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▶ Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial.

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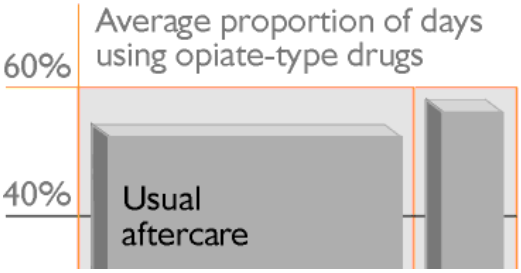
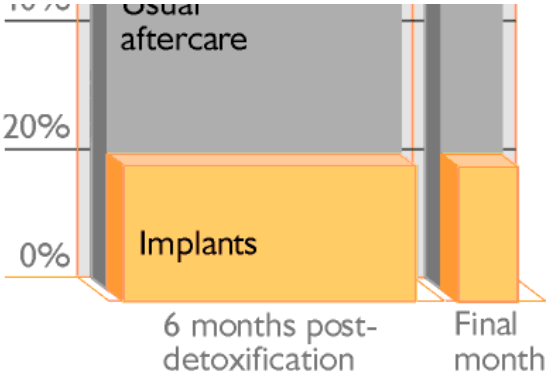
In the first randomised trial, implants which block opiate-type drugs for months helped heroin addicts in Norway avoid relapse after detoxification. If these or allied products gain a UK licence, they could help pave the way to abstinence for the minority of suitable addicts.

Summary Naltrexone is a medication which blocks the effects of heroin and other opiate-type drugs. Its considerable potential in helping to prevent post-detoxification relapse has not been realised because patients generally refuse to take it or quickly discontinue. However, these limitations apply to the oral formulation which has be taken daily. Longer-lasting formulations in the form of a depot injection or an implant inserted under the skin avoid the need to take the medication daily. This is the first randomised trial of an implant whose opiate-blocking effects last for about six months.

Over 18 months from January 2006, staff at inpatient drug clinics in south-eastern Norway invited opiate-dependent patients on abstinence–oriented programmes to participate in the study. Patients who agreed were contacted by researchers at the end of their detoxification or residential treatment. The 56 who joined the study were told that for the first six months they would be randomly allocated to the implant or to usual aftercare arrangements, but that then all would be offered (re)implantation. Typically they were male injectors in their 30s who had used heroin for on average seven years; nearly all also used other drugs.





Three of the implant group left the clinic before they could be implanted and another three had the implants removed. All but three of the surviving (there were two deaths) patients were reassessed six months later. The main analysis included all the patients whether or not they had received or retained their implants. Over the six months of the follow-up, usual-care patients recalled using opiate-type drugs on average on 97 days, the implant group on just 37 days ▶ *chart*. This differential remained in the last month of the follow-up, when the corresponding figures were 17 and six days, a statistically significant difference. Average frequency of use was also significantly higher among the usual-care patients. At the six-month follow-up assessment, 18 out of 27 usual-care patients but just 9 of the 29 implant patients continued to meet criteria for opioid dependence. In line with this, implant patients were much less likely to experience craving. Nevertheless, during the study over half (18 of 29) tried opioids at least once.

In the last month of the follow-up, implant patients scored significantly lower on an index of multiple drug use and injected less often, but there were no significant differences in drinking or use of non-opioid drugs. Over the follow-up, usual-care patients averaged significantly more repeat detoxifications (0.71 versus 0.21); there were no significant differences in outpatient treatment attendance or use of aftercare services. By the end of the follow-up, implant patients expressed greater satisfaction with their lives but there were no significant differences in levels of depression, work, or criminal activity.

One patient in the implant group reported three non-fatal overdoses (there were four in the usual-care group) while using combinations of opioids, amphetamines and benzodiazepines. Three had implants removed due to infection, discomfort or side-effects. In another two, wound-opening required antibiotic treatment, and three had allergic reactions treated with antihistamines. The single death among patients allocated to implants was an overdose prior to implantation. There was also one overdose death among the usual-care patients.

