

ORIGINAL ARTICLE

Counseling plus Buprenorphine–Naloxone Maintenance Therapy for Opioid Dependence

David A. Fiellin, M.D., Michael V. Pantalon, Ph.D., Marek C. Chawarski, Ph.D., Brent A. Moore, Ph.D., Lynn E. Sullivan, M.D., Patrick G. O'Connor, M.D., M.P.H., and Richard S. Schottenfeld, M.D.

ABSTRACT

BACKGROUND

The optimal level of counseling and frequency of attendance for medication distribution has not been established for the primary care, office-based buprenorphine–naloxone treatment of opioid dependence.

METHODS

We conducted a 24-week randomized, controlled clinical trial with 166 patients assigned to one of three treatments: standard medical management and either once-weekly or thrice-weekly medication dispensing or enhanced medical management and thrice-weekly medication dispensing. Standard medical management was brief, manual-guided, medically focused counseling; enhanced management was similar, but each session was extended. The primary outcomes were the self-reported frequency of illicit opioid use, the percentage of opioid-negative urine specimens, and the maximum number of consecutive weeks of abstinence from illicit opioids.

RESULTS

The three treatments had similar efficacies with respect to the mean percentage of opioid-negative urine specimens (standard medical management and once-weekly medication dispensing, 44 percent; standard medical management and thrice-weekly medication dispensing, 40 percent; and enhanced medical management and thrice-weekly medication dispensing, 40 percent; $P=0.82$) and the maximum number of consecutive weeks during which patients were abstinent from illicit opioids. All three treatments were associated with significant reductions from baseline in the frequency of illicit opioid use, but there were no significant differences among the treatments. The proportion of patients remaining in the study at 24 weeks did not differ significantly among the patients receiving standard medical management and once-weekly medication dispensing (48 percent) or thrice-weekly medication dispensing (43 percent) or enhanced medical management and thrice-weekly medication dispensing (39 percent) ($P=0.64$). Adherence to buprenorphine–naloxone treatment varied; increased adherence was associated with improved treatment outcomes.

CONCLUSIONS

Among patients receiving buprenorphine–naloxone in primary care for opioid dependence, the efficacy of brief weekly counseling and once-weekly medication dispensing did not differ significantly from that of extended weekly counseling and thrice-weekly dispensing. Strategies to improve buprenorphine–naloxone adherence are needed. (ClinicalTrials.gov number, NCT00023283.)

From the Departments of Internal Medicine (D.A.F., L.E.S., P.G.O.) and Psychiatry (M.V.P., M.C.C., B.A.M., R.S.S.), Yale University School of Medicine, New Haven, Conn. Address reprint requests to Dr. Fiellin at Yale University School of Medicine, 333 Cedar St., P.O. Box 208025, New Haven, CT 06520, or at david.fiellin@yale.edu.

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BUPRENORPHINE–NALOXONE TREATMENT of patients dependent on heroin and prescription opioids is more efficacious than placebo and as efficacious as moderate doses of methadone.¹⁻⁴ Because of its low risk of respiratory depression and abuse, buprenorphine–naloxone is a Schedule III controlled medication.⁵ Specially certified office-based physicians can provide this treatment.⁶ Previous research has demonstrated the effectiveness of transferring patients from opioid-treatment programs to treatment through physicians' offices.^{7,8} Buprenorphine–naloxone allows physicians to initiate and manage the treatment of opioid-dependent patients directly in the office.

The appropriate level of contact (e.g., the degree of counseling services and the frequency of prescriptions received) for patients who are receiving buprenorphine–naloxone has not been established. Early studies of buprenorphine involved obligatory counseling and daily or thrice-weekly medication dispensing.^{1-4,9-14} Physicians providing office-based treatment with buprenorphine–naloxone are required only to refer patients to counseling and may provide 30-day prescriptions. The purpose of this study was to evaluate two levels of counseling and medication dispensation for patients receiving buprenorphine–naloxone treatment in primary care.

METHODS

PATIENTS

All enrolled patients met the criteria for opioid dependence¹⁵ and for opioid-agonist maintenance treatment. Patients were excluded if they were dependent on alcohol, benzodiazepines, or sedatives; were dangerous to themselves or others; were psychotic or had major depression; were unable to comprehend English; or had life-threatening medical problems. Women of childbearing age agreed to use contraception and undergo monthly pregnancy monitoring. Enrollment began on August 11, 2000, and ended on February 11, 2004. Informed written consent was obtained from all patients. The study was approved by the Human Investigation Committee of the Yale University School of Medicine.

