A Randomized Trial of Buprenorphine Maintenance for Heroin Dependence in a Primary Care Clinic for Substance Users versus a Methadone Clinic

Patrick G. O’Connor, MD, MPH, Alison H. Oliveto, PhD, Julia M. Shi, MD, Elisa G. Trifileman, MD, Kathleen M. Carroll, PhD, Thomas R. Kosten, MD, Bruce J. Rounsaville, MD, Juliana A. Pakes, Richard S. Schottenfeld, MD

PURPOSE: Buprenorphine is an alternative to methadone for the maintenance treatment of heroin dependence and may be effective on a thrice weekly basis. Our objective was to evaluate the effect of thrice weekly buprenorphine maintenance for the treatment of heroin dependence in a primary care clinic on retention in treatment and illicit opioid use.

SUBJECTS AND METHODS: Opioid-dependent patients were randomly assigned to receive thrice weekly buprenorphine maintenance in a primary care clinic that was affiliated with a drug treatment program (n = 23) or in a traditional drug treatment program (n = 23) in a 12-week clinical trial. Primary outcomes were retention in treatment and urine toxicology for opioids; secondary outcomes were opioid withdrawal symptoms and toxicology for opioids; secondary outcomes were opioid withdrawal symptoms and toxicology for opioids.

RESULTS: Retention during the 12-week study was higher in the primary care setting (78%, 18 of 23) than in the drug treatment setting (52%, 12 of 23; P = 0.06). Patients admitted to primary care had lower rates of opioid use based on overall urine toxicology (63% versus 85%, P < 0.01) and were more likely to achieve 3 or more consecutive weeks of abstinence (43% versus 13%, P = 0.02). Cocaine use was similar in both settings.

CONCLUSIONS: Buprenorphine maintenance is an effective treatment for heroin dependence in a primary care setting.

mostly opioid-free urine samples (25). We therefore conducted a 12-week randomized clinical trial to compare the effects of thrice weekly buprenorphine in a primary care setting with those in a traditional drug treatment setting on retention in treatment and rates of opioid use.

METHODS

Patients
Patients were recruited from a methadone maintenance program waiting list and word-of-mouth referrals. Inclusion criteria were current opioid dependence according to DSM III-R criteria (26) and opioid-positive urine toxicology. Exclusion criteria were current DSM III-R diagnosis of other drug or alcohol dependence (other than tobacco), current cocaine use (defined as any use within the past month by self-report or by a positive urine toxicology for cocaine at the time of screening for admission to the study), complex medical comorbidity (eg, major cardiovascular, renal or gastrointestinal disease), complex psychiatric comorbidity (eg, psychosis, suicidality, schizophrenia, major depression), and pregnancy.

Treatment Settings
Eligible patients were randomly assigned to either a primary care clinic or a methadone maintenance clinic.

Primary care setting. Primary care-based buprenorphine maintenance was administered at the Central Medical Unit, a licensed, free-standing primary care clinic (27) that provides care for substance users who are enrolled in drug treatment programs affiliated with the Yale University Substance Abuse Treatment Unit, as well as for patients with psychiatric disorders enrolled in an affiliated mental health program. Approximately 1,300 patients receive medical services from the Central Medical Unit, which is staffed by primary care physicians (general internists), nurse practitioners, and physician associates. We utilized a manual-guided clinical management protocol developed by Fawcett and colleagues (28) adapted for use in the treatment of drug abuse (25,29). The protocol included taking a complete history, identifying medical problems, providing advice about changing behavior, prescribing medication, and referring patients to services. The initial session (week 1), designed to correspond to a “new patient” visit in primary care, was up to 1 hour in length to assure that patients received full clinical and research assessment. In this session the patient met the clinician who provided care during the entire course of therapy. The goals of this session were to review the medical and substance abuse history and complications associated with the patient’s substance abuse; to develop a substance abuse treatment plan including the benefits and risks of buprenorphine, and a treatment plan for medical issues; to provide a referral to group therapy; and to review program guidelines, and goals for subsequent sessions. Subsequent 20-minute sessions (weeks 2 through 12) corresponded to the “follow-up” visit format employed in primary care settings. These sessions reviewed substance use since the prior visit, urine toxicology results, commitment to treatment, attendance at group sessions, medication use, and medical and psychosocial issues, to determine goals for subsequent sessions. Patients met weekly in a 50-minute semistructured group session that was facilitated by a primary care nurse practitioner, and that utilized a self-help approach in which patients attempted to learn from each other concerning strategies to promote abstinence.

