

Methadone Maintenance in Primary Care

A Randomized Controlled Trial

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THE CURRENT NARCOTIC TREATMENT system is able to provide the most effective medical treatment for opioid dependence, opioid agonist maintenance,¹⁻⁴ to only 170 000 of the estimated 810 000 opioid-dependent individuals in the United States.^{1,4} A recent increase in heroin use due to greater drug purity and intranasal administration has resulted in increased admissions to treatment centers⁵ and greater use of emergency services for medical conditions related to illicit opioid use.⁶ This shortage of adequate treatment persists despite the demonstrated effectiveness of methadone maintenance in decreasing the medical,² legal,² and infectious^{2,7-9} complications associated with heroin use.

The marginalization of medical care for opioid dependence and the stigma attached to this diagnosis and methadone maintenance treatment play an important role in untreated opioid dependence.¹⁰ Current federal regulations restrict the care of opioid-dependent patients to federally licensed narcotic treatment programs (NTPs) with little to no involvement by community-based physicians.¹¹ Recent calls from federal and scientific bodies, including the Institute of Medicine,¹² a National Insti-

Context Methadone maintenance is an effective treatment for opioid dependence, yet its use is restricted to federally licensed narcotic treatment programs (NTPs). Office-based care of stabilized methadone maintenance patients is a promising alternative but no data are available from controlled trials regarding this type of program.

Objective To determine the feasibility and efficacy of office-based methadone maintenance by primary care physicians vs in an NTP for stable opioid-dependent patients.

Design Six-month, randomized controlled open clinical trial conducted February 1999-March 2000.

Setting Offices of 6 primary care internists and an NTP.

Patients Forty-seven opioid-dependent patients who had been receiving methadone maintenance therapy in an NTP without evidence of illicit drug use for 1 year and without significant untreated psychiatric comorbidity were randomized; 1 patient refused to participate after treatment assignment to NTP.

Interventions Patients were randomly assigned to receive office-based methadone maintenance from primary care physicians, who received specialized training in the care of opioid-dependent patients (n=22), or usual care at an NTP (n=24).

Main Outcome Measures Illicit drug use, clinical instability (persistent drug use), patient and clinician satisfaction, functional status, and use of health, legal, and social services, compared between the 2 groups.

Results Eleven of 22 (50%; 95% confidence interval [CI], 29%-71%) patients in office-based care compared with 9 of 24 (38%; 95% CI, 21%-57%) of NTP patients had a self-report or urine toxicology test result indicating illicit opiate use ($P=.39$). Hair toxicology testing detected an additional 2 patients in each treatment group with evidence of illicit drug use, but this did not change the overall findings. Ongoing illicit drug use meeting criteria for clinical instability occurred in 4 of 22 (18%; 95% CI, 7%-39%) patients in office-based care compared with 5 of 24 (21%; 95% CI, 9%-41%) NTP patients ($P=.82$). Sixteen of the 22 (73%; 95% CI, 54%-92%) office-based patients compared with 3 of the 24 (13%; 95% CI, 0%-26%) NTP patients thought the quality of care was excellent ($P=.001$). There were no differences over time within or between groups in functional status or use of health, legal, or social services.

Conclusions Our results support the feasibility and efficacy of transferring stable opioid-dependent patients receiving methadone maintenance to primary care physicians' offices for continuing treatment and suggest guidelines for identifying patients and clinical monitoring.

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tutes of Health consensus panel,¹ and the Office of National Drug Control Policy,⁴ have recommended restructuring the regulatory processes involved in the treatment of opioid-dependent patients, including increased involvement of primary care physicians.

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See also pp 1715 and 1764.

Office-based methadone maintenance administered by appropriately trained primary care and specialist physicians has the potential to provide an alternative for selected patients to the current narcotic treatment system that would allow for greater physician involvement and perhaps increased quality of care.¹³ Potential benefits from this type of care include increased attention to comorbid medical and psychiatric conditions, decreased stigma associated with the diagnosis and treatment, decreased contact with active heroin users, and increased access to treatment. These benefits may increase patient satisfaction and enhance clinical outcomes.

