Buprenorphine Implants for Treatment of Opioid Dependence

A Randomized Controlled Trial

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Context Limitations of existing pharmacological treatments for opioid dependence include low adherence, medication diversion, and emergence of withdrawal symptoms.

Objective To determine the efficacy of buprenorphine implants that provide a low, steady level of buprenorphine over 6 months for the treatment of opioid dependence.

Design, Setting, and Participants A randomized, placebo-controlled, 6-month trial conducted at 18 sites in the United States between April 2007 and June 2008. One hundred sixty-three adults, aged 18 to 65 years, diagnosed with opioid dependence. One hundred eight were randomized to receive buprenorphine implants and 55 to receive placebo implants.

Intervention After induction with sublingual buprenorphine-naloxone tablets, patients received either 4 buprenorphine implants (80 mg per implant) or 4 placebo implants. A fifth implant was available if a threshold for rescue use of sublingual buprenorphine-naloxone treatment was exceeded. Standardized individual drug counseling was provided to all patients.

Main Outcome Measure The percentage of urine samples negative for illicit opioids for weeks 1 through 16 and for weeks 17 through 24.

Results The buprenorphine implant group had significantly more urine samples negative for illicit opioids during weeks 1 through 16 ($P=.04$). Patients with buprenorphine implants had a mean percentage of urine samples that tested negative for illicit opioids across weeks 1 through 16 of 40.4% (95% confidence interval [CI], 34.2%-46.7%) and a median of 40.7%; whereas those in the placebo group had a mean of 28.3% (95% CI, 20.3%-36.3%) and a median of 20.8%. A total of 71 of 108 patients (65.7%) who received buprenorphine implants completed the study vs 17 of 55 (30.9%) who received placebo implants ($P<.001$). Those who received buprenorphine implants also had fewer clinician-rated ($P<.001$) and patient-rated ($P=.004$) withdrawal symptoms, had lower patient ratings of craving ($P<.001$), and experienced a greater change on clinician global ratings of severity of opioid dependence ($P<.001$) and on the clinician global ratings of improvement ($P<.001$) than those who received placebo implants. Minor implant site reactions were the most common adverse events: 61 patients (56.5%) in the buprenorphine group and 29 (52.7%) in the placebo group.

Conclusion Among persons with opioid dependence, the use of buprenorphine implants compared with placebo resulted in less opioid use over 16 weeks as assessed by urine samples.

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DEPENDENCE ON OPIOIDS, IN THE form of heroin or prescription pain medications, is a significant health concern.[1-3] Methadone maintenance treatment for opioid dependence reduces morbidity, mortality, and the spread of infectious diseases[4] but is restricted to licensed specialty clinics in the United States, requires frequent clinic visits, and has a risk of mortality with overdose.[5] These issues have led to increased use of buprenorphine, and numerous studies support the efficacy of sublingually administered buprenorphine.[6] In the United States, buprenorphine can be prescribed in office-based physician practice.[7] Because it is a partial agonist, buprenorphine has less risk of overdose than methadone.[8] However, there are concerns about diversion and nonmedical use of sublingual buprenorphine, even when a buprenorphine-naloxone combination (designed to reduce misuse) is used.[9-11] Poor treatment adherence, resulting in craving and withdrawal symptoms that increase the likelihood of relapse, is also a concern with sublingual buprenorphine.[12]

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To address these problems with adherence, diversion, and nonmedical use, an implantable formulation of buprenorphine has been developed. This implant is a polymeric matrix composed of ethylene vinyl acetate and buprenorphine that delivers buprenorphine over 6 months. Following an initial pulse release, a constant and low level of buprenorphine is released, avoiding plasma peaks and troughs observed with sublingual administration. A preliminary open-label phase 2 study reported favorable results with this implant in opioid-dependent patients.[13]

The present study reports results of a phase 3 multicenter, randomized, placebo-controlled investigation of buprenorphine implants for treatment of opioid dependence.

METHODS

Participants

Patients were recruited for the study from 6 academic, 3 Veterans Affairs, and 9 nonprofit community addiction treatment centers in the United States between April 2007 and June 2008. The study was approved by institutional review boards at each site, and written informed consent was obtained from all participants.

