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Research Article

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Long-Term Buprenorphine Implants for Treatment of Opioid Dependence: Safety Outcomes from Two Open-Label Extension Trials

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Abstract

Objective: To assess long-term exposure to buprenorphine implants (BIs) for opioid dependence in two open-label extension clinical trials.

Methods: Two six-month, open-label, multicenter extension studies of BI (Clinicaltrials.gov NCT01262261, NCT00630201) were conducted with opioid-dependent adult participants who had completed 24 weeks of BI treatment in prior phase 3 trials. Subjects received four subdermal implants, each containing 80 mg buprenorphine hydrochloride. Supplemental sublingual buprenorphine or insertion of a fifth implant were available for patients meeting criteria for opioid craving or withdrawal at investigator discretion. Safety of BI was evaluated using adverse events (AEs), abnormalities in physical exams, and vital signs. Additional outcomes included plasma concentrations of buprenorphine, ratings of opioid withdrawal symptoms, and craving and treatment retention.

Results: A total of 62/88 and 85/163 eligible participants continued in Study 1 and Study 2, respectively. Patient retention rates were 74.2% (46/62) and 78.8% (67/85) in Study 1 and 2, respectively. In Study 1, 47/62 participants (75.8%) experienced 329 treatment-emergent AEs; in Study 2, 57/85 participants (67.1%) experienced 172 AEs. Modifications to the implantation procedure between Study 1 and Study 2 resulted in a numerical decrease in AEs. Of these AEs, 103/329 (31.3%) in Study 1 were implant site-related; 19/57 (11.0%) in Study 2 were implant site-related. Mean concentrations of buprenorphine were stable from weeks 4 to 24, and cravings and withdrawal were well controlled.

Conclusion: The use of BI up to one year appears safe. Modifications in the surgical technique resulted in a reduction in the overall number of AEs.

Keywords

Introduction

Opioid abuse and dependence have reached epidemic proportions in the United States, resulting in premature death, criminal activity, and other serious consequences that cost almost $56 billion annually [1-6]. In 2014, nearly 50,000 people in the United States died from drug overdoses, more than any previous year on record [7]. Since 2000, rates of death involving opioid overdoses have increased by 200% [7]. Recent increases in opioid-related overdoses are particularly concerning, with three- and six-fold increases in overdose deaths related to prescription opioids and heroin, respectively, between 2001 and 2014 [8].

Extended maintenance with sublingual buprenorphine (SL BPN) is an efficacious treatment for opioid addiction [9-13]. However, the widespread adoption of buprenorphine by treatment providers may be limited by concerns regarding patient nonadherence, abuse, or accidental pediatric exposure to the medication [14-17]. Indeed, recent reports have noted some degree of buprenorphine nonadherence among patients, which could erode the clinical benefits being produced by the expansion of buprenorphine into general medical settings [16,18]. Even under supervision, between 15% and 30% of participants reported removing or diverting an oral buprenorphine dose over a six-month period [19].

A novel, sustained-release formulation of buprenorphine, delivered via subdermal implants, was designed to provide sustained plasma concentrations of buprenorphine for up to six months, which may eliminate the need for daily dosing and reduce need for take-home doses. Previous phase 3, double-blind, placebo-controlled trials were conducted with opioid-dependent subjects treated for six months with urine toxicology testing conducted thrice weekly [20,21]. In these studies, buprenorphine implants (BI) were superior to placebo on outcomes of illicit opioid abstinence, retention in treatment, and ratings of opioid withdrawal and cravings. Further, BI was superior to SL BPN for control of withdrawal and cravings. The purpose of this study was to evaluate long-term exposure to BIs for opioid dependence in two open-label extension clinical trials in which subjects who had previously completed 24 weeks of BI treatment subsequently received BI for an additional 24 weeks. The present study represents the longest duration exposure evaluated to date with this novel, sustained-release formulation of buprenorphine.

Materials and Methods

Study design

Two six-month, open-label, multicenter clinical trials of BI were conducted with adult participants with a history of opioid dependence who had completed 24 weeks of treatment in prior phase 3 trials evaluating BI [20,21]. In Study 1, all participants had previously received active or placebo implants. In Study 2, participants had previously received active implants, placebo implants, or SL BPN. Both trials were conducted in compliance with regulations and guidelines governing Good Clinical Practice and in accordance with the Declaration of Helsinki, with all participants providing written consent prior to participation.