Prior evaluations of office-based methadone services in the United States are limited to the description of 3 programs.¹⁴⁻¹⁸ Two of these were uncontrolled case series in which patients who had been stabilized while receiving methadone for at least 5 years were transferred to receive care at physicians' offices.¹⁵⁻¹⁸ One trial was conducted with patients who had been stabilized for 1 year and were subsequently randomized either to a specialized methadone clinic or to remain in their NTP.¹⁴ Therefore, to our knowledge, no data exist regarding the efficacy of treating stabilized patients in an NTP vs in the office of a primary care physician. The purpose of the current study was to investigate the feasibility and efficacy of office-based methadone maintenance by primary care physicians for the treatment of clinically stable opioid-dependent patients.

METHODS

Study Design

This study was a 6-month randomized controlled open clinical trial, conducted in February 1999-March 2000, intended to evaluate whether relapse to illicit drug use would occur more frequently among patients transferred to office-based treatment compared with patients continuing treatment in an NTP. Stable opioid-dependent patients from an NTP were randomly assigned to office-based methadone main-

tenance or continuation of methadone maintenance at their current NTP.

We anticipated that a low proportion of patients in the NTP would relapse to illicit drug use during the 6-month clinical trial since study eligibility criteria required that all patients had evidence of abstinence for at least the past year while treated in the NTP. Since previous uncontrolled trials of office-based methadone treatment, performed with stricter eligibility criteria or in specialized settings, noted ongoing illicit drug use in 18% to 27% of patients, we anticipated a higher rate of relapse in patients who were transferred to office-based treatment.^{14,17} The intended a priori sample size of 60 was designed to provide sufficient power (>80%) to detect a medium to large effect-size difference^{19,20} (eg, 30%-40% difference) in the proportion of patients relapsing to illicit drug use. The actual number of patients enrolled during the allotted recruitment period was 47. There were no differential fees for the 2 treatment conditions and patients in both groups continued to pay their usual fees to the NTP.

Research assistants, who did not participate in treatment allocation, assessed all patients for eligibility. Study identification numbers were assigned to eligible subjects. Randomization and treatment allocation for all patients were determined using a computer-generated random-number table for an intended sample size of 60 patients, using a block size of 60, according to a 1:1 allocation ratio by an investigator who had no information aside from the study identification number. Treatment allocation was communicated by this investigator to a separate investigator, not involved in assessment for eligibility or randomization, who notified each patient of his/her treatment assignment in a sequential manner.

Participants

Opioid-dependent patients receiving methadone maintenance were evaluated for the following eligibility criteria: treatment at the NTP for more than 1 year, age 18 to 60 years, absence of positive urine toxicology results for il-

licit opioids or cocaine during the prior 12 months, anticipated continued methadone maintenance for at least 6 months, no significant psychiatric or medical condition that would be compromised by leaving the NTP, no evidence of current dependence on cocaine, alcohol, or drugs other than nicotine, transportation to and from the NTP or physician's office, evidence of a legal income, and evidence of a consistent place of residence.

Written informed consent was obtained from all participants and this study was approved by the Human Investigations Committee at Yale University School of Medicine.

Treatment

Office-Based Methadone Maintenance. Methadone maintenance was provided in the offices of 6 general internal medicine physicians. Patients had weekly contact with the physician's office, at which time they ingested 1 dose of methadone and received a 6-day supply of liquid methadone. Patients met monthly with their physician. The initial physician visit was modeled after a "new patient" visit and allowed the physician to review the patient's medical and substance abuse history, perform a physical examination, and outline the components of office-based methadone maintenance. Subsequent monthly physician visits consisted of 30-minute counseling sessions that discussed signs and symptoms of relapse, potential complications of prior substance use (eg, medical, psychiatric, social), medication issues (including methadone dose), health promotion (eg, smoking cessation), and participation in self-help or relapse prevention activities. Patients provided random urine samples in the physician's office for toxicology testing.

Physician Selection and Training. Physician recruitment followed a survey of potential patients asking for the names of their current primary care providers. From a total of 9 physicians contacted based on interest, 6 physicians, all general internists, 4 of whom had certification from the American Society of

Addiction Medicine (ASAM), were recruited. The practice settings included 3 community group practices, 1 suburban solo practice, 1 hospital-based primary care clinic, and 1 urban federally qualified health center. Physician training was conducted using a training and resource guide that was developed in conjunction with the Addiction Technology Transfer Center of New England.²¹ Two initial 1/2-day training sessions were supplemented with an onsite manual (available at the Substance Abuse and Mental Health Services Administration Web site: <http://www.samhsa.gov/centers/csat/csat.html>) and 24-hour consultation by pager for clinical questions or concerns. Project physicians performed monthly onsite reviews using structured instruments that covered medical records, documentation, clinician's questions and concerns, and included feedback to the physician regarding appropriate clinical practice. Finally, an in-service training was conducted at each physician's office with nurses and office personnel that covered the nature of opioid dependence, treatment strategies, the rationale for opioid agonist maintenance, and the importance of expanding care into office-based settings.

