Drug Treatment Outcomes Among HIV-Infected Opioid-Dependent Patients Receiving Buprenorphine/Naloxone

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Background: Buprenorphine/naloxone allows the integration of opioid dependence and HIV treatment.

Methods: We conducted a prospective study in HIV-infected opioid-dependent patients to investigate the impact of buprenorphine/naloxone treatment on drug use. Self-report and chart review assessments were conducted every 3 months (quarters 1–4) for 1 year. Outcomes were buprenorphine/naloxone treatment retention, drug use, and addiction treatment processes.

Results: Among 303 patients enrolled between July 2005 and December 2007, retention in buprenorphine/naloxone treatment was 74%, 67%, 59%, and 49% during Quarters 1, 2, 3, and 4, respectively. Past 30-day illicit opioid use decreased from 84% of patients at baseline to 42% in retained patients over the year. Patients were 52% less likely to use illicit opioids for each quarter in treatment (Odds ratio = 0.66; 95% CI: 0.61 to 0.72). Buprenorphine/naloxone doses and office visits approximated guidelines published by the United States Department of Health and Human Services. Urine toxicology monitoring was less frequent than recommended.

Conclusions: Buprenorphine/naloxone provided in HIV treatment settings can decrease opioid use. Strategies are needed to improve retention and address ongoing drug use in this treatment population.

Key Words: Buprenorphine, heroin dependence, HIV, methadone, opioid-related disorders

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INTRODUCTION

Opioid dependence, defined as the uncontrolled use and misuse of opioids such as heroin or prescription pain medication,[1] is a chronic and relapsing medical disorder with a well-established biopsychosocial basis.[2] Medications such as methadone and buprenorphine are the most effective treatments for opioid dependence.[3] Methadone and buprenorphine treatment of HIV-infected individuals have both been shown to decrease HIV transmission risk and improve HIV biological outcomes.[4–7] Nonetheless, few sites integrate the treatment of HIV and opioid dependence; consequently patients must often seek and receive care at 2 separate locations. This situation is due in part to regulations that restrict the provision of methadone for the treatment of opioid dependence to opioid treatment programs that are governed by federal regulations, limited in number and geographical distribution, and often have limited capacity to provide HIV specialty care.

Since late 2002, buprenorphine (primarily as buprenorphine/naloxone) has been used in the United States to treat opioid dependence. One potential advantage of buprenorphine/naloxone over methadone is the ability for qualifying physicians, including those with expertise in treating HIV infection, to prescribe this medication for dispensing at a pharmacy. This integration of addiction and HIV treatment provides an opportunity to coordinate care of these 2 medical

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The BHIVES Collaborative members are listed in Appendix 1.

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conditions in 1 setting, the HIV primary care clinic. The impact of integrating the care of opioid dependence and HIV on drug use has not been firmly established. Although initial studies demonstrate promise,[4,8] data are not yet available from multiple sites and in a large number of patients. Therefore, the purpose of the current study is to investigate the impact of buprenorphine/naloxone treatment on drug use outcomes in opioid-dependent patients who are HIV-infected.

METHODS

Study Design

The overall design of the Buprenorphine and Integrated HIV Care Model Demonstration Project (BHIVES) has been described elsewhere.[9,10] Briefly, 9 sites, with 10 unique implementation protocols, participated in this evaluation and contributed data to the current analysis. Each protocol included at least one arm that provided buprenorphine/naloxone to opioid-dependent HIV-infected individuals in a HIV primary care setting. Patients were allowed to switch between treatment arms in some protocols. In the current analysis, we report on patients who received buprenorphine/naloxone, defined as those patients who were prescribed buprenorphine/naloxone at the beginning of the study period and received at least 1 dose of buprenorphine/naloxone regardless of subsequent treatment (ie, intention to treat).

Clinician Training and Support

The HIV clinicians at most sites had limited or no experience providing buprenorphine/naloxone to opioid-dependent patients before the project although each site had affiliated personnel with expertise in the use of the medication. The BHIVES Evaluation and Support Center (Center) included 4 clinical experts, each with greater than 5 years of experience providing buprenorphine/naloxone.[9] Before patient enrollment, the Center, in conjunction with the American Society of Addiction Medicine, provided an 8-hour training for physicians and clinical staff of all the sites. The Center coordinated monthly 1-hour-long technical assistance conference calls to discuss issues related to clinical management. The sites also participated in a restricted access listserv that allowed for discussion of clinical issues via email and dissemination of appropriate clinical support materials. Finally, additional technical assistance was provided to clinicians during annual meetings, site visits, and individually, as needed, by telephone and email.