DOSE OF BUPRENORPHINE–NALOXONE

Patients were seen at the Primary Care Center of Yale–New Haven Hospital, which provides no specialty addiction treatment other than buprenor-

phine–naloxone. Buprenorphine was provided by the National Institute on Drug Abuse, which played no role in the trial design, data accrual or interpretation, or manuscript preparation. We used the buprenorphine–naloxone combination tablet (Suboxone), which includes buprenorphine and naloxone in a 4:1 ratio. After a 2-week induction and stabilization period (mean, 14.5 days; 95 percent confidence interval, 14.2 to 14.8), during which patients were seen thrice weekly, 16 mg of buprenorphine daily was provided for 24 weeks. Successive increases to 20 mg and 24 mg were permitted depending on the patient's level of discomfort or evidence of ongoing (for three successive weeks) illicit drug use. Take-home medication was provided for the days on which the patients did not receive medication in the office. The mean (\pm SD) dose of buprenorphine during the maintenance phase was 17.5 ± 2.5 mg and did not differ significantly across the three treatment groups ($P=0.65$).

ASSIGNMENT OF TREATMENT

After induction and stabilization, patients were randomly assigned to receive one of three treatments: standard medical management and once-weekly medication dispensing, standard medical management and thrice-weekly medication dispensing, or enhanced medical management and thrice-weekly medication dispensing. An urn randomization procedure¹⁶ was used to ensure that the groups were similar with regard to sex ratio, employment status, presence of cocaine abuse, and presence of personality disorders.

MEDICATION DISPENSING AND COUNSELING

Buprenorphine–naloxone was dispensed by nurses either once weekly or thrice weekly (on Monday, Wednesday, and Friday), according to treatment group. Trained primary care nurses, with no previous experience treating addiction and limited concurrent responsibilities, provided weekly manual-guided standard or enhanced medical management to individual patients. Each session of standard medical management was scheduled to last 20 minutes and involved a counseling approach with demonstrated efficacy.^{10,13,17} The sessions covered recent drug use or efforts to achieve or maintain abstinence, attendance in self-help groups, support for efforts to reduce drug use or remain abstinent, advice for the achievement or maintenance of abstinence, and the results of analysis of weekly urine specimens. Each session of enhanced medical management was approximate-

ly 45 minutes long and covered similar issues but provided more in-depth drug counseling than did the standard approach.¹⁸ All patients also met with a physician monthly for approximately 20 minutes. The content of these sessions paralleled that of the standard-medical-management sessions, with the addition of an assessment of employment, legal, family or social, medical, and psychiatric problems related to addiction.

The nurses, a physician, and a psychologist met weekly to review the counseling. To assess counseling fidelity, all sessions were audiotaped, except when the patients did not consent or the equipment malfunctioned (<10 percent of sessions). Approximately 16 percent of the audiotapes (337 of 2139) were randomly selected, according to a block randomization scheme that ensured an equal likelihood of selecting a tape from each phase of treatment (i.e., early, middle, or late), from a session run by each nurse counselor, from each study year, and from each treatment group. The selected audiotapes were coded for session length and were rated by independent persons with regard to each nurse's adherence to the manual and competence as a counselor.¹⁹ The mean length of the sessions were 23±8 minutes for standard medical management and 43±12 minutes for enhanced medical management. Prescribed counseling components were provided in both standard medical management and enhanced medical management, with greater frequency in the latter. Competency ratings did not differ significantly between the two types of counseling.

PROTECTIVE TRANSFER

Patients with unremitting illicit-drug use (three consecutive weeks of urine specimens positive for opioids, cocaine, or both after the buprenorphine-naloxone dose had been increased to 24 mg) met the criteria for protective transfer.^{11,20} Patients in whom marked psychiatric symptoms developed were evaluated by an independent psychiatrist, who weighed the safety and appropriateness of continued treatment as compared with protective transfer. Patients who were protectively transferred were removed from the study and were referred to alternative treatment.

OUTCOMES

The primary outcome measures, defined before the study began, were the self-reported frequency of illicit opioid use, the percentage of opioid-negative urine specimens, and the self-reported maxi-

imum number of consecutive weeks of abstinence from illicit opioids (verified by urinalysis). The secondary outcomes included the proportion of patients remaining in the study (the percentage of patients who did not meet the criteria for protective transfer, did not miss medication for more than seven days, or did not miss three or more counseling sessions), the number of days of the study that were completed, the percentage of cocaine-negative urine samples, patient satisfaction, and the use of health and social services. Because patients received buprenorphine-naloxone for unsupervised self-administration and medication adherence could be influenced by the treatment and could affect treatment outcome, the adherence to medication was assessed through a review of nurses' notes in the patient's clinical record and through the monitoring of the computerized caps of medication bottles (Medication Event Monitoring System, Apres). These caps contain a microprocessor that records, but does not display, the date and time at which each bottle is opened. Patients were classified as adherent to buprenorphine-naloxone for a given day if adherence was documented by means of a nurse's note or a recording of a bottle's having been opened on that day.

ASSESSMENT OF OUTCOMES

Illicit-drug use was measured weekly by means of the patient-reported frequency of drug use and the testing of urine samples. Urinalyses were conducted with the use of a semiquantitative homogeneous enzyme immunoassay for opioids and cocaine. Since the proportion of patients abusing prescription opioids increased during the course of the trial, we also tested all patients for oxycodone and methadone.

Patient satisfaction was measured at week 12 with the use of a questionnaire adapted from a previously published one.⁷ Nineteen items were rated on a 5-point Likert scale, with a higher score corresponding to greater satisfaction and a highest possible score of 95.

STATISTICAL ANALYSIS

On the basis of data from a pilot study and published data,^{10,20} we anticipated an absolute difference of 18.5 percent in the percentage of opioid-negative urine specimens, favoring enhanced medical management over standard medical management; no data were available to estimate the predicted difference between standard medical

management and once-weekly versus thrice-weekly medication dispensing. The enrollment of 166 patients provided the study with a statistical power of more than 80 percent to detect an absolute difference of at least 18.5 percent among the three groups, with a two-sided type I error of 0.05.

The patients' characteristics at enrollment were compared among the three groups with the use of the chi-square test and analysis of variance, as appropriate. Analyses were planned in advance and were based on the intention-to-treat principle.

The proportion of patients remaining in the study was evaluated with the use of the chi-square test, and the number of study days completed was evaluated with the use of the Kaplan–Meier product-limit method and the log-rank test. A mixed-model analysis of variance was used to conduct a repeated-measures analysis of the frequency of illicit opioid use. Analysis of variance was used to evaluate differences among groups in the percentage of opioid-negative and cocaine-negative urine specimens, the maximum number of consecutive weeks of abstinence, patient satisfaction during treatment, the use of health and social services, and adherence to buprenorphine–naloxone. If significant differences were detected among the groups, Scheffé's adjusted pairwise comparisons were used to examine those differences. Correlation coefficients were used to evaluate the association of buprenorphine–naloxone adherence with the percentage of opioid-negative urine specimens and the mean maximum number of consecutive weeks of abstinence.

Given the association between treatment discontinuation and the relapse to illicit opioid use, we coded missing urine specimens as positive for opioids in our analysis. The pattern of results did not differ significantly in additional analyses that used other assumptions regarding missing urine specimens (e.g., coding them as missing, coding them as positive only when patients were still receiving treatment, or carrying the last result forward).

The results regarding urinalyses are based on 2386 urine samples (60 percent of the 3984 total possible urine samples anticipated had all patients remained in treatment during the entire study and provided all planned samples). During the study, 12 percent of the scheduled urine samples (312 of 2698) were missed. The percentage of collected urine samples for the complete cohort did not differ significantly according to treatment ($P=0.17$):

802 of the 1296 possible urine samples (62 percent) were collected from the patients receiving standard medical management and once-weekly medication dispensing, 784 of the 1344 possible (58 percent) were collected from the patients receiving standard medical management and thrice-weekly medication dispensing, and 800 of the 1344 possible (60 percent) were collected from the patients receiving enhanced medical management and thrice-weekly medication dispensing.

The results regarding the self-reported frequency of illicit opioid use are based on 2930 assessments (65 percent of the 4482 total possible assessments, including baseline assessments and weekly assessments during induction, that were anticipated had all patients remained in treatment for the 24-week trial; and 92 percent of the 3196 assessments scheduled while patients remained in treatment). The percentage of completed self-reported assessments differed significantly among the treatment groups ($P=0.001$): 1018 of the 1512 possible assessments (67 percent) were provided by patients receiving standard medical management and once-weekly medication dispensing, 933 of the 1512 possible (62 percent) were provided by patients receiving standard medical management and thrice-weekly medication dispensing, and 979 of the 1458 possible (67 percent) were provided by patients receiving enhanced medical management and thrice-weekly medication dispensing.

There were no interim analyses. All analyses involved two-tailed tests of significance and were performed with the use of SPSS software, version 13.0. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The baseline demographic and clinical characteristics of the patients enrolled (Fig. 1) are given in Table 1. None differed significantly among the three treatment groups.

OPIOID USE

All three treatments resulted in a reduction in the mean self-reported frequency of opioid use, from 5.3 days per week (95 percent confidence interval, 5.1 to 5.5) at baseline to 1.1 days (95 percent confidence interval, 0.9 to 1.3) during induction to 0.4 day (95 percent confidence interval,

0.2 to 0.7) during maintenance ($P < 0.001$ for the comparisons of induction and maintenance with baseline), but there were no significant differences among the three groups ($P = 0.73$) or among the treatments over time ($P = 0.83$) (Fig. 2). The mean percentage of opioid-negative urine specimens did not differ significantly among the three groups ($P = 0.82$), and there were no significant differences in the mean maximum number of consecutive weeks of abstinence among the groups ($P = 0.54$) (Table 2).

COMPLETION OF THE STUDY

The mean percentage of patients who had completed the study (did not meet the criteria for protective transfer, did not miss medication for more than 7 days, or did not miss three or more coun-

seling sessions) at 24 weeks did not differ significantly among the three groups: 48 percent of the patients receiving standard medical management and once-weekly medication dispensing, 43 percent of the patients receiving standard medical management and thrice-weekly medication dispensing, and 39 percent of the patients receiving enhanced medical management and thrice-weekly medication dispensing ($P = 0.64$) (Fig. 3). The number of patients who were protectively transferred also did not differ significantly among the three treatment groups ($P = 0.32$).

COCAINE USE

The proportion of patients with at least one cocaine-positive urine specimen during the trial did not differ significantly among the three groups:

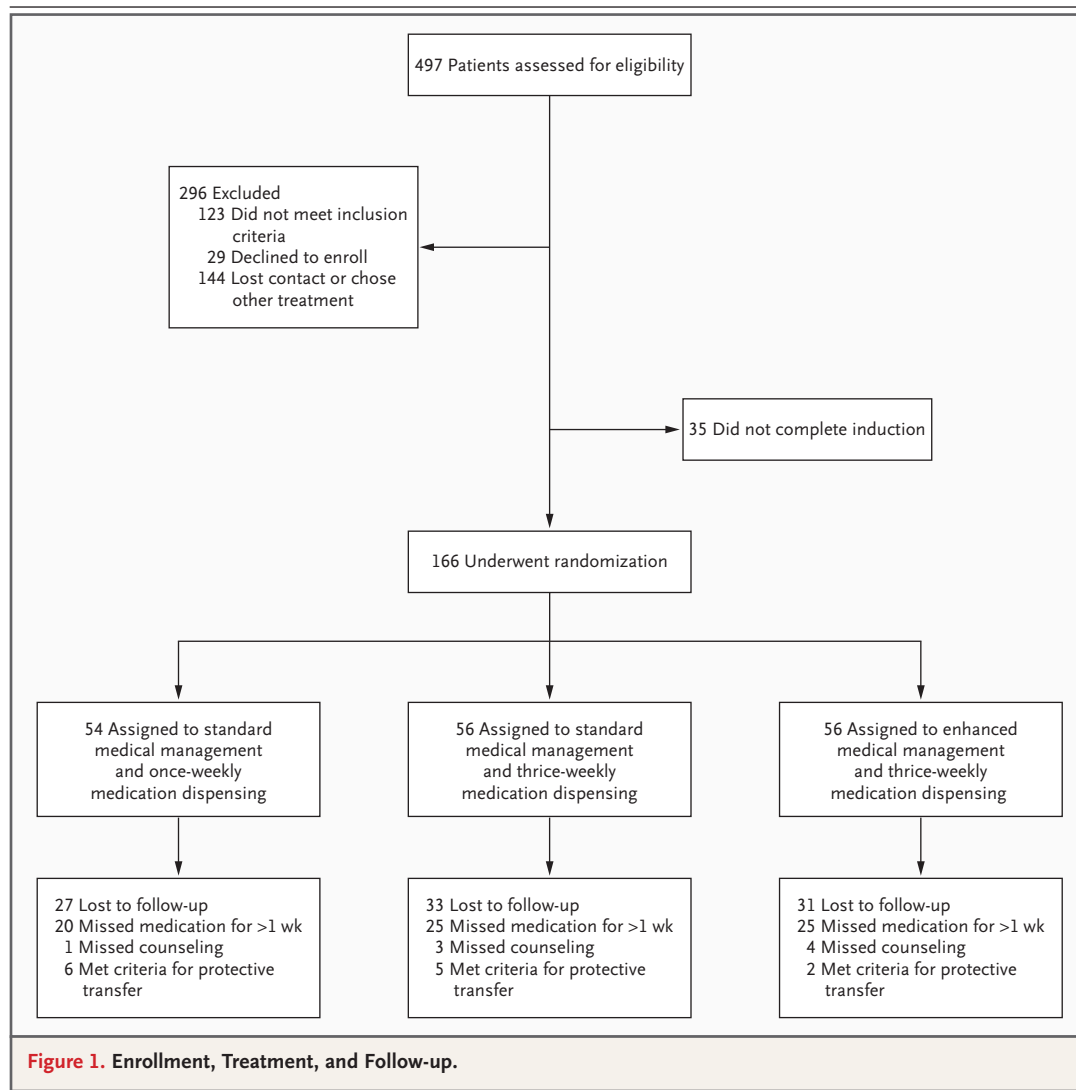


Table 1. Baseline Demographic and Clinical Characteristics of Opioid-Dependent Patients Receiving Buprenorphine–Naloxone in Primary Care.*

| Characteristic | Standard Medical Management and Once-Weekly Medication Dispensing (N=54) | Standard Medical Management and Thrice-Weekly Medication Dispensing (N=56) | Enhanced Medical Management and Thrice-Weekly Medication Dispensing (N=56) | P Value |
|---|--|--|--|---------|
| Age — yr | 37.1±8.4 | 35.9±9.7 | 35.1±9.7 | 0.55 |
| Male sex — no. (%) | 42 (78) | 43 (77) | 44 (79) | 0.97 |
| White race — no. (%)† | 38 (70) | 43 (77) | 46 (82) | 0.35 |
| Full-time employment — no. (%) | 25 (47) | 31 (55) | 23 (42) | 0.36 |
| High-school graduate — no. (%) | 41 (77) | 47 (84) | 46 (84) | 0.61 |
| Monthly income — \$ | 1,571±1,457 | 1,210±1,240 | 1,330±1,760 | 0.46 |
| Never married — no. (%) | 30 (57) | 32 (57) | 33 (60) | 0.93 |
| Duration of opioid dependence — yr | 8.1±7.7 | 8.6±8.6 | 7.5±7.7 | 0.77 |
| Prescription-drug use — no. (%) | 9 (17) | 8 (15) | 11 (20) | 0.94 |
| History of intravenous drug use — no. (%) | 16 (30) | 17 (32) | 19 (34) | 0.88 |
| Use of other substances during previous 30 days — days | | | | |
| Alcohol | 3.1±5.5 | 2.8±5.4 | 2.6±5.1 | 0.89 |
| Cocaine | 1.2±2.4 | 1.6±3.6 | 1.5±3.1 | 0.79 |
| Cocaine-positive urine specimen at treatment entry — no. (%) | 11 (20) | 11 (20) | 12 (21) | 0.96 |
| Previously attempted detoxification — no. (%) | 34 (67) | 40 (71) | 35 (64) | 0.68 |
| History of participation in methadone-maintenance program — no. (%) | 35 (67) | 33 (59) | 35 (71) | 0.40 |

* Plus-minus values are means ±SD. Some characteristics could not be assessed for all patients.

† Race was self-reported.

31 of 54 patients (57 percent) receiving standard medical management and once-weekly medication dispensing, 28 of 56 patients (50 percent) receiving standard medical management and thrice-weekly medication dispensing, and 31 of 56 patients (55 percent) receiving enhanced medical management and thrice-weekly medication dispensing ($P=0.73$). There were no significant differences in the mean percentage of cocaine-negative urine specimens among the groups during treatment ($P=0.79$) (Table 2).

PATIENT SATISFACTION AND USE OF SERVICES

Treatment satisfaction was significantly associated with the treatment group ($P=0.049$); patients reported greater satisfaction with standard medical management and once-weekly medication dispensing than with standard medical management and thrice-weekly medication dispensing ($P=0.04$) (Table 2). The groups did not differ sig-

nificantly in their use of ancillary health and social services (data not shown).