Regulatory Requirements. To ensure compliance with federal regulations, the Food and Drug Administration (FDA) provided approval for the physicians' offices to operate as methadone dispensing units. In addition, the FDA provided an exemption to allow patients who had been receiving methadone for fewer than 3 years to receive weekly take-home medication. The Drug Enforcement Administration provided special methadone registrations to each physician participating in the clinical trial.

Narcotic Treatment Program. The NTP had a census of approximately 600 to 700 patients during the conduct of the study. The program provides the standard set of services to opioid-dependent patients through a combination of physician, certified drug and alcohol counselor, social work, and employment services. Patients presented

to the NTP on a once-a-week to 3-times-weekly schedule to ingest 1 dose and to receive their supply of methadone depending on their duration of maintenance and according to federal regulations that stipulate the frequency of patient contact. The regulations that were in place at the time of this study, for instance, prohibited weekly medication pick-up for patients with fewer than 3 years in treatment. Weekly group and monthly individual counseling was available and was provided by a clinician certified in addiction counseling. A random urine sample for toxicology testing was obtained on a monthly basis at the NTP.

Assessments

All assessments were performed uniformly in the 2 treatment conditions and were not shared with the clinical team. All urine and hair toxicology testing was performed blinded to treatment condition. Illicit drug use was measured by patient self-report and urine and hair toxicology testing. Urine samples were collected during monthly scheduled research assessments (nonrandomly) and randomly during clinical sessions. The collection of urine samples was supervised. Patients were observed entering and leaving the bathroom facilities and temperature determinations were performed on all samples. Urine toxicology analysis was performed using a semi-quantitative homogeneous enzyme immunoassay for opiates, cocaine, and methadone. Hair samples were collected at baseline and 3 and 6 months but were not analyzed until completion of the study and thus were not considered when assessing subjects for study eligibility or clinical care. Hair samples sufficient to detect opiate and cocaine use over a 90-day period were analyzed using radioimmunoassay (Psychemedics Corporation, Cambridge, Mass).²² This method provides a qualitative rather than a quantitative measure of opiate and cocaine metabolites.

Patient and clinician satisfaction items were measured on a 5-point Likert scale using standard questionnaires modified for the purpose of this study. Func-

tional status was measured using the Medical Outcomes Study Short-Form 36.²³ This 36-item structured questionnaire measures function in the following realms: physical, general health, vitality, social, emotional, and mental health. We used the Addiction Severity Index (ASI)²⁴ and a modified Treatment Services Review (TSR)²⁵ to measure, on a monthly basis, the impact of each patient's addiction on his/her function and service utilization in the realms of employment, drug use, alcohol use, and legal, family, and psychiatric problems. We used the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item inventory, to assess depressive symptoms. A CES-D score of 16 or higher is suggestive of a diagnosis of depression.²⁶

Clinical Instability and Retention

To ensure patient safety and prevent unremitting use of illicit substances, a priori criteria were established as evidence of clinical instability and the need for protective transfer to guarantee increased treatment services. A patient was considered to be clinically unstable if both of the following criteria were met: a random clinical urine sample had evidence of opiates or cocaine or lacked evidence of methadone; and a repeat urine sample, conducted within 1 week of the original sample, had evidence of opiates or cocaine or lacked evidence of methadone.

These criteria were applied equally in both treatment groups. Patients randomized to office-based methadone maintenance who met criteria for clinical instability were returned to the NTP for increased clinical monitoring, including medication pick-up 6 times per week, more frequent counselor sessions as needed, weekly group counseling, and more frequent urine toxicology testing. Patients in the NTP who met criteria for clinical instability also received increased clinical monitoring in this manner.

