Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults with Opioid Dependence Treated with Sublingual Buprenorphine: A Randomized Clinical Trial

BACKGROUND:

- Opioid dependence is a chronic, relapsing disorder that is associated with the spread of HIV and hepatitis C and has become a growing concern in the United States.
- Medical treatment of opioid dependence decreases illicit opioid use at a greater rate compared with psychosocial intervention or placebo alone.
- In a previous trial, buprenorphine implants were superior to placebo implants in reducing illicit opioid use over the initial 6-month treatment period.

OBJECTIVE

- To determine if 6-month subdermal buprenorphine implants maintained low to no illicit opioid use relative to daily sublingual buprenorphine among currently stable opioid-dependent patients receiving buprenorphine maintenance treatment.

METHODS

- **Design:** Randomized, double-blind, double-dummy, active-controlled, 26-week, multisite study
- **Inclusion Criteria:** Participants must have a primary diagnosis of opioid dependence, be 18 to 65 years old, have received sublingual buprenorphine for at least 24weeks as an outpatient at a stable dosage of 8 mg/d or less, and showed no evidence of opioid withdrawal or illicit opioid-positive urine samples for at least 90 days prior to study entry. Female participants of childbearing potential agreed to use contraception during the study.
- **Exclusion Criteria:** Pregnancy, lactation, or planning pregnancy; lack of appropriate implant sites (recent scars, history of keloids); coagulopathy within 90 days; screening serum aspartate and alanine aminotransferase levels 3-fold higher than upper limits of normal; total bilirubin or creatinine levels 1.5-fold higher than upper limits of normal; clinically significant thrombocytopenia; use of strong cytochrome P450 3A4 inhibitors (azole antifungals, macrolide antibiotics, or protease inhibitors) or an anticoagulant; chronic pain requiring opioids; AIDS; significant medical problems potentially affecting volunteer safety if enrolled; primary diagnosis of substance dependence other than opioids or nicotine; or pending legal action or other factors/conditions that could adversely affect participant safety and adequate adherence.
- **Primary Outcome Measure:** The difference in proportion of responders, defined as participants with at least 4 of 6 months without evidence of illicit opioid use (based on urine test and self-report composites) by treatment group.
- **Secondary Outcome Measures:** Treatment retention, time to first illicit opioid use, percentage of illicit opioid use by month, and cumulative percentage of negative illicit opioid urine results at 6months. Opioid craving, withdrawal, and supplemental use of sublingual buprenorphine were also measured. Safety (based on adverse event reporting, including implant site reactions) was assessed in all participants receiving study medication.
- 177 patients were randomized into two groups
    - 87 patients to receive daily sublingual buprenorphine tablets (dosage same as pre-randomization) with 4 placebo subdermal implants.
    - 90 patients to receive daily sublingual placebo tablets with 4 active buprenorphine implants.
- Power 87.3% with non-inferiority established for a lower bound of the 95% CI greater than -0.20 (calculated based on a sample size of 90 participants per group [180 participants overall], assuming a 75% responder rate for both treatment groups).
- Data handling method was intent-to-treat.

RESULTS

- 165 patients completed the study (81 in the implant group and 84 in the tablet group).
- **Primary Outcome Measure:** In the implant and tablet groups, 81 of 84 participants (96.4%) and 78 of 89 participants (87.6%), respectively, were responders. The difference was 8.8% (1-sided 97.5%CI, 0.009 to ∞; P < .001 for non-inferiority; P = .03 for superiority)
- **Secondary Outcome Measures:** There was a significant difference 13.8% in cumulative 6 months without evidence of opioid use (95% CI, 0.018-0.258; P < .03). Time to first evidence of illicit opioid use was significantly longer for implants relative to tablets (hazard ratio, 0.49; 95% CI, 0.25-.97; P = .04). There were no significant differences in craving, withdrawal, and supplemental use (P = .83, P = .92, and P > .05, respectively). Serious adverse events occurred in 5 participants (3 in the tablet group and 2 in the implant group).
- **Author's conclusion:** Among adults with opioid dependence maintaining abstinence with a stable dose of sublingual buprenorphine, the use of buprenorphine implants compared with sublingual buprenorphine did not result in an inferior likelihood of remaining a responder.

STRENGTHS

- Study design was gold standard: Double-blind, double-dummy, active controlled
- Adherence was measured by visual inspection and palpitation of each implant and via pill counts at each study visit,
- Urine screenings were not only performed at monthly visits, but also 4 times randomly throughout the course of the trial.

LIMITATIONS

- Not powered to detect differences in adverse outcomes
- Generalizability is limited because the majority of participants were white, employed, and had at least a high school education.
- Participants were clinically stable, maintained abstinence for at least 90 days, and prior to randomization, were in buprenorphine treatment for an average of 3.5 years.
- Dose of buprenorphine was not uniform among all participants.
- Many conflicts of interest between the authors and the pharmaceutical companies.

CONCLUSION

- Although this study both proved the non-inferiority and superiority of buprenorphine implants to sublingual tablets, these results are not generalizable to the population.
- Future research:
    - A study should be done to determine the effectiveness of buprenorphine implants in people that are newly diagnosed with opioid dependency and who are not yet clinically stable.

Reference: Rosenthal RN, Lofwall MR, Kim S, Chen M, Beebe KL, Vocci FJ. Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial. JAMA. 2016 Jul 19;316(3):282-90.

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