Participants

Participants aged 18 to 65 years were eligible for inclusion if they had successfully completed 24 weeks of prior study treatment and volunteered to continue. Participants in the core blinded studies

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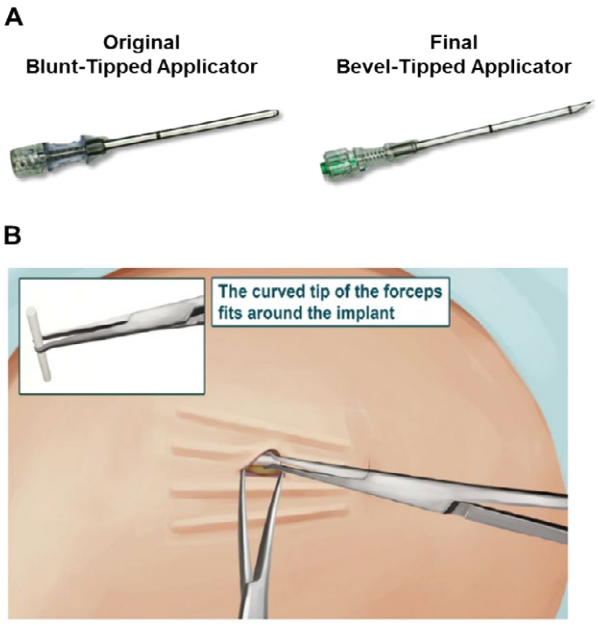
were required to meet *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for current opioid dependence at screening and without active agonist maintenance treatment in the past 90 days [22]. Key patient exclusion criteria included aspartate aminotransferase or alanine aminotransferase levels ≥ 3x the upper limit of normal (ULN) or total bilirubin or creatinine levels ≥ 1.5x ULN at screening; a current diagnosis of chronic pain requiring opioid treatment; use of agents metabolized through cytochrome P450 3A4; a history of coagulopathy or current anticoagulant therapy; medical or psychiatric factors precluding study inclusion; or medical or legal conditions potentially affecting study participation or protocol adherence.

Study treatment and patient care

Each participant received four subdermal implants, each containing 80 mg buprenorphine hydrochloride, inserted by trained healthcare professionals under sterile conditions into the upper inner side of the opposite arm used in the prior trial (dominant arm) using a specialized applicator. Participants were seen for a minimum of 12 study visits: one baseline visit, at least one induction visit, one implant visit, one postimplant visit, six treatment visits, one end-of-treatment visit (implant removal, 24 weeks), and a follow-up visit (four weeks after implant removal). Vital signs, implant site and treatment compliance, illicit drug use self-report, withdrawal symptoms, adverse events, and concomitant medications and procedures were assessed at each study visit.

Implantation procedures and training were modified during Study 1; prior to Study 2, the implant equipment, procedures, and training were also modified. A blunt-tipped applicator was used in Study 1; based on investigator feedback and safety, a new bevel-tipped applicator was used throughout Study 2 (Figure 1A). Additionally, the procedure for implant removal was also modified between Study 1 and Study 2. In Study 1, implants were removed via an incision at the original insertion site. As some investigators found that implants were susceptible to breakage when grasped at the end, a new removal technique was developed with an incision at the midpoint of the implants. The implant was then grasped in the middle and bent into a U-shape for removal using a custom 2.5-mm no-scalpel vasectomy clamp (Figure 1B). Modifications to the training program included a switch from a video-based program to a live, hands-on training program using a model for practice of insertion and removal procedures.

In both studies, participants underwent induction to SL BPN (Suboxone®, Indivior, Richmond, VA) at 12 to 16 mg/day and were maintained at a consistent dose for at least three consecutive days immediately prior to BI administration. Throughout the studies, participants were eligible to receive supplemental SL BPN in increments of 2 mg or more if they met one or more of the following criteria: withdrawal symptoms >12 on Clinical Opiate Withdrawal Scale (COWS) [23], cravings >20 mm on the opioid-craving visual analog scale (VAS) [24] or SL BPN increase deemed appropriate by the investigator. Subjects could be provided with an additional BI as early as two weeks following the initial implant visit if they had received supplemental SL BPN for ≥ 3 days per week for two consecutive weeks or ≥ 8 days over four consecutive weeks. Subjects who received an additional BI who required SL BPN ≥ 3 days per week for two consecutive weeks or on ≥ 8 days total over four consecutive weeks were considered treatment failures and were withdrawn from the study.



AE- Adverse event; BI- Buprenorphine implant; SL BPN- Sublingual buprenorphine.

Figure 1: Buprenorphine implant procedural modifications.
A) Original and final applicators used for implantation procedure.
B) Illustration of the implant removal technique employed in Study 2.

Outcome measures and patient assessments

The primary objective was to assess long-term exposure to extended BI delivery via evaluation of adverse events (AEs), abnormalities in physical exams, and vital signs. Serious AEs (SAEs) were defined as any adverse drug experiences that resulted in death, were life-threatening, required inpatient hospitalization or prolonged existing hospitalization, resulted in disability or incapacity, or otherwise jeopardized the participant or required medical or surgical intervention. Plasma concentrations of buprenorphine and norbuprenorphine, ratings of opioid withdrawal symptoms (measured by Subjective Opiate Withdrawal Score [SOWS] [25] and COWS), ratings of craving (assessed by VAS), and retention in treatment were also evaluated.

Venous blood samples were collected contralateral to the implant arm for assessment of buprenorphine plasma concentrations at baseline; induction; day of implant; weeks 4, 8, 12, 16, and 20; and at end of treatment. Samples were collected ≥ 24 hours following the previous dose of SL BPN; any SL BPN doses taken 24 hours prior to collection were documented with the date, time of dose, and dosage taken.

In Study 2, participants completed a patient satisfaction survey instrument with questions regarding induction, implant insertion, and removal and control of opioid-related symptoms at baseline and at week 28.

Statistics

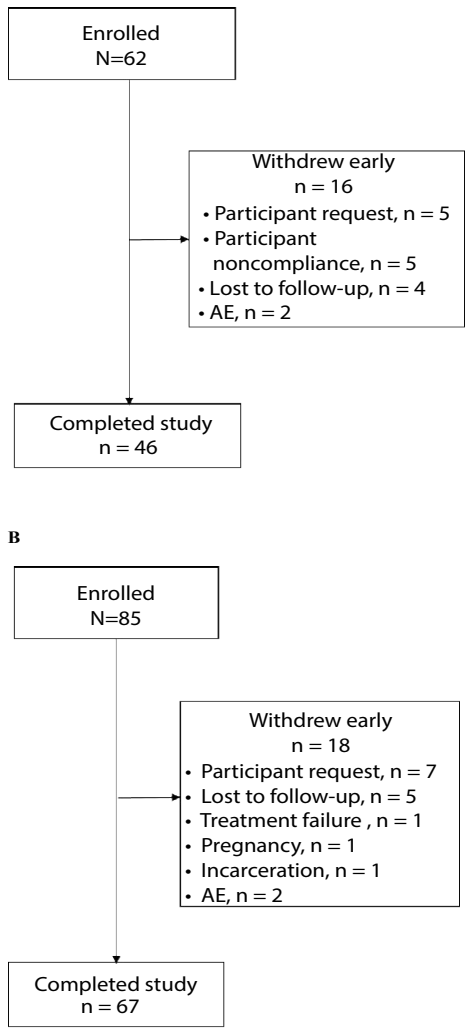
All data were summarized using descriptive statistics calculated using SAS version 9.1 (SAS Institute, Cary, NC). SOWS and COWS scores were summarized by symptom or score and by timepoint; total rating scores were summarized at each visit. Values and change from

baseline for craving scores were summarized by time point. A weighted average approach was used to calculate total scores for SOWS and COWS assessments missing <20% of values. No total scores were calculated if ≥ 20% of SOWS or COWS scores were missing and a last observation carried forward mechanism was used to calculate postbaseline scores. Missing postbaseline VAS scores were imputed using the last observation carried forward method.

Results

Participants

From March 20, 2008, to February 19, 2009, 62 individuals at 15 sites participated in Study 1; from November 29, 2010, to November 30, 2011, 85 individuals at 18 sites participated in Study 2. In Study 1, 12/62 (19.4%) and 50/62 (80.6%) participants had previously received placebo or active BI, respectively (Figure 2). In Study 2, 57/85 (67.1%) participants had previously received BI, 20/85 (23.5%) had previously received SL BPN, and 8/85 (9.4%) had previously received a placebo implant. In both trials, the majority of participants were male, white, and not Hispanic or Latino (Table 1).



AE- Adverse event.

Figure 2: CONSORT diagram for A) Study 1 and B) Study 2.

Safety

Overall adverse events: Of the 62 participants enrolled in Study 1, 47 (75.8%) experienced 329 treatment-emergent AEs. A total of 22 participants experienced 57 AEs related to study drug (35.5%). Adverse events occurring in >2% of participants are presented in Table 2. A total of nine SAEs occurred, including five implant site SAEs in a single participant (erythema, edema, pain, site reaction, and hematoma) and three other SAEs in two participants (nausea and decreased orgasmic sensation, and pneumonia in a separate participant). The nausea and pneumonia were considered not related to study drug; the decreased orgasmic sensation was possibly related to study drug. One SAE, an incidence of pneumonia that was not considered related to either the study drug or the implant procedure, occurred during treatment induction. Two participants discontinued, one due to erythema, edema, infection, and bleeding at the implant site and one due to implant site infection. No deaths occurred in the study.

Of the 85 participants enrolled in Study 2, 57 (67.1%) experienced 172 AEs. Adverse events occurring in >2% of participants are presented in Table 2. Only two treatment-emergent SAEs were reported in two participants—one instance of cellulitis and one instance of suicidal ideation—which were not considered related to either the study drug or insertion or removal of the implant. One patient experienced elevated alanine aminotransferase levels prior to induction that were not reported until after induction; this patient was withdrawn from the study. No AEs during treatment led to discontinuation from the study. A total of six SAEs were reported in Study 2; of these, four occurred in participants who had previously received BI (cellulitis, back pain, emotional disorder, and depression and suicidal ideation; 7.0%, 4/57), one who had previously received placebo (implant site reaction; 12.5%, 1/8) and one (insomnia; 5.0%, 1/20) who had previously received SL BPN. No deaths occurred during the study.

Implant site-associated adverse events: In Study 1, 103 implant site AEs occurred in 28 participants (45.2%) (Table 3). The majority of these AEs were mild or moderate in intensity. A total of five AEs possibly related to implant insertion/removal were also reported for four of 62 participants (6.5%). This included contusion, dizziness, hypoesthesia (two participants), and skin lesion; these AEs were mild in intensity. One participant experienced five SAEs including implant site erythema, edema, pain, reaction, and hematoma.

A total of 19 events occurred in 12 of 85 participants (14.1%) in Study 2. These AEs included implant site hematoma (two events, two participants), implant site hemorrhage (three events, three participants), and implant site rash (three events, two participants). All AEs were mild or moderate in intensity with the exception of one SAE (implant site reaction) in one participant who had previously received placebo.

Completion rate

In Study 1, 46 of 62 (74.2%) participants completed the six-month trial. In Study 2, 67 of 85 participants (78.8%) completed the six-month study. While not all patients attended all study visits, the number of subjects missing at each visit ranged from 0-17 in Study 1, and from 0-20 in Study 2. No evidence of removal or attempted removal of the implant was observed in any subjects at any visit.

Supplemental BPN and additional implants

During Study 1, a total of six of 62 (9.7%) subjects received a fifth BI. Supplemental SL BPN was given to 26 of 62 (41.9%) participants

Table 1: Study Demographics.

	Study 1 N = 62	Study 2 N = 85
Age, mean ± SD, y	38.6 ± 11.31	37.5 ± 11.92
Male sex, n (%)	44 (71.0)	56 (65.9)
Race, n (%) White Black Asian American Indian or Alaskan Native Native Hawaiian or Pacific Islander Other	 48 (77.4) 5 (8.1) 0 2 (3.2) 0 7 (11.3)	 72 (84.7) 11 (12.9) 0 1 (1.2) 0 1 (1.2)
Ethnicity, n (%) Hispanic or Latino Not Hispanic or Latino	 9 (14.5) 53 (85.5)	 19 (22.4) 66 (77.6)

SD- Standard deviation.

Table 2: All AEs reported in ≥ 5% of participants.

