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▶ Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial.

Tiihonen J., Krupitsky E., Verbitskaya E. et al.

The American Journal of Psychiatry: 2012, 169(5); p.531–536.

Would dually addicted heroin and stimulant users fitted with an opiate-blocking naltrexone implant simply escalate their stimulant use? The issue is important because multi-drug use is the norm. In this Russian study it was the reverse - amphetamine use decreased as well as heroin use.

SUMMARY Naltrexone is an opiate antagonist which has no psychoactive effects of its own but blocks the effects of heroin and other opiate-type ('opioid' drugs. Oral naltrexone has been used as a treatment for people dependent on opiates, in the hope that its blocking effect will lead to them using less often, but this has been ineffective as people do not continue taking the naltrexone. Previous studies have shown that longer-acting naltrexone implants or depot injections may be an effective treatment for people who use heroin alone, but many people addicted to heroin are also addicted to other drugs. It is not known if long-acting naltrexone is effective for these people, or if they might use heroin less often but compensate by using other drugs instead. This trial in Russia (where opiate substitute prescribing using drugs like methadone is not permitted) therefore aimed to test the effectiveness of a naltrexone implant at reducing heroin and amphetamine use in people dependent on both drugs. A small capsule was surgically implanted under the skin of 50 participants living in and around St Petersburg, Russia. The capsule contained 1000mg of naltrexone to be released slowly, blocking the effects of opioid drugs for eight to ten weeks. Another 50 randomly selected patients were implanted with a placebo, forming a control group against whom to benchmark the effect of the active implant. Allocation was also 'double-blinded'; to reduce the risk of bias, neither patients nor researchers knew who had been assigned to which group. After the implant was fitted, patients were scheduled to attend the clinic weekly to be urine-tested for heroin or amphetamine use and to complete research interviews.

Patients were typically men in their late twenties who averaged over eight years of dependent heroin use and nearly six of amphetamine use. Over half whose status was known were infected with HIV.

To select the participants for the trial, several inclusion criteria were specified, including having been diagnosed as dependent on both amphetamine and heroin for at least a year, having a stable address and telephone number, and having at least one relative willing to help with the trial. Applicants were ineligible for the trial if they had drunk alcohol recently, had one of a number of serious physical or mental illnesses, were facing possible imprisonment, or were already in treatment. It was also required that, although they were dependent on heroin, they did not use it for three to four days before the implant was fitted. Whilst the criteria seem strict, only 16% of people assessed for the study were excluded, resulting in a sample assumed by the authors to be typical of people seeking drug treatment. One possible indication of the strictness of the criteria is that it took from March 2008 until February 2011, over three years, to recruit 100 patients.

Main findings

By the end of the ten week period, the group who received the naltrexone implant were significantly more likely to be retained in the study (52%) than those who received a placebo (38%), and significantly less likely to either test positive for heroin or amphetamine use, or miss a test (62% versus 84%). Separating the two drugs, naltrexone patients were significantly more likely (52% versus 20%) to deliver urine samples free from heroin; similarly for amphetamine (40% versus 24%), but not to a statistically significant degree. Those in the naltrexone group also used amphetamine less on average (4.5 times a week versus 5.7), a finding which narrowly missed statistical significance. On a measure of addiction severity called the Clinical Global Impression Scale, those given naltrexone (56%) were significantly more likely to rate as much improved at the end of the ten weeks than the control group (14%). The group who received naltrexone were also significantly less likely to report that use of amphetamine had its full euphoric effect (14% versus 83%). Craving for heroin and amphetamines and practices which risked HIV transmission diminished to roughly the same degree in both sets of patients.

The authors' conclusions

This study offers the first evidence of an effective pharmacological treatment for people dependent on both heroin and amphetamine. Compared to a placebo, patients implanted with naltrexone stayed in the study longer, made greater reductions in their heroin and amphetamine use, and were judged by clinicians to have experienced greater overall improvement. Concerns that patients would substitute amphetamine for the heroin they could no longer experience proved unfounded. Implants caused no serious adverse effects and there were no deaths during the study.