To be eligible for the study, men or nonpregnant women, aged 18 to 65 years, were required to meet *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) diagnosis of current opioid dependence at a screening visit as determined by the Mini International Neuropsychiatric Interview.[14] Exclusion criteria were AIDS, met *DSM-IV* criteria for current dependence on psychoactive substances other than opioids or nicotine, currently using nonprescribed benzodiazepines, had received medication treatment for opioid dependence within the previous 90 days, or had a current diagnosis of chronic pain that required opioid treatment. Patients were also excluded if they had any of the following: aspartate aminotransferase (AST) levels at least 3 times higher than the upper limit of normal, alanine aminotransferase (ALT) levels at least 3 times the upper limit of normal, total bilirubin levels of at least 1.5 times the upper limit of normal, or creatinine levels at least 1.5 times the upper limit of normal.

Demographics and history were collected by patient self-report based on a list of choices.

Study Intervention and Randomization

Eligible patients entered into an open-label induction phase designed to ensure that buprenorphine could be safely administered. Patients were required to complete induction within 10 days of screening and receive a fixed dose of 12 to 16 mg/d sublingual buprenorphine-naloxone tablets for at least 3 consecutive days immediately before randomization. Patients were excluded from participation if during the induction phase they had reported significant withdrawal symptoms, defined as more than 12 on the Clinical Opiate Withdrawal Scale,[15] or significant cravings for opioids, defined as more than 20 mm on a 100-mm opioid craving visual analog scale (VAS).

At the end of the induction phase, patients were randomized (stratified by sex and site) at a 2:1 ratio to double-blind treatment with either 4 buprenorphine implants (80 mg each) or 4 placebo implants. The 2:1 ratio was used to reduce patient exposure to placebo implants. The implants (26 mm in length × 2.5 mm in diameter) were placed in the subdermal space (2-3 mm below the skin) all at the same time in the inner side of the nondominant arm by a physician who had participated in a 1-day training in implant insertion and removal or who had prior similar experience. No sutures are required for implantation (sutures were used at removal). The physicians who placed and removed the implants were from various medical specialties (eg, family practice, psychiatry, dermatology, obstetrics and gynecology) and had surgical training but did not serve as the site investigator. The implants were removed after 6 months.

After implant placement, patients could receive supplemental sublingual buprenorphine-naloxone tablets, beginning with 4 mg and increasing in 2-mg increments as clinically necessary and tolerated up to 12 to 13 mg, if they experienced significant withdrawal symptoms or significant craving or if they had requested a dose increase that the treating physician judged to be appropriate. The supplemental sublingual buprenorphine-naloxone tablets were administered at the clinic under observation, except for weekends and holidays, for which participants received a maximum of 3 days of dosing to take at home. Patients could receive an additional implant if they required 3 or more days per week of any supplemental sublingual buprenorphine-naloxone tablets for 2 consecutive weeks, or 8 or more days of any supplemental buprenorphine-naloxone tablets over 4 consecutive weeks.

Because the placebo implants had a slightly different appearance than buprenorphine implants, steps were taken to maintain the blind: (1) the physician and staff involved in the implant insertion and removal procedures did not participate in efficacy evaluations or discuss with other study staff any information regarding a patient's implants, (2) surgical draping prevented patients from viewing the implants during insertion or removal procedures, (3) staff not involved in implant insertion and removal procedures were forbidden from asking those involved in these procedures about the rod's appearances, (4) each implant was sealed in an opaque, foil-lined pouch that hid the contents from view and was only opened by those involved with the implanting procedures.

All patients received manual-guided individual drug counseling.[16] Sessions were held twice a week during the first 12 weeks and then weekly for the subsequent 12 weeks. If a patient missed 6 consecutive counseling sessions, this was judged to be clinically meaningful nonadherence, causing the patient to be withdrawn from the study. Because experienced drug

counselors at each site who were familiar with the drug-counseling treatment model provided services, they received no formal training.

Urine samples were obtained 3 times per week throughout the entire 6-month treatment period. Drug screens were performed by a central laboratory and study staff, and patients remained blind to results. If a patient did not provide 9 consecutive urine samples, they were considered nonadherent and withdrawn (ie, 3 weeks was considered a clinically important interval). Participants could continue in the study regardless of test results. Urine toxicology samples were verified at collection by measurement of urine temperature. Patients provided another sample if a urine sample was outside of a valid temperature range. If the second sample was outside of the temperature range, the sample was designated as missing.

