

Long-Term Treatment with Buprenorphine/Naloxone in Primary Care: Results at 2–5 Years

David A. Fiellin, MD,¹ Brent A. Moore, PhD,² Lynn E. Sullivan, MD,¹
 William C. Becker, MD,³ Michael V. Pantalon, PhD,² Marek C. Chawarski, PhD,²
 Declan T. Barry, PhD,² Patrick G. O'Connor, MD, MPH,¹ Richard S. Schottenfeld, MD²

¹Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

²Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut

³Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania

To examine long-term outcomes with primary care office-based buprenorphine/naloxone treatment, we followed 53 opioid-dependent patients who had already demonstrated six months of documented clinical stability for 2–5 years. Primary outcomes were retention, illicit drug use, dose, satisfaction, serum transaminases, and adverse events. Thirty-eight percent of enrolled subjects were retained for two years. Ninety-one percent of urine samples had no evidence of opioid use, and patient satisfaction was high. Serum transaminases remained stable from baseline. No serious adverse events related to treatment occurred. We conclude that select opioid-dependent patients exhibit moderate levels of retention in primary care office-based treatment. (Am J Addict 2008;17:116–120)

Buprenorphine/naloxone is a viable treatment for patients with prescription opioid or heroin dependence. Certified office-based physicians are increasingly providing this treatment.¹ However, patients and providers express uncertainty regarding the efficacy, appropriate duration, and long-term safety of buprenorphine/naloxone treatment. There are reasons to believe long-term treatment with buprenorphine may be effective. First, a substantial literature supports the efficacy of long-term methadone treatment when compared to short-term treatment or detoxification.² In addition, long-term retention in treatment is an important predictor of abstinence from illicit drug use.

Retention in opioid agonist treatment varies by site and medication. Roughly one-third of patients enrolled in treatment program-based methadone are retained for one to five years.^{3–6} Office-based and addiction treatment program-based

buprenorphine has been associated with retention of 39–55% at six months^{7,8} and 54% at three years.⁹

Since the introduction of buprenorphine/naloxone into the United States in 2003, no study has provided information on long-term outcomes with this formulation when provided in clinical practice. To describe the clinical course of opioid-dependent patients receiving office-based buprenorphine/naloxone treatment in primary care, we conducted an exploratory analysis of the efficacy and safety of this treatment in patients who received this treatment for up to five years.

METHODS

Patients

Patients became eligible for entry into this observational study at the completion of their participation in a clinical trial. Of the 166 randomized patients, fifty-three, or 32%, had achieved at least nine weeks of abstinence at any point during the trial and were serially entered into a compassionate use extension phase for this long-term study. The design and results of the six-month trial have been previously reported.⁷ Briefly, at entry into the six-month trial, all patients met criteria for opioid dependence¹⁰ and were excluded if they were dependent upon alcohol or benzodiazepines; were a danger to themselves or others; psychotic or experiencing major depression; unable to comprehend English; or experiencing life-threatening medical problems. Women of childbearing age agreed to adequate contraception and monthly pregnancy monitoring. Enrollment into the long-term phase of the study began on 3/4/2001 and ended on 9/28/2004. Data presented here was collected until 08/25/06. Therefore, all patients were eligible for at least two years of follow-up while receiving buprenorphine. The study was approved by the Human Investigation Committee of Yale University School of Medicine.

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Address correspondence to Dr. Fiellin, Yale University School of Medicine, 333 Cedar St., P.O. Box 208025, New Haven, CT 06520-8025. E-mail: david.fiellin@yale.edu.

Setting

The setting was the Primary Care Center of a large, urban, academically-affiliated hospital.

Buprenorphine/Naloxone

Buprenorphine was provided as the buprenorphine/naloxone combination tablet, which includes buprenorphine and naloxone in a 4:1 ratio. The initial target dose of buprenorphine was 16 milligrams daily. Dose increases to a maximum of 24 milligrams were provided based upon patient discomfort or evidence of ongoing illicit drug use. There was no attempt on the part of the physicians to taper medication doses over time. Dose reductions were made after discussion with the physician and based on patient request.

Medication Dispensing

Buprenorphine-naloxone was dispensed for take-home administration by nurses thrice weekly, weekly, or every two weeks, depending upon patients' clinical stability.

Counseling

All patients met with one of four physicians monthly for approximately 20 minutes and received a counseling approach with demonstrated efficacy.^{7,11–13} The content of the physician sessions was outlined in a structured clinical note and covered the following:

1. recent drug use or efforts at abstinence;
2. self-help group attendance;
3. support for efforts to reduce drug use or remain abstinent;
4. advice for achieving or maintaining abstinence;
5. review of urine specimen results; and
6. assessment of addiction-related employment, legal, family/social, medical or psychiatric problems or progress.

In addition, care was provided for those patients with primary medical care needs (eg, hypertension, asthma) and psychiatric diagnoses (eg, anxiety, depression) if they did not have an alternate provider.

Protective Transfer

Patients who had evidence of illicit drug use (eg, opioids, cocaine, or benzodiazepines) were provided increased intensity of services, including more frequent urine monitoring (weekly to thrice weekly), ancillary off-site counseling, and increased frequency of physician visits (weekly to every two weeks). If patients experienced unremitting illicit drug use despite these measures, they were offered protective transfer to an alternate form of treatment, typically methadone maintenance via an opioid treatment program.

Outcome Assessments

Data were collected from those patients who remained in treatment as part of routine clinical care (eg, urine toxicology analyses) and at research assessments conducted at 12-week intervals. Urine samples were scheduled to be collected at

each physician visit, scheduled no more than 4–5 weeks apart, and as clinically indicated. All urines were assessed for the presence of opioids and cocaine metabolites. In addition, urines were analyzed for methadone, oxycodone, and benzodiazepines, as clinically indicated. Self-report of illicit drug use was assessed every 12 weeks.

Patient satisfaction was measured every 12 weeks using the Primary Care Buprenorphine Satisfaction Scale (PCBSS), a questionnaire adapted from previous work.^{14,15} The PCBSS comprised nineteen items that included satisfaction ratings in three areas: overall and specific service components; staff expertise, concern, and responsiveness; and helpfulness of overall and specific treatment components. PCBSS items were scored on a five-point Likert-type scale (possible satisfaction scores ranged from 15 to 95).

To evaluate for any hepatotoxic effects of long-term buprenorphine/naloxone,^{16,17} serum transaminases were collected and analyzed every 12 weeks. Adverse events were recorded as they were spontaneously reported by patients and as noted at each contact with a clinician (physician or nurse) or research assistant.

Outcomes

The primary outcome measures were retention in treatment (adherence to physician visits and medication dispensing visits) and the percentage of opioid-negative urine specimens. Patients were considered lost to treatment if they did not attend a physician visit within eight weeks or did not present for medication greater than seven days after the assigned date of dispensing. Patients were not allowed to re-enter treatment. Secondary outcomes included the percentage of cocaine-negative urine specimens, buprenorphine dose, patient satisfaction, serum transaminases, and adverse events.

Statistical Analysis

Demographic and clinical characteristics were analyzed using descriptive statistics, chi-square and ANOVA as appropriate. All analyses used two-tailed tests of significance and were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois, USA). *p* values <.05 were considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the 53 patients enrolled are displayed in Table 1.

Treatment Retention

Patients completed 741 (75%) of scheduled physician visits over the data collection period (see Figure 1). The mean (SD) number of days between visits was 36.9 (21). Based on when they completed the initial six months of treatment in the randomized clinical trial, 53 patients began entering the long-term phase between 3/04/2001 and 9/28/2004. As of 08/25/06, the number of patients (and the minimum period of time they

TABLE 1. Demographic and clinical characteristics of opioid-dependent patients receiving buprenorphine/naloxone in primary care

Characteristic	N = 53
Age [years; mean, (SD)]	36.0 (9.4)
% Male, (n)	81% (43)
% White, (n)	77% (41)
% Full-time employment, (n)	47% (25)
% High school or greater, (n)	85% (45)
Monthly income, \$, mean (SD)	\$1720 (\$1858)
% Never married, (n)	57% (30)
Opioid dependence [years; mean (SD)]	8.7 (8.8)
% Prescription drug use only, (n)	27% (14)
% History intravenous drug use, (n)	30% (16)
% Hepatitis C antibody positive, (n)	25% (13)
Days of use of other substances in previous 30 days, mean, (SD)	
Alcohol	2.6 (5.4)
Cocaine	1.2 (2.5)
% with cocaine-positive urine at treatment entry, (n)	11% (6)
% Prior attempted detoxification, (n)	26% (14)
% History of participation in methadone maintenance program, (n)	38% (20)
Serum AST, mean (range)	25.5 (11–121)
Serum ALT, mean (range)	30.7 (4–142)
Buprenorphine dose at entry into extension phase, mean (SD, range)	17.5 (3.8) (6 to 24)

remained in treatment following the initial six months) was 28 (one year), 20 (two years), 13 (three years), 6 (four years), and 3 (five years).

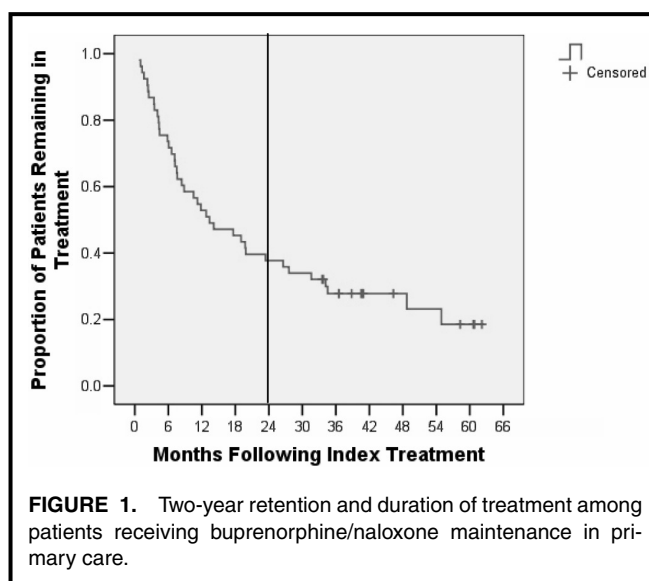
Disposition

During the follow-up period, 40 patients left treatment:

- 38% (20/53) dropped out of treatment;
- 15% (8/53) had persistent drug use and elected not to transfer to an outpatient specialty treatment program for methadone and/or increased services;
- 11% (6/53) were transferred to an outpatient specialty treatment program for methadone and/or increased services;
- 6% (3/53) requested and completed a taper off of buprenorphine/naloxone;
- 4% (2/53) elected to remain on buprenorphine/naloxone but declined further research assessments; and
- 2% (1/53) elected transfer to inpatient substance abuse treatment.

Drug Use

Patients provided urine specimens at 668/741 (90%) of physician visits. In addition, patients provided urine specimens between physician visits for a total of 1106 urine specimens.

**FIGURE 1.** Two-year retention and duration of treatment among patients receiving buprenorphine/naloxone maintenance in primary care.

One thousand and five of the 1106 specimens (91%) had no evidence of illicit opioids (see Table 2). One thousand sixty-two of the 1106 specimens (96%) had no evidence of cocaine. One thousand and fifty-three of 1073 (98%) tested urines had no evidence of benzodiazepines, and 569/574 (99%) tested urines had no evidence of methadone.

Patient Satisfaction

The mean score on the patient satisfaction instruments was 86 out of a possible 95. Scores were negatively skewed, with 79% having scores of 80 or above, and the lowest value of 63. Lowest satisfaction was reported with referral to NA and for monitoring of drug use.

Serum Transaminases

Serum transaminases remained stable from baseline over the period of observation. No patients developed elevations in their aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values that required changes in buprenorphine/naloxone dose or discontinuation.

TABLE 2. Outcomes among opioid-dependent patients receiving long-term buprenorphine/naloxone maintenance in primary care

Primary outcomes	N = 53
Percentage of opioid-negative urine specimens, n/N	91% (1005/1106)
Secondary outcomes	
Percentage of cocaine-negative urine specimens, n/N	96% (1062/1106)
Dose of buprenorphine/naloxone, mean, SD	17.0 (4.2)
Treatment satisfaction score, mean (range)	86.3 (69–93)
Serum AST, mean (range)	29.6 (9–169)
Serum ALT, mean (range)	22.6 (4–119)

Adverse Events

No serious adverse events directly related to buprenorphine/naloxone treatment occurred over the 2–5-year follow-up period. A small number of patients had visits to the emergency department for acute painful events (eg, renal colic, wrist fracture) that were not related to opioid dependence or buprenorphine/naloxone treatment. Minor (eg, carpal tunnel release) and major (ie, hip replacement) surgical procedures were successful and well-tolerated by patients. During periods that required short-term management with full opioid agonist pain medication (eg, morphine), buprenorphine/naloxone administration was terminated and reinstated following the discontinuation of opioid analgesic medications.

DISCUSSION

Our results demonstrate the natural history, over a 2–5-year period, of prescription opioid- and heroin-dependent patients receiving primary care office-based buprenorphine/naloxone treatment. These findings demonstrate that nearly 40% of patients who have previously demonstrated significant abstinence over a six-month period of time will remain in treatment for an additional two years. Illicit drug use is uncommon, but it does occur among these patients. Patients express high levels of overall satisfaction with this model of care. The mean rating of 86 is somewhat higher than the mean score of 83 found in the larger clinical trial earlier in treatment. Serum transaminases were stable throughout the duration of therapy, and no patients needed to leave treatment due to hepatotoxicity. Finally, adverse events were rare, and episodes of acute pain management were generally handled without incident.

It is useful to contrast our results with those reported for patients receiving methadone in clinics and office-based settings.^{5,14,18,19} A large observational cohort study of clinic-based methadone documented three-year retention of 42%.⁵ Prior studies have demonstrated that methadone dose is positively associated with retention,^{20–22} whereas the level of ancillary services has no clear association.²³ This study extends previous findings in the United States that have found that patients seeking buprenorphine, in contrast to those receiving methadone, treatment tend to be younger, with relatively fewer years of opioid dependence, and have lower levels of heroin dependence.^{24,25} Similarly, prior studies have demonstrated that buprenorphine dose is positively associated with retention,²⁶ while level of counseling is not associated with retention.⁷ The current results extend the period of follow-up beyond the six months reported in prior studies in patients receiving buprenorphine.^{7,8,27–29} The low level of ongoing drug use is consistent with prior investigations of office-based treatment of opioid dependence with methadone, although the retention rate is not as high.^{14,19} Finally, the lack of change in serum transaminases over this period of time is reassuring regarding the long-term hepatic safety of buprenorphine/naloxone and contrasts with mild elevations previously described with shorter durations of buprenorphine therapy.¹⁶

Our results are not without limitations. First, while this is the largest cohort of patients followed for up to five years while receiving buprenorphine/naloxone in a primary care office-based setting, the results reflect the experience of one group practice and will need to be replicated in other settings with a larger numbers of patients. Of note, less than one-third of all patients who were randomized in the original clinical trial were retained and exhibited our criteria for stability in order to enter the long-term phase. Second, these results were obtained in a limited cohort of patients who met specific eligibility criteria and may not be generalizable to patients with active untreated comorbid psychiatric disorders, untreated addiction to alcohol or benzodiazepines, or significantly elevated transaminases (eg, greater than three times normal) at the time of treatment entry. Third, patients had clinical assessments and urine toxicology monitoring conducted on a routine basis. Self-report or objective evidence of ongoing illicit drug use was met with attempts to help the patient achieve abstinence with a discussion of transfer to methadone maintenance for those patients who were not able to achieve abstinence with office-based buprenorphine. These efforts and discussions had an impact on treatment retention with some patients opting to accept a transfer to methadone and others resisting increased treatment structure and opting to leave treatment. Fourth, our measurement of patient satisfaction, although previously used, has not been validated. Finally, due to serial entry into the long-term phase, we had variable lengths of follow-up and were not able to systematically track patients once they left treatment, so long-term outcomes in those who elected to taper their buprenorphine or left treatment abruptly are not known.

Our results provide novel information regarding the efficacy and the long-term safety of buprenorphine/naloxone treatment. The findings of moderate levels of treatment retention highlight the potential chronic and relapsing nature of the diagnoses of opioid dependence.³⁰ Similar to patients with other chronic medical conditions, our patients often exhibited periods of control interspersed with periods of relapse.³¹ Treatment systems that address opioid dependence should strive to minimize barriers to treatment re-entry while attempting to match patients' disease severity to appropriate levels of care (eg, opioid treatment program vs. office-based settings). While research in this area is nascent, early results demonstrate that there are patient populations who can benefit from the lower level of services available in office-based settings, with our current study demonstrating that a minority appear to benefit for a prolonged period of time.

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