The authors concluded that naltrexone implants safely and significantly reduced opioid use in a motivated population of patients.

FINDINGS In the UK, neither implants nor 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.

As with oral naltrexone, the main limitation of the treatment is its acceptability to patients. In Norway acceptability will have been heightened by restricted access to substitute prescribing programmes, particularly for people unwilling to contract to forgo not just heroin, but persistent substance use of any kind. Nevertheless, recruitment to

the study seems to have been slow. The 56 out of 667 patients who joined the study were probably unusually highly motivated to sustain abstinence from opiates, yet over half the implant patients tried resuming opiate use, and those who did used for on average 60 days. This degree of persistence seems incompatible with the implant having totally eliminated opiate-type effects. The reduction in multiple drug use seems to have been mainly due to the effect on opiate use, since drinking and use of other drugs were not significantly affected. As this study shows, implants and depot injections do not guarantee abstinence. Implants can be removed and both these and depot injections can be sidestepped by turning to non-opiate drugs (as may have happened in Australia) or overridden by very high doses of opiate-type drugs, attempts which risk overdose.

The implants were compared against relatively weak aftercare arrangements; more active and structured aftercare (for example, regular monitoring, continued well organised care from the initial service, or active referral) might have narrowed the differences between the groups. However, highly motivated patients and imperfect aftercare arrangements probably reflect the conditions in which implants would be deployed in normal practice, as does the fact that patients knew whether they had an active implant; unlike some other studies, there was no placebo comparison group.

Of the 26 patients who were implanted, eight (nearly 1 in 3) experienced complications which led three to have the implant removed. One other potential problem is that implants impede opiate-based pain relief. To cater for this, participants were given a card to carry which specified the presence of a naltrexone implant, its expected duration, possible pain relief options, and contact details for study staff. Without this (as reported in Australia) hospital staff sometimes make futile attempts to relieve pain using opiate-type medications. The same report of hospital admissions after implantation identified severe withdrawal symptoms after rapid detoxification to the point where hospitalisation was required. Long-acting naltrexone means one effective way of relieving these symptoms (using opiate-type drugs) is denied to the patient, though others remain.

Norwegian prison study

Other related reports from Norway have also been analysed by Findings. Two concerned a sister study from the same research team of prisoners dependent on opiates before their sentence who in their final month in prison were randomly allocated to naltrexone implants or methadone maintenance to promote continuity of treatment on release and avoid relapse. One focused on the acceptability of the attempt to randomly allocate prisoners, while a second focused on drug use and other outcomes after six months.

The prison study found that inmates refused treatment usually because they misjudged their ability to maintain abstinence on release. At the same time this misplaced confidence and features of the prison environment impeded treatment entry. Motivating inmates to accept treatment in prison involves cooperation between prison health services, criminal justice staff and (to ensure continuity and support on release) community treatment providers, as well as researchers if the treatment offer is part of a study. For methadone in particular, continuity often could not be arranged. Unless removed, naltrexone implants automatically continued on release, but fewer inmates were prepared to go through with this treatment.

Despite the fact that 17 of the 44 patients did not initiate treatment in prison, compared to the six months before their imprisonment, on average in the six months after release frequency of use of heroin and illicit benzodiazepines had significantly declined. From using heroin nearly every day before prison, after release use was down to 15–20 days a month. Days per month on which crimes were committed also fell significantly by 4–5 days a month to on average every other day. Neither on these measures nor on the days the former prisoners 'survived' before relapsing to heroin use were there any significant differences between prisoners allocated to methadone versus those allocated to naltrexone.

Data from implanted patients in these and another Norwegian study have been amalgamated in a report which assessed the degree to which the implants actually did block the effects of opiate-type drugs and prevent opiate use. Drawing on data from the same patients, a further report assessed how many would continue the treatment by having a second implant after six months.

