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▶ Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone.

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The first trial of implanted versus oral naltrexone found that the implants' extended opiate-blocking action helps avoid relapse to regular opiate use – but the action was not as extended as hoped, non-opiate use was greater, and there were more unpleasant side-effects.

Abstract Naltrexone blocks the effects of opiate-type drugs, in theory helping to prevent post-detoxification relapse to heroin and allied drugs. As a medication taken daily by mouth, its potential has not been realised because patients generally refuse to take the pills or quickly discontinue. New longer-acting formulations in the form of a depot injection or an implant surgically inserted under the skin avoid the need to take medication daily, promising to improve retention on the medication and outcomes.

This Australian study compared the oral form of naltrexone with a naltrexone implant thought to block the effects of heroin and allied drugs for several months. Of 236 people referred to the study or who responded to ads, 70 were assessed as heroin dependent and met safety and other criteria for inclusion the study. Typically they were men in their late 20s and early 30s who had on average been using heroin regularly for nearly ten years. Following outpatient detoxification they were randomly allocated to an active implant and inactive placebo pills, or the reverse. Neither they nor the researchers knew who had been given the active implant and who the active pills. Trial treatments lasted six months, during which patients were dispensed monthly supplies of the pills. Arrangements were made for their consumption to be supervised and encouraged by a non–drug using associate such as a family member or partner. All patients were encouraged to attend weekly individual, group, or family therapy sessions and were regularly monitored by researchers including blood samples to check on naltrexone levels and urine samples to test for drug use.

By the end of the six months of treatment a range of alternative measures confirmed that the implants had helped prevent relapse to heroin use. Just two of the 34 patients originally prescribed active implants had been withdrawn from the study and offered alternative treatments due to relapse to daily heroin (and often other drug) use; in contrast, this rescue procedure had to be applied to 13 of the 35 originally prescribed active oral medication. Just six of the 35 patients prescribed implants either could not be followed up (4) or had according to their own accounts relapsed to frequent heroin use. In contrast, this was the norm (21 out of 34, of whom five could not be followed up) among patients prescribed oral naltrexone, creating a statistically significant difference between the groups. Abstinence from opiate-type drugs throughout the six months could be confirmed by urine tests for half (17) the implant patients but just a fifth (7) of the oral naltrexone patients. Oral naltrexone patients who returned to heroin use generally relapsed to regular use, not the case among those prescribed implants. Though both groups typically used non-opiate drugs, this was more common (94% v. 76%) among the implant patients; all but two had used other drugs, of whom 11 had used cannabis daily (versus seven oral patients) and four stimulants (versus one oral patient).

Greater desistance from heroin use in the implant group was related to the longer period they maintained blood levels of naltrexone sufficient to at least partly block opiate-type drugs. However, this new implant did not maintain these levels for as long as the earlier product not subject to the same manufacturing standards. In men an accepted therapeutic level was maintained for on average just under two months and among women for six weeks. A partially effective level was maintained for just over three months and four months respectively. Three of the 35 implant patients experienced complications around the injecting site and a few others experienced diarrhoea, nausea, and vomiting, experiences absent in the oral group. No opiate overdoses were noted. Altogether a fifth of the active implant patients had implants removed though three of the seven later had them reinserted.

The authors concluded that, compared with oral naltrexone, implants effectively reduced relapse to regular heroin use and were not associated with major adverse events. Often patients appear to have 'tested' the implant by using heroin but found the effects unrewarding and did not carry on using. Though at the cost of a minor surgical procedure, the featured implant has the advantage over other formulations of sustaining partially effective naltrexone levels for three to four months, providing an extended period during which the patient can make significant life changes, and/or reducing the frequency of repeat implantations.

FINDINGS The featured study seems the first to have randomised patients to an implant or to the oral form of the drug. It convincingly demonstrated the superiority of the implant version in the limited but important area of short-term reduction in use of opiate-type drugs. It was also the first trial to use implants manufactured in accordance with an international code which aims to ensure medicines meet certain production quality standards. This more controlled manufacturing process seems to have accounted for the dramatically shortened duration of action, meaning that implants would have to be repeated every six to eight weeks to sustain the blockade. Briefer duration increases the risks and expense and offers more opportunities for patients to return to opiate use, possibly before their lives have stabilised in other ways. In the study at least 14 of the 34

implant patients had no signs of a return to using opiate-type drugs, despite the fact that for the last half of the six months the implants would have partially or altogether lost their potency. However, the study offers no indications of how far this opiate-abstinent period was used to create a life sustainably free of regular drug use. All of these 14 could have been among the patients who resorted to regular use of non-opiate drugs, an unintended impact also seen in other Australian reports (1 2). Gains from the implant were also bought at the cost of a higher incidence of unwelcome side-effects, one of which was a case of MRSA infection, potentially a very serious incident, though in this highly monitored research study, one quickly resolved. One methodological concern is that recruitment was partly through newspaper ads, possibly meaning the patients were not typical of usual caseloads. Another is that reduced craving for heroin was to have been one of the primary measures of effectiveness, yet these results were not reported. A big gap is the absence of data on drinking, clearly a possible route to continued intoxication for patients on implants denied the effects of opiate-type drugs.

Other randomised trials (see below) have tested implants as a supplement to medication-free psychosocial support. Presuming that patients join these studies primarily for the chance of receiving a long-acting implant or injection, they suggest that patients motivated for this radical treatment do considerably better when they receive it than when offered just modest outpatient aftercare support, even if this includes support to keep taking oral naltrexone. As yet untested is whether such patients would do better if maintained on opiate-type drugs such as methadone or buprenorphine. In all randomised trials to date, more active and structured aftercare (for example, regular monitoring, continued well organised care from the initial service, or active referral to support groups) might have narrowed the advantages gained by supplementing aftercare with implants or depot injections. However, motivated patients and imperfect aftercare arrangements probably reflect the conditions in which implants would be deployed in normal practice. The featured study's findings are consistent with those 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 and sometimes too by resort to non-opiate drugs (1 2).

A trial in Norway tested an earlier form of the implant used in the featured study, one whose blocking effects typically last nearly six months. Staff at inpatient drug clinics invited opiate-dependent patients on abstinence–oriented programmes to participate in the study. 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, after which all would be offered (re)implantation. Over the six months of the follow-up, implanted patients used opiate-type drugs far less often, and 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 this study implants supplemented relatively weak aftercare arrangements.

Another randomised trial conducted in the USA tested a long-acting form of naltrexone administered by injection which blocks opiates for about four weeks. Compared to placebo, this 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. In this study all the patients

were offered twice weekly relapse prevention therapy and monthly psychiatric consultations.

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, an unusual degree of commitment. In the featured study for example, despite responding to ads or agreeing to a referral, of 129 people screened by the study who might otherwise have qualified to join it, nearly half (59) declined. But from the control groups in naltrexone implant/depot studies, we know that motivation alone is usually insufficient; without long-acting medication, even among 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.

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. Some possible safety concerns are outlined below.

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, possibly because opiate use too remains suppressed. Another potential problem is that implants impede opiate-based pain relief. To cater for this, at least one study gave patients 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 the most effective way of relieving these symptoms (using opiate-type drugs) is denied to the patient. As the featured study illustrates, any surgical procedure carries risks. No implant has yet been through the safety tests required for registration as a medical product. See background notes to an earlier Findings analysis for more on adverse effects and overdose protection.

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