Patients

To participate in the BHIVES study, all patients were required to meet the following inclusion criteria: 18 years or older, HIV-infected, meet DSM-IV criteria for opioid dependence,[1] aspartate transferase or alanine transferase less than 5 times the upper limits of normal per the local reference laboratory, willing and able to participate for 1 year, able to provide informed consent, and fluency in English or Spanish. Patients were excluded if they met criteria for benzodiazepine dependence or alcohol dependence, were pregnant or trying to become pregnant, were acutely suicidal or had psychiatric conditions affecting their ability to provide informed consent (eg, dementia, delusional, actively psychotic) or were deemed otherwise inappropriate for the study according to the clinical judgment of the prescribing physician.

Measures

Uniform measures were collected on patients at predetermined intervals. Data were collected at the time of study enrollment (baseline) and quarterly for a year. Demographic and clinical data were collected via self-report and chart abstraction by research assistants.

Substance Use and Psychiatric Data

Drug and alcohol use data were collected at baseline (lifetime and past 30 days) and at each follow-up interval (past 30 days) using the Addiction Severity Index (ASI)–Lite. The ASI-Lite is a validated self-report measure used to assess the severity of drug and alcohol use and associated psychosocial impairment.[11,12] Patients were asked to provide information about their use of opioids such as heroin, nonprescribed methadone, other opioids (nonmedical use of oxycodone, hydrocodone, morphine, hydromorphone), stimulants: cocaine or methamphetamines, alcohol, and sedatives/barbiturates (eg, benzodiazepines, referred to as sedatives from hereon). Because sites were not consistent in their timing or use of urine toxicology analysis, these data are not included. Depression was assessed using the Center for Epidemiologic Studies Depression Scale.[13]

Addiction Treatment Process Data

To assess the impact of process measures that might affect drug treatment outcomes, we collected information on buprenorphine/naloxone dose prescribed, the number of buprenorphine/naloxone-related office visits attended, and number of urine toxicology analyses performed. Buprenorphine/naloxone dose was assessed via chart abstraction. Buprenorphine/naloxone-related office visits were assessed via chart abstraction and included any visit to a buprenorphine/naloxone clinician (physician, nurse, nurse practitioner, pharmacist, counselor) and any related visits (eg, urine collection, prescription pick up).

HIV Data

Data on years since HIV diagnosis, current HIV treatment, and biologic markers (CD4 lymphocyte counts and HIV RNA) was collected via self-report, chart extraction or direct measurement via blood collection and analysis. Antiretroviral adherence was measured using the CASE adherence index.[11]

Data Analyses

Analyses of baseline measures used descriptive statistics, χ^2 and t tests as appropriate. Buprenorphine/naloxone dose, methadone dose, CASE index score, number of buprenorphine/naloxone-related office visits, number of urine toxicologies collected, and ASI scores were analyzed within quarters using Analysis of Variance. The primary outcome measure was retention in buprenorphine/naloxone treatment over the 1 year period. Treatment retention was assessed on

a quarterly basis. Patients were considered retained in buprenorphine/naloxone treatment only if the chart abstraction data indicated that they received any buprenorphine/naloxone treatment during a quarter. Therefore, patients were categorized as in buprenorphine/naloxone treatment, not in buprenorphine/naloxone treatment, or lost to study follow-up at each quarter. Patients were re-induced onto buprenorphine/naloxone if there were treatment interruptions (no buprenorphine/naloxone for at least 7 days). Because patients were allowed to reinitiate treatment with buprenorphine/naloxone within a 1-year window of their initial entry into the study, we catalogued the number and timing of their re-inductions onto buprenorphine/naloxone. Retention was analyzed using the Kaplan–Meier product limit method and the generalized Wilcoxon test. To determine those factors associated with retention in buprenorphine/naloxone treatment at quarter 4, we performed a stepwise forward logistic regression using the following variables; age, gender, race/ethnicity (black vs. other), housed, primarily prescription opioid user, years of opioid dependence, recent stimulant use, Center for Epidemiologic Studies Depression Scale score, ASI alcohol score, ASI drug score, years since HIV diagnosis, receiving antiretroviral treatment, CASE score, CD4, and log HIV RNA. We included variables in the model if they were associated with the outcome at the $P < 0.10$ level. The final model only included those variables significant at $P < 0.05$. Secondary outcomes included self-reported illicit opioid, stimulant, and sedative use by quarter. Generalized Estimating Equations were used to evaluate time effects. Odds ratios (ORs) and 95% confidence intervals (CIs) controlled for site and were calculated using generalized estimating equations, Logit link function.