ADHERENCE TO BUPRENORPHINE–NALOXONE

The overall mean percentage of days on which patients adhered to buprenorphine–naloxone was 71 ± 22 percent (range, 7 to 100), and the mean percentage did not differ significantly among the groups ($P=0.87$) (Table 2). The percentage of days of adherence correlated significantly with the percentage of opioid-negative urine specimens and the mean number of consecutive weeks of abstinence from opioids ($r=0.30$ and $r=0.35$ across all groups, respectively; $P<0.001$).

DISCUSSION

We investigated the use of counseling and different frequencies of medication dispensing in primary care treatment with buprenorphine–nalox-

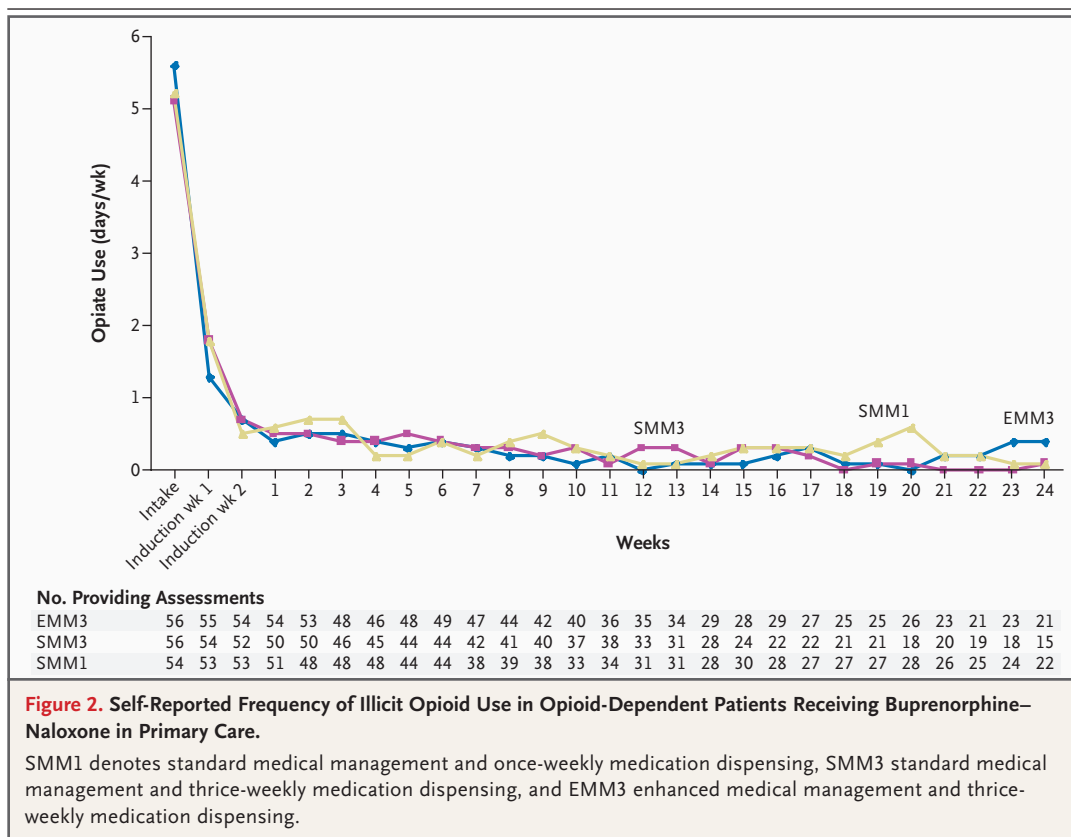


Figure 2. Self-Reported Frequency of Illicit Opioid Use in Opioid-Dependent Patients Receiving Buprenorphine–Naloxone in Primary Care.

SMM1 denotes standard medical management and once-weekly medication dispensing, SMM3 standard medical management and thrice-weekly medication dispensing, and EMM3 enhanced medical management and thrice-weekly medication dispensing.

one. Neither the primary outcomes (the frequency of illicit opioid use, the percentage of opioid-negative urine specimens, and the maximum number of consecutive weeks of abstinence from illicit opioids) nor the proportion of patients who completed the study differed significantly among the three groups. Specifically, outcomes among patients receiving brief counseling combined with once-weekly medication dispensing did not differ significantly from outcomes among patients receiving either extended counseling or thrice-weekly medication dispensing. Patient satisfaction was significantly higher with once-weekly than with thrice-weekly medication dispensing, although because of the large number of statistical tests conducted, this may represent a chance finding.

