]

Craving

The Desire to Use Drugs Inventory was administered every 4 weeks, and scores were analyzed with respect to dose, visit frequency, and time. Dose and visit frequency interacted ($F(1,87) = 4.402$; $P = .038$). Subjects attending the clinic five times per week and receiving 80 mg methadone reported a greater "desire to use" than did those visiting the clinic five times and receiving 50 mg methadone (means = 2.19 vs 1.49), but they were less likely to do so. The opposite pattern was observed for those attending the clinic twice a week (means = 1.60 vs 2.25 for 80- and 50-mg groups, respectively). A dose-by-time interaction ($F(5,344) = 2.267$; $P = .0476$) was observed with equivalent "desire" in months 1 and 2, increased "desire" for the 50-mg group in months 3 and 4, and crossover for the 50-mg group (decreasing) and 80-mg group (increasing).

Addiction Severity Index

Composite scores on the Addiction Severity Index were analyzed as a function of dose, visit frequency, and time (pre-post). All measures declined over time (F ratios from 2.765 to 56.67, P values from .10 to < .0001), with the exception of the legal severity rating (parolees and probationers had been excluded). The two indices of drug severity evidenced the
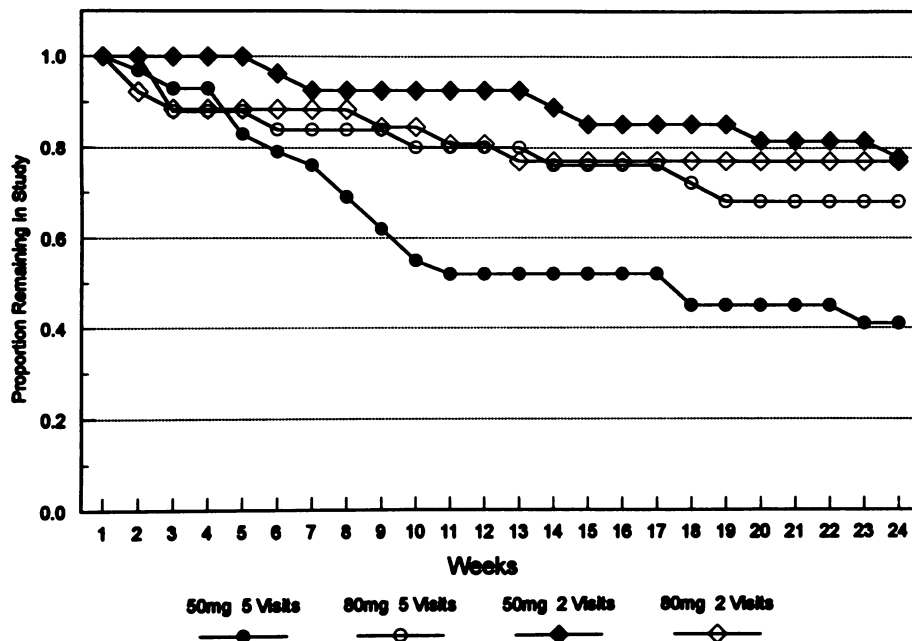
Note. Joint actions of visit frequency and methadone dose are evident. Retention was better with 2 visits per week than 5 visits per week. Eighty mg of methadone facilitated retention in the 5-visit-per-week condition, and the 2-visit requirement diminished the adverse effect of the lower methadone dose. The worst outcome resulted from 50 mg and the 5-visit-per-week requirement. Diamonds = 2 visits per week; circles = 5 visits per week; open = 80 mg/day; closed = 50 mg/day.

FIGURE 1—Effects of visit frequency and methadone dose on retention.

most reliable declines (severity rating $F(1,66) = 56.67$ and composite score $F(1,65) = 38.33$).

Discussion

This study's design paralleled that of a large clinical trial of cocaine dependency treatment that examined visit frequency and medication dose.[7] Parallel designs permit generalization where common findings emerge. The results here, combined with those of the earlier report, are pivotal on the question of visit frequency. The dose-effect data are also clear. Discussion of these two main points, collateral data, and recommendations follow.