Data Analysis

The primary outcomes of interest were prospectively defined as relapse to il-

licit drug use, retention in the study protocol, and patient and clinician satisfaction. Secondary outcomes included functional status and the use of health and social services. Also, we were interested in evaluating the additional utility of hair toxicology testing for opiates and cocaine to the standard measures of patient self-report and urine toxicology in assessing illicit drug use and predicting treatment outcomes. Planned analyses for the primary end points included comparisons between treatment groups for proportion of patients with any evidence of illicit drug use, clinical instability leading to protective transfer from study protocol according to the established criteria, and ratings on patient and clinician satisfaction instruments.

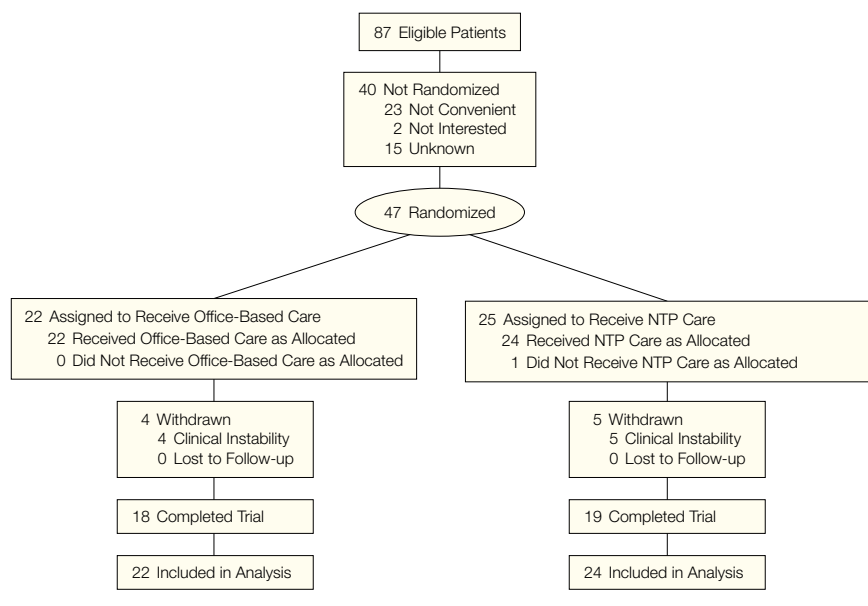
Baseline characteristics and outcomes were compared using the χ^2 test for dichotomous variables and the *t* test for continuous variables. We excluded from analysis urine and hair toxicology test results that indicated the presence of opiates in patients who had documentation of receiving medically prescribed opiate analgesics following medical procedures. Due to low attrition following randomization ($n=1$), the primary analyses were conducted on all enrolled and randomized patients who attended at least 1 assigned session. All analyses used 2-tailed tests of significance and were performed using SPSS version 10.0 (SPSS Inc, Chicago, Ill). $P<.05$ was considered statistically significant.

RESULTS

Patient Recruitment

Of the 115 patients who were referred by the NTP for participation in the study, 87 (76%) met the eligibility criteria. Of these 87 eligible patients, 47 (54%) were enrolled into the study protocol and were randomly assigned to office-based care ($n=22$) or usual care at the NTP ($n=25$). One patient randomized to NTP refused to participate, stating that he wanted only office-based care. Of the 41 patients who decided not to participate, 26 (63%) provided a reason. Twenty-three of the 41 nonparticipants (56%) declined due to a con-

Figure. Flow of Patients Through the Study



NTP indicates narcotic treatment program.

flict with their work schedule or perceived inconvenience (FIGURE).

Baseline Patient Characteristics

Baseline characteristics of patients in both groups are presented in TABLE 1. There were no significant differences between the groups for most major demographic and clinical characteristics including age, sex, employment, marriage status, duration of methadone treatment or dose of methadone, or HIV (human immunodeficiency virus) status. There were, however, significant differences between the groups by white race, history of intravenous drug use, and previous participation in an opioid detoxification program (Table 1).

Relapse to Illicit Drug Use

Using patient self-report and urine toxicology testing data, 12 of the 22 (55%; 95% confidence interval [CI], 34%-76%) patients in office-based care compared with 10 of 24 (42%; 95% CI, 22%-62%) NTP patients had any evidence of illicit drug use during the 6-month treatment period ($P=.38$). Eleven (50%; 95% CI, 29%-71%) office-based care patients compared with 9 (38%; 95% CI, 21%-57%) NTP patients had self-

report or urine toxicology testing that was positive for illicit opiates ($P=.39$). Four (18%; 95% CI, 3%-33%) office-based care patients and 4 (17%; 95% CI, 2%-30%) NTP patients had self-report or urine toxicology testing that was positive for cocaine ($P=.89$) (TABLE 2).

The frequency of drug use was investigated by determining the proportion of urine toxicology samples that had evidence of illicit drug use. Overall, there were 622 and 620 clinical and research urine toxicology procedures performed for opiates and cocaine, respectively. Of these, 63 (10%; 95% CI, 8%-13%) were positive for opiates and 24 (4%; 95% CI, 3%-6%) were positive for cocaine (Table 2). The proportion of opiate-positive urine results for those patients in office-based care was 22 of 252 (9%; 95% CI, 6%-13%) and 41 of 370 (11%; 95% CI, 8%-14%) in the NTP ($P=.34$). The proportion of cocaine-positive urine tests for patients in office-based care was 9 of 251 (4%; 95% CI, 2%-6%) and 15 of 369 (4%; 95% CI, 2%-6%) for those in the NTP ($P=.76$). Hair toxicology testing detected an additional 2 patients in each treatment group with evidence of illicit drug use, but this did not change the overall findings.

Clinical Instability and Retention

Criteria for clinical instability were met in 4 (18%; 95% CI, 7%-39%) office-based care patients compared with 5 (21%; 95% CI, 9%-41%) NTP patients ($P = .82$) (Table 2).

Patient and Clinician Satisfaction

On patient satisfaction questionnaires, 17 of 22 (77%; 95% CI, 59%-95%) office-based patients vs 9 of 24 (38%; 95% CI, 19%-57%) NTP patients reported that they were very satisfied with the treatment they received ($P = .01$). Additionally, 16 (73%; 95% CI, 54%-92%) of the office-based patients compared with 3 (13%; 95% CI, 0%-26%) of the NTP pa-

tients thought the quality of the care they received was excellent ($P = .001$). When asked at the completion of the study whether they would like to receive their medication in a physician's office or an NTP, 20 (91%; 95% CI, 79%-100%) of the office-based patients and 14 (58%; 95% CI, 38%-78%) of the NTP patients indicated that they would prefer to receive their medication from a physician's office ($P = .01$). In addition, questionnaire responses revealed that patients who received office-based care thought that the physicians' offices were conveniently located and had convenient appointments, that they were seen on time and received their medication on time,

that they were treated in a manner similar to other patients and rarely felt out of place, and that the staff and physicians were courteous and responsive to their concerns.

Both office-based physicians and NTP clinicians indicated that they were extremely satisfied with treating patients (11/20 office-based patients; 55% [95% CI, 33%-77%] and 14/23 NTP patients; 61% [95% CI, 41%-81%]) ($P = .99$). Office-based physicians believed that they had a good to excellent rapport with 19 (95%; 95% CI, 86%-100%) patients compared with 19 (83%; 95% CI, 68%-98%) for NTP clinicians ($P = .21$). In addition, questionnaire responses revealed that office-based physicians thought that their patients were on time for their appointments, followed clinical advice, were compliant with taking their medications, picking up and returning their medication bottles, and making their payments, were honest about their drug and alcohol use, and had an excellent attitude toward office staff and other patients. Office-based physicians did report, however, that their methadone maintenance patients had higher needs for emotional support and had more psychosocial stressors compared with their other patients.

Table 1. Baseline Characteristics of Patients Receiving Methadone in a Primary Care Office-Based Setting and in a Narcotic Treatment Program (NTP)*

Characteristic	Office-Based (n = 22)	NTP (n = 24)	P Value
Age, mean (SD), y	42 (5.7)	41 (5.8)	.38
Men, No. (%) [95% CI]	14 (64) [43-80]	16 (67) [47-82]	.92
White, No. (%) [95% CI]	13 (59) [39-77]	23 (96) [80-99]	.01
Employed full-time, No. (%) [95% CI]	13 (59) [39-77]	18 (75) [55-88]	.40
Monthly income, mean (SD), \$	1311 (849)	1751 (1337)	.21
Never married, No. (%) [95% CI]	8 (36) [20-57]	9 (38) [21-57]	.82
High school education or greater, No. (%) [95% CI]	19 (86) [67-95]	21 (88) [69-96]	.91
Previous detoxification attempt, No. (%) [95% CI]	18 (82) [62-93]	24 (100) [86-100]	.05
History of IV drug use, No. (%) [95% CI]	12 (55) [35-73]	21 (88) [69-96]	.03
Lifetime methadone maintenance, mean (SD), y	9.4 (8.4)	5.8 (4.4)	.07
Current methadone maintenance, mean (range), y	3.4 (1-9)	4.6 (1-14)	.24
Methadone dose, mean (range), mg/d	69 (20-100)	70 (25-100)	.91
Known HIV positive, No. (%) [95% CI]	6 (27) [13-48]	2 (8) [2-26]	.09
SF-36 score, mean (SD)†	115 (19)	113 (21)	.75
CES-D score, mean (SD)‡	10 (8)	11 (9)	.43

