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Buprenorphine implants in medical treatment of opioid addiction

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ABSTRACT

Introduction: Opioid use disorder is a chronic, relapsing disease that encompasses use of both prescription opioids and heroin and is associated with a high annual rate of overdose deaths. Medical treatment has proven more successful than placebo treatment or psychosocial intervention, and the partial μ-opioid receptor agonist and κ-opioid receptor antagonist buprenorphine is similar in efficacy to methadone while offering lower risk of respiratory depression. However, frequent dosing requirements and potential for misuse and drug diversion contribute to significant complications with treatment adherence for available formulations.

Areas covered: This review describes the development of and preliminary data from clinical trials of an implantable buprenorphine formulation. Efficacy and safety data from comparative studies with other administrations of buprenorphine, including tablets and sublingual film, will be described. Key premises of the Risk Evaluation and Mitigation Strategy program for safely administering buprenorphine implants, which all prescribing physicians must complete, are also discussed.

Expert commentary: Long-acting implantable drug formulations that offer consistent drug delivery and lower risk of misuse, diversion, or accidental pediatric exposure over traditional formulations represent a promising development for the effective treatment of opioid use disorder.

1. Introduction

Opioid dependence is a chronic, relapsing disease characterized by compulsive drug seeking and drug use, despite harmful consequences [1], resulting in long-lasting structural and functional changes in the brain. In a 2014 survey in the US, an estimated 4.3 million people aged 12 years and older (1.6% of the total US population) reported current nonmedical use of prescription opioids [2]. An opioid use disorder was reported by an estimated 1.9 million people aged 12 years or older, and 586,000 people reported a heroin-use disorder [2]. In total, 47,055 people in the US died from drug overdoses in 2014; of these deaths, 18,893 were from prescription opioid overdose and 10,574 were from heroin overdose [3]. Intravenous heroin users additionally have an increased risk of contracting HIV and hepatitis C [4,5].

Medical treatment of opioid use increases treatment retention, reduces craving for opioids, and provides relief from opioid withdrawal syndrome [6]. Medical treatment of opioid abuse reduces illicit opioid use at a greater rate relative to psychosocial intervention or placebo alone [6–10] and reduces morbidity, mortality [11], and the spread of infectious diseases [12–14]. Three medications—methadone, naltrexone, and buprenorphine—are approved by the US FDA for the treatment of opioid dependence [8,15]. Methadone has long been the gold standard for medical treatment of opioid use. Methadone reduces heroin craving and blocks the euphoric effect of heroin [16]. It is provided once daily, has a long duration of efficacy, and blocks opiate withdrawal for 24–36 h [17]. Methadone can be started at any time during treatment, but it takes time to achieve a therapeutic steady state dose [6]. However, as methadone is a full μ-opioid receptor agonist, it is associated with some disadvantages, including the potential to produce or maintain opioid dependence, as well as respiratory depression or sedation in the event of overdose [18].

Buprenorphine is a partial μ-opioid receptor agonist and a κ-opioid receptor antagonist [19]. Its ceiling effect limits the potential for respiratory depression and, therefore, fatal overdose [19], resulting in a better safety profile relative to methadone [20]. Although effective as a treatment, sublingual buprenorphine tablets and film may be susceptible to diversion, misuse, and abuse [21–26]. Globally, 18–28% of patients enrolled in outpatient methadone or buprenorphine treatment programs report that they have sold, given away, or removed medication while under supervision or shared other prescribed medications [23]. The misuse and diversion of opioids contribute to poor treatment adherence [27] and can also result in accidental pediatric exposures [28–30]. Notably, 9.5% of emergency hospitalizations for drug ingestion among children under 6 years of age were due to buprenorphine/naloxone, although buprenorphine only accounts for 2.2% of opioid prescriptions and 0.16% of all prescriptions [30]. Critical...
factors in reducing misuse or diversion of medical treatment of opioid abuse include supervising consumption, restricting exposure for children, abuse-deterrent formulations, and encouraging the use of formulations that are more difficult to divert [26].

