ORIGINAL ARTICLE

Office-Based Treatment of Opiate Addiction with a Sublingual-Tablet Formulation of Buprenorphine and Naloxone

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ABSTRACT

BACKGROUND

Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone has been proposed, but its efficacy and safety have not been well studied.

METHODS

We conducted a multicenter, randomized, placebo-controlled trial involving 326 opiate-addicted persons who were assigned to office-based treatment with sublingual tablets consisting of buprenorphine (16 mg) in combination with naloxone (4 mg), buprenorphine alone (16 mg), or placebo given daily for four weeks. The primary outcome measures were the percentage of urine samples negative for opiates and the subjects' self-reported craving for opiates. Safety data were obtained on 461 opiate-addicted persons who participated in and open-label study of buprenorphine and naloxone (at daily doses of up to 24 mg and 6 mg, respectively) and another 11 persons who received this combination only during the trial.

RESULTS

The double-blind trial was terminated early because buprenorphine and naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. The proportion of urine samples that were negative for opiates was greater in the combined-treatment and buprenorphine groups (17.8 percent and 20.7 percent, respectively) than in the placebo group (5.8 percent, $P<0.001$ for both comparisons); the active-treatment groups also reported less opiate craving ($P<0.001$ for both comparisons with placebo). Rates of adverse events were similar in the active-treatment and placebo groups. During the open-label phase, the percentage of urine samples negative for opiates ranged from 35.2 percent to 67.4 percent. Results from the open-label follow-up study indicated that the combined treatment was safe and well tolerated.

CONCLUSIONS

Buprenorphine and naloxone in combination and buprenorphine alone are safe and reduce the use of opiates and the craving for opiates among opiate-addicted persons who receive these medications in an office-based setting.

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Addiction to opiates, usually to heroin, remains a continuing problem in the United States and is increasing in Europe.[1-5] Opiate-substitution pharmacotherapy reduces the use of illicit opiates and the high-risk and criminal behaviors associated with it.[6-8] However, two currently available opiate-substitution therapies, methadone and levomethadyl acetate, are provided only in a strictly regulated environment in which medication is taken under clinical observation, with limited provision for take-at-home dosing.[9] Such monitoring is necessary because of concern about the diversion of these drugs to illicit use but is also known to dissuade many addicted persons from seeking help.[10] Furthermore, under the same regulations, access to opiate-substitution pharmacotherapy is limited to persons with defined histories of documented, chronic opiate addiction; those with relatively recent addiction are ineligible.[9]

Buprenorphine is a partial μ-opiate–receptor agonist and a κ-opiate–receptor antagonist[11,12] that is used in many countries for the treatment of moderate to severe pain. Sublingual administration of buprenorphine circumvents first-pass drug inactivation. Although this agent, like methadone and levomethadyl acetate, has the potential to be abused,[13-15] its potential for abuse can be diminished by combining it with naloxone.[16] Indeed, buprenorphine, alone or in combination with naloxone, has recently been approved in the United States and other countries for the treatment of opiate addiction. Recent legislation in the United States[17] allows physicians to administer buprenorphine or a combination of buprenorphine and naloxone to treat opiate-addicted patients in their offices.

We conducted a randomized, placebo-controlled, multicenter trial to evaluate the safety and efficacy of a sublingual-tablet formulation of buprenorphine and naloxone in an office-based setting. The ratio of buprenorphine to naloxone in the formulation was 4:1, with the aim of reducing or preventing potential misuse of buprenorphine by the parenteral route.[18-20]

METHODS

SUBJECTS

Men and women who met the diagnostic criteria for opiate dependence according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),[21] who were seeking opiate-substitution pharmacotherapy, who were between the ages of 18 and 59 years, and who were able to give informed consent and comply with study procedures were eligible to participate. Participants were enrolled between October 21, 1996, and September 30, 1997. Women who were pregnant or nursing were excluded. Other criteria for exclusion included any medical condition that made study participation medically hazardous; aspartate or alanine aminotransferase levels greater than three times the upper limit of normal; a current, primary, Axis I psychiatric diagnosis (according to the DSM-IV) other than opiate, caffeine, or nicotine dependence; and use of methadone, levomethadyl acetate, or naltrexone within the 14 days before enrollment. Subjects were compensated $10 per day to complete the study assessments during the double-blind trial; they were not paid for taking any of the study treatments.