TABLE 1. Baseline Characteristics of 303 HIV-Infected Opioid-Dependent Patients Receiving Buprenorphine/Naloxone

Characteristic	
Age, mean (SD)	45.2 (8.1)
% Male	67.7
Race/ethnicity	
% White	22.7
% Black	51.5
% Hispanic	22.4
% Other	3.3
% High school education or greater	57.6
% Employed	25.7
% Heroin user*	61.3
% Heroin/other opioid user*	21.1
% Other opioids*	17.6
% Injection drug use at treatment entry	60.1
Years of opioid dependence, mean (SD)	17.21 (11.1)
% Recent alcohol use	49.2
% Recent cocaine use	66.0
% Recent methamphetamine use	6.0
CES-D score, mean (SD)	2.45 (0.73)
ASI Alcohol Score score, mean (SD)	8.56 (11.9)
ASI Drug Score score, mean (SD)	32.03 (12.9)
Years of HIV diagnosis, mean (SD)	12.2 (6.5)
% Antiretroviral treatment at treatment entry	59.9
Case adherence index score	11.1 (6.5)
Baseline CD4, mean (SD)	353 (261)
Baseline log HIV RNA, mean (SD)	3.47 (1.1)

*Two hundred and fifty-six of 303 reported heroin or prescription opioid use within 30 days of starting buprenorphine/naloxone.
CES-D, Center for Epidemiologic Studies Depression Scale.

RESULTS

Characteristics

Table 1 shows the demographic and clinical characteristics of the 303 patients who received at least 1 dose of buprenorphine/naloxone. The majority of patients were male, black, high school graduates, unemployed, and reported recent injection drug use and recent cocaine use.

Treatment Retention

Table 2 shows the number and percentage of patients who received buprenorphine/naloxone treatment, did not receive buprenorphine/naloxone treatment, and were lost to follow-up at baseline and during each quarter. Retention in buprenorphine/naloxone treatment was 225 of 303 (74%), 204 of 303 (67%), 179 of 303 (59%), and 149 of 303 (49%) during Quarters 1,2, 3, and 4, respectively. During the 1-year period, 23 (8%) patients transferred from buprenorphine/naloxone to methadone and 8 patients (3%) switched to other (eg, inpatient, detoxification) treatments. Female gender (OR: 1.72; CI: 1.04 to 2.87), black race (OR: 1.7; CI: 1.05 to 2.73), and a greater number of years since the diagnosis of HIV (OR: 1.05; CI: 1.01 to 1.09) were associated with retention at quarter 4.

Re-inductions

Eighty-two of the 303 (27%) patients underwent re-induction onto buprenorphine/naloxone during study enrollment. Sixty-two patients (76%) had 1 re-induction, 17 (21%) had 2, and 3 (4%) had 3 re-inductions. Of the re-inductions, 73 (88%) took place within quarter 1 or quarter 2. Patients who underwent re-induction during quarter 1 or 2 were 3.56 times less likely than those without re-inductions to be retained in buprenorphine/naloxone treatment during the course of treatment.

Illicit Drug Use

Table 3 shows the prevalence of illicit drug use by quarter. Self-reported illicit opioid use in the past 30 days

TABLE 2. Treatment Retention in HIV-Infected Patients Receiving Buprenorphine/Naloxone (n = 303)

	% Retained	% Not Retained	% Lost to Follow-Up
Baseline	100.0	NA	NA
Quarter 1	74.3	9.9	15.8
Quarter 2	67.3	11.6	21.1
Quarter 3	59.1	14.2	26.7
Quarter 4	48.2	17.2	33.7