Adherence to daily dosing for management of chronic disorders is challenging [31]. Unlike methadone, buprenorphine does not require daily clinic visits; patients are provided with medication for up to 1 month of treatment at a time following stabilization [32]. In a survey of 703 subjects receiving buprenorphine therapy, 142 subjects (20%) reported relapse to opioid use at month 2 or 3 [32]. Further, patients who were noncompliant with treatment were significantly more likely to relapse [32]. An implantable buprenorphine delivery system may reduce adherence issues.

In May 2016, a 6-month buprenorphine implant (Probuphine®, Braeburn Pharmaceuticals, Princeton, NJ, USA) was approved for maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on no more than 8 mg/day sublingual buprenorphine [33]. The long-acting implantable buprenorphine formulation was developed with the goal of reducing the risks associated with sublingual buprenorphine tablets and film, while increasing treatment options for opioid dependence. Like other buprenorphine formulations, the implant is used as part of a comprehensive treatment program, including counseling and psychosocial support. Here, we discuss the role of buprenorphine in medical treatment of opioid dependence and review clinical data supporting the safety and efficacy of the buprenorphine implant.

2. The role of buprenorphine in medical treatment of opioid dependence

Buprenorphine was first shown in 1980 to suppress heroin self-administration in addicted volunteers to a greater degree relative to placebo [34]. In 1992, it was demonstrated to have a similar efficacy to methadone 60 mg in reducing illicit opioid use and maintaining retention over 25 weeks of outpatient treatment [35]. Subsequent studies demonstrated the safety and efficacy of buprenorphine in combination with naloxone for reducing craving in opiate-addicted patients in an office-based environment [7]. Following this study, buprenorphine and the buprenorphine/naloxone combination was established as a first-line therapy in this population [36].

The superiority of buprenorphine relative to placebo in retaining patients in treatment has been demonstrated in multiple trials [15]. Buprenorphine, at daily doses ranging from 7 to 15 mg, and methadone, at daily doses ranging from 40 to 85 mg, produce equivalent rates of patient retention in treatment and numbers of positive urine samples for heroin or cocaine [15]. Additionally, in pharmaceutical opioid-addicted individuals, buprenorphine is equally effective as methadone in preventing illicit opioid use, as measured by drug-free urine samples, and in retention in treatment [37]. Some studies suggest retention rates in treatment are improved with methadone treatment relative to buprenorphine [38,39]. At 4–6 months of treatment, rates of retention with methadone were higher relative to buprenorphine/naloxone (74% vs. 46%) [38]. Relative to methadone (60–120 mg), flexible-dose buprenorphine is less effective in retaining patients in treatment; however, it produces similar suppression of opioid use relative to patients remaining in treatment [18]. Medium-dose buprenorphine (8–15 mg) did not have an advantage over medium-dose methadone in treatment retention and was inferior to methadone in suppressing heroin use [18]. Higher treatment doses of buprenorphine and methadone have been shown to be more effective in many patients relative to lower doses [15,16].

There are three phases of buprenorphine treatment: induction, stabilization, and maintenance [19]. The Substance Abuse and Mental Health Services Administration clinical guidelines for medication-assisted treatment for opioid addiction recommend treatment initiation with buprenorphine 4 mg on the first day of treatment, increasing to a maximal dose of 8 mg [40]. After the first day of treatment, induction is completed with a combination therapy of buprenorphine and naloxone, increasing dosages up to a maximum daily dose of 32 mg buprenorphine/8 mg naloxone over a 1-week period [19]. Once patients no longer experience withdrawal symptoms, have minimal or no side effects, and do not experience uncontrollable cravings for opioid agonists, stabilization is initiated [19]. Most patients stabilize on daily buprenorphine/naloxone doses of 16/4 mg to 24/6 mg; frequent assessments may be needed to adjust dosages [19]. Stabilization is usually achieved within 1 to 2 months of treatment [19]. Following stabilization on the lowest dose to maximize benefits and minimize side effects, the maintenance period begins [19]. Maintenance is the longest-lasting period of treatment and may extend for months or years, depending on patient and physician goals [19,41]. Maintenance treatment serves to eliminate or reduce illicit opioid use and reduce its associated negative outcomes; it is not considered an abstinence treatment [20]. In conjunction with medical therapy, patients should be treated for psychosocial and family issues contributing to addiction [19].