The study was approved by the Human Rights Committee of the Veterans Affairs Cooperative Studies Program Coordinating Center (Perry Point, Md.) and by the institutional review boards of participating sites and was conducted in accordance with the Declaration of Helsinki. All the subjects provided written informed consent. A data and safety monitoring board provided independent monitoring of the study. Haybittle–Peto horizontal boundaries,[22] with a criterion of 3 SD, were used in the interim analyses conducted to determine whether the study should be terminated early.

PROCEDURES

There were two parts to the study: first, a 4-week, double-blind, placebo-controlled efficacy trial, and second, an open-label safety phase lasting 48 weeks (for persons who had participated in the efficacy trial) or 52 weeks (for those who had not participated in the efficacy trial). The double-blind trial was conducted at eight sites (in Boston; Cincinnati; Hines, Ill.; Los Angeles; New York; Philadelphia; San Francisco; and West Haven, Conn.). The open-label phase was conducted at four other sites as well (in Baltimore, Miami, New Orleans, and San Juan, Puerto Rico). Subjects who received at least one dose of the combined medication consisting of buprenorphine and naloxone (but not those who received buprenorphine alone) in either part of the study constituted the group in whom safety was assessed. All study visits took place in a physician's office in a clinical research program located in an environment distinct from the clinic where methadone and levomethadyl acetate were provided.

During the double-blind trial, subjects were ran-

domly assigned to daily treatment with buprenorphine (16 mg) in combination with naloxone (4 mg), buprenorphine alone (16 mg), or placebo. A 16-mg dose of buprenorphine was chosen on the basis of results of previous studies,[23-25] after adjustment for the bioavailability of the sublingual-tablet formulation.

Subjects came to the clinic each weekday and were administered medication on site. Take-home doses were dispensed on Fridays for use on the weekends and were also provided for use on clinic holidays. Those who were assigned to active treatment with buprenorphine alone received a dose of 8 mg on day 1 of the study; those who were assigned to the combination treatment received buprenorphine alone on days 1 and 2 (8 mg on day 1 and 16 mg on day 2) to minimize the risk of naloxone-induced opiate withdrawal. All the tablets were identical in appearance and taste and were provided by Reckitt Benckiser Healthcare (Hull, United Kingdom), through a Cooperative Research and Development Agreement between Reckitt and Colman Pharmaceuticals (Richmond, Va.; currently Reckitt Benckiser Pharmaceuticals) and the National Institute on Drug Abuse, National Institutes of Health. The data were held by the National Institute on Drug Abuse; Reckitt and Colman was not involved in the study design, in the collection of data, in the preparation of the manuscript, or in the decision to submit the manuscript for publication.

All the subjects received counseling regarding human immunodeficiency virus infection and up to one hour of individualized counseling per week. Emergency counseling (e.g., after a relapse) and referrals (e.g., to community legal aid programs) could be provided, but no other counseling or services (e.g., regarding family or employment issues) were offered.[26]

During the open-label phase of the study, subjects who were to receive the combined treatment were given buprenorphine alone for the first two days of therapy (8 mg on day 1 and 8 or 12 mg on day 2), after which they were given the combination tablet, up to a total daily dose of 24 mg of buprenorphine and 6 mg of naloxone. For the first two weeks, the medication was administered each weekday at the clinic (as it had been in the double-blind trial). After that, up to a 10-day supply of medication could be provided, at the discretion of the investigators, for subjects' use at home. Individualized counseling was available at the clinics, but the subjects were also encouraged to obtain behavioral-treatment services outside the study.

MEASURES OF TREATMENT EFFICACY

The primary outcome measures in the double-blind trial were the percentage of opiate-negative urine samples and subjects' self-reported craving for opiates. Urine samples were collected on Mondays, Wednesdays, and Fridays with the use of a urine-collection cup containing a temperature sensor (Franklin Collectors, Francus Medical Marketing) and specimen authenticity verified by measurement of urine temperature; direct observation was used when an assessment of urine temperature might not have been reliable (e.g., in febrile persons). The samples were analyzed centrally (at Northwest Toxicology, Salt Lake City) for the presence of opiates (e.g., morphine, codeine, and the corresponding metabolites) and for other substances of abuse (Abuscreen Online Immunoassay, Roche Diagnostic Systems). A few compounds (e.g., oxycodone and meperidine) cross-react only poorly with this assay, but other assay procedures were not used.

Criteria for a positive test were based on general clinic practices and on federal guidelines for immunoassay testing in place at the time. Urine samples containing less than 300 ng of drug or metabolite per milliliter were considered negative for that substance, except in the case of amphetamines, for which the cutoff value was 1000 ng per milliliter. Samples not provided when due were recorded as missing. The subjects' craving for opiates was assessed at each clinic visit in terms of the peak craving during the preceding 24 hours, measured with a 100-mm visual-analogue scale (where 0 represented "no craving" and 100 "the most intense craving I ever had"). The initial (base-line) assessment was obtained on day 1 before administration of the study medication.

