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▶ Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial.

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Krupitsky E., Nunes E.V., Ling W. et al.
Lancet: 2011, 377, p. 1506–1513.
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In Russia, injecting detoxified opiate addicts with long-acting naltrexone which blocks opiates for a month meant more were able to stay off the drugs, findings which helped persuade US authorities to approve it for this role. Others argue this was precipitate given the lack of evidence on overdose protection.

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. An implant form inserted under the skin lasts up to six months, but involves minor surgery with occasional adverse reactions at the injection site. An alternative long-acting formulation approved in the USA and Russia for medical use instead takes the form of an intramuscular depot injection which blocks the action of opiate-type drugs for a month or possibly longer. Both avoid the need to take the medication daily, in theory overcoming the main shortcoming of oral naltrexone – that patients usually stop taking the tablets and resume heroin use.

In this trial in Russia (where opiate substitute prescribing using drugs like methadone is not permitted), the long-acting injection was tested as a way of sustaining abstinence from opiate-type drugs among opiate addicts who had been withdrawn from these drugs at 13 inpatient centres. Of 335 screened for the study, 250 voluntary patients completing their detoxifications joined it and were randomly allocated to naltrexone injections or to injections of a similar looking but inactive placebo. Injections started within a week of the completion of detoxification and were then scheduled to be re-administered every four weeks until 24 weeks, after which patients were to be offered long-acting naltrexone for another year. During the 24 weeks of the study patients could attend fortnightly counselling sessions.

Patients were typically young men in their late twenties and early thirties who had already spent nearly three weeks in inpatient detoxification. Over 4 in 10 were HIV positive and about 9 in 10 infected with hepatitis C. Of primary interest was whether they were opioid-abstinent (according to urine tests and their own accounts) during each week of the final 20 weeks of the 24-week follow-up; before this, some were expected to 'test' whether the injections really did block the effects of heroin or other opioids.

Main findings

Results were analysed on the basis that missing urine tests would have revealed that the patient had used opiate-type drugs. Over 4 in 10 tests were missing, almost exclusively because treatment had been prematurely terminated. Retention was, however, significantly better on the active naltrexone injections. By the end of the study just over half (67 of 126) of these patients remained in the study and in treatment compared to just over a third (47 of 124) assigned to placebo injections. Nearly 60% of naltrexone patients had all six of their scheduled injections compared to just over 40% on placebos.

In either group only a minority were known to have been totally abstinent, but the key finding was that on average naltrexone patients could be shown to have sustained abstinence in 18 of the 20 weeks of the assessment period compared to just 7 for placebo patients, a highly statistically significant difference. The gap between the proportions of patients sustaining abstinence became apparent by the second week of the trial and remained to the final week, when just over half the naltrexone patients could be shown not to have used opiate-type drugs compared to just over a third on placebos. On the assumption that patients not re-assessed were continuing with their pre-treatment opioid use, according to their own accounts, over the full 24 weeks of the follow-up on virtually no days had naltrexone patients lapsed to opioid use compared to 40% on placebos. The severity of relapse was indicated by the fact that 17 placebo patients were known to have become once again physically dependent on opioids compared to just one on naltrexone.

Compared to placebo patients, in each week of the follow-up period naltrexone patients on average reported less intense craving for opiate-type drugs and their craving remained lower than at the start of the study. In contrast, the impulse to use remained high among placebo patients. More generally too, and much more so than placebo patients, naltrexone patients had reduced their risk of infection and improved their health and quality of life, on several measures to the point where they no longer scored substantially worse than Russian norms.

Though naltrexone patients were more likely (over a quarter did) to experience some adverse side effects thought due to the treatment, none were judged serious and just two patients stopped treatment as a result, the same as on placebos. No overdoses or deaths were documented and no patient experienced pain which could not be relieved. However, liver enzyme abnormalities were more commonly found among naltrexone patients.

The authors' conclusions

The results of this study suggest that extended release naltrexone offers a new approach – distinct from maintenance using opioid agonists like methadone – which helps patients abstain from opioids and prevents relapse to opioid dependence. It found that detoxified,

opioid-dependent adults voluntarily seeking treatment who received naltrexone experienced more weeks free of opioid drugs than those who received a placebo, and did so regardless of age, sex, or duration of opioid dependence. Naltrexone patients experienced a persistent anti-craving effect, fewer confirmed relapses to dependence, and nearly double the typical retention in treatment of placebo patients. These benefits were rapid and persisting and more apparent than in studies which have used oral naltrexone, which patients have to take every day, and which less effectively maintains blood levels of the active ingredient.

Injectable extended release naltrexone was generally well tolerated by the patients and no new safety concerns were reported. Though more naltrexone than placebo patients adverse events, similar numbers stopped treatment as a result or experienced serious adverse events. Abnormal liver function tests occurred only in patients infected with hepatitis C. Pain at the injection site pain was more common when naltrexone was injected but was not severe. No patient suffered intractable pain, though those in pain or who might be were excluded from the trial.