*CI indicates confidence interval; IV, intravenous; and HIV, human immunodeficiency virus.

†Scoring for the Medical Outcomes Study Short-Form 36 (SF-36) is described in the "Methods" section.

‡Scoring for the Center for Epidemiological Studies Depression Scale (CES-D) is described in the "Methods" section.

Table 2. Urine Toxicology and Self-report of Illicit Drug Use*

Results	No. (%) [95% CI]		P Value
	Office-Based (n = 22)	NTP (n = 24)	
Patients with evidence of illicit drug use	12 (55) [34-76]	10 (42) [22-62]	.38
Patients with evidence of opioid use	11 (50) [29-71]	9 (38) [21-57]	.39
Patients with evidence of cocaine use	4 (18) [3-33]	4 (17) [2-30]	.89
Urine test with evidence of illicit opiate use	22/252 (9) [6-13]	41/370 (11) [8-14]	.34
Urine test with evidence of cocaine use	9/251 (4) [2-6]	15/369 (4) [2-6]	.76
Patients meeting criteria for clinical instability†	4 (18) [7-39]	5 (21) [9-41]	.82

*CI indicates confidence interval; NTP, narcotic treatment program.

†Clinical instability was defined as a random clinical urine sample with evidence of opiates or cocaine or without evidence of methadone and a repeat urine sample, conducted within 1 week, with evidence of opiates or cocaine or without evidence of methadone.

Functional Status and Service Use

There were no significant differences over time within or between treatment groups in functional status as reflected by SF-36 scores. The mean (range) frequency of patient contact with the NTP for medication, nursing encounter, or counseling was 2.3 (1.1-5.1) per week compared with 1.6 (1.1-2.0) per week for those in office-based care ($P = .003$). The use of health, legal, and social services as measured on the ASI and a detailed TSR was similar between the 2 groups, and there were no significant changes over time. Few patients in either group required or received additional counseling sessions.

Predictive Value of Baseline Hair Toxicology

Following study completion, hair samples obtained at baseline were ana-

lyzed for evidence of illicit drug use. Despite all patients demonstrating baseline clinical stability with at least 1 year of urine toxicology testing without evidence of illicit opioid or cocaine use, 20 of 46 (44%; 95% CI, 30%-58%) patients had evidence of illicit opiate or cocaine use on baseline hair toxicology testing, including 11 (50%; 95% CI, 29%-71%) patients assigned to office-based methadone and 9 (38%; 95% CI, 19%-57%) patients assigned to the NTP.

Among the patients with evidence of illicit drug use on baseline hair toxicology results, 18 of 20 (90%; 95% CI, 77%-100%) had evidence of subsequent illicit drug use during the 6-month study period, compared with 5 of 26 (20%; 95% CI, 5%-35%) without evidence of illicit drug use on baseline hair toxicology tests ($P=.001$). A similar pattern was found for any opiate use (13/15; 85% [95% CI, 67%-100%] vs 5/31; 16% [95% CI, 3%-29%]; $P=.001$) and any cocaine use (6/10; 60% [95% CI, 30%-90%] vs 2/36; 4% [95% CI, 0%-10%]; $P=.001$). Similarly, 8 of 20 patients (40%; 95% CI, 19%-61%) with evidence of illicit drug use on baseline hair testing met criteria for clinical instability compared with 1 of 26 (4%; 95% CI, 0%-11%) without evidence of illicit drug use on baseline hair testing ($P=.005$).