The principal secondary outcome measures included the subjects' and the clinicians' impressions of overall status since enrollment in the study and since the previous visit. Other secondary measures were the percentages of urine samples that were negative for other drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, and methadone), subject retention, the rates of adverse medical events, findings on electrocardiography, and the results of clinical (chemical and hematologic) analyses. Impressions of overall status were rated on Mondays, Wednesdays, and Fridays with the use of

a 100-mm visual analogue scale (where 0 represented "much worse," 50 "no change," and 100 "much better"). Adverse medical events were assessed weekly; in addition, any events spontaneously reported during daily visits to the clinic were recorded.[27] Electrocardiography and laboratory testing were performed at screening before enrollment and at the end of week 4.

During the open-label phase, urine samples were collected randomly two times each month, and the results were made available to the investigators. Other evaluations were performed during screening and at the following intervals: clinical (chemical and hematologic) evaluations, monthly; pregnancy tests, monthly; electrocardiography, weeks 4, 12, 24, 36, and at the end of the study; and physical examination, at the end of the study. Adverse events were evaluated weekly.

STATISTICAL ANALYSIS

Estimates of the sample size that would be required for the double-blind trial were derived with the use of effect sizes and variances obtained from a previous study.[24] To detect a difference of 10 percentage points between the combined-therapy group and the placebo group in the percentage of urine tests negative for opiates or a 10-point difference between the two groups in the craving score with a type I error of 0.05 and a power of 0.80, the inclusion of 63 and 86 subjects per group, respectively, would be required. To assess the craving for opiates, a total of 384 subjects (128 per group) was needed (with a total of 48 per site [16 per group per site]), after allowance for approximately 33 percent attrition. Comparison of the combined-therapy group and the placebo group was the primary comparison; the group that received buprenorphine alone served as an active control. All statistical tests were performed as two-sided tests with an alpha level of significance of 0.05.

The base-line characteristics of the groups were compared with the use of the following tests: the Kruskal–Wallis test for the duration of opiate use and household income; the Cochran–Mantel–Haenszel test, stratified according to site, for race, sex, any past enrollment in a methadone or levomethadyl acetate maintenance program, employment status, and living arrangement; and a two-factor (group and site) analysis of variance for other variables. Adverse effects were compared among groups with the use of Fisher's exact test.

The percentage distribution of opiate-negative urine samples was analyzed with a two-factor (site and group) analysis of variance. Least-squares means analysis was used for each of the three pairwise comparisons. No adjustments were made for multiple comparisons. Participants provided a maximum of 11 or 12 urine samples, depending on the day of the week on which treatment was initiated. According to the most conservative approach, missing samples (including those from subjects who did not complete the trial) were considered "not negative" for opiates. The percentage of negative urine samples for each subject was based on the expected number of samples (11 or 12).

Opiate-craving scores and subject- and clinician-rated impressions of overall status were analyzed as four weekly averages by a three-factor (site, group, and week), repeated-measures analysis of covariance (for craving) or analysis of variance (for global impressions).

RESULTS

DOUBLE-BLIND TRIAL

The data and safety monitoring board and the Human Rights Committee of the Veterans Affairs Cooperative Studies Program Coordinating Center recommended termination of the double-blind trial because buprenorphine alone and the combination of buprenorphine and naloxone had been found to have greater efficacy than placebo. At the time the study was terminated, 451 persons had been screened, 326 had been enrolled and assigned to a study group, 323 had received at least one dose of study medication, and 243 had completed the trial. The three subjects (one in each group) who had not received study medication after randomization were excluded from the analyses. Of the 323 subjects who had received at least one dose, 109 received the combination of buprenorphine and naloxone, 105 received buprenorphine alone, and 109 received placebo. Of the 27 subjects who had not completed the double-blind trial when it was stopped, 11 had begun receiving the combined treatment, 4 had begun receiving buprenorphine alone, and 12 had begun receiving placebo. After termination of the study, all 27 subjects were enrolled in the open-label phase. For the 296 subjects who were not affected by the early termination, 243 (82 percent) completed the trial (82 in the combined-treatment group, 86 in the buprenorphine-only group, and 75 in the placebo group); the differences among the groups in the proportion of subjects who completed the tri-

al were not significant. Overall, the subjects received medication for 90 percent of the days that they remained in the study.