The study took place where the main alternative pharmacotherapy for opioid dependence – substitute opioids like methadone – was unavailable; findings may not generalise to other jurisdictions. But even where methadone and allied agonist options are available, extended release naltrexone might attract patients whose employment prohibits opioid use, those early in their addiction careers, and those who want to secure their recovery after a successful course of agonist therapy.

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.

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 possibly weeks or months without the effects of heroin or other opiate-type drugs. 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 (perhaps because due to employment or other pressures, they have to) 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.

Naltrexone implants and depot injections impede opiate-based pain relief. This is a greater problem with the irreversible long-acting naltrexone injection than with implants which can be removed. Possible adverse effects of naltrexone on liver function – seen in the featured study among patients infected with hepatitis C – are also a concern based

on early studies, but not one confirmed in several later studies.

About the study

The featured study demonstrated both the advantages and the limitations of an opiate-blocking agent which patients have to be motivated enough to renew every four weeks. The sample seem relatively promising: their major drug problems were limited to opiate-type drugs, they were in relatively good psychological health, had voluntarily submitted themselves to several weeks inpatient detoxification, completed this, remained opiate-free and stable enough to about a week later commence longer term treatment, had someone close and supportive enough to supervise them, and were prepared to take a 50-50 chance of being injected with a drug which would extend by four weeks the period during which they would not experience opiate effects. Even those assigned to placebo avoided opiate use on most days during the 24-week follow-up and − after on average 10 years of dependence − over a third could be shown to be abstinent from opioids in the final week.

This performance was achieved with the support of one counselling session a fortnight and an inactive injection. 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 the injections would be deployed in normal practice. Set against this backdrop of perhaps inadequate aftercare, active injections substantially elevated opioid use outcomes and substantially improved general health and welfare. Yet it seems these benefits were concentrated in about half the patients who took all their injections, completed the study, and were abstinent from opioids in the final week. For the other half, four-weekly naltrexone injections and infrequent counselling were insufficient.

As with any abstinence-based treatment, relapse risking overdose due to lost tolerance to opiate-type drugs is a serious concern. Criticism of the trial has focused on the apparent lack of comprehensive enquiries to establish whether patients who dropped out of the study had died. The few studies to date of naltrexone implants suggest these 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. However, implants last up to six months while injections last four weeks, offering more opportunity to discontinue the treatment, re-experience opiate-type drugs, and risk taking too much.

Given excess drop-out on placebos, some of the advantage found for the naltrexone injections must have been due to the assumption that drop-outs were still using opiate-type drugs and doing so at the same rate as before treatment. Though the 'worst case' is a common and defensible assumption in research, it also seems possible that some of these motivated patients, discovering they had been allocated to placebo, discontinued treatment and participation in the trial yet managed well without treatment, or found alternative sources of support for their recovery.

Another issue is less a criticism of the trial, than of its acceptance in the process of approving the injections for the treatment of opioid dependence in the USA, where opiate substitute prescribing is available and has a proven lifesaving record. The argument is that in such countries the issue is not whether depot naltrexone is better than an inactive placebo, but whether it at least matches methadone maintenance, the standard pharmacotherapy, an argument which would apply also to the UK. In response, US authorities have pointed out that even where methadone treatment is available, many patients do not or cannot enter it, and that naltrexone is intended for a different caseload − one which has already overcome physical dependence on heroin and allied

drugs and wishes to sustain this without dependence on similar-acting medications.

The study was sponsored and (with the researchers and others) designed, analysed and interpreted by the pharmaceutical company which manufactures depot naltrexone. The first author was a consultant to the company and the only author to have had full access to the original data without having to make a specific request. He also made the final decisions on all parts of the featured report. Three other authors were full-time employees of the company. This degree of involvement raises concerns over the independence of the study from pharmaceutical industry influences with a strong interest in finding positive results. Studies have found that industry-sponsored research is significantly more likely to reach conclusions favourable to the sponsor than studies not sponsored by the pharmaceutical industry. This seems partly because industry-sponsored trials are more likely to compare their products with an inactive placebo than an active alternative treatment.

Other similar trials

Another randomised trial of the same 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.

Results echoed those of a similar study in Norway, where − though permitted − access to substitute prescribing programmes is restricted, particularly for people unwilling to contract to forgo not just heroin, but persistent substance use of any kind. There a randomised trial used a naltrexone implant whose opiate-blocking effects last about six months. Over these six months, usual-care patients leaving inpatient detoxification recalled using opiate-type drugs on average on 97 days, implant patients on just 37. By the end, 18 out of 27 usual-care patients but just 9 of 29 implant patients continued to meet criteria for opioid dependence. As in the featured study, patients assigned to long-acting naltrexone were much less likely to experience craving. Again in this study, implants were compared against relatively weak aftercare arrangements.

Though in Russia methadone is not an alternative treatment, oral naltrexone is and might have been used as a comparator instead of placebo. The chances are however that the long-acting formulation would still have proved superior. This was the case in an Australian study of patients who had completed outpatient detoxification and were assigned either to naltrexone tablets or to an implant thought to block opiate effects for several months. 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, despite the fact that for the last half of this period the implants would have partially or altogether lost their potency.

For more Findings analyses of long-acting naltrexone treatment for opiate dependence click here.

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