The promise and challenges of buprenorphine implant for treatment of opioid dependence

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SUMMARY

This was a randomized, active-controlled, double-blind, double-dummy clinical trial conducted across 18 office-based/outpatient sites in the USA. It aimed to determine whether long-acting subdermal buprenorphine implants (BI) were non-inferior to sublingual (SL) buprenorphine in former opioid-dependent subjects who are already stable on opioid substitution therapy (OST) with SL buprenorphine–naloxone combination and are abstinent from illicit opioids. The participants were randomly assigned to two groups. Group 1 (n=90) received four active 80 mg subdermal BI and SL placebo tablets daily. Group 2 (n=87) continued to receive their stable daily dose of active SL buprenorphine tablets and four placebo subdermal implants. The primary outcome was the proportion of 'responders' defined as participants with at least 4 of 6 study months without evidence of illicit opioid use (based on urine test and/or self-report). In addition, several secondary outcome measures were included such as treatment retention, time to first illicit opioid use, opioid craving, severity of withdrawal symptoms, supplemental use of SL buprenorphine and safety/adverse effects if any in both groups.

The authors used a non-inferiority design and had predetermined a non-inferiority margin of –0.20. This means that BI would be non-inferior to SL buprenorphine if the lower bound of the 95% confidence interval of the inter-group difference in the proportion of responders was <0.2.

Both groups were comparable in demographic and clinical characteristics at baseline. Intention-to-treat analysis was used for comparison. Primary analysis showed that at the end of 6 months, 96.4% patients in group 1 (BI) were responders, vis-à-vis 87.6% in group 2 (SL buprenorphine). The lower bound of the 97.5% CI of the inter-group difference in the proportion of responders was 0.009, far less than the non-inferiority margin of 0.2, thus showing that subdermal BI was non-inferior to the benchmark comparison product. Secondary analysis suggested better response also in terms of cumulative duration of abstinence. On sensitivity analysis, where the worst case scenarios were considered, cumulative 6-month abstinence was significantly more in the BI group. Additionally, the authors found no difference in craving and withdrawal between the groups. The study was not adequately powered to detect the implant site-related side-effects in the BI group. The retention rate in this study was unusually high in both the groups.

COMMENT

Opioid dependence is a cause of morbidity and mortality. OST can significantly bring down the harm caused by illicit opioid use. The current gold standard for OST is oral methadone and SL buprenorphine. However, serious concerns regarding the abuse and diversion potentials of these preparations, treatment adherence and accidental exposure to children have led to the search for long-acting injectable or implantable preparations. Two earlier published trials[1,2] of BI had compared it with placebo or non-blinded SL buprenorphine. Hence, the importance of this trial, which almost concurred with the recent approval of the patented product Probuphine (Titan Pharmacuticals) by the US Food and Drug Administration on 26 May 2016.

The study design (non-inferiority trial) and methodology were appropriate. However, we have a few concerns. The patients included in the study were those with former opioid dependence stabilized on SL buprenorphine OST for a mean duration of 3 years and abstinent from illicit opioid use for at least 3 months. This group represents only a small proportion (around 10%) of people on OST in the real world, with the best biopsychosocial recovery-oriented prognosis. Hence, there would be a possibility of gradual discontinuation of OST and a transition from medication-assisted recovery to medication-free recovery.[3] It also explains the surprisingly good outcome (nearly 88% responders!) in the SL control group. Thus, it appears to be a case of 'self-fulfilling prophecy' with the selection of the best-prognosis patients for the trial. Further, treating these patients with a long-acting implant appears to contradict the philosophy of recovery-oriented OST, which has become the official stand in many countries. As opposed to time unlimited OST which permits OST for an indefinite period, recovery-oriented OST is goal-directed. The mutually agreed goal takes into account complete psychosocial and substance use-related recovery. Once the goal is achieved, OST is discontinued gradually with the person's consent.

Our second concern is that there is no mention of allocation concealment before the intervention leading to the possibility of selection bias. It has been shown that trials that used inadequate or unclear allocation concealment yielded 40% larger effect estimate as compared to those with adequate concealment.[4] Third, we are not sure if the non-inferiority margin set at –0.20 was appropriate, as studies which the authors had mentioned were based on subjects stabilized on methadone and were conducted for a shorter duration (10–12 weeks). Fourth, determination of medication adherence solely with the basis of self-report and pill count appears inadequate. Non-adherence with OST is an extremely important contributor for relapse.[5] In the present study, urine test for buprenorphine could have been done to examine adherence. Finally, the higher requirement of supplemental buprenorphine in the implant group though not statistically significant could be clinically meaningful and might indicate episodic craving which might have resulted from an inadequate level of buprenorphine during the time of need. As craving was modestly associated with subsequent relapse in patients on buprenorphine substitution, this observation needs special mention.[6] A related comment is that the measurement of craving once a month through visual analogue scale may not capture the real picture. To identify real-life episodic craving, ecological momentary assessment should have been done.

Despite these issues, we believe that this study has an important clinical potential. Phase 4 studies and post-marketing surveillance are urgently needed to shed more light on its effectiveness, safety and acceptability in the real world. We look forward to such data.

Relevance for India

Proximity to the Golden Crescent and the Golden Triangle has left India perpetually vulnerable to illicit opioid use, in addition to its

own home-grown opioids. Clinical data and experience suggest that the number of people with illicit opioid use is on the rise especially in certain parts of India.[7] The proportion of these affected individuals on OST is low because of low coverage, legal restrictions, lack of trained manpower, and concerns regarding treatment adherence, abuse and diversion.[8] Because of its limited possibility of abuse/diversion and potential to improve treatment adherence, this new modality of treatment in the form of BI, if approved, is likely to reduce legal constraints and increase treatment coverage. However, several questions need to be answered before its official approval. An acceptability and feasibility study needs to be carried out. The mean stable dose of buprenorphine is much lower in the Indian population when compared to the West. Therefore, the dose of BI must be adjusted. Affordability could be another important issue in the Indian context.

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