Base-line demographic data were similar in all three treatment groups (Table 1). Both of the buprenorphine-based treatments reduced opiate use; the percentages of urine tests that were opiate-negative were 17.8 percent in the combined-treatment group and 20.7 percent in the buprenorphine group, as compared with 5.8 percent in the placebo group ($P<0.001$ for both comparisons). There was a significant site effect ($P<0.001$), but there was no significant site-by-group interaction; that is, the effect of treatment was about the same at all sites.

Both of the buprenorphine-based treatments also reduced the craving for opiates (Fig. 1A). During each of the four study weeks, the mean craving scores in the combined-treatment and buprenorphine groups were significantly lower than those in the placebo group ($P<0.001$ for both comparisons). The effects of the site ($P=0.03$), group ($P<0.001$), and week of treatment ($P<0.001$) on craving scores were significant; there was also a significant group-by-week interaction ($P<0.001$), indicating that the effects of treatment varied from week to week during the trial.

The overall health and well-being of the subjects in the combined-treatment and buprenorphine-only groups improved to a significantly greater extent than they did in the placebo group, as measured by a global-impression rating scale with which the subjects assessed their own status each week relative to their status at the start of the study (Fig. 1B) ($P<0.001$ for both buprenorphine-based groups vs. placebo at all assessments). In all the groups, subjects' self-assessments of their overall status relative to the previous assessment also showed improvements, but these improvements were not statistically significant. Each week, those who received either the combined treatment or buprenorphine alone had significantly higher scores than those who received placebo ($P<0.001$) (data not shown).

The clinicians' ratings of their impressions of the subjects' status relative to the start of the study were generally lower than the subjects' own ratings but showed similar improvements (Fig. 1C). Each week, subjects who received either the combined treatment or buprenorphine alone had higher scores than those who received placebo ($P<0.001$ for both comparisons). The improvements in clinicians' ratings relative to the previous assessment were similar to the improvements relative to the start of the study, except that scores in the group that received buprenorphine alone were significantly higher than those in the placebo group only at week 1 ($P<0.001$) and week 2 ($P=0.002$).

The drug (other than opiates) most commonly detected in the urine in all three groups was cocaine; the frequency of cocaine-positive samples did not differ significantly among the groups (45 percent in the combined-treatment group, 44 percent in the group that received buprenorphine alone, and 40 percent in the placebo group). Overall, benzodiazepines were detected in 83 of 813 samples (10 percent), and amphetamines, barbiturates, and methadone were each detected in less than 5 percent of the samples. There was no appreciable increase or decrease in the use of any of these drugs during the four-week study period in any of the groups.

Buprenorphine was well tolerated when given alone or in combination with naloxone. The overall rate of adverse events did not differ significantly among the groups (78 percent in the combined-treatment group, 85 percent in the buprenorphine-only group, and 80 percent in the placebo group), and there were few differences among the groups in the rates of specific adverse events (Table 2). Fourteen serious adverse events (four in the combined-treatment group, three in the buprenorphine-only group, and seven in the placebo group) were reported in 13 subjects. Inpatient detoxification treatment was the most common (in five subjects), and suicidal ideation or a suicide attempt was reported by two subjects, both in the buprenorphine-only group. Treatment with the combination of buprenorphine and naloxone or with buprenorphine alone did not result in appreciable electrocardiographic changes. Changes from base line in clinical (chemical and hematologic) values were small and not clinically relevant.

OPEN-LABEL STUDY

A total of 461 subjects (268 of whom had participated in the double-blind trial) took part in the open-label safety study. These 461 subjects and an additional 11 subjects who had participated only in the double-blind trial constituted the group in whom safety was assessed (Table 1). Of these 472 subjects, 385 received at least eight weeks and 261 received at least six months of treatment consisting of buprenorphine and naloxone in combination. There were a total of 92,930 subject-days of exposure to this medication. Fourteen subjects discontinued therapy because of adverse events, of which detox-

Table 1. Base-Line Demographic Characteristics of the Subjects in the Double-Blind Trial and of Those Who Constituted the Group in Whom Safety Was Assessed.*