Amalgamated findings from Norway

From all these Norwegian reports it seems that six-month naltrexone implants can be an effective and lasting aid to curbing opiate use for the minority of patients motivated to aim for opiate abstinence and prepared to accept that opiate effects may be unavailable to them for six months. Because it does not require the patient to choose to enter aftercare treatment, the option may have a particular role in safeguarding patients emerging opiate-free from prison or other protected environments such as inpatient detoxification centres. However, and despite being motivated to sustain abstinence and being implanted, many if not most patients try opiates again and some do so repeatedly. Details below.

As in the featured study, recruitment in prison seems to have been very slow and no patient volunteered as opposed to being referred by staff. In both studies the minority of potential participants who joined were probably highly motivated to sustain abstinence from opiates because they were prepared to risk random allocation to a procedure which promised to enforce this for up to six months. In the aftercare study they had just completed abstinence-oriented residential care and in the prison study were keen to sustain their enforced abstinence on release.

Across the Norwegian studies implant patients substantially reduced their opiate use during the six months the initial implants were active and in the aftercare study, did so substantially and significantly more than patients allocated to normal aftercare arrangements. However, even among this selected and presumably motivated set of patients, the implants did not totally abolish use of opiate-type drugs and nor did they reduce some other forms of drug use. Just over half the implant patients tested the naltrexone blockade by using opiate-type drugs, and about a quarter of the sample did so repeatedly. Most of this opioid use occurred when naltrexone levels were above those known to block the pleasurable effects of heroin and few patients experienced the usual opiate-induced euphoria or 'high'. Perhaps because nearly a third allocated to implants refused these, in the prison study in particular, the reduction in opiate use was on average modest and no greater than among patients allocated to methadone maintenance.

Of the 61 patients implanted in all the studies, three had the initial implant removed. After six months, 44 said they wanted to be re-implanted and 31 actually were, showing that for some patients the implants can be a long-term treatment rather than simply an enforced break from opiates.

Other studies

In studies a minority of patients experience complications at the insertion site which lead the implant to be removed. Another potential problem is that implants impede opiate-based pain relief. Other occasionally severe reactions to implants and injections have been observed, but generally side effects are mild and/or short-lived and treatable. As with any abstinence-based treatment, overdose due to lost tolerance to opiate-type drugs is a serious concern. However, the few studies to date suggest these products protect against overdose while they are active, and that in caseloads prepared to undertake these procedures, opiate overdose reductions can outlast the active period of the implants. These findings are consistent with findings from Britain (1) and elsewhere (1 2 3 4 5) tentatively suggesting that long-acting naltrexone can be used to create an opiate-free period which extends beyond the initial blockade, sometimes aided by further administrations (1 2). See background notes for more on these important issues of adverse effects and overdose protection.

Another randomised trial of a different long-acting form of naltrexone has been conducted in the USA. Compared to placebo, this injection lasting four weeks nearly doubled the time heroin dependent patients were retained in aftercare following inpatient detoxification. On the credible assumption that drop-outs relapsed, there was a similar impact on heroin use. At the four-week choice point when the naltrexone patients could have refused the second set of injections, few did so, most committing themselves to another period without (or with reduced) opiate effects. Though encouraging, multiple exclusions (such as psychiatric conditions or dependence on other drugs) and the recruitment procedures (partly through newspaper ads) meant the patients may not have been typical of usual caseloads.

A criticism of trials to date is that they included highly selected patients. However, in this they may have reflected normal practice. Patients will only opt for such procedures if they are prepared (irreversibly in the case of depot injections) to commit to weeks or months without the effects of heroin or other opiate-type drugs, or with severely attenuated effects requiring higher than usual doses. From the control groups in naltrexone implant/depot studies, we know that even in these caseloads, treatment drop-out and relapse are common. Long-acting naltrexone helps these highly motivated patients sustain their resolve. The clearest candidates for the treatment are patients who are motivated to return to a life without opiate-type drugs (including prescribed substitutes), have the resources, stability and support to sustain this, are unlikely to simply 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.

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