FINDINGS **COMMENTARY** This study clearly shows improved outcomes for the people given naltrexone implants compared to those who only received placebos, in particular with regard to the percentage of people testing free from heroin. The lower level of amphetamine use for the same group is also particularly encouraging, suggesting that participants are not simply using amphetamine more in order to compensate for the effect of heroin having been blocked. This may be influenced by more naltrexone patients staying in the study, and the assumption that this meant better drug use outcomes. However, levels of alcohol and other drug use during or at the end of the programme were not measured, so it remains possible that people did compensate for heroin and amphetamine use with alcohol, cocaine, cannabis or benzodiazepines, for example. Whilst the group were tested for benzodiazepine, cannabis and alcohol use at the beginning of the programme, the researchers decided not to continue testing for use of these drugs once the programme had started. This severely limits the ability to infer that the naltrexone implants are a safe and effective treatment for this group of people, who were already addicted to two drugs, and might suffer serious health harms and yet more addiction problems if they increased use of others.

One important limitation of this study with regard to its implications for UK practice is that the comparison is between the naltrexone implant and a placebo – nothing at all. Perhaps of more relevance for UK practitioners is the unasked and unanswered question: 'is a naltrexone implant better than existing pharmacological treatments, such as methadone or buprenorphine?'. One study in Australia has suggested that, at least with regard to mortality rates, naltrexone implants might be better than buprenorphine. It is important to note that these results may have been influenced by the different characteristics of people drawn to each treatment, and in particular the poor retention rates of those on buprenorphine. Another study in Norwegian prisons found that naltrexone implants had some advantages over methadone, including better continuity of treatment in the period when prisoners returned to the community. This period is important because there is a risk of overdose in people returning to the community after being drug-free in prison. In

fact it may be that naltrexone implants are suitable for different people than methadone, as US authorities have pointed out, naltrexone may be best suited for people who have overcome physical dependence on heroin, and want to sustain this without dependence on similar-acting medications.

It should also be noted that the participants of this study, although described by the authors as typical of people in drug treatment, were all people who had relatively unchaotic lives for people addicted to heroin – low alcohol use, a stable address, educated to at least high school graduate level, relatives willing to help, none of several serious mental and physical health problems, and not least the desire to engage in this treatment process. As has been noted when analysing previous research, "patients will only opt for such procedures if they are prepared... to commit to possibly weeks or months without the effects of heroin or other opiate-type drugs...Long-acting naltrexone helps these highly motivated patients sustain their resolve". Nonetheless, only just over half of people given the implant were retained in the study for the ten week period. The vital questions of what happened next are also unanswered – did those who had avoided heroin and amphetamine use at ten weeks get fitted with another implant, and if so, did they continue to avoid using? Is it expected that they be fitted with new implants every ten weeks, or will there be a transition to no pharmacological treatment at all, in which case how will the risk of relapse be managed? This point may be especially important given that after the ten weeks, the implant had not led to a greater reduction in drug cravings than placebo. Finally, and of huge importance, what can be done for the 62% of people who received the implant but were still known or assumed to be using heroin or amphetamine at the end of the ten weeks?

This study is one of a growing number of recent research reports which suggest that naltrexone implants may have a positive role to play in addiction treatment, and a search of the Drug & Alcohol Findings Effectiveness Bank gives information and analysis on this body of evidence. To examine the issue in general, readthis Hot Topic article, which explains why naltrexone implants may, even if their effectiveness is proven, still arouse controversy.

The clearest candidates for the treatment are patients who are motivated (perhaps due to employment or other pressures) to return to a life without opiate-type drugs including prescribed substitutes, have the resources, stability and support to sustain this, are unlikely simply to use other drugs instead, but who when free to experience heroin and allied drugs, cannot resist using them, possibly reflected in their poor compliance with oral naltrexone regimens. The treatment may also be considered for unstable patients at very high risk of overdose, but who will not accept or do poorly in substitute prescribing programmes. Other candidates might include those unwilling or unable to accept daily supervised consumption if this is a requirement of being prescribed substitute medications. Many patients will still at least initially try out the blockade by taking opioid drugs and do so perhaps repeatedly, but they are safeguarded from overdose while the naltrexone is active, and some studies (but not all) found rapidly stop wasting their time and money.

In the UK, neither implants nor long-lasting depot injections of naltrexone have been licensed for medical use; they can still be (and have been; 1 2 3 4) used, but patient and doctor have to accept the added responsibility of a product which has not yet been shown to meet the safety and efficacy requirements involved in licensing.

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