Consistent with the findings of previous research with buprenorphine,¹⁻⁴ the frequency of illicit opioid use decreased significantly from baseline to induction and was lowest during maintenance for all three groups. The mean percentages of patients who completed the 24-week study, which ranged between 39 and 48 percent, were similar to those found in previous studies, includ-

ing one conducted in an office-based setting.¹⁻⁴ Therefore, the majority of patients who entered this study either left treatment or were considered appropriate for transfer to a more structured treatment setting with methadone. Nonetheless, although we did not demonstrate the superiority of extended counseling or thrice-weekly medication dispensing over the relatively limited nurse-administered counseling and once-weekly dispensing, our findings support the feasibility of buprenorphine–naloxone maintenance in primary care.^{10,13,21}

Although previous studies establishing the effectiveness of buprenorphine involved weekly counseling, the available evidence suggests wide variability in the counseling provided in office-based practices in the United States, France, and other countries, where many patients receive little or no formal drug counseling. A study in France reported that 54 percent of physicians met with the patient once per week during induction and 47 percent met with the patient once per month during maintenance.²² In a previous study of methadone maintenance, weekly or more frequent drug counseling and ancillary services resulted

Table 2. Outcomes for Opioid-Dependent Patients Receiving Buprenorphine–Naloxone in Primary Care.*

| Outcome | Standard Medical Management and Once-Weekly Medication Dispensing (N=54) | Standard Medical Management and Thrice-Weekly Medication Dispensing (N=56) | Enhanced Medical Management and Thrice-Weekly Medication Dispensing (N=56) | P Value |
|---|--|--|--|---------|
| Primary | | | | |
| Opioid-negative urine specimens — % | | | | 0.82 |
| Mean | 44 | 40 | 40 | |
| 95% CI | 34–53 | 31–50 | 31–49 | |
| Maximum duration of continuous abstinence from illicit opioids — wk | | | | 0.54 |
| Mean | 6.7 | 5.7 | 5.5 | |
| 95% CI | 5.0–8.3 | 4.0–7.3 | 3.8–7.0 | |
| Secondary | | | | |
| Days of the study completed† | | | | 0.72 |
| Mean | 120 | 115 | 126 | |
| 95% CI | 105–134 | 101–128 | 112–141 | |
| Patients who met criteria for protective transfer — no. (%) | 6 (11) | 5 (9) | 2 (4) | 0.32 |
| Cocaine-negative urine specimens — % | | | | 0.79 |
| Mean | 75.5 | 71.1 | 73.6 | |
| 95% CI | 66.4–84.7 | 62.3–79.9 | 64.8–82.3 | |
| Treatment satisfaction score | | | | 0.04 |
| Mean | 85.2 | 80.3 | 82.6 | |
| 95% CI | 82.5–88.0 | 77.6–83.0 | 80.0–85.3 | |
| Days adherent to buprenorphine–naloxone — % | | | | 0.87 |
| Mean | 75 | 73 | 69 | |
| 95% CI | 68–81 | 67–79 | 63–74 | |

* CI denotes confidence interval.

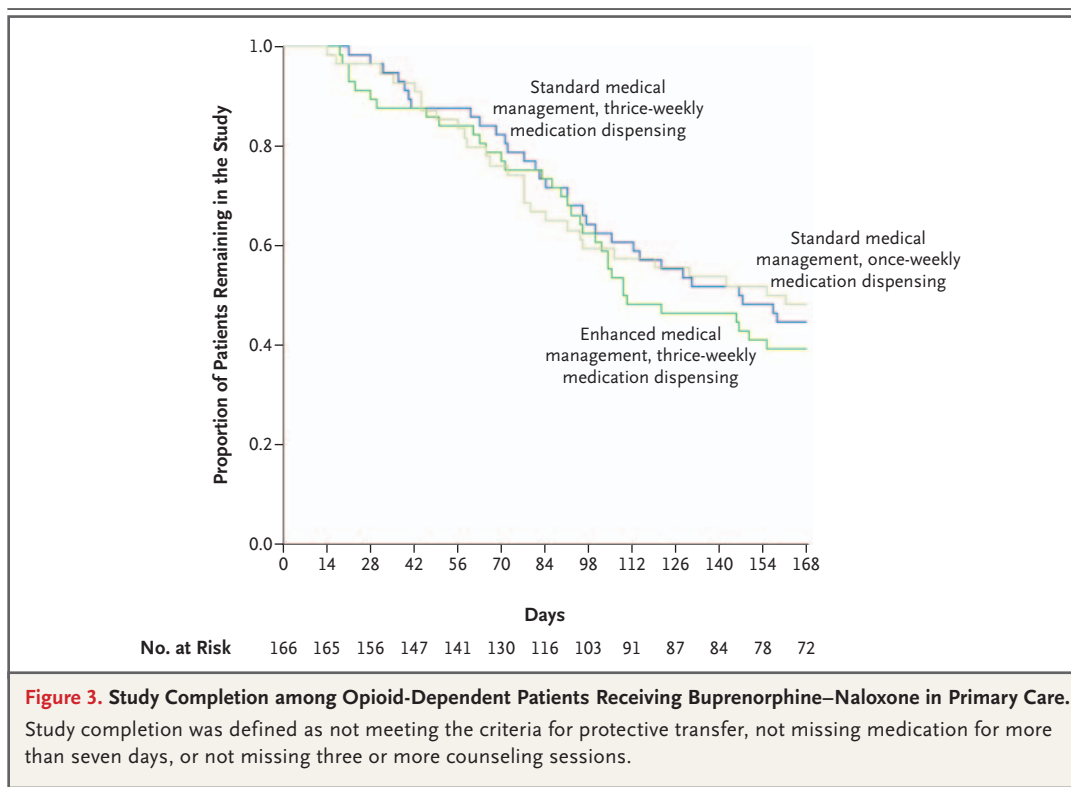
† Study completion was defined as not meeting the criteria for protective transfer, not missing medication for more than seven days, or not missing three or more counseling sessions.