Efficacy Assessments

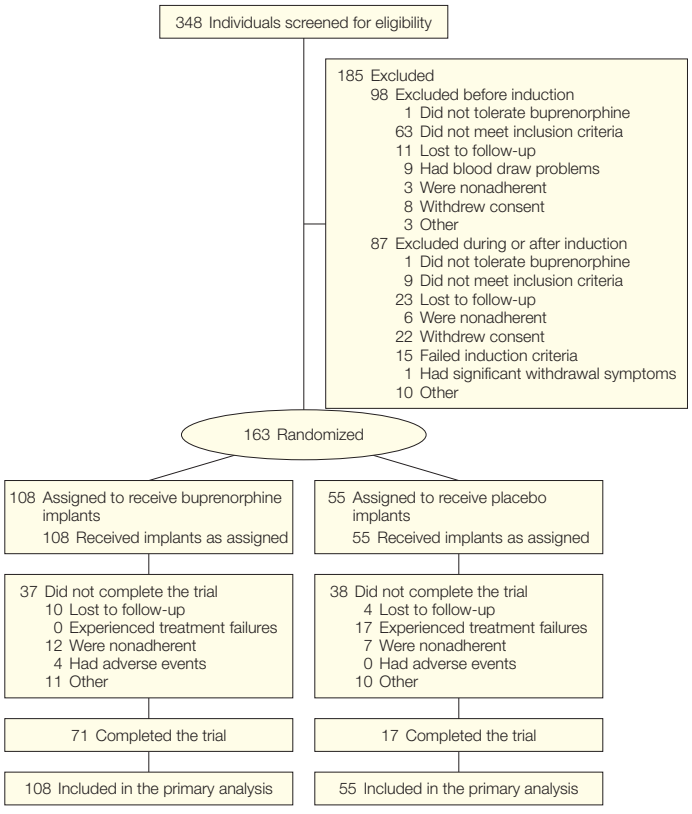
The primary outcome measure was the percentage of the 48 urine samples that were negative for illicit opioids during the first through 16th week of the trial. This 16-week period was selected because of the interest in examining early-treatment response in the context of this longer-term treatment.

The secondary outcome measure was assessed as the percentages of the 24 urine samples that were negative for illicit opioids during weeks 17 through 24. Additional outcomes measured included the proportion of treatment failures, the proportion of study completers, the patient-report and clinician-report withdrawal scales, a craving scale, and clinician severity and improvement ratings.

Treatment failure was defined as receiving a fifth implant and subsequently requiring 3 or more days per week of supplemental sublingual buprenorphine-naloxone treatment for 2 consecutive weeks or 8 or more days of supplemental sublingual buprenorphine-naloxone treatment over 4 consecutive weeks at any time after the implant dosage increase. Patients who met this definition of treatment failure were withdrawn from the study.

Patient report of withdrawal symptoms was assessed by the Subjective Opiate Withdrawal Scale.[17] Clinician report of withdrawal symptoms was measured with the Clinical Opiate Withdrawal Scale, administered by the investigator or other qualified clinical staff. Craving for opioids was measured using a 100-mm VAS: 0 indicates no cravings; and 100, the maximum craving experienced. All 3 measures were obtained at baseline and at weeks 1, 4, 8, 12, 16, 20, and 24. The clinician-rated Clinical Global Impressions-Severity (CGI-S)[18] (of opioid dependence) and Improvement scales (CGI-I)[18] were obtained at baseline and at weeks 16 and 24 (or end point).

Figure 1. Flow Diagram of Participants Through the Trial



Safety and Pharmacokinetic Assessments

Vital signs, blood and urine laboratory tests (hematology, liver function tests, coagulation, pregnancy test), and electrocardiograms were obtained at regular study visits. The assessment protocol required that study investigators visually inspect the surgical implant location of each participant during each study visit. Levels of plasma buprenorphine were obtained and analyzed from blood samples taken at baseline and monthly thereafter.

Statistical Analyses

Baseline variables were compared across treatment groups using χ^2 for categorical variables and *t* tests for continuous variables.

The primary analysis was conducted using an intention-to-treat approach that included all randomized patients. The primary statistical analysis specified in the study protocol was a van Elteren Wilcoxon rank sum test,[19] stratified by sex and treatment site, comparing study groups on the distributions

of the percentages of urine samples that tested negative for illicit opioids over 16 weeks. Sample size determination was conducted using a 2-sided α of .05 and 80% power to detect a shift of 20% (a difference deemed to be clinically relevant) between the placebo and buprenorphine groups on the distributions of the percentage of urine samples negative for illicit opioids over 16 weeks. Approximately 150 patients were required, taking into account the 2:1 randomization scheme, normal distributions without stratification with a common standard deviation of 30% as a conservative powering model, and an attrition rate of approximately 40%.