	Study 1 N = 62	Study 2 N = 85
Total AEs, n	85	51
Headache	16	10
Insomnia	10	2
Constipation	9	2
Subcutaneous abscess	-	10
Back pain	6	5
Upper respiratory tract infection	3	7
Fatigue	3	4
Implant site bruising/hematoma	3	2
Urinary tract infection	-	5
Depression	-	4
Implant site erythema	4	-
Implant site pain	4	-
Implant site pruritus	3	-
Rash	4	-
Stomach discomfort	4	-
Toothache	4	-
Excoriation	3	-
Increased ALT	3	-
Increased GLT	3	-
Pharyngolaryngeal pain	3	-

Dash indicates event occurred in <5% of participants.
AE- Adverse event; ALT- Alanine aminotransferase; GLT- Gamma-glutamyl transferase.

during the study for a mean ± standard error (SE) of 10.5 ± 1.98 days; the mean total dose of supplemental SL BPN dispensed per participant throughout the study was 146 ± 31.0 mg. During Study 2, nine of 85 (10.6%) of participants received a fifth BI. In total, 17/85 (21.2%) participants received supplemental SL BPN for a mean of 9.6 ± 1.96 days and a mean total dose of 74.7 ± 20.7 mg dispensed per participant throughout the trials.

Plasma buprenorphine concentrations

Concentrations of plasma buprenorphine varied due to participant differences in administration of supplemental SL BPN as well as differences in sampling times relative to administration of SL BPN. Overall, the mean buprenorphine concentrations were stable over 24 weeks (Figure 3).

SOWS/COWS

At baseline in Study 1, the SOWS score mean ± SE was 5.0 ± 1.00; at week 24, the mean SOWS score was 2.6 ± 0.55. The baseline mean COWS score was 2.8 ± 0.49; at week 24, the mean COWS score was 1.9 ± 0.31 (Figure 4A,4B). In Study 2, the baseline mean SOWS score was 3.41 ± 0.86; at week 24, the mean SOWS score was 3.73 ± 0.68. The mean baseline COWS score was 1.72 ± 0.23; at week 24, the mean COWS score was 1.55 ± 0.24 (Figure 4A,4B).

Cravings

Out of a maximum possible score of 100 mm, the baseline mean ± SE cravings score in Study 1 was 12.3 ± 2.75 mm; at week 24, the mean cravings score was 7.5 ± 1.45 mm. In Study 2, baseline mean cravings score was 4.3 ± 1.18 mm; at week 24, the mean cravings score was 6.8 ± 1.54 mm (Figure 4C).

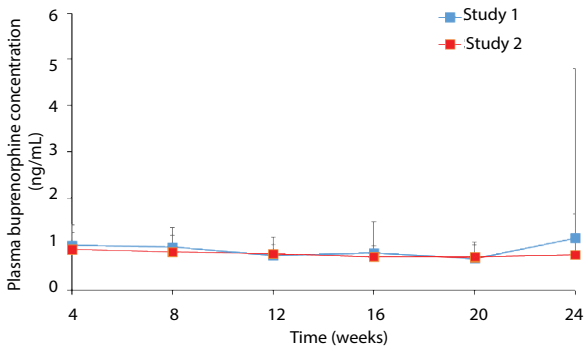
Self-report of illicit drug use

In Study 1, the incidence of self-reported drug use was 41.9% overall at baseline and 54.8% at end-of-treatment. Marijuana was the

Table 3: All implant-site-associated AEs.

	Study 1 N = 62	Study 2 N = 85
Any Implant Site AE, n	103	19
Erythema	20	1
Pain	18	0
Pruritus	16	1
Edema	9	0
Bleeding	11	0
Reaction	6	1
Bruising/Contusion	6	1
Hemorrhage	4	3
Infection	4	1
Rash	1	3
Hematoma	1	2
Discoloration	1	0
Necrosis	1	0
Scar	1	0
Abscess	0	1
Cellulitis	1	1
Implant expulsion	2	0
Contact dermatitis	0	1
Impaired healing	1	0
Procedural site reaction	0	1
Subcutaneous abscess	0	1
Wound dehiscence	0	1

AE- Adverse event.