Characteristic	Double-Blind Trial†				Safety Sample (N=472)
	Buprenorphine and Naloxone (N=109)	Buprenorphine Alone (N=105)	Placebo (N=109)	P Value‡	
Male sex — no. (%)	68 (62.4)	70 (66.7)	71 (65.1)	0.85	327 (69.3)
Age — yr	38.1±8.3	36.6±8.9	38.0±9.3	0.42	38.9±8.3
Race — no. (%)§				0.74	
White, non-Hispanic	65 (59.6)	62 (59.0)	70 (64.2)		238 (50.4)
Black, non-Hispanic	32 (29.4)	35 (33.3)	25 (22.9)		142 (30.1)
Hispanic	8 (7.3)	6 (5.7)	9 (8.3)		79 (16.7)
Native American	2 (1.8)	0	2 (1.8)		4 (0.8)
Asian or Pacific Islander	2 (1.8)	2 (1.9)	3 (2.8)		9 (1.9)
Weight — kg	72.3±13.9	73.4±13.6¶	75.8±16.4	0.21	74.5±16.0‖
Height — cm	172.0±9.6	173.5±8.8**	172.7±9.6	0.50	172.9±9.3††
Rating of need for drug-abuse treatment‡‡	7.6±1.4	7.6±1.1	7.5±1.1	0.82	7.4±1.4§§
Duration of heroin abuse — mo				0.74	
Median	84	84	84		120
Interquartile range	180	168	144		192
Range	6–393	3–420	6–468		3–468
Past enrollment in a methadone or levomethadyl acetate maintenance program — no. (%)¶¶	55 (50.5)	57 (54.8)	52 (48.1)	0.58	233 (49.5)
Household income — $‖‖				0.94	
Median	15,500	18,000	15,000		15,500
Interquartile range	17,000	20,400	20,000		19,000§§
Range	0–150,000	0–78,000	0–110,000		0–500,000
Employment pattern in past 3 yr — no. (%)***				0.45	
Full-time	59 (54.1)	53 (51.0)	49 (45.0)		226 (48.0)
Unemployed	14 (12.8)	20 (19.2)	26 (23.9)		85 (18.0)
Lack of stable living arrangements in past 3 yr — no. (%)	1 (0.9)	1 (1.0)	3 (2.8)	0.65	12 (2.5)

* Plus–minus values are means ±SD. The interquartile range is the difference between the 75th percentile and the 25th percentile and is represented as a single number.
† Data are shown for the 323 subjects who received at least one dose of study medication.
‡ P values are for the overall comparison among the three groups.
§ Race was reported by the subjects.
¶ The value shown is based on data from 103 subjects.
‖ The value shown is based on data from 468 subjects.
** The value shown is based on data from 104 subjects.
†† The value shown is based on data from 470 subjects.
‡‡ Scores were determined by an Addiction Severity Index interview and could range from 0 (no real problem and treatment not indicated) to 9 (extreme problem and treatment absolutely necessary).
§§ The value shown is based on data from 466 subjects.
¶¶ The values shown are based on data on 109, 104, 108, and 471 subjects who received buprenorphine and naloxone, buprenorphine alone, and placebo and who were included in the safety sample, respectively.
‖‖ The values shown are based on data from 106, 102, and 108 subjects who received buprenorphine and naloxone, buprenorphine alone, and placebo, respectively.
*** The values shown are based on data on 109, 104, 109, and 471 subjects who received buprenorphine and naloxone, buprenorphine alone, and placebo and who were included in the safety sample, respectively.