That two large clinical trials with patients dependent on different drugs produced parallel results with respect to visit frequency firmly substantiates the generalizability of the findings. Regulations and therapeutic lore requiring that patients receiving methadone attend a clinic 7 days per week during the first 90 days can be viewed as having little benefit and potential harm, and as wasting limited treatment funds. The strength of the effect is further evidenced by a reduced dropout rate at the lower visit
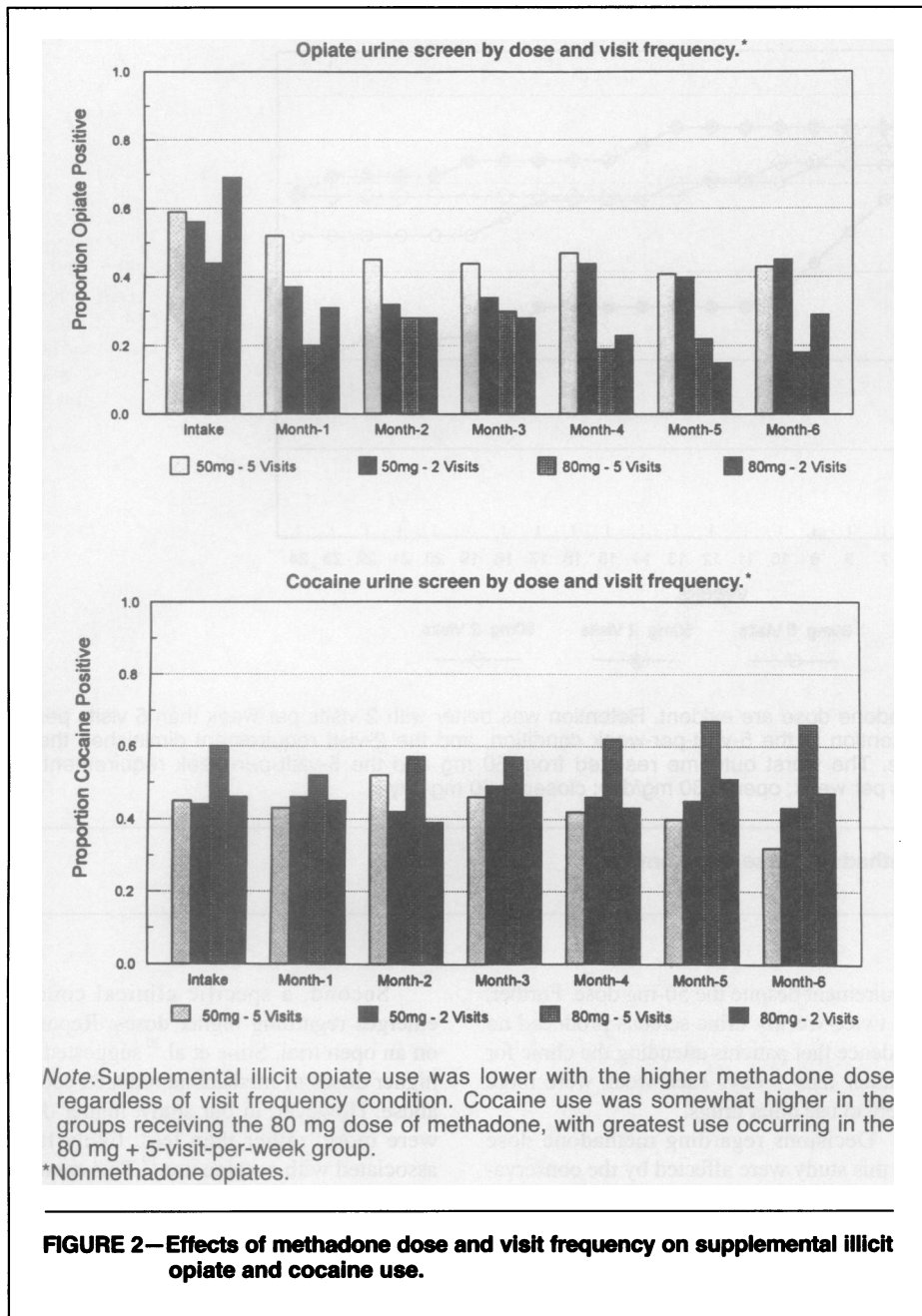
requirement despite the 50-mg dose. Further, the twice-weekly urine screens produced no evidence that patients attending the clinic for 2 rather than 5 days each week were more likely to use other drugs.

Decisions regarding methadone dose for this study were affected by the conservative tendency in the clinical science community. The National Institute on Drug Abuse peer-reviewed proposal specified comparison of 50 and 100 mg of methadone. However, pre-study discussion resulted in strong recommendations by consultants that the high dose be 80 mg. The data presented here strongly support the case of greater benefit from higher methadone doses.