The denominator for the primary end point was all possible urine samples that could have been collected from implantation through week 16. Missed samples were considered positive for opioids. After a patient was withdrawn from the study, urine samples from the point of withdrawal onward were also considered positive.

A secondary analysis examined the percentage of urine samples over weeks 17 through 24 (using a van Elteren Wilcoxon test stratified for sex and site). Hypothesis testing for the primary analysis and the first secondary analysis was conducted using a fixed-sequence testing procedure. First, the primary hypothesis was tested using a 5% α level. Only if the null hypothesis was rejected for the primary analysis did testing proceed to the first secondary analysis. In accordance with this procedure, no α adjustment for multiple tests is required and the accepted alternative hypotheses may be claimed significant at the 5% level. An additional van Elteren Wilcoxon rank sum test examined the percentage of urine samples negative for the full 24-week period (72 samples per patient).

The proportions of participants who completed the study (defined as completing 24 weeks) were compared between treatment groups with a Cochran Mantel-Haenszel test, stratified by sex and site. The clinical and subjective withdrawal scales and the craving VAS were analyzed using a mixed-effects repeated-measure analysis of covariance using all available assessments and adjusting for sex, site, and baseline value. A spatial power law correlation structure was specified for these analyses. This covariance structure was used because it is appropriate for modeling data when the measurement time points are continuous (unequally spaced) rather than discrete categories, and the correlations decline as a function of the time difference. The CGI-I and CGI-S were analyzed as categorical variables using a Cochran Mantel-Haenszel test stratified by sex and site.

The incidence of specific adverse events was compared across treatment groups using χ^2 tests. All statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient Characteristics and Disposition

Of 348 patients screened for the study, 185 were excluded: 98 before and 87 during or after the induction period (FIGURE 1). There were no significant differences between the treatment groups (TABLE 1).

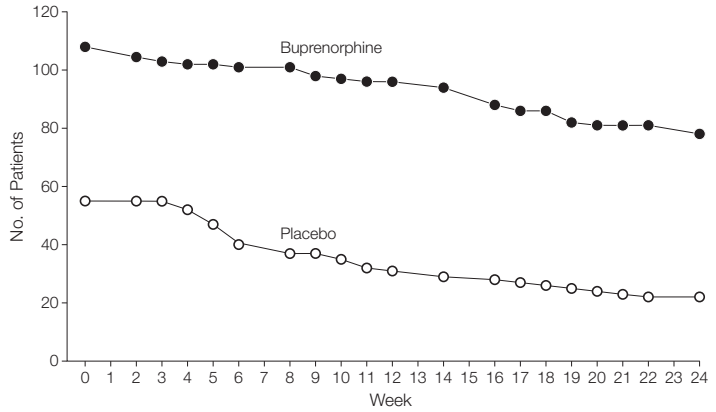
Treatment Exposure

The median number of weeks of exposure to the implants (before they were removed) was 24 (range, 0-43 weeks) for buprenorphine and 16.6 (range,

Table 1. Baseline Characteristics of Patients

Characteristic	Implant Group, No. (%)		*P* Value
	Buprenorphine (n = 108)	Placebo (n = 55)	
Age, mean (SD), y	35.8 (11.0)	39.3 (11.7)	.07
Male	72 (66.7)	40 (72.7)	.43
Race			
White	82 (75.9)	40 (72.7)	.62
African American	14 (13.0)	6 (10.9)	
Other	12 (11.1)	9 (16.4)	
Ethnicity			
Hispanic or Latino	12 (11.1)	12 (21.8)	.07
Primary opioid of abuse			
Heroin	69 (63.9)	34 (61.8)	.80
Prescription pain medication	39 (36.1)	21 (38.2)	
Diagnosis of opioid dependence for >5 y, (range)	15.5 (11-71)	14.3 (6-42)	.86
Previous pharmacotherapy for opioid dependence	25 (23.1)	14 (25.5)	.74