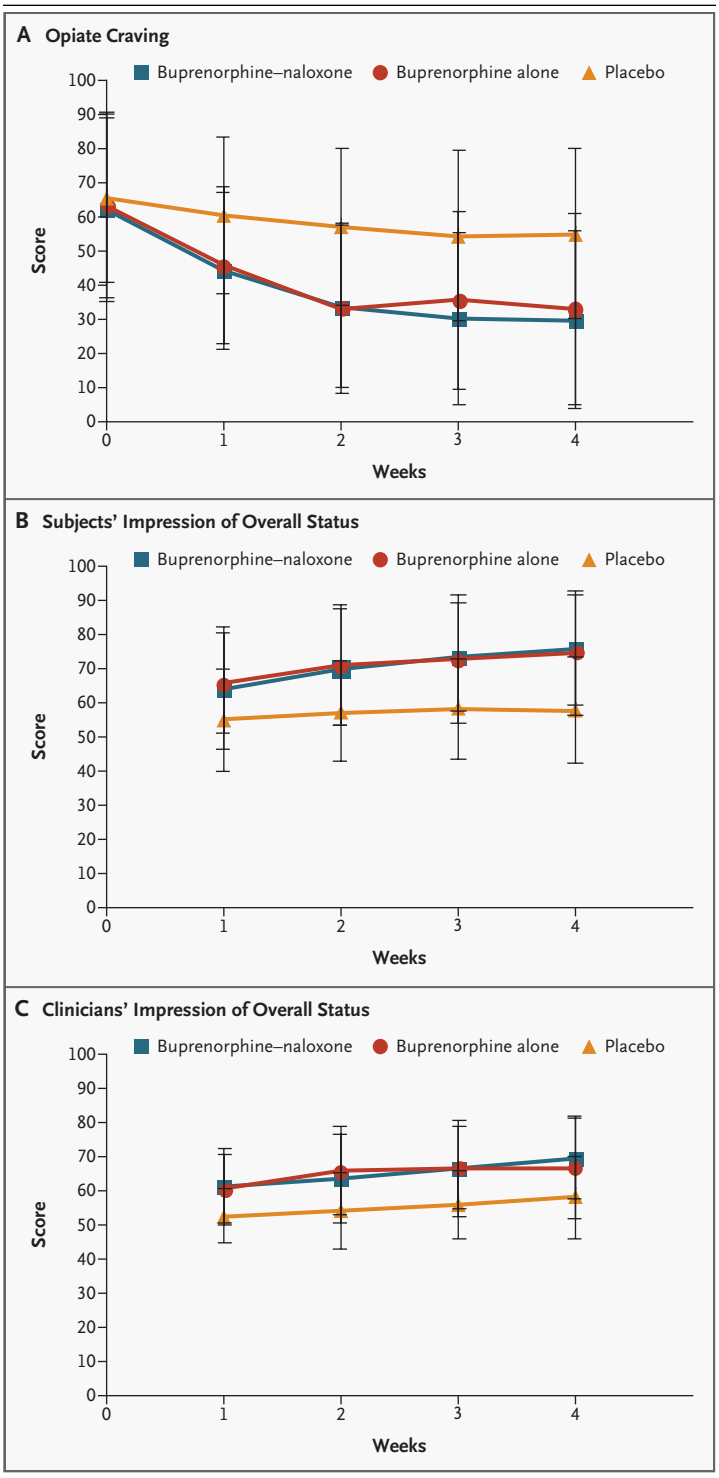


Figure 1. Mean (±SD) Scores for Opiate Craving and Subjects' and Clinicians' Impression of Overall Status.

For each of the four study weeks, the mean scores for opiate craving in the combined-treatment and buprenorphine groups were significantly lower than those in the placebo group ($P<0.001$ for both comparisons each week), and the scores for subjects' and clinicians' global impressions were significantly higher than those in the placebo group ($P<0.001$ for both comparisons each week). Panel A shows opiate-craving scores for subjects for whom data were available at a given time point (range, 79 to 109 subjects). Panel B shows subjects' impression of their own overall status since enrollment in the study for those for whom data were available at a given time point (range, 75 to 108 subjects). Panel C shows clinicians' impression of the subjects' overall status since enrollment for those for whom data were available at a given time point (range, 75 to 108 subjects). In Panels B and C higher scores indicate better perceived status.

ification or withdrawal symptoms (for example, rhinitis and diarrhea) were the most common. Eight subjects discontinued therapy because of medical conditions considered unrelated to the study medication, and two subjects discontinued therapy because of conditions possibly related to it.

Eighty-one serious adverse events were reported. The most common (in 10 subjects) were increases in hepatic alanine or aspartate aminotransferase or lactate dehydrogenase levels that were judged to be not related (in 3 cases), possibly related (in 6 cases), or probably related (in 1 case) to the study medication. In 8 of these 10 cases, serologic evidence of hepatitis B or hepatitis C infection was present at base line. Nonserious adverse events reported by at least 20 percent of the subjects were headache, pain, withdrawal syndrome, infection, insomnia, back pain, and constipation. There were no clinically important changes from base line in the results of clinical (chemical and hematologic) tests or in the findings on electrocardiography.

The percentages of urine samples negative for opiates, cocaine, and benzodiazepines are shown in Figure 2. The percentage of opiate-negative urine samples ranged from 35.2 percent to 67.4 percent in multiple assessments. The overall rate of opiate use was lower than that in the double-blind trial, whereas the use of cocaine or benzodiazepines remained relatively constant.