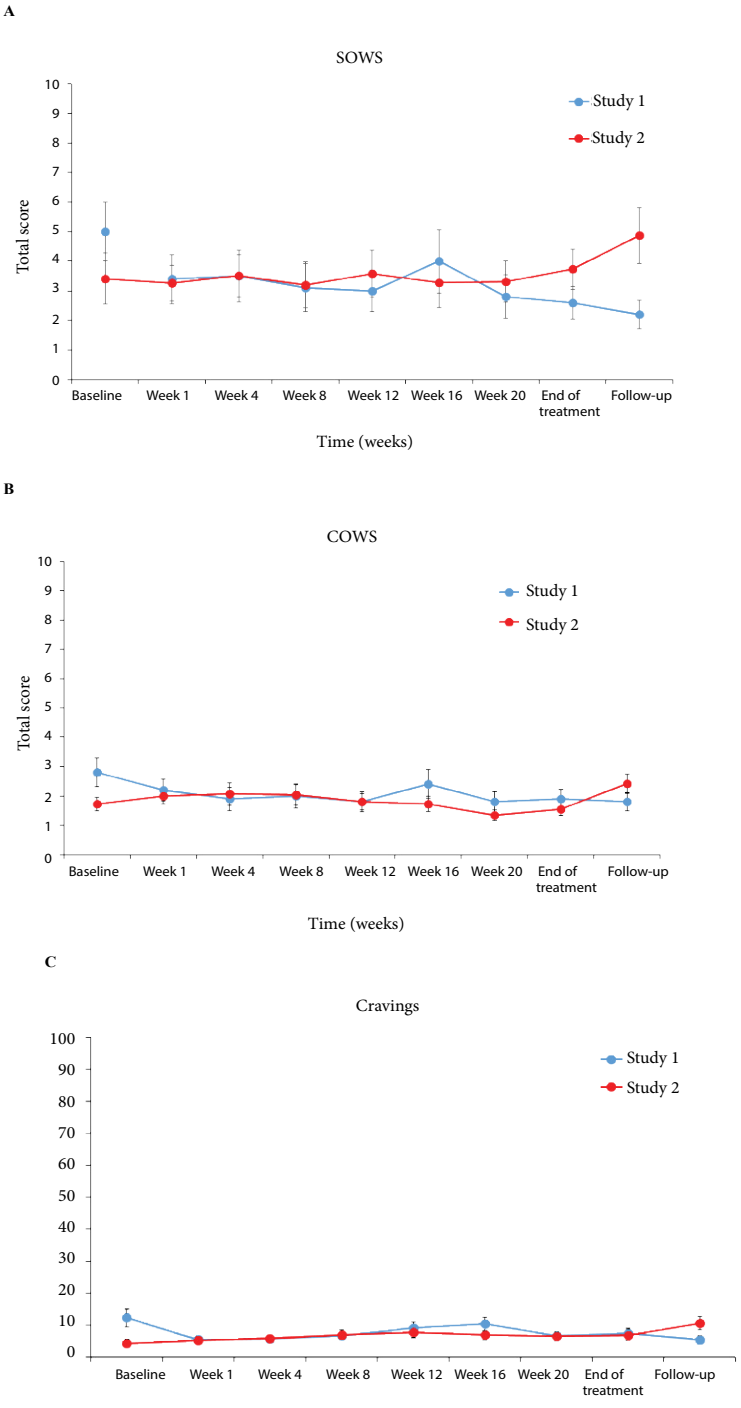


Error bars denote standard deviation.

Figure 3: Mean plasma buprenorphine concentrations over 24 weeks.

most frequently used drug at baseline (22.6%) and marijuana and heroin were the most frequently used drugs at the end of the study (both 27.4%).

In Study 2, self-reported baseline illicit drug use (34.1%) overall was similar among the three prior treatment groups (33.3%, 37.5%, and 35.0% in subjects who received prior BI, placebo, and SL BPN, respectively). At end-of-treatment, self-reported illicit drug use was similar to that observed at baseline (38.8% overall; 38.6%, 37.5%, and 40.0% in subjects who had received prior BI, placebo, and SL



Error bars denote standard error.
COWS- Clinical opiate withdrawal scale; SOWS- Subjective opiate withdrawal scale.

Figure 4: Mean ratings of A) subjective and B) clinical opioid withdrawal symptoms and C) ratings of opioid withdrawal.

BPN, respectively). Marijuana was the most commonly used drug at baseline (72.4%), and marijuana (51.5%) and heroin (48.5%) were the most frequently used drugs at end of study.