Figure 2. Retention of Patients Through the Trial



3-34 weeks) for placebo. Additional implants were received by 20.3% (22 of 108) of those in the buprenorphine group and 58.2% (32 of 55) of those in the placebo group. During weeks 1 through 16, 64 of 108 participants (59%) in the buprenorphine implant group received supplemental sublingual buprenorphine-naloxone tablets for a median of 7.5 days for emergent withdrawal or craving, whereas 50 of the 55 patients in the placebo group (91%) received the buprenorphine-naloxone tablets for a median of 19.5 days. The buprenorphine implant group received a mean dose of 94.1 mg (95% confidence interval [CI], 71.3-117.0 mg) for the weeks 1 through 16 and received an average daily dose of 9.8 mg (95% CI, 8.8-10.8 mg), whereas the placebo group received a mean of 208.3 mg (95% CI, 163.1-253.5 mg) for an average daily dose of 10.4 mg (95% CI, 9.3-11.4 mg). For weeks 17 through 24, 12% (13 of 108) in the buprenorphine implant group received a mean dose of 56.9 mg (95% CI, 29.2-84.6 mg) and an average daily dose of 12.7 mg (95% CI, 10.1-15.2 mg) for a median of 3 days, whereas 20% (11 of 55) in the placebo group received a mean of 175.8 mg (95% CI, 21.0-330.6 mg) and an average daily dose of 12.8 mg (95% CI, 9.8-15.8 mg) for a median of 7 days.

The most frequent reasons for early discontinuation in the buprenorphine implant group were nonadherence with the protocol and being lost to follow-up. In the placebo group, patients most frequently withdrew early because of treatment failure or nonadherence (Figure 1).

Of those who discontinued because of protocol nonadherence, 2 participants in the buprenorphine implant group and 1 in the placebo group missed 6 consecutive counseling sessions and were therefore withdrawn. There was no evidence of unscheduled implant removal or attempted removal.

Table 2. Secondary Efficacy End Points[a]

	Mean (95% Confidence Interval)[b]		
	Buprenorphine (n = 108)	Placebo (n = 55)	*P* Value
Scores over 24 wk			
Clinical Opiate Withdrawal Scale	2.3 (1.9-2.7)	3.4 (2.8-4.0)	<.001
Subjective Opiate Withdrawal Scale	4.1 (3.1-5.1)	6.5 (5.1-7.9)	.004
Visual analog scale–opioid craving	9.9 (7.8-12.0)	15.8 (12.7-18.9)	<.001
	No. (%)[c]		
	(n = 91)	(n = 47)	
CGI-severity at week 24 (or end point)			
Normal, no symptoms	34 (37.4)	9 (19.1)	<.001
Borderline	18 (19.8)	7 (14.9)	
Mild	21 (23.1)	12 (25.5)	
Moderate	16 (17.6)	12 (25.5)	
Marked	1 (1.1)	7 (14.9)	
Severe	1 (1.1)	0	
Among the most extreme symptoms	0	0	
CGI-improvement at week 24 (or end point)			
Very much	51 (56.0)	11 (23.4)	<.001
Much	22 (24.2)	13 (27.7)	
Minimally	14 (15.4)	14 (29.8)	
No change	3 (3.3)	8 (17.0)	
Minimally worse	1 (1.1)	1 (2.1)	
Much worse	0	0	
Very much worse	0	0	

Abbreviation: CGI, Clinical Global Impressions

[a] Significance tests for Clinical Opiate Withdrawal Scale, Subjective Opiate Withdrawal Scale, or the visual analog scale for opioid craving are based on mixed-effects repeated measures analysis of variance using scores from weeks 1, 4, 8, 12, 16, and 20, with baseline scores, sex, and site as covariates. Significance tests for CGI-severity and CGI-improvement based on Cochran Mantel-Haenszel test stratified by sex and site. The Clinical Opiate Withdrawal Scale potentially ranges from 0 to 48, with a score of 5 to 12 considered mild; 13 to 24, moderate; 25 to 36, moderately severe; and more than 36, severe withdrawal. The Subjective Opiate Withdrawal Scale scores potentially range from 0 to 64, with each of 16 questions rated on intensity of withdrawal on a 0 (not at all) to 4 (extremely) scale. The visual analog scale ranges from 0 (no craving) to 100 mm (maximum experienced).

[b] Means are adjusted for sex, site, and baseline value.

[c] Data were missing for 17 in the buprenorphine implant group and 8 in the placebo group.

