Your selected document

▶ Oral naltrexone maintenance treatment for opioid dependence.

Minozzi S., Amato L., Vecchi S. et al.
Cochrane Database of Systematic Reviews: 2011, 2, Art. No.: CD001333.

Authoritative synthesis of research confirms that the general run of opiate-addicted patients do almost as well given no active medication as when prescribed the opiate-blocking drug naltrexone, though it does have limited role among highly motivated and/or monitored patients with much to lose from relapsing.

Summary Naltrexone is a an opioid 'antagonist', meaning that it blocks the effects of opiate-type drugs such as heroin. With sufficient naltrexone in their system, someone who takes heroin will not feel any of its characteristic effects. For this reason it has for decades been considered a potential way of enabling dependent users to avoid the temptation to take opiate-type drugs. Since in active dependent users it precipitates a withdrawal syndrome, it is used to maintain abstinence in patients already withdrawn or 'detoxified' from opiates. Though the drug works when taken, the problem has been that most dependent users simply stop taking it (typically it is taken orally once a day or once every two or three days) and drop out of treatment so they can re-experience the effects of heroin or allied drugs. While it cannot help people who plan to use heroin so stop taking the drug, it can help patients resist unplanned and impulsive use, acting as a kind of 'insurance policy' in case their resolve weakens. It is therefore particularly useful when motivation to abstain is high. In practice these are generally patients who are closely monitored and have much to lose from being exposed as having relapsed to opiate use; among the general run of patients, prescribing it does little to foster abstinence because the pills are simply not taken.

The featured review aimed to assess whether this general picture remained valid, taking in studies available since the last review conducted for the Cochrane collaboration published in 2005. It based its conclusions on a search for studies (in whatever language) which randomly (or in some other way ensured comparability between patients) allocated detoxified opioid-dependent patients to naltrexone-based treatment or treatment which

did not feature an opioid antagonist. It was concerned solely with naltrexone taken by mouth, not depot or implant preparations which are injected or inserted under the skin and 'drip-feed' blockade doses for several months. Since abstinence is the main objective of naltrexone treatment, this was the prime outcome assessed, either assumed because patients remained in treatment and taking their naltrexone, or directly assessed by self-report or urine tests. The review also aimed to assess whether studies have shown that the medication reduces crime, the degree to which it produces unwelcome side-effects, and the impact on death rates. The latter is a prominent concern over naltrexone − some patients stop taking the drug, return to heroin and then die from overdose − but none of the studies assessed mortality.

Main findings

The searches uncovered 13 relevant studies of altogether 1158 outpatients followed up for at most 10 months in either the USA, Israel, Russia, Italy, Spain, China, Malaysia or Germany. All 13 involved a comparison between patients (891 in all) prescribed naltrexone versus either an identical but inactive placebo pill or simply no medication at all. Most also offered all the patients psychosocial therapy. The outcomes were all in favour of naltrexone, but on only one measure − the proportion of patients re-imprisoned − was the difference statistically significant. Over all the studies, prescribing naltrexone had not reliably improved retention or abstinence rates.

The most common measure was the proportion of patients retained in treatment and who at the end were no longer taking opiate-type drugs. Across these six studies, 24 in every 100 naltrexone patients met this criteria compared to 17 in every 100 not prescribed naltrexone, but the variability was such that this difference could not be relied on as truly indicating that naltrexone was superior. Naltrexone's non-significant advantage was due largely to studies (three in all) in which patients had been in some way made to take the pills. Among this subset of studies [Editor's note: and specifically the two Russian studies ▸ comments below] there was a statistically significant difference in favour of naltrexone; 39 of 116 naltrexone patients − almost exactly a third − were retained and abstinent compared to just 13 of 114 not prescribed the medication.

Across the fewer studies reporting retention in treatment, or abstinence at the end of the treatment period (whether or not the patient had been retained) or at a follow-up, on no measure did prescribing naltrexone lead to a statistically significant advantage compared to placebo or no medication. The same was true in studies which compared naltrexone to psychotherapy or other combinations of comparison treatments, including other medications.

Naltrexone's sole statistically significant advantage arose from two US studies which assessed the proportion of patients imprisoned during the treatment period. A quarter (13 of 54) naltrexone patients had been imprisoned but half (16 of 32) not prescribed the medication. [Editor's note: a study of opiate-dependent offenders on probation or parole was the main contributor to this finding ▸ comments below.]

The authors' conclusions

Compared to placebo, or to no medication or alternative medications, prescribing oral naltrexone led to no statistically significant differences in the primary retention/ abstinence outcomes. The main problem associated with oral naltrexone was high

treatment drop-out – across the 13 included studies, 72% of patients did not complete treatment. Newer implant and depot preparations which patients cannot simply stop taking are intended to overcome this problem, but a parallel Cochrane review of these preparations found insufficient evidence to evaluate their effectiveness.