3. Buprenorphine implant

The buprenorphine implant is 26 mm in length and 2.5 mm in diameter and contains buprenorphine (74.2 mg, equivalent to 80 mg buprenorphine hydrochloride) within an ethylene vinyl acetate implant [33]. A total of four implants are inserted subdermally into the inner side of either upper arm [33]. Once placed, implants provide 6 months of treatment, after which the implants are removed and new implants can be inserted into the alternate arm [33]. Reinsertion into prior administration sites or sites other than the upper arm has not been studied.

The pharmacokinetics of buprenorphine implants were consistent between six human clinical trials and were consistent with published data on other routes of buprenorphine administration (Table 1). Buprenorphine single-dose exposures (maximum plasma concentration \(C_{\text{max}}\) and area under the concentration curve \(AUC\)) increase linearly, but not in a direct dose-proportional manner, with increasing single sublingual doses from 4 to 16 mg [42]. Maximal buprenorphine plasma concentrations are reached within 24 h of subcutaneous
administration of four implants and decline exponentially to a stable, low concentration from 4 to 24 weeks post-administration [33]. Following implant removal, plasma buprenorphine concentrations rapidly decline. The extended-release formulation of the buprenorphine implant reduces peak and total exposure in a dosing interval compared to the rapid absorption from sublingual administration; concentrations following implant administration are shown in Figure 1.

The relative bioavailability on day 28 of buprenorphine from the implant treatment was 31% relative to daily sublingual administration of 16 mg at steady state, reflecting reduced relative exposure after achievement of a steady state plateau [33]. Maximum concentrations reached on the first day following insertion of four implants were lower than those following administration of 16-mg daily sublingual tablets and remained lower throughout the 24-week treatment period (Figure 1).

Buprenorphine undergoes N-dealkylation to norbuprenorphine and glucuronidation, mediated primarily by cytochrome P450 isozyme 3A4 [33]. Thus, patients who require azole antifungal agents, such as ketoconazole, macrolide antibiotics, such as erythromycin, or HIV protease inhibitors, such as ritonavir, may require dosing adjustments [46]. The subcutaneous buprenorphine implant avoids first-pass metabolism, leading to fewer CYP3A4 interactions compared to buprenorphine absorbed in the gastrointestinal tract. The risk of respiratory depression leading to overdose death is increased if buprenorphine is used in combination with other central nervous system depressants, including benzodiazepines and alcohol [47]. The primary metabolite of buprenorphine, norbuprenorphine, is a partial agonist of the µ- and κ-opioid receptors and a full agonist of the δ-opioid receptor in vitro [48]; it has not been studied clinically.

Buprenorphine is cleared 30% in urine and 69% in feces for up to 11 days after dosing [42]. The impact of hepatic impairment on buprenorphine concentrations following implant administration has not been studied. Since buprenorphine is extensively metabolized, hepatic impairment may increase exposure and prolong the half-life of buprenorphine. Based on a small study, patients on dialysis had similar buprenorphine concentrations relative to patients with normal renal function following administration of 0.3-mg intravenous buprenorphine, suggesting a limited effect of renal impairment on buprenorphine exposure [46].

4. Buprenorphine implant clinical trial data
4.1. Efficacy
The efficacy of buprenorphine was assessed in a randomized controlled study conducted in patients stabilized to ≤8 mg daily sublingual buprenorphine prior to study enrollment [49]. A qualified physician implanted either four placebo or four buprenorphine implants in the upper inner nondominant arm. Active or placebo implants were administered with placebo or active sublingual buprenorphine tablets, respectively. Supplemental buprenorphine was available as needed to both treatment arms, and all participants underwent manual-guided drug counseling; no additional implants were allowed. Primary efficacy outcomes were based on the percentage of urine samples negative for illicit opioids;
efficacy was also assessed by a subjective opiate withdrawal scale, clinician report of withdrawal symptoms, and craving for opioids measured by a 100-mm visual analog scale.