Among the 25 patients with no evidence of illicit drug use by hair toxicology testing at baseline, 3 of 10 (30%; 95% CI, 2%-58%) office-based care patients vs 2 of 15 (13%; 95% CI, 0%-30%) NTP patients had subsequent evidence of any illicit drug use during the 6-month study period ($P=.31$). Two of 10 (20%; 95% CI, 0%-45%) office-based care patients with no hair toxicology evidence of illicit drug use at baseline vs 2 of 15 (13%; 95% CI, 0%-30%) NTP patients with no hair toxicology evidence of illicit drug use at baseline had any evidence of illicit opiate use during treatment ($P=.66$). Among patients with no hair toxicology evidence of illicit drug use at baseline, 1 of 10 office-based care patients (10%; 95% CI, 0%-29%) and 0% of NTP patients had any evidence of illicit co-

caine use during the 6-month study ($P=.21$).

COMMENT

This study represents the first randomized clinical trial of primary care-based methadone maintenance compared with standard care in an NTP for clinically stable opioid-dependent patients. Findings from this study support the generally comparable efficacy of this office-based approach compared with continued treatment in an NTP and are also notable for the unexpectedly high prevalence of illicit drug use among otherwise clinically stable patients in both treatments both before and during the study. Our results demonstrate that methadone maintenance using weekly physician office-based dispensing is feasible, that treatment retention and patient and clinician satisfaction are high, and that illicit drug use does not differ significantly compared with continued treatment in an NTP. Stable patients demonstrated high functional status and low levels of health and social service use on transfer from an NTP to office-based care. The high level of patient and clinician satisfaction with office-based care and the outcomes observed with office-based treatment run counter to concerns regarding the potential quality of this type of care²⁷ and the ability to identify a group of physicians interested in providing treatment for opioid-dependent patients.²⁸⁻³⁰

Despite these important findings, at least 1 episode of illicit drug use was detected in 22 of 46 (52%) patients overall, and 9 (20%) patients met criteria for clinical instability. This rate was unexpectedly high for patients who had been selected for clinical stability based on results of urine toxicology testing. Nonetheless, the proportion of patients with evidence of illicit drug use and the frequency of positive urine toxicology results were generally comparable and did not differ significantly between groups. This level of illicit drug use during treatment demonstrates the importance of ongoing clinical evalu-

ation in these patients and the role that physicians need to play in monitoring for evidence of lapses even among patients who have been selected for clinical stability.

Our results also demonstrate that hair toxicology testing provided important prognostic information. In this cohort of patients who were presumed abstinent based on at least 1 year of routine clinical urine toxicology testing, baseline hair toxicology testing revealed illicit drug use during the prior 90 days in 20 patients. Importantly, evidence of illicit drug use on hair toxicology testing at baseline was associated with ongoing drug use in 18 patients during treatment. This demonstrates the potential prognostic utility of this test to identify patients receiving methadone maintenance with a low likelihood of abstinence in either office-based or NTP-based care.

Our results provide information regarding the potential impact of this type of program on the overall narcotic treatment system. Office-based care, using the eligibility criteria for the current study, will likely be appropriate for a minority of patients in NTPs because only a small proportion of patients met the eligibility criteria for sufficient clinical stability to participate. The 87 eligible patients represented 12% to 14% of the 600 to 700 patients in the NTP. Use of hair toxicology to determine patient eligibility would likely reduce this percentage further.

Our results support and extend prior research that has demonstrated the efficacy of transferring stabilized opioid-dependent patients to physicians' offices.¹⁴⁻¹⁸ Prior studies, however, have been restricted to patients who had received care in an NTP for a minimum of 5 years, had documented abstinence for 3 years¹⁶⁻¹⁸ to 5 years,¹⁵ and were treated in hospital-based physicians' offices.¹⁶⁻¹⁸ In a specialized clinic pilot study,¹⁴ medical maintenance was provided to patients who had received methadone treatment for at least 1 year. These patients continued to attend their NTP on a monthly basis for counseling and urine toxicology testing.¹⁴ In

contrast to this early literature on medical maintenance, our study provided office-based care to patients who had received methadone maintenance for only 1 year, did not require contact with the NTP, and treated patients in community offices by trained primary care physicians.