DISCUSSION

This two-part study demonstrated the efficacy and safety of a novel sublingual-tablet formulation of buprenorphine and naloxone in combination. The superiority of buprenorphine over placebo has been previously reported,[23,28,29] but the efficacy of buprenorphine or of this medication in combination with naloxone has not been previously evaluated in

Table 2. Adverse Events Reported by at Least 5 Percent of the Subjects in Any Treatment Group during the Double-Blind Trial.*

Adverse Event	Buprenorphine and Naloxone (N=107)	Buprenorphine Alone (N=103)	Placebo (N=107)	P Value†
	no. of subjects (%)			
Headache	39 (36.4)	30 (29.1)	24 (22.4)	0.08
Withdrawal syndrome	27 (25.2)	19 (18.4)	40 (37.4)	0.008
Pain	24 (22.4)	19 (18.4)	20 (18.7)	0.74
Insomnia	15 (14.0)	22 (21.4)	17 (15.9)	0.37
Nausea	16 (15.0)	14 (13.6)	12 (11.2)	0.73
Sweating	15 (14.0)	13 (12.6)	11 (10.3)	0.70
Abdominal pain	12 (11.2)	12 (11.7)	7 (6.5)	0.37
Rhinitis	5 (4.7)	10 (9.7)	14 (13.1)	0.09
Diarrhea	4 (3.7)	5 (4.9)	16 (15.0)	0.005
Infection	6 (5.6)	12 (11.7)	7 (6.5)	0.24
Chills	8 (7.5)	8 (7.8)	8 (7.5)	1.0
Constipation	13 (12.1)	8 (7.8)	3 (2.8)	0.03
Back pain	4 (3.7)	8 (7.8)	12 (11.2)	0.12
Vasodilation or flushing	10 (9.3)	4 (3.9)	7 (6.5)	0.28
Vomiting	8 (7.5)	8 (7.8)	5 (4.7)	0.66
Weakness	7 (6.5)	5 (4.9)	7 (6.5)	0.87

* Data were unavailable for two of the subjects in each group.
† P values are for the overall comparison among the three groups.

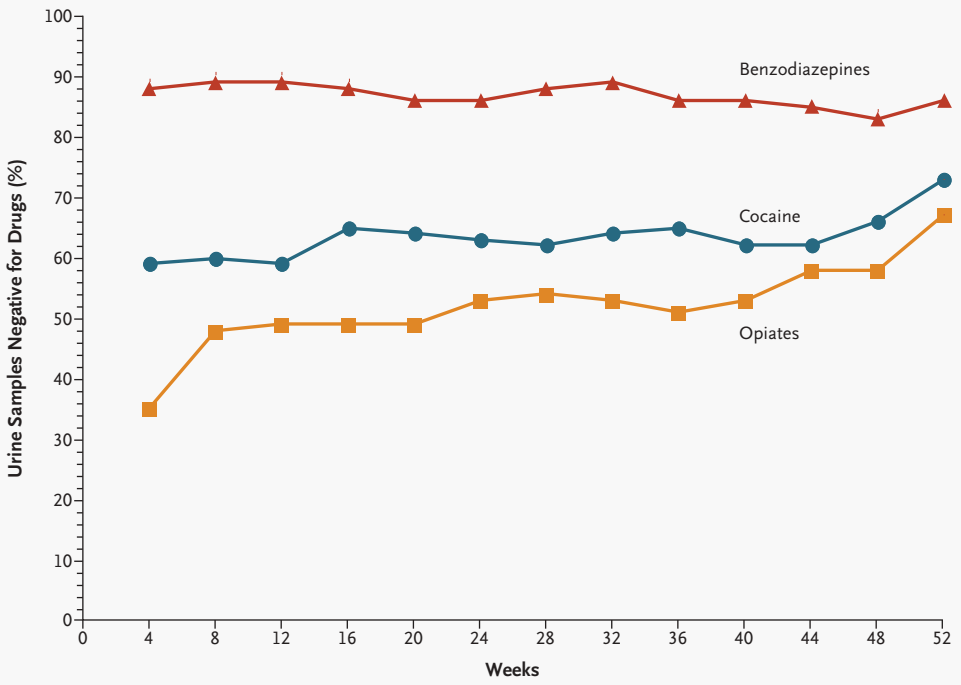
an office-based setting. The subjects in the double-blind trial were examined and given medication daily in an office setting. Medication was provided for at-home use on weekends and clinic holidays during the double-blind trial and for up to 10 days during the open-label phase. The Drug Addiction Treatment Act of 2000,[17] which allows the use of schedule III, IV, and V narcotic medications for the treatment of opiate addiction, and the approval by the Food and Drug Administration in October 2002 of buprenorphine and buprenorphine and naloxone in combination permit office-based treatment with these medications.