In patients stable on ≤8 mg sublingual buprenorphine, buprenorphine implants were noninferior to sublingual buprenorphine on the a priori specified primary outcome measure of 4 of 6 months without evidence of opioid use (Figure 3) \[49\]. Additionally, post hoc sensitivity analyses applying more stringent parameters for defining responders to treatment support the noninferiority of buprenorphine implants to sublingual buprenorphine. In conservative sensitivity assessments including imputation of missing urine samples as positive for opioid use and adjudication of subjects receiving buprenorphine as responders, buprenorphine implants were noninferior to supplemental buprenorphine for efficacy based on proportion of responders. In patients stable on ≤8 mg sublingual buprenorphine relative to buprenorphine implants, there were no significant differences in craving or withdrawal scores prior to study entry or at study end \[49\]. Additionally, the time to first evidence of illicit opioid use, based on the proportion of negative urine samples, was longer in participants treated with buprenorphine implants relative to those treated with sublingual buprenorphine (Figure 4). The percentages of participants who required supplemental sublingual buprenorphine did not significantly differ between treatment groups; 15/84 (17.9%) participants with buprenorphine implants and 13/89 (14.6%) participants receiving sublingual buprenorphine required supplemental sublingual buprenorphine \[49\]. For the majority of these participants, the prescribed doses of supplemental sublingual buprenorphine

Figure 2. Study design schematic for phase 3 study. R, randomization; SL, sublingual; SL BPN, sublingual buprenorphine.

Figure 3. Evidence for efficacy of buprenorphine implant in individuals stable on >8 mg sublingual buprenorphine \[49,50\] BI, buprenorphine implant; CI, confidence interval; SL BPN, sublingual buprenorphine.

Figure 4. Number of events of illicit opioid use \[48\]. BI, buprenorphine implant; HR, hazard ratio; MCF, mean cumulative function; SL BPN, sublingual buprenorphine.
were small (2 mg/day) and prescribed four or fewer occasions within the 6-month period [49].

Secondary post hoc analyses were also performed to evaluate whether patient demographics or baseline characteristics were predictive of treatment response. Age, gender, abuse of heroin vs. prescription pain reliever, supplemental buprenorphine use, number of times entering treatment, duration of treatment, and the dose of buprenorphine at enrollment were not predictive of treatment response (data on file).

4.2. Safety

The safety of buprenorphine was assessed in the phase 3 clinical trial enrolling patients stable on buprenorphine, as well as in other clinical trials using buprenorphine implants [43,51] and in two 6-month, open-label extension trials [52]. In the extension trials, participants received four subdermal implants into the upper inner aspect of the opposite arm used in the prior trial for an additional 24 weeks of treatment [52].

Throughout the clinical development of buprenorphine implants, refinements were made to the equipment and procedures used for implantation, as well as to the training provided to implanters, to minimize adverse events (AEs) related to implantation. Specifically, the applicator used for implant placement was altered from a blunt tip to a bevel tip, the removal technique was modified to reduce the risk of implant breakage, and the training program was refined from a video-based program to a live, hands-on training program.

One death occurred over all three trials; that participant was randomized to sublingual buprenorphine and experienced an accidental overdose 3 days after initiating early withdrawal from the study [51]. Combined rates of implant site-associated AEs were 37.2% for the buprenorphine implants and 27.3% for participants receiving placebo implants; pain and pruritus were the most commonly reported implant site AEs (Table 2) [33]. Notably, modifications to the procedures for implant insertion and removal effectively reduced rates of implant-associated AEs; following revisions to the insertion procedures, 23.0% of participants receiving the active implant and 13.5% of participants receiving the placebo implant had more than one implant-associated AE [49].

The extension trials support the safety of buprenorphine implants for up to 1 year. In the extension trials, most AEs were transient and not serious [52]. Further, systemic AEs associated with buprenorphine implants occurred at a low incidence [52] and were similar to the known safety profile of buprenorphine [42]. For comparison, the overall safety profile of buprenorphine based on a dose-controlled study of 731 subjects receiving between 1-mg and 16-mg sublingual solution over 4 months of treatment is provided in Table 3 [33].

5. Practical considerations for use of buprenorphine implants

The implant is approved for maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on a maintenance dose of ≤8 mg/day of a transmucosal buprenorphine-containing product for at least 3 months or longer without any need for supplemental dosing or adjustments and should be used as part of a treatment program, including counseling and psychosocial support [33]. Determination of clinical stability should include evaluation of the patient’s duration of time free from illicit opioid use; living environment stability; participation in structured activities or employment; consistency of participation in behavioral therapy or peer support programs; consistency in compliance with clinic visit requirements; minimal or no desire to use illicit opioids; duration of time without episodes of hospitalization, emergency room visits, or crisis interventions for addiction-related or mental health-related concerns; and social support system [33]. Patients who are new to treatment or who have not achieved prolonged clinical stability should not be given buprenorphine implants [33]. Buprenorphine implants are contraindicated in patients who are hypersensitive to buprenorphine or ingredients in the implant [33].
Implantation and removal of the buprenorphine implants may result in rare but serious complications. Improper implantation may result in implant migration causing nerve damage, embolism or death, local migration, or protrusion or expulsion of the implant. Additionally, infections or improper insertions may result in protrusion or expulsion of the implant [33]. To mitigate this risk, all health-care providers in the US who wish to utilize the implants must complete a training program on insertion and removal procedures and become certified in the Risk Evaluation and Mitigation Strategy (REMS; described below) program prior to performing insertions or prescribing the implants [33].

There have been no well-controlled studies of the use of buprenorphine or buprenorphine implants in pregnant women [33]. Newborns exposed to prolonged use of opioids during pregnancy may experience neonatal opioid withdrawal syndrome, which may be fatal if not recognized and treated. Pregnant women should be advised of the risks associated with and the importance and benefits of managing opioid addiction during pregnancy.

6. REMS program

Buprenorphine implants are available only through an approved REMS program. This program was developed in conjunction with the FDA to mitigate the risk of complications of migration, protrusion, expulsion, and nerve damage associated with the insertion and removal of implants, as well as risks of accidental overdose, misuse, and abuse. Health-care providers who perform insertions and or removals of buprenorphine implants are required to complete a live training program and demonstrate competency on the procedure prior to inserting or removing implants.

The REMS program was developed following a rigorous evaluation of independent human factors. As a result, a 28-step process was developed for inserting buprenorphine implants, and a 22-step process was developed for implant removal. To maximize safety, these processes are taught to health-care providers as part of a training certification process.

As part of the REMS program, health-care providers who are certified to perform the buprenorphine surgical procedures are trained to understand the potential risks associated with implant insertion and removal, proper and aseptic implant insertion and removal procedures, care of the incision and removal site, and managing potential complications associated with implant insertion and removal. Providers must attest to performing a surgical procedure with aseptic technique in the 3 months preceding enrollment in REMS program and demonstrate proficiency in implant insertion and removal in a live practicum.

Health-care providers who do not have the interest or background in performing the surgical procedures can become certified as prescribers only. These providers must still attend the training session and complete a knowledge test. Providers certified as prescribers must verify that a certified health-care provider will perform the implantation and removal procedures.

In addition to training and educating physicians, the goals of the REMS program include patient education and establishment of a safe, closed distribution system for the implants (Figure 5). As of the writing of this review, more than 2800 physicians have attended training sessions.

7. Conclusions

Buprenorphine is a well-established treatment for opioid abuse. In patients stable on ≤8 mg sublingual buprenorphine, buprenorphine implants are noninferior to sublingual buprenorphine and have a similar safety profile for up to 1 year of use. Decreases in pediatric exposures, diversion and misuse of buprenorphine, and increased treatment adherence are anticipated.

Figure 5. Overview of REMS program for practicing physician. OTP, opioid treatment program; REMS, risk evaluation and mitigation strategies.
for patients using the implantable formulation; however, future studies in real-world populations are required for corroboration.