Efficacy

A mean of 40.4% (95% CI, 34.2%-46.7%; median, 40.7%) of the 48 urine samples taken for each patient in the buprenorphine group during the first 16 weeks of the study tested negative for opiate use vs a mean 28.3% (95% CI, 20.3%-36.3%; median, 20.8%) in the placebo group ($P = .04$). The distributions of the percentage of 24 urine samples taken from week 17 through 24 that tested negative for opioid use also showed a statistically significant difference ($P < .001$). For the full 24-week treatment period for a total of 72 urine samples from each patient, the buprenorphine group had a mean 36.6% (95% CI, 30.5%-42.6%; median, 29.9%) of urine samples that tested negative for opioids vs 22.4% (95% CI, 15.3%-29.5%; median, 13.9%) for the placebo group ($P = .01$).

A mean of 42.9 (44.0%) urine samples were actually provided by patients for weeks 1 through 16 and 17.5 (31.1%) for weeks 17 through 24 for the buprenorphine group vs 31.9 (43.2%) for weeks 1 through 16 and 8.5 (14.1%) for weeks 17 through 24 for the placebo group. Retention in the study is shown in FIGURE 2.

Treatment group differences were also evident on additional efficacy measures (TABLE 2). During weeks 1 through 16, 88 of 108 (81.5%) in the buprenorphine implant group remained in the study vs 28 of 55 (50.9%) in the placebo group ($P < .001$). A sig-

nificant difference ($P<.001$) was also evident in completion rates for the full 24-week study period: 71 of 108 (65.7%), buprenorphine implant group; 17 of 55 (30.9%), placebo group. The buprenorphine implant group had lower scores for clinical ($P<.001$) and subjective ($P=.004$) opiate withdrawal and for opioid craving ($P<.001$) than those in the placebo group across 24 weeks of treatment. At week 24, there were significant differences between the treatment groups on the CGI-S ($P<.001$) and CGI-I ($P<.001$) rating scales favoring buprenorphine (Table 2).

No patients in the buprenorphine implant group met the definition of treatment failure; 30.9% (17of 55) of placebo patients were classified as treatment failures.

Table 3. Treatment-Emergent Adverse Events Across 24 Weeks With Incidence of More Than 10% in Either Group

	Events, No. (%)		
	Buprenorphine (n = 108)	Placebo (n = 55)	*P* Value
Adverse event			
Constipation	15 (13.9)	3 (5.5)	.10
Diarrhea	6 (5.6)	7 (12.7)	.11
Nausea	15 (13.9)	7 (12.7)	.84
Toothache	12 (11.1)	3 (5.5)	.24
Nasopharyngitis	15 (13.9)	3 (5.5)	.10
Upper respiratory tract infection	14 (13.0)	6 (10.9)	.71
Back pain	13 (12.0)	3 (5.5)	.18
Headache	27 (25.0)	10 (18.2)	.33
Anxiety	11 (10.2)	5 (9.1)	.82
Insomnia	23 (21.3)	12 (21.8)	.94
Serious adverse events	2 (1.9)	4 (7.3)	.08
Implant site adverse events			
Any event	61 (56.5)	29 (52.7)	.65
Erythema	27 (25.0)	12 (21.8)	.65
Edema	14 (13.0)	5 (9.1)	.47
Itching	27 (25.0)	8 (14.5)	.12
Pain	24 (22.2)	6 (10.9)	.08
Bleeding	13 (12.0)	7 (12.7)	.90

Safety

Ninety-three (86.1%) of those in the buprenorphine implant group had at least 1 adverse event vs 45 (81.8%) of those in the placebo group (TABLE 3). Implant site adverse events were the most common; these events were normal and expectable consequences of the surgical procedure (not due to difficulties with insertion or removal).

Among adverse events not related to implant site, headache and insomnia were the most common in the buprenorphine group. No significant treatment group differences were apparent for adverse events that occurred with 10% or greater frequency (Table 3). No adverse events resulted in discontinuation of treatment in the placebo group. In the buprenorphine group, 3.7% of the patients experienced adverse events for which they were discontinued. These adverse events were implant site pain and infection (2 cases), implant site pain, and elevated liver enzymes. Two patients (1.9%) in the buprenorphine implant group experienced serious adverse events compared with 4 (7.3%) in the placebo group. One patient with a history of pulmonary embolism and chronic obstructive pulmonary disease in the buprenorphine group had a pulmonary embolism and an exacerbation of chronic obstructive pulmonary disease, and these events were judged as possibly related to treatment (because of the effect of opioids on respiratory function). The other patient experienced a burn injury. In the placebo group, 1 patient experienced suicidal ideation, another had pneumonia and cellulitis (related to implant site), another had a relapse of opioid dependence resulting in hospitalization, and another had respiratory failure. The patient with pneumonia and cellulitis was hospitalized for 1 day, during which time an incision and drainage were performed on the infected site, and the patient was treated with intravenous and oral antibiotics.

