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▶ Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial.

Ling W., Casadonte P., Bigelow G. et al. Request reprint

JAMA: 2010, 304(14), p. 1576–1583.

According to an editorial in the same journal, this study of implants providing six months of 24-hour a day maintenance to suppress heroin use represents a "potentially important step forward" in expanding treatment options for opioid dependence.

Summary After an initial pulse, implants surgically inserted under the skin deliver a steady stream of buprenorphine in to the patient's bloodstream, promising to reduce the problem of the drug in tablet or liquid form being diverted on to the illicit market and to virtually ensure that patients receive their opiate-substitute medication as intended by the prescriber without relapse-precipitating troughs in blood levels.

Whether this is how it works out in practice was the question addressed by this study, the first to test buprenorphine implants against an alternative treatment, in this case, the same counselling schedule with placebo implants instead of real ones. In each case, four thin rods about two and a half centimetres long were inserted under the skin of the inner arm. The plan was to remove them six months later, the active period of the real implants.

From 18 US treatment centres the researchers recruited 163 patients dependent on heroin or other opiate-type drugs. Despite long addiction careers, only about a quarter had previously been prescribed drugs in the treatment of their dependence. In a 2:1 ratio they were randomly allocated to active (108 patients) or placebo (55 patients) implants. Before this point, another 185 patients had been screened for the study but were then excluded or withdrew. Among this number were 15 who did not complete a short prior trial period on buprenorphine/naloxone tablets or who during this period experienced significant withdrawal or cravings for opiates.

Once implanted, patients who it was judged needed this (for example, due to withdrawal

or craving) could be prescribed additional buprenorphine in the form of buprenorphine-naloxone tablets. In the first 16 weeks of the trial this was needed for 59% of buprenorphine patients and 91% on placebo. If tablets were needed regularly for several weeks, an extra implant could be inserted. Additional implants were received by just a fifth of the buprenorphine group but most (58%) in the placebo group. If these patients then still regularly needed buprenorphine tablets, the treatment was considered a failure and the patient was withdrawn from the study. Patients were also withdrawn if they missed six consecutive counselling sessions. 44% of placebo patients were withdrawn for these reasons, mostly for 'treatment failure', but just 11% on real implants, none due to 'treatment failure'.

Results of urine tests taken three times a week to detect unauthorised use of opiate-type drugs were the main outcome measure; missed tests were treated as positive for opiates. In the first 16 weeks of the 24-week implant period, among buprenorphine patients, on average 40% of scheduled tests were clear of opiates (ie, negative) compared to 28% of placebo patients; corresponding figures for the entire period were 37% and 22%. In both cases there was a statistically significant advantage for the buprenorphine patients. They were also over twice as likely to complete the study (66% v. 31%), during that time experienced less craving and less severe withdrawal symptoms, and by the end nearly 30% more (80% v. 51%) were judged by their doctors to have improved much or very much since the start of the study.

In both groups over 8 in 10 patients recorded a medical problem. For over half the patients these included the anticipated consequences of the surgery required to insert the implant such as inflammation or bleeding. Among the six serious conditions noted during the study (two of which were in the buprenorphine group), one buprenorphine patient had serious breathing problems which might have been aggravated by the drug, and one placebo patient developed pneumonia and cellulitis due to an implant site infection which required a day in hospital and intravenous and oral antibiotics.

Tests showed that due to rescue tablet prescribing or illicit supplies, the placebo group retained in the study had on average an appreciable amount of buprenorphine in the blood, nearly 60% of the level in patients with active implants.

The authors' conclusions

This study showed that buprenorphine implants are effective in the treatment of opioid dependence over the following 24 weeks. Nearly two thirds of patients completed treatment without experiencing craving or withdrawal symptoms which necessitated leaving the study, compared to other studies in which just over a third of patients have been retained for six months on sublingual buprenorphine. This was despite the (relative to typical sublingual administration) low blood concentrations of buprenorphine achieved by the implants. More implants creating higher blood levels may have worked better, but the initial four implants, in some cases supplemented by a fifth, was sufficient to avoid craving or withdrawal symptoms forcing treatment termination. There was just one major adverse response to the implants and no evidence of attempted removal. It should be borne in mind that, in the event, the comparator was not nil buprenorphine, but an appreciable level in the placebo group, making the relative benefits of the implants more notable.

FINDINGS As an editorial on the study commented, it represents a "potentially important step forward" in expanding treatment options for opioid dependence, offering the proven efficacy of maintenance treatment with, from the patient's point of view, the added benefit of not having to attend a clinic or pharmacy daily or several times a week to be dispensed medication and often also to take it. The concerns which drive these precautions (diversion of medication on to the illicit market; not taking medication as prescribed risking relapse or overdose; medication being taken by children or adults who might not be able to tolerate it) could be virtually eliminated by implants if they are sufficiently effective at suppressing illicit opiate use, paving the way for widespread adoption of this technology (implants are reportedly simple to insert) even in primary care-based treatment. In the future they may achieve this potential, but this study shows that we are not there yet.

One key to understanding the study is to appreciate the weakness of the comparator against which the implants were pitted. As the editorial pointed out, "Detoxification has been conclusively demonstrated to have exceedingly high long-term failure rates and is not nearly as effective as opioid maintenance". Yet the placebo group underwent an unprepared, blind and abrupt form of detoxification from the quite high-dose sublingual buprenorphine prescribed in the run-up to the implants, with no standard tapering procedure to ease the process. Not surprisingly, all but a few required additional buprenorphine in the form of buprenorphine-naloxone tablets, but this just postponed abrupt withdrawal to either when the patient stopped being given the extra medication, or they had taken it for so long and so regularly that they were withdrawn from the study. After this point, all the urine tests which could have been taken were counted as indicative of illicit opiate use, helping to create (perhaps entirely accounting for) the advantage gained by buprenorphine.

A different rule enabling, for example, patients to be prescribed more buprenorphine than the 12mg per day limit (in the run-up period doses could range up to 16mg) and/or for longer, or to be prescribed methadone, might have 'rescued' more placebo patients, who would then have been in a position to submit urines clear of illicit opiates. This would of course have further diluted the intention to establish the absolute efficacy of the implants compared to a non-active placebo, but would arguably have asked a more relevant clinical question: given the well established oral and sublingual maintenance options, is there any added value from implants? According to the *JAMA* editorial, only if there was could this innovation be considered to have moved beyond a "potentially important step" to a "major advance". Put in a more challenging way, it might be said that the crunch issue for a new treatment – especially one which causes common if non-serious side effects – is not whether it is better than a weak alternative which should never be offered in clinical practice, but whether it is sufficiently preferable to established treatments to warrant its introduction.

Pitted against unstructured detoxification, the active implants clearly were preferable, but their performance was far from perfect. In the first 16 weeks and over the whole 24 weeks of the study, most (60% and 63% respectively) urine tests were missed or positive for opiates. From these figures it is possible to calculate that in weeks 17 to 24 about 81% of urine tests on buprenorphine patients were either missed or indicated illicit opiate use – better than the roughly 92% in the placebo group, but not a tally a well run

methadone programme would hope for.

Methodologically, a possibly major concern is the representativeness of the patients. All were already in treatment, raising the issue of why they volunteered for a study which gave them a 1 in 3 chance of an inactive implant, especially when one of the main advantages of an implant − not having to visit the clinic several times a week − was denied them due to the need to be tested for urine and to attend counselling sessions. Over the 15 months, 18 treatment centres recruited 163 patients − nine each; if recruitment was continuous at each clinic over this period, on average just over one every two months. It seems possible that this sample was in some respects atypical.

Another concern is the extensive involvement of the implant manufacturers in not just the funding but the conduct, analysis and reporting of the trial. They were also heavily involved in a predecessor study which established that the implants did deliver steady dose of buprenorphine over six months.

Thanks for their comments on this entry in draft to Roy Robertson of Edinburgh University and the Muirhouse Medical Group. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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