Patient satisfaction

A patient satisfaction survey was administered to participants at follow-up in Study 2 only. Data at follow-up were provided by 53 participants, of whom 36 (67.9%) had previously received BI, five (9.4%) had previously received placebo, and 12 (22.6%) had previously received SL BPN. At the follow-up visit, 92.4% of participants agreed or strongly agreed that their problems with opioids decreased after starting the study. The majority of participants (77.4%) also somewhat or strongly agreed that the implants helped them to avoid the temptation of skipping doses of medication in order to use other opioids to get high. The majority of participants agreed or strongly agreed that the implants reduced their cravings for opioids (92.5%), use of opioids (92.4%), and feelings of withdrawal (86.8%) relative to their experience without medication for opioid addiction.

The majority of participants (90.6%) agreed with the statement, "I didn't mind having the BI inserted under my skin." In a follow-up, two (3.8%) participants indicated dissatisfaction with the implantation procedure, one indicated dissatisfaction with scars, and one found the insertion and healing painful/uncomfortable. A total of six (11.3%) participants indicated dissatisfaction with implant removal due to a painful/uncomfortable insertion process (three participants), painful/uncomfortable healing process (one participant), incision healing time (one subject), scars (three participants), or "other" reasons (three participants); participants could select more than one reason for dissatisfaction.

Participants who previously received SL BPN agreed or strongly agreed with statements that BI provided better reduction in cravings for opioids (83.4%), actual use of opioids (75.0%), and feelings of withdrawal (75.0%) compared with SL BPN. The majority of these participants also agreed or strongly agreed with statements that compared with SL BPN, BI better helped them stick with taking their medication (91.7%), kept their treatment private (75.0%), prevented other people from getting access to their medication (83.3%), and allowed them to worry less about their children or pets accidentally taking their medication and becoming sick (91.7%).

Discussion

Here, we present data assessing long-term BI exposure from two open-label extension trials in which subjects who had previously completed 24 weeks of BI treatment subsequently received BI for an additional six months. These extension trials represent the longest duration exposure evaluated to date with this novel, sustained-release formulation of buprenorphine. In Study 1, implant site-related AEs occurred in 45.2% of participants; in Study 2, implant site-related AEs occurred in 14.1% of participants. This reduction in AEs demonstrates that the revisions to the surgical procedure between Study 1 and Study 2 were successful in improving safety. Additionally, most AEs in either study were transient and not serious. Systemic AEs associated with BIs occurred at a low incidence and closely mirrored the known safety profile of buprenorphine [26]. These results support the safety of BI for up to one year.

The majority (74.2% and 78.8%) of enrolled participants completed each study. In prior studies with BI, retention rates were 64% to 66% [20,21]. Here, the completion rates in the extension studies were slightly larger than in the parent studies. This modest increase is consistent with most open-label extension studies. In both open-label extension studies, BI produced stable mean buprenorphine concentrations during weeks 4 to 24. Assessment of efficacy, based on participants' COWS, SOWS, and VAS scores indicate cravings and withdrawal symptoms were well controlled for the duration of the study. These pharmacokinetic and efficacy measures demonstrated the presence of buprenorphine in the systemic circulation throughout the testing period. A limited amount of supplemental buprenorphine was dispensed in either study; over the six months of testing, an average of 146.2 mg per participant in Study 1 and 74.7 mg per participant in Study 2 was administered.

In Study 2, a patient satisfaction instrument was implemented for the first time as an experimental outcome measure. This survey indicated that the majority of participants viewed their BI treatment positively, and further, BI was preferable to SL BPN for helping patients adhere to treatment; maintain privacy; and restrict drug access to others, including children and pets. The positive signal achieved here suggests that further research using this patient satisfaction instrument is warranted. However, it should be noted that the results of the patient satisfaction survey were based on a subset of completers, thus it is subject to unknown bias, which represents a potential study limitation.

The two trials reported here had similar but slightly different designs. Additionally, only participants who successfully completed 24 weeks of prior study treatment were eligible for inclusion. Further, participants who required SL BPN $\geq$ 3 days per week for two consecutive weeks or $\geq$ 8 days total over four consecutive weeks after receiving an additional implant were considered treatment failures and were withdrawn from the study. Additionally, a limited number of participants were available for the patient satisfaction survey. Outstanding questions regarding maximum treatment duration and potential use of additional implantation sites remain, as neither insertion into sites other than the upper arm, nor reinsertion into a previously used site after six months of treatment has been investigated at this time.