Based on the generally small studies available to date, maintaining patients on oral naltrexone cannot yet be considered scientifically proven to be superior to other kinds of treatment. It may however be an effective supplement in the treatment especially of patients who fear severe consequences if they relapse, such as health-care professionals who might lose their jobs, or parolees who risk imprisonment. Other highly motivated addicts may also profit from naltrexone. However, further studies are required to confirm this impression. As with treatment generally, so too with naltrexone, the chances of a positive outcome may be improved if the patient has a stable social circle (spouse, family, friends), an occupation, a confidential relationship with the therapist, clear instructions on the treatment, and give their informed consent.

FINDINGS The typical opiate-addicted patient in Britain does not do well with a detoxification plus naltrexone package as normally implemented in the UK, illustrated recently in a study from Birmingham in which just eight of 71 patients were free of opiate-type drugs six months later, following what was generally a rapid relapse during or shortly after detoxification. Just two patients completed detoxification and avoided a return to opiate-type drugs over the following six months. Without pill-taking being monitored by someone with the leverage to ensure they were taken, even patients with the resolve to complete detoxification generally succumbed to the temptation to stop treatment and resume opiate use. In doing so they exposed themselves to what internationally has been documented as a high risk of death from overdose, in Australia, as high as 1 in 12 within three months of completing detoxification.

This risk is applicable not just to detoxification followed by naltrexone, but opiate detoxification in general. Naltrexone may, however, aggravate the risk. Experts convened by the World Health Organization have pointed out that patients who stop naltrexone in order to resume heroin use can find that same ineffective dose they took hours before is later fatal as naltrexone levels gradually fall and the blockade effect weakens.

Post-detoxification overdose risk is one reason why UK national guidelines caution careful selection of patients fully committed to the process and who will have supportive and stable social environments available after discharge, among which may be seamless entry to residential rehabilitation. The preparation phase and the detoxification interlude itself should be used to bolster psychological resilience and social supports.

In respect of naltrexone in particular, the guidelines echo recommendations from Britain's National Institute for Health and Clinical Excellence (NICE) that the drug is suitable for detoxified patients who are highly motivated to remain in an abstinence programme, and should be administered under adequate supervision as part of a programme of supportive care to people who have been fully informed of the risks. Despite an unpromising record among the generally randomly allocated patients in clinical trials, NICE's experts were convinced that among selected individuals and in the recommended circumstances, naltrexone can greatly aid abstinence from opiate-type drugs with associated improvements in the patient's quality of life. The World Health Organization is clear that

the overdose risk means naltrexone is best reserved for patients who have a reasonable chance of remaining abstinent, and that those severely dependent should be cautious about embarking on the treatment.

The featured review confirms such guidance in that positive results were largely confined to studies in which the drug was administered to the patient or the patient was supervised while taking the drug, and the population was highly motivated either intrinsically or because they had much to lose if they dropped out of treatment, or if close monitoring including urine tests revealed they had relapsed.

Other more promising options (because they are much less vulnerable to planned or impulsive drop out) for highly motivated patients are long-acting formulations of naltrexone more or less irreversibly injected or implanted under the skin. The indecisiveness of the parallel review of these preparations was probably due to the lack of evidence at the time; just one trial met the review's stringent criteria. A more optimistic impression is gained by looking more widely at the evidence, and taking in later trials (1 2), including one which convincingly demonstrated that the implant was better at suppressing opiate use than the oral formulation. Though not without drawbacks (including problems at the implant site and the interference with opiate-based pain control), long-acting naltrexone helps sustain the resolve of the minority of patients prepared to more or less irreversibly commit to weeks or months without the effects of opiate-type drugs. 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.

Notwithstanding these technological advances, a defining characteristic of opiate addiction − an overwhelming desire to experience opiate-type effects − means that any treatment which relies mainly on the patient's sustained resolve to abstain is likely to remain a minority approach. After reviewing the entire spectrum of medication-based treatments for opiate dependence, experts convened by the World Health Organization concluded that agonist maintenance with drugs like methadone, which substitute for rather than block illegal opiates, should form the backbone of treatment systems. Their conclusion has been supported by the sole head-to-head comparison of post-detoxification outcomes when patients have been allocated to naltrexone or the substitute drug buprenorphine. Treatment retention and heroin use outcomes were clearly and universally superior for the buprenorphine patients, significantly better than placebo, and generally also significantly better than naltrexone.