TABLE 3. Percent of Illicit Opioid, Stimulant, and Sedative Use in HIV-Infected Patients Receiving Buprenorphine/Naloxone

	n	Opioids	Stimulants	Sedatives
Baseline	302	84.4	58.3	17.9
Quarter 1	219	43.8	40.2	13.2
Quarter 2	196	38.8	41.8	9.7
Quarter 3	185	41.6	41.6	10.3
Quarter 4	191	42.4	38.7	11.5

decreased from 84% of patients at baseline to 42% of patients over the 4 quarters. On average, patients were 33% less likely to use illicit opioids in the past 30 days for each quarter they were prescribed buprenorphine/naloxone (OR: 0.67; CI: 0.61 to 0.72). Self-reported illicit stimulant use in the past 30 days decreased from 58% of patients at baseline to 41% of patients over the 4 quarters of treatment. On average, patients were 17% less likely to use stimulants in the past 30 days for each quarter that they were prescribed buprenorphine/naloxone (OR: 0.83; CI: 0.76 to 0.90). Self-reported sedative use in the past 30 days decreased from 18% of patients at baseline to 12% of patients over the 4 quarters of treatment. On average, patients were 13% less likely to use sedatives in the past 30 days for each quarter that they were prescribed buprenorphine/naloxone (OR: 0.87; CI: 0.77 to 0.98).

Addiction Treatment Process Measures

Table 4 shows the dose of buprenorphine/naloxone prescribed, number of buprenorphine/naloxone-related office visits, and number of urine toxicology analyses performed by quarter. The mean dose of buprenorphine/naloxone per quarter ranged between 16.9 mg and 18.2 mg; range 2 mg to 44 mg. The dose of buprenorphine/naloxone increased across quarters by approximately 0.5 mg (Beta = 0.42; CI: 0.03 to 0.80). The mean number of buprenorphine/naloxone-related office visits per quarter decreased from 7.1 to 5.3 from the first to last quarter (range 0–54 per quarter). The mean number of urine toxicology analyses conducted per quarter decreased from 3.8 to 1.5 from the first to last quarter (range from 0 to 16 per quarter).

TABLE 4. Process Data on Office-Based Treatment of HIV-Infected Patients Receiving Buprenorphine/Naloxone or Methadone

Variable	Mean (SD), Median, Range
Buprenorphine/naloxone dose	
Quarter 1	16.9 (6.6), 16, 2–40
Quarter 2	17.1 (7.3), 16, 2–44
Quarter 3	17.5 (6.8), 16, 2–40
Quarter 4	18.2 (7.1), 16, 2–44
Number of buprenorphine/naloxone-related office visits	
Quarter 1	7.1 (7.3), 5, 0–39
Quarter 2	5.9 (7.0), 4, 0–39
Quarter 3	7.3 (9.3), 4, 0–50
Quarter 4	5.3 (6.9), 3, 0–38
Number of urine toxicologies obtained	
Quarter 1	3.8 (3.8), 3, 0–14
Quarter 2	2.7 (3.1), 2, 0–16
Quarter 3	2.7 (3.3), 2, 0–16
Quarter 4	1.5 (2.2), 1, 0–12

DISCUSSION

Our data represent the largest reported cohort to date of HIV-infected patients who received buprenorphine/naloxone treatment and have been followed systematically over a 1-year period. The retention findings are overall similar to those observed among HIV-infected opioid-dependent patients who received buprenorphine in an earlier small trial and a French observational cohort.[4,14] This finding may reflect the low threshold for treatment re-entry employed in the current study.

Our study provides novel data on the frequency of re-induction onto buprenorphine/naloxone in this patient population and the poor prognosis associated with re-induction. Nearly one third of patients required re-induction onto buprenorphine/naloxone and re-induction during the first 6 months of treatment was associated with poorer retention in treatment overall. Our data on retention reflects the subsequent use of other treatment options by patients initiated on buprenorphine/naloxone. It is notable that more than 10% of patients who initiated treatment with buprenorphine/naloxone went on to receive another treatment during the course of the year-long study. The treatment retention and opioid and stimulant use findings are consistent, also, with those observed with buprenorphine treatment among HIV-negative patients in specialty and office-based treatment settings.[15–18] The rate of ongoing abuse of sedatives is a concern given that benzodiazepine dependence was an exclusion criterion and the potential for overdose when benzodiazepines are abused in combination with buprenorphine administration.[19]

Most patients received doses of buprenorphine/naloxone and office visits at a frequency that is consistent with prior research and federal guidelines.[15,16,20] Urine toxicology monitoring was less frequent, however, than what is recommended by existing guidelines on the use of buprenorphine/naloxone in the treatment of opioid dependence.[20] There is limited literature that reports process data on office-based treatment of opioid dependence in the United States. A prior study presented data on processes of care in a clinical trial of office-based methadone.[21] Federal evaluations have provided limited descriptions of physician practice patterns with office-based treatment using buprenorphine/naloxone.[22] The current findings demonstrate substantial adherence by clinicians to guidelines for treatment of opioid dependence, although they highlight 2 areas of concern. The first area is that of buprenorphine/naloxone dosing. There are no clinical trials that demonstrate a benefit to prescribing doses of buprenorphine/naloxone greater than 24 mg. The package inserts for the commercial products that are currently available in the United States indicate that the highest recommended dose is 24 mg. Despite this recommendation, there is evidence that at least 1 physician prescribed up to 44 mg of buprenorphine/naloxone to a patient. This practice raises concerns about potential diversion of extra medication doses and hepatotoxicity.[23–26]

The second area of concern is that of urine toxicology monitoring. Infrequent monitoring of illicit drug use via objective measures such as urine toxicology analyses raises concern for undetected relapse or use of other substances, such as cocaine and benzodiazepines, that might require independent treatment. Guidelines for the use of buprenorphine/naloxone recommend monthly urine toxicology monitoring in patients with demonstrated abstinence. More frequent monitoring is recommended in patients with ongoing illicit drug use.[20,27–29] All sites in the current study included protocols that planned for urine toxicology analyses on a monthly basis. Despite this, urine toxicology screening was obtained a median of 1–2 times over a 3-month period of time during quarter 2–4. This occurred despite patients receiving buprenorphine/naloxone-related visits at a higher rate during the same time. This level of urine toxicology screening is below that required by current federal regulations in patients receiving care in opioid treatment programs (8 urine toxicology analyses per year), and raises the possibility that there are structural or attitudinal barriers to conducting urine toxicology screening as planned and as is recommended. Of note, the technical assistance conference calls did not systematically review the treatment provided to patients in the study but rather responded to questions raised by the clinicians who attended the calls. Future technical assistance and support for new providers of buprenorphine/naloxone treatment may benefit from routine surveillance of key indicators such as buprenorphine/naloxone dosage and urine toxicology testing.

The current study has limitations. First, the lack of a randomized design with a control group prevents us from making comparisons between treatments. Second, our measure of buprenorphine/naloxone treatment retention, any receipt of treatment during a specified quarter, likely overestimates therapeutic treatment retention. In addition, patients were allowed to undergo re-induction onto buprenorphine/naloxone, a practice not included in prior reports of controlled trials. Third, we were able to obtain complete follow-up data on 201 of 303 (66%) of all participants. The statistical approaches we used to account for missing data only partially address this limitation. All prospective research faces challenge of study retention. In studies on opioid dependence, lack of retention in treatment is often associated with relapse and nonadherence to study assessments. Illicit drug use is likely higher in those who were not retained in treatment but could reflect prolonged successfully treated addiction. Fourth, the results were obtained in practice settings that had limited prior experience with the use of buprenorphine/naloxone at the initiation of the study and that received training and ongoing clinical feedback and support. The results obtained may not directly transfer to settings with more experience or with less clinical support and mentorship. Fifth, there was significant variation in the personnel, visit frequency, and type and frequency of counseling across the sites.[9] Finally, 3 sites contributed 46% of patients, raising the possibility that outcomes would have differed if the distribution of patients was more uniform across the models of care that were implemented.

Our study has implications for clinical care and research. The results demonstrate the feasibility of providing buprenorphine/naloxone treatment in a variety of HIV primary care settings. The sites in the current study included academic medical centers and community health centers that receive funding through the Health Resources Service Administration's Ryan White Care Act. The current findings should provide encouragement to sites that are planning to implement buprenorphine/naloxone in HIV primary care. In particular, attention should be paid to the level of staffing and resources that were used to develop and sustain integrated programs.[30] The question of which model of integrated care delivery results in optimal resource use and addiction and HIV outcomes may be contingent upon local services and is addressed in separate papers in the current volume.[9,30] Further research on strategies to improve retention, the optimal type and intensity of counseling, the impact of varying intensities of urine toxicology monitoring, and the role of concomitant substance use on addiction and HIV outcomes would help refine the integration of treatment for these 2 medical conditions.

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APPENDIX 1: BHIVES COLLABORATIVE

The CORE Center (Chicago, IL), El Rio Santa Cruz Neighborhood Health Center (Tucson, AZ), Johns Hopkins University (Baltimore, MD), Miriam Hospital (Providence, RI), Montefiore Medical Center (Bronx, NY), OASIS (Oakland, CA), Oregon Health Sciences University (Portland, OR), University of California San Francisco Positive Health Program at San Francisco General Hospital (San Francisco, CA), University of Miami Medical School (Miami, FL), Yale University School of Medicine (New Haven, CT), and The New York Academy of Medicine (New York, NY).