Approximately half of the subjects enrolled in the study reported having received no prior opiate-substitution treatment, either by choice or because of regulatory ineligibility for such treatment. The remainder had discontinued methadone or levomethadyl acetate pharmacotherapy; no direct induction from either of these medications was undertaken in this study. These results support the use of a sublingual tablet consisting of a combination of buprenorphine and naloxone as a first-line, office-based treatment for opiate addiction. The results also extend treatment options for persons who have previously undergone opiate-substitution pharmacotherapy.

The inclusion of naloxone in the sublingual-tablet formulation is not intended to increase the efficacy of treatment but, rather, to help deter the possible diversion of buprenorphine to misuse by the parenteral route. Combinations of buprenorphine and naloxone have been shown to precipitate withdrawal signs and symptoms when administered intravenously to opiate-dependent persons.[18-20] According to published data,[30] the buprenorphine–naloxone combination would not be expected to precipitate opiate withdrawal in persons whose condition had stabilized with the use of a therapeutic dose of buprenorphine. Although this study was not intended to compare the two active-treatment groups, the absence of an apparent difference in efficacy between them supports the idea that naloxone does not reduce the efficacy of buprenorphine.

The percentages of opiate-negative urine samples in both active-treatment groups were significantly greater than those in the placebo group during the double-blind trial. Although the percentages, averaged over four weeks, may appear low, this finding was neither unexpected nor indicative of a poor treatment response. The trial was designed to show efficacy by the four-week point, not the achievement of a full clinical effect. As a conservative approach, all the missing urine samples, including those missing because of early termination of the study, were coded as "not negative." Thus, it is likely that the actual percentage of negative samples was higher than that estimated. The pattern of results is similar to that observed in the initiation of treatment with other therapies currently approved for persons with opiate addiction.[31] In addition, other factors probably negatively affected the outcome of treatment. These factors include the fixed-dosing design, which did not permit individual dose titration; the blinding of clinicians to the results of urine testing, which are typically used to tailor individual treatment plans; and the absence of concomitant behavioral treatment. The percentages of urine samples negative for opiates during the open-label phase (generally between 50 percent and 60 percent) exceeded those in the double-blind trial and more closely resembled those reported in studies in which therapeutic dosages of buprenorphine, methadone, and levomethadyl acetate were used.[31-33]

The strengths of this study include the placebo-



No. of Samples Tested													
For cocaine or benzodiazepines	824	667	632	563	537	494	448	449	408	383	361	323	178
For opiates	943	675	633	564	537	494	449	449	408	383	361	323	178

Figure 2. Percentage of Urine Samples Negative for Opiates, Cocaine, or Benzodiazepines among Subjects Who Received Combination Treatment with Buprenorphine and Naloxone.

The data shown for week 4 include results from subjects in the double-blind trial and the open-label study; only the first urine sample collected during week 4 was analyzed for both opiate and nonopiate drugs. The differences between the numbers of samples analyzed for cocaine or benzodiazepines and the number analyzed for opiates at weeks 8, 12, 16, and 28 reflect missing data.

controlled design, the inclusion of both women and men, and the consistency of the findings among multiple outcome measures. Its limitations include a potentially restricted capacity for generalization to the population of opiate-addicted persons, because the criteria for enrollment excluded some persons, primarily for reasons related to safety. In addition, the expertise of the investigators and the resources available to them in the clinics may exceed those available in some office-based settings.

No unexpected safety issues emerged during the study, and the reported adverse events were those known to be generally associated with opiate-agonist treatment. We conclude that both buprenorphine alone and buprenorphine and naloxone in combination provide safe and effective treatment of opiate-addicted persons in an office-based setting.

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APPENDIX

Other members of the Buprenorphine/Naloxone Collaborative Study Group were as follows: Principal investigators in the open-label study — R. Douyon, the Veterans Affairs Medical Center, Miami; M. Fe-Bornstein, the Veterans Affairs Medical Center, New Orleans; J.G. Liberto, the Veterans Affairs Medical Center, Baltimore; and E. Santos, the Veterans Affairs Medical Center, San Juan, Puerto Rico; other members of the study group — K. Ajir, K. Annon, J.M. Buckelew, K. Conley, B.L. Curtis, T. Doane, D. Gaughan, L.D. Gorgon, C. Haakenson, M. Hanrahan-Boshes, R.L. Hawks, J. Hill, P. Lane, J. Leal, D. Leiderman, D. Lokhorst, P. Manning, F. McSherry, D. Preston, M. Sather, S. Scott, E. Somoza, S. Stinnett, K.B. Thomas, D. Wagner, J. Wagner, and R. Walsh.

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