There were no clinically meaningful changes from baseline in vital signs, physical examinations, or electrocardiograms. No clinically significant changes from baseline were observed in hematology or coagulation values in either group. There was a minor increase in mean ALT and mean AST levels in the buprenorphine group, which was attributable to 1 patient who had significant increases in ALT and AST levels that were likely related to a hepatitis C infection and history of alcohol and drug use.

Pharmacokinetics

Mean (SD) steady state plasma buprenorphine concentrations over weeks 4 through 24 were 941 (832) pg/mL vs 495 (720) pg/mL in the placebo group, and the respective medians were 775 pg/mL (range, 378-8070 pg/mL) vs 237 pg/mL (range, 0-3070 pg/mL). The plasma buprenorphine in the placebo group can be attributed to use of rescue sublingual buprenorphine-naloxone tablets and possibly buprenorphine obtained from outside the study.

COMMENT

This study demonstrated that buprenorphine implants are effective in the treatment of opioid dependence over a 24-week period following implantation. Of particular clinical importance are the favorable urinalysis toxicology results

and the good patient retention—with 65.7% of patients who received the active implants completing 24 weeks of treatment without experiencing craving or withdrawal symptoms that necessitated withdrawal from the study. In contrast, a recent study reported a median duration of 40 days for individuals who received sublingual buprenorphine in clinical settings.[12] Available 6-month trials of sublingual buprenorphine have reported retention rates of 35%,[20] 38%,[21] and 35%.[22]

The improved retention rate was found in the current study despite the buprenorphine implants resulting in relatively low plasma concentrations of buprenorphine. Given the known pharmacokinetics of buprenorphine,[23] the steady state plasma concentration levels are consistent with a constant buprenorphine release of 1 to 1.3 mg/d from 4 to 5 buprenorphine implants. Results from the prior phase 2 study showed that average plasma concentrations of buprenorphine implants were lower than trough plasma concentrations of sublingual buprenorphine measured in the same patients (prior to implants) and that the initial pulse of buprenorphine in the 24 hours following implant insertion was less than half of peak plasma concentration observed with sublingual buprenorphine prior to implant insertion.[13] Extrapolating from the low buprenorphine plasma concentrations, it is possible that a higher number of implants would result in greater efficacy. However, no patients in the buprenorphine implant group exceeded the criterion for treatment failure based on the need for sublingual buprenorphine-naloxone tablets. Thus, it appears that 4 or 5 implants are sufficient to control most cravings and withdrawal symptoms.

Minor implant site reactions were common. However, only 1 patient in the placebo group experienced a major implant site reaction (cellulitis). There was no evidence of unscheduled implant removal or attempted removal. Thus, diversion of the buprenorphine implants appears unlikely.

Several limitations of this study are important to consider: (1) All patients received psychosocial counseling in addition to implants. The extent to which the efficacy of the implants is dependent on this ancillary counseling is not known, although this is the standard of care in addiction treatment. (2) Placebo patients had an average buprenorphine plasma concentration that was almost half that of the active implant group due to the need for rescue buprenorphine-naloxone treatment. The use of rescue buprenorphine-naloxone treatment complicates the interpretation of study results, particularly the plasma buprenorphine levels. (3) The current trial was not statistically powered to examine efficacy within subgroups of patients. The number of implants and extent of supplemental sublingual buprenorphine-naloxone treatment may need to vary depending on initial severity of opioid dependence, duration of opioid dependence, or type of opioid. (4) Attrition was high because of the regulatory requirement to include a placebo control.

In summary, this study found that the use of buprenorphine implants compared with placebo resulted in less opioid use over 16 weeks and also across the full 24 weeks.

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Author Contributions: Drs Ling and Casadonte had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Beebe, Ling, Casadonte.
Acquisition of data: Beebe.
Analysis and interpretation of data: Ling, Casadonte, Bigelow, Kampman, Patkar, Bailey, Rosenthal, Beebe.
Drafting of the manuscript: Ling, Casadonte, Bigelow, Kampman, Patkar, Bailey, Rosenthal, Beebe.
Critical revision of the manuscript for important intellectual content: Ling, Beebe, Patkar.
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