This study has important findings that update the literature on office-based methadone maintenance. First, the model of dispensing methadone directly from physicians' offices on a weekly basis, developed to ensure at least weekly contact with the office, also appeared to create a restriction for patients who found the office hours inconvenient. Of note, however, the frequency of contact in the physicians' offices was lower than that in the NTP partly due to the regulatory requirements that dictated the frequency of contact in the standard care of an NTP. The model of dispensing medication from the physician's office also placed logistical burdens on the clinicians and required them to maintain separate records regarding transfer and storage of methadone. Second, this study provided a level of ancillary support and oversight through the monthly on-site reviews and 24-hour coverage for clinical concerns that might not be routinely provided in most clinical settings. The monthly continuing consultation and clinical education were important in developing each physician's clinical competence and ability to handle complicated clinical scenarios, such as self-reports of drug use or abnormal urine results. Future programs should consider a similar system to help ensure adequate physician oversight and training.

This study has some limitations. The power of the study to detect significant differences is limited by the study's relatively small sample size and the relatively short duration. Findings of no significant differences do not necessarily imply that outcomes were equivalent with the 2 treatments, and a larger sample size would be needed to have sufficient power to detect significant differences in the observed proportions of

patients with any evidence of illicit drug use or clinical instability. The findings of low incidences of clinical instability among the treatment groups in the current study (18% in office-based care and 21% in the NTP), consistent with prior research,¹⁴⁻¹⁸ suggest that a randomized clinical trial of approximately 5000 patients, using a 1:1 allocation ratio, would have sufficient power ($\beta = .80$) to detect a statistically significant difference in this outcome. A randomized clinical trial with a sample size of 492 patients, using a 1:1 allocation ratio, would be necessary to have sufficient power ($\beta = .80$) to detect a statistically significant difference of 13 percentage points, as was observed for the proportion of patients with illicit drug use (55% for office-based care and 42% for NTP). This limitation, however, does not compromise the demonstration of the feasibility of this model of office-based care.

One potential limitation of a randomized controlled open clinical trial with blocked randomization is that of selection bias due to lack of concealment of treatment allocation.^{31,32} In the current study this potential bias was minimized by the use of 3 distinct individuals, blinded to each other's work, to determine subject eligibility, perform randomization, and notify patients of treatment allocation. In this manner, the investigator who determined patient eligibility was removed from the process of treatment allocation.

Our study was limited to patients without other drug dependencies or untreated comorbid psychiatric conditions. Prior research demonstrates lifetime prevalence rates of 47% of comorbid psychiatric disease among patients who are entering methadone maintenance.³³ While management of patients with opioid dependence and untreated psychiatric disorders may be possible in a psychiatrist's office, these patients are likely to require services beyond those available in primary care physicians' offices. The finding of cocaine use in approximately one quarter of patients is consistent with prior

literature on patients receiving methadone maintenance^{34,35} and points out the importance of vigilance in screening for and treating this comorbid disorder.^{36,37}

The level of interest and expertise among the 4 physicians certified by ASAM is greater than that in the majority of practicing general internists and may limit the generalizability of our findings. Despite these qualifications, however, only 2 of the physicians had any prior experience in supervising the care of patients receiving opioid agonist maintenance therapy.

This study has implications for future treatment of opioid dependence. First, the results support the feasibility of transferring stable patients from NTPs to the offices of trained primary care physicians and extends prior research in this field.¹⁴⁻¹⁸ These findings, along with recent trials demonstrating the effectiveness of buprenorphine for untreated opioid-dependent patients in primary care settings,^{38,39} offer encouragement regarding the use of primary care offices to help expand access to treatment for opioid dependence. Second, baseline hair toxicology testing identified patients with evidence of recent illicit drug use who met eligibility criteria based on routine clinical data, and these patients were substantially more likely to use illicit drugs during treatment. Future programs should consider baseline hair toxicology testing to help determine patient eligibility for office-based care. Future research should evaluate the utility of hair toxicology results compared with other criteria for determining eligibility such as length of time in treatment. Third, as recently stated,^{27,40} the relatively low number of patients in the NTP who were eligible for office-based care has important implications for policy makers who might look to this model of care as a mechanism to achieve significant treatment expansion.^{1,4} Fourth, the inconvenience to the physician's office of dispensing medication on a weekly basis will make imperative the evaluation of models that use monthly supplies of methadone or community

pharmacy dispensing.^{41,42} Recent changes in the regulatory processes governing methadone maintenance that will allow greater flexibility in the provision of take-home medication may facilitate the development of monthly medication dispensing.⁴³ Finally, the high levels of patient and clinician satisfaction with the office-based model, detected using unvalidated standard questionnaires modified for this study, indicate that implementation of office-based programs will likely be well received by patients and clinicians.

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