in better outcomes than brief monthly counseling,²⁰ and a recent systematic review concluded that the addition of psychosocial services to methadone maintenance leads to a reduction in the number of days on which a patient uses heroin but does not affect the time the patient remains in treatment.²³ Our findings do not establish that extended weekly counseling is more effective than brief weekly counseling, but we did not include a control group receiving minimal or no counseling.

Our study provides data regarding patients' adherence to buprenorphine–naloxone and the association between adherence and abstinence. Problems with medication adherence are not unique

to opioid-dependent patients; for some health conditions, adherence to less than the recommended amount of medication is sufficient to attain the goals of treatment.²⁴ Nevertheless, low doses of buprenorphine have been found to be less efficacious than higher doses in studies in which overall adherence is quite high and is ensured by observed ingestion.¹⁴

Our study has limitations. The sample size was adequate to detect medium-sized differences in effect but did not account for loss to follow-up. Because the confidence intervals around the observed means are wide, we cannot conclude that there are no clinically significant differences among the three treatments. As in other studies,



the loss to follow-up at 24 weeks was greater than 50 percent. The approaches we used to account for missing data only partially address this limitation. The eligibility criteria limit the generalizability of the findings to patients who do not have severe and untreated coexisting psychiatric conditions or a concomitant dependence on alcohol, benzodiazepines, or sedatives, although patients with personality disorders and cocaine abuse were included in our study. Most studies of buprenorphine–naloxone have been in patients similar to those in our study who have seemed well-suited to office-based settings when directly admitted for treatment with buprenorphine–naloxone^{10,13} or have been conducted in patients who have transferred to physicians' offices while receiving methadone.⁷

Our trial compared counseling interventions that differed primarily in duration, not content, and were not tailored to individual patients; the least intensive intervention in this study is likely to provide more counseling and other types of contact than some practices can. The study design did not include a group assigned to enhanced medical management and once-weekly buprenorphine–naloxone dispensing, and thus we cannot

directly compare enhanced medical management and standard medical management for patients who were provided buprenorphine–naloxone once weekly.

Finally, our study was conducted in an urban, academically affiliated medical center. Other practices will need to consider the implications of this study with regard to resources, primarily for eligibility screening and nurse staffing.

Our study also has implications for clinical care and research. The fact that many patients can receive efficacious care in a primary care, office-based setting with weekly brief counseling and medication dispensing is important. The recent finding that the availability of buprenorphine–naloxone attracts new patients to treatment for addiction²⁵ provides support for federal efforts to expand access to the treatment.⁶ Our findings also show that supervised nurses can provide appropriate counseling. The finding of ongoing cocaine use among patients treated for opioid dependence is consistent with findings among patients receiving methadone maintenance^{26,27} and supports efforts to monitor and address this coexisting disorder.^{28–30} Finally, the variability in buprenorphine–naloxone adherence highlights

the need both to measure adherence in future research and to monitor and encourage adherence in practice in order to reduce the potential misuse of the medication and to improve the treatment outcomes.

No potential conflict of interest relevant to this article was reported.

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