Comments on dosing are warranted. First, while higher rather than lower doses are recommended, flexible rather than fixed dosing is reasonable. On the basis of this and other work, we now administer methadone at 1.1 mg/kg. Typically, upward adjustment is needed at lower weights and downward adjustment is needed at higher weights. Doses over 100 mg require informing regulatory agencies. However, agency personnel are responsive to requests from clinics with systematic protocols. Therefore, this regulatory issue is not a deterrent to higher dose administration.

Second, a specific clinical concern emerges regarding higher doses. Reporting on an open trial, Stine et al.[20] suggested that higher doses of methadone reduced cocaine abuse. However, in our study, higher doses were more, rather than less, likely to be associated with cocaine use.[19] This creates a clinical conundrum. Higher methadone doses reduce injection heroin use, thereby reducing the risk of HIV transmission. However, injection heroin users were more likely to use cocaine intravenously, potentially increasing the risk of HIV and other disease transmission. Nevertheless, this should not lead to recommendations for a reduction in methadone dose. Rather, astute clinical effort must be applied to cocaine use. The opportunity to intervene is lost if imposed treatment conditions produce high dropout rates, the consequence of high visit frequency and low doses.

These data have been extensively scrutinized. First, the few predictors of retention and success were dominantly related to three interrelated factors: older patients (after the stabilization period), patients with methadone experience, and patients who had not used drugs in recent days all did better. These findings dictate the need to focus on retaining young drug

Opiate urine screen by dose and visit frequency.*

☐ 50mg - 5 Visits ■ 50mg - 2 Visits ▨ 80mg - 5 Visits ■ 80mg - 2 Visits

Cocaine urine screen by dose and visit frequency.*

▨ 50mg - 5 Visits ■ 50mg - 2 Visits ▨ 80mg - 5 Visits ■ 80mg - 2 Visits

*Note.*Supplemental illicit opiate use was lower with the higher methadone dose regardless of visit frequency condition. Cocaine use was somewhat higher in the groups receiving the 80 mg dose of methadone, with greatest use occurring in the 80 mg + 5-visit-per-week group.
*Nonmethadone opiates.

FIGURE 2—Effects of methadone dose and visit frequency on supplemental illicit opiate and cocaine use.

parameters for other forms of drug abuse. The data strongly point to the need for policymakers and agencies to substantially revise regulations that (1) limit access to methadone, (2) encourage low-dose regimens, and (3) thus exacerbate the myriad problems associated with opiate dependence, including HIV transmission. This point applies as well to developing regulations for new opiate replacement medication such as buprenorphine.

The benefits of these empirically based recommendations will outweigh the risks characterized by the historic concerns of overdose and diversion. Data-based changes in regulations will reduce the burden on the Drug Enforcement Administration, the Food and Drug Administration, and state agencies, and will permit attention to be paid to other aspects of drug control and drug abuse policy. Further, the irony of increased availability of nicotine replacement products along with the current NIDA focus on developing cocaine substitution strategies should persuade the science community, the federal authorities, and the public of the need to reduce impediments in access to opiate substitution treatment. At the same time the expectations of substitution medications are specific: they are to reduce the use of the drug for which they are substituting and thus improve retention. Secondary improvements (e.g., employment) may emerge but depend on the quality of collateral behavior therapy and other factors. Other features of patient behavior will not inherently follow from the direct drug effects. Yet the HIV data support the concept of using substitution as a vehicle for interventions benefiting individual and public health. □

users in treatment, presumably with strategies to make treatment more accessible. Second, the data also suggest the need to maximize opportunities to *expose* patients to methadone treatment. This parallels findings on smoking cessation, for which success is linked to sequential "quit attempts." Increased opportunities for treatment, and thus exposure to methadone, become possible when treatment slots can be freed by requiring fewer visits. Third, more attention clearly should be focused on those patients who have opiate-positive results on urine screens at intake. In both this study and the cocaine dependency study,[7] entry urine screen was a profound

predictor of dropout. The combined results suggest a need for more rational allocation of resources related to severity. Finally, self-reported craving or desire to use drugs was not meaningfully related to any dimension of treatment.

The findings concerning HIV risk behaviors are reassuring. In brief, beyond demonstrating that drug abuse treatment "works," the findings also demonstrate that drug abuse treatment is an excellent vehicle for reducing HIV transmission.

The results commend strategies for effective use of treatment resources. And combined with other data, they have even broader implications for basic treatment

Acknowledgments

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