Drug treatment setting. The drug treatment site was the Legion Avenue Methadone Maintenance Program, which has been in operation since 1968 and has a census of over 300 patients. The clinic has been the site of several studies of buprenorphine maintenance (18,20). Patients randomly assigned to buprenorphine maintenance in the drug treatment setting received the standard set of services provided to patients in the clinic including assignment to a substance abuse counselor, medication, urine toxicology, and group therapy sessions. During the initial session (week 1), patients attended an extended intake session with their counselor (2 to 3 hours in length). Thereafter they attended clinic thrice weekly to receive medication, provide urine samples, and complete a self-report detailing drug use and opioid withdrawal symptoms. Once weekly, blood pressure and side effects were also evaluated, and patients attended a 60-minute group therapy session with their counselors, based on a 12-week manual-guided relapse prevention program designed for use in alcoholic patients (30) and modified for methadone-maintained individuals (31). On a monthly basis and as needed, patients met individually with their counselors to discuss psychosocial issues and their treatment plan.

Buprenorphine administration. In both treatment settings, sublingual liquid buprenorphine administration occurred in two phases. During buprenorphine stabilization in week 1, treatment was begun at a dose of 2 mg on day 1 and gradually increased to 4 mg (day 2), 8 mg (day 3), 16 mg (day 4), and 32 mg (day 5). During buprenorphine maintenance in weeks 2 to 13, treatment was administered thrice weekly at doses of 22 mg on Monday and Wednesday and 40 mg on Friday. Clinicians dispensing buprenorphine observed the patients, who were instructed to hold it under their tongue for up to 5 minutes to assure adequate absorption. Upon completion of the study, buprenorphine was tapered during a 3-week period, and patients were referred to drug treatment programs in the community.

Study outcomes. The primary outcomes of interest for this study were retention in treatment and urine toxicol-
ogy for opioids. Patients were discharged from the study if they missed medication on three successive occasions or if they failed to attend a weekly group therapy session. Discharged patients were referred to alternative drug treatment programs in the community. Urine toxicology testing was performed 3 times a week for the presence of opioids and cocaine using the Abbott Tdx system (32). Withdrawal symptoms were measured using an Opioid Withdrawal Symptom Scale that assessed self-reported experience of each of 17 opioid withdrawal symptoms on a 0 to 3 scale (none, mild, moderate, severe) (33).

**Statistical Analysis**

Baseline characteristics were compared with chi-square and t tests. Differences in retention rates were analyzed using the Kaplan-Meier product limit method and the generalized Wilcoxon test (34,35). Random regression models were chosen for the principal analysis of the effect of setting (primary care clinic or drug treatment program) on urine toxicology results and opioid withdrawal symptoms (36). This approach was designed for unbalanced repeated measures with missing data, allowing for intrasubject serial correlation and unequal variance and covariance structures across time, by incorporating data for each individual group. We estimated 95% confidence intervals (CI) to compare differences in rates or proportions (as relative risks [RR]). The BMDP statistical package was used. The primary intention to treat analyses were conducted on all 46 enrolled patients who met eligibility criteria.

**RESULTS**

**Baseline Patient Characteristics**

Of 46 heroin-dependent individuals enrolled in this study, 23 were assigned to each treatment group. Baseline sociodemographic and clinical features of the treatment groups were similar (Table). Most patients had used heroin intravenously during the past 30 days. Both groups had similar experience with prior methadone maintenance treatment.

**Treatment Outcomes**

Overall, 65% (30 of 46) of patients completed treatment. Of the 16 patients who left treatment, 2 were transferred to other treatment programs for reasons not directly related to the treatment protocol. One patient in the primary care group was transferred to inpatient treatment after becoming suicidal, and 1 patient in the drug treatment setting was transferred to methadone maintenance for medical reasons. The remainder (14) dropped out of treatment prior to the end of the study.

The proportions of patients remaining in treatment are shown in Figure 1. Rates of completion of the 12-week trial were 78% (18 of 23) in the primary care setting and 52% (12 of 23) in the drug treatment setting (RR = 1.5, 95% CI = 0.96 to 2.3, P = 0.06). There were significant effects of treatment setting and time on the rates of opioid-positive urine samples (Figure 2). Mean rates were lower in the primary care clinic (63%) than in the drug treatment program (85%, P < 0.01). The proportion of patients who achieved 3 or more consecutive weeks of abstinence from opioids, as determined by thrice weekly urine toxicology testing, was also higher in the primary care setting (44%, 10 of 23) than in the drug treatment setting (13%, 3 of 23; RR = 3.33, 95% CI = 1.05 to 10.56, P = 0.02). While the rate of opioid use decreased over

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Proportions of patients remaining in treatment protocol by study group.

<p>| Table. Baseline Demographic and Clinical Characteristics of the Study Groups |
|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Primary Care (n = 23) (%)</th>
<th>Drug Treatment (n = 23) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33 ± 10</td>
</tr>
<tr>
<td>Male</td>
<td>59</td>
</tr>
<tr>
<td>Caucasian</td>
<td>77</td>
</tr>
<tr>
<td>Never married</td>
<td>41</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.9 ± 1.2</td>
</tr>
<tr>
<td>Currently employed</td>
<td>44</td>
</tr>
<tr>
<td>Heroin use in past 30 days</td>
<td>29</td>
</tr>
<tr>
<td>Intravenous drug use in past 30 days</td>
<td>55</td>
</tr>
<tr>
<td>Previous methadone maintenance</td>
<td>96</td>
</tr>
<tr>
<td>Days of alcohol use in past 30 days</td>
<td>3.1 ± 6.6</td>
</tr>
</tbody>
</table>

Plus-minus values are mean ± SD. There were no significant differences between the two groups.
between setting and time (P < 0.001), it remained stable in the drug treatment program setting. Opioid withdrawal symptoms decreased over time in both settings (P < 0.001); there was no significant effect of setting on withdrawal symptoms (P = 0.6) or interaction between setting and time (P = 0.77). Although no patients reported cocaine use in the month prior to admission to the study and all had negative urine toxicology at that time, a substantial proportion of urine toxicology screens during the study were positive for cocaine: 30.5% in the primary care and 38.5% in the drug treatment groups. No substantial adverse effects were noted in either group.

Patients in the primary care treatment group were offered the option of continuing in that setting beyond the completion of the trial for an additional 10 weeks. All 18 patients who completed the 12-week trial accepted this option, 13 of whom remained in treatment for the full 22 weeks. Among these 18 patients, 38% of urine toxicology samples were positive for opioids during the continuation study.

**DISCUSSION**

Our results support the effectiveness of the primary care setting as an alternative to a drug treatment setting for providing thrice weekly opioid maintenance therapy to heroin-dependent patients “off-the-street.” Although a previous study evaluated methadone maintenance in a general medicine practice, patients in that study were required to have been on methadone maintenance at least 5 years with a high level of compliance, including clean urine toxicologies (9,37). This study also suggests that less than daily buprenorphine maintenance is effective. Most previous clinical trials have focused on daily buprenorphine, typically in doses of 8 to 16 mg sublingually (22–24). Amass et al (23) demonstrated that buprenorphine can be safely administered every 48 hours by doubling the maintenance dose. Similarly, Johnson et al (22) found that alternate-day dosing may also be effective in many patients. Because buprenorphine’s effects may last up to 72 hours, we were able to design a regimen that would be practical for primary care providers’ routine schedules (Monday, Wednesday, Friday dosing) (24,25).

Primary care-based opioid maintenance treatment may improve access to treatment. Properly trained clinicians could offer this treatment to their patients. This approach also offers the possibility of opioid maintenance treatment in communities, such as smaller towns, where methadone maintenance programs are not available. The treatment protocol used in this study was designed to be applicable to most primary care settings. We employed brief counseling techniques routinely used by primary care physicians (6,38); intervention approaches with a content similar to ours are effective in decreasing alcohol use in these settings (39–42). The visit sessions in this study were similar in time and effort to usual follow-up visits, and used an advice and clinical management approach that is well within the capabilities of most primary care providers (6,28,39,41). However, the number of visits was greater than that seen in typical brief intervention studies (41), and one might argue that weekly visits may be impractical. Other primary care patients may require a similar level of care, including selected patients with chronic conditions such as depression (43), diabetes (44), and HIV disease (45). It is possible that the frequency of visits may be diminished as patients remain in therapy for longer periods of time (25).

Our initial aim in this study was to demonstrate that primary care-based buprenorphine maintenance would be at least as effective in promoting retention in treatment and decreasing opioid use as a drug treatment program approach. We were surprised to find that patients assigned to the primary care-based treatment actually did better than those assigned to a traditional methadone maintenance setting. Patients assigned to the primary care setting may have received more intensive individual attention than those treated in the methadone maintenance clinic, given the weekly visits with the primary care providers (46). The retention rates and urine toxicology results in our primary care patients were similar to those reported in other studies of patients given buprenorphine maintenance (14,17,47) as well as traditional methadone maintenance (18,47). Urine toxicology results may continue to improve after the 12-week duration of the randomized trial, as was seen in our continuation study (25,38). Finally, the willingness of our primary care patients to remain in this setting (as opposed to being transferred to opioid maintenance in a traditional setting) and their continued retention for 22 weeks suggests that patients are satisfied with this approach.

Primary care-based drug treatment may have other unique advantages. Traditional primary care settings, more so than the primary care setting used in this study, may avoid some of the “negative” aspects of opioid main-
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The high rate of concurrent cocaine use and to consider strategies in providing this treatment need to be aware of the positive for cocaine during the study. Clinicians interested in offering this treatment to patients who were dependent on cocaine, able in primary care settings. Despite our attempt to screen out patients who were dependent on cocaine, psychiatric disease require more services than are available in primary care settings. The doses of buprenorphine that we used were based on our previous experience with daily buprenorphine use (18), published literature concerning the potential use of buprenorphine as less than daily medication (23), and our pilot study of thrice weekly buprenorphine maintenance (25). There is controversy concerning the optimal daily dose of buprenorphine. In general, lower doses (4 to 8 mg/day) are thought to be less effective than standard doses of methadone (48) or higher doses (12 to 16 mg/day) of buprenorphine (49). The weekly total dose of buprenorphine (84 mg) received by our patients is equivalent to daily administration of 12 mg, a dose that is generally considered to be effective (48). Given that 16 mg/day may be more effective (47), patients may do better on a thrice weekly regimen with a greater total dose, such as 32 mg on Monday and Wednesday and 48 mg on Friday.

Enrollment in this study was limited to patients without other drug dependence or severe psychiatric comorbidity. Patients with multiple substance dependencies or psychiatric disease require more services than are available in primary care settings. Despite our attempt to screen out patients who were dependent on cocaine, approximately one third of urine toxicology reports were positive for cocaine during the study. Clinicians interested in providing this treatment need to be aware of the high rate of concurrent cocaine use and to consider strategies to address this problem. More effective screening procedures may also be needed to minimize cocaine use in patients treated in primary care settings.

Our results need to be interpreted in light of the small sample size and the relatively short follow-up period of 12 weeks. Although data from our pilot study demonstrated that this approach was successful for up to 6 months in most patients (25), additional studies with larger numbers of patients and longer term follow-up are needed before this approach can be generalized.

Properly trained primary care physicians, including general internists, are well suited to care for patients with opioid dependence (13,50). Prior research suggests that the pharmacologic and nonpharmacologic treatments employed in this study can be provided by appropriately trained primary care providers (7,8,10,25,41,42,46,51). New approaches to managing substance use in primary care settings are central to ongoing efforts to link substance abusers to primary medical care (53). An additional barrier that would need to be addressed is the method of reimbursement for these services in primary care settings. Capitated, full-risk managed care plans may provide an impetus for this type of comprehensive treatment.

In summary, this study demonstrates that thrice weekly primary care-based buprenorphine maintenance is an effective approach to promoting retention in treatment and deceased opioid use in managing heroin-dependent patients. Future research should more precisely define the dose schedules of buprenorphine, examine this approach in other primary care settings, and identify the subpopulation of drug users for whom primary care-based treatment may be suitable.

REFERENCES

8. O’Connor PG, Carroll KM, Shi JM, et al. Three methods of opioid...