Conclusions

Taken together, the data from these extension trials support the safety of treatment with BI for up to one year. Fewer implant-associated adverse events were reported by patients in the second study using a modified implant insertion and removal procedure. As opioid addiction may require lifelong treatment, future long-term studies of BI are needed, including examination of the safety and efficacy of implant reinsertion into the same site.

Trial registration

Clinicaltrials.gov

NCT01262261, https://clinicaltrials.gov/ct2/show/NCT01262261;

NCT00630201, https://clinicaltrials.gov/ct2/show/NCT00630201

References

1. Becker WC, Fiellin DA, Merrill JO, Schulman B, Finkelstein R, et al. (2008) Opioid use disorder in the United States: insurance status and treatment access. Drug Alcohol Depend 94: 207-213.

2. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, et al. (2011) Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med 12: 657-667.

3. Clausen T, Waal H, Thoresen M, Gossop M (2009) Mortality among opiate users: opioid maintenance therapy, age and causes of death. Addiction 104:1356-1362.
4. Jones CM, Mack KA, Paulozzi LJ (2013) Pharmaceutical overdose deaths, United States, 2010. JAMA 309: 657-659.
5. Shah NG, Lathrop SL, Reichard RR, Landen MG (2008) Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: combinations of heroin, cocaine, prescription opioids and alcohol. Addiction 103: 126-136.
6. The NSDUH Report: Substance Use and Mental Health Estimates from the 2013 National Survey on Drug Use and Health: Overview of Findings. Rockville, USA.
7. Rudd RA, Aleshire N, Zibbell JE, Gladden RM (2016) Increases in Drug and Opioid Overdose Deaths--United States, 2000-2014. MMWR Morb Mortal Wkly Rep 64: 1378-1382.
8. Overdose Death Rates. National Institute on Drug Abuse website. Revised December 2015.
9. Connery HS (2015) Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. Harv Rev Psychiatry 23: 63-75.
10. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, et al. (2003) Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med 349: 949-958.
11. Johnson RE, Strain EC, Amass L (2003) Buprenorphine: how to use it right. Drug Alcohol Depend 70: S59-77.
12. Mattick RP, Breen C, Kimber J, Davoli M (2014) Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev CD002207.
13. Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, et al. (2008) Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA 300: 2003-2011.
14. Bailey JE, Campagna E, Dart RC (2009) The underrecognized toll of prescription opioid abuse on young children. Ann Emerg Med 53: 419-424.
15. Centers for Disease Control and Prevention (CDC) (2013) Emergency department visits and hospitalizations for buprenorphine ingestion by children--United States, 2010-2011. MMWR Morb Mortal Wkly Rep 62: 56.
16. Lofwall MR, Walsh SL (2014) A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. J Addict Med 8: 315-326.
17. Sigmon SC (2015) The untapped potential of office-based buprenorphine treatment. JAMA Psychiatry 72: 395-396.
18. Fiellin DA, Pantalon MV, Chawarski MC, Moore BA, Sullivan LE, et al. (2006) Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Engl J Med 355: 365-374.
19. Larance B, Lintzeris N, Ali R, Dietze P, Mattick R, et al. (2014) The diversion and injection of a buprenorphine-naloxone soluble film formulation. Drug Alcohol Depend 136: 21-27.
20. Ling W, Casadonte P, Bigelow G, Kampman KM, Patkar A, et al. (2010) Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. JAMA 304: 1576-1583.
21. Rosenthal RN, Ling W, Casadonte P, Vocci F, Bailey GL, et al. (2013) Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. Addiction 108: 2141-2149.
22. American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, 4th edtn, Washington, DC, USA.
23. Wesson DR, Ling W (2003) The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 35: 253-259.
24. Kozlowski LT, Mann RE, Wilkinson DA, Poulos CX (1989) "Cravings" are ambiguous: ask about urges or desires. Addict Behav 14: 443-445.
25. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, et al. (1987) Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse 13: 293-308.
26. SUBOXONE® (buprenorphine and naloxone) sublingual film for sublingual or buccal use (2015), Full prescribing information. Richmond, VA.

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