8. Expert commentary

The approval of buprenorphine implants marks an important advance in the field of addiction medicine. The long-acting implantable formulation of buprenorphine shifts the paradigm away from the requirement of daily dosed maintenance medications. Additionally, the implantable formulation addresses the long-held concerns over medication diversion, misuse, abuse, and accidental exposure, while providing improved medication adherence along with consistent dosing. Despite the potential clinical and societal benefits offered by buprenorphine implants, several challenges remain regarding clinical management, namely, patient access and patient selection. While the implementation of an REMS program may greatly contribute to reducing the potential for medication diversion, and the likelihood of procedure-related AEs, it can, at least in the initial period after FDA approval, slow patient access to the treatment. Providers will require time to achieve certification in buprenorphine implantation and removal, and a certified provider may not be immediately available to potential patients in their geographic area. It is anticipated that this issue will be resolved as buprenorphine implant awareness grows and more providers are certified to prescribe and perform the implantation procedure. Additionally, experience with an REMS training program involving multiple medical specialties will offer valuable insights into the viability, safety, and general acceptance of novel procedural-based interventions.

Determination of clinical stability remains a more pressing challenge. Buprenorphine implants are indicated for the maintenance treatment of opioid use disorder in clinically stable individuals; however, a single unified definition of clinical stability has not been ratified. Based on experience in clinical trials, patients are considered stable on consistent doses of ≤8 mg/day transmucosal buprenorphine for a prespecified duration. Other considerations include urine toxicology testing and biopsychosocial factors, such as employment, home life stability, comorbid behavioral health disorders, as well as duration of time free from illicit opioid use and current involvement in a treatment program. These variables, combined with the attitudes, experience, and understanding of individual providers, contribute to a nonuniform picture of clinical stability. Further research to better define what constitutes the clinically stable patient should ensure that buprenorphine implant is utilized most effectively and, in a broader sense, will ultimately assist the treatment of opioid use disorder.

9. Five-year view

Looking toward the future for opioid use disorder treatment, buprenorphine implants represent a movement away from daily-dose maintenance medications. As the clinical effectiveness of longer duration maintenance treatment becomes better understood, development and utilization of depot/long-acting medications would be expected to increase. Additionally, formulations that provide consistent dose delivery and improved patient adherence while reducing opportunities for accidental exposure, diversion, and misuse and abuse of medications will likely be favored.

Key issues

- The partial µ-opioid receptor agonist and a κ-opioid receptor antagonist buprenorphine has a better safety profile relative to methadone, and its use is well established as a therapy for prevention of illicit opioid use.
- Misuse and diversion of opioids, such as sublingual buprenorphine can contribute to poor treatment adherence and result in accidental pediatric exposures.
- A long-acting implantable buprenorphine formulation was developed with the goal of reducing the risks associated with sublingual buprenorphine tablets and film while increasing treatment options for opioid dependence.
- In patients stable on ≤8 mg sublingual buprenorphine, buprenorphine implants were noninferior to sublingual buprenorphine on the a priori specified primary outcome measure of 4 to 6 months without evidence of opioid use.
- Phase 3 clinical testing of buprenorphine implants and open-label extension trials support the safety of buprenorphine implants for up to 1 year of use.
- Buprenorphine implants are available only through an approved Risk Evaluation and Mitigation Strategy program, which was developed in conjunction with the FDA to mitigate the risk of complications of migration, protrusion, expulsion, and nerve damage associated with the insertion and removal of implants, as well as risks of accidental overdose, misuse, and abuse.

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Declaration of interest

Steven E. Chavoustie has received honoraria/speaking fees from Medicis Global Services Corporation and serves as a consultant and master trainer for Braeburn Pharmaceuticals. Ole W. Snyder serves as a consultant and master trainer for Braeburn Pharmaceuticals. Michael P. Frost serves as a consultant and master trainer for Braeburn Pharmaceuticals. Joel Owen is an employee of and owned stock in Braeburn Pharmaceuticals. Victoria Sanjurjo is an employee of and owns stock in Braeburn Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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A phase 3, multicenter, randomized, placebo-controlled study in opioid-dependent adults supporting the safety of buprenorphine implants for up to 6 months.


Open-label extension trials supporting the safety of buprenorphine implant treatment for up to 1 year.