Family supervision helps ensure compliance

In the featured review, two Russian studies (1 2) from the same research team were largely responsible for the non-significant advantage naltrexone recorded on the retention plus abstinence measure. They were the only ones to find a statistically significant difference in favour of the medication. Across the remaining studies, a slightly higher proportion of patients (22% v. 18%) met this criterion of success without than with the aid of naltrexone. The Russian studies illustrate naltrexone's positive potential among patients early in their addiction careers and with sufficient ties to mainstream society for their families to exert leverage over them to take the medication, even if they have previously been unable to exert sufficient leverage to directly prevent heroin use. In these circumstances, the medication, taken at a time when the patient is not in a position to use heroin and

is under the influence of whoever is supervising their medication, extends that influence to situations later in the day where heroin is potentially available.

What was distinctive about these studies is that they took place in a country where the main alternative type of drug treatment – 'agonist' drugs like methadone – was unavailable, and that opioid-dependent Russians are mostly young people living with their parents, who usually initiate treatment and can control the daily process of taking naltrexone. Both studies required patients to have a stable address and at least one relative willing to participate in treatment and monitor administration of medications, assist in follow-up, and provide outcome data. The first of the two studies adds that all the patients lived with their families, on whom generally they relied for accommodation. They were usually brought to treatment by their parents who were closely involved in the treatment. In both studies too patients were almost all in their early 20s and had been using/dependent on heroin for on average two to three years. Treatment lasted six months and included fortnightly counselling visits during which urine tests were completed and which were usually attended by parents or close relatives living with the patients who knew whether they had relapsed. Under these circumstances, more than twice as many patients were retained in treatment and avoided relapse with the aid of naltrexone. In these cases the drug acted as an arm's length extension of parental monitoring, making sure that the parent's influence (in ensuring the pill is taken) remained active in the form of the naltrexone blockade even when the parent was not there to help prevent heroin use.

Imprisonment outcomes

In the featured review, across the two (both US) studies which measured this, in the six months of the studies a smaller proportion of naltrexone than non-naltrexone patients were imprisoned.

The main contributor to this finding, and the only study which on its own found a statistically significant effect, concerned opiate-dependent offenders on probation or parole. Of the 300 potentially eligible offenders, 51 joined the study. They were randomly allocated to fairly intensive weekly contact with their probation officers during which they would be urine tested, or to this plus naltrexone administered by researchers in the same building and at the same time as one of their probation appointments. The researchers too confidentially urine-tested the offenders, and found that though more naltrexone patients were retained in the study (52% v. 33%), on average they were much less likely (8% v. 30% of tests) to test positive for opiates. Greater rates of non-attendance and illegal drug use probably contributed to the fact that over the six months 56% of the probation-only offenders were imprisoned for violating their probation but just 26% administered naltrexone. The study exemplifies the conclusion that naltrexone has a role among closely monitored patients who have much to lose (in this case, their freedom) from dropping out of treatment and returning to opiate use, especially when pill-taking is supervised.

The contrast between findings in this study and another from the same researchers but not included in the featured review illustrates the importance of monitoring. Encouraged by their earlier findings, they tried psychosocial treatment with versus without naltrexone on opiate-dependent offenders under legal supervision in the community. As before, the drug was administered by the research team, but this time there was no impact on recorded crime. While retained in treatment naltrexone patients submitted more opiate-free urines, but this result was overwhelmed by the high treatment drop-out rate (about two-thirds) in both groups of patients. The big difference with the previous study was the much less intense criminal justice supervision, and consequently the lower risk of non-compliance being spotted and resulting in sanctions. Only among the relatively closely supervised and regularly urine-tested offenders referred to the project from a drug court did naltrexone help patients complete treatment – 57% did so compared to none not administered naltrexone, though numbers were small.

The second study included in the featured review was not concerned with offenders under legal supervision. In this case its positive results may have been due to applicants having to complete a two-week induction during which they were required to demonstrate they were opiate free and had complied with the programme's

requirements. Only a third of patients allocated to the study's treatments got through and joined the study. Among this highly selected group prepared to do what it took to enter this intensive rehabilitation programme, being assigned to naltrexone taken under supervision at the centre helped them stay in treatment and opiate-free, and over the 12 months of the study, non-significantly more avoided imprisonment. The study seems to illustrate that dependent patients who are highly motivated to overcome their dependence can make good use of clinic-administered naltrexone and that without this, their motivation is usually not enough to sustain their resolve.

Thanks for their comments on this entry to Silvia Minozzi of the Department of Epidemiology, ASL RM/E, in Rome. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

Last revised 15 July 2011

▶ Comment on this entry• ▶ Give us your feedback on the site (one-minute survey)

Top 10 most closely related documents on this site. For more try a subject or free text search

Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial STUDY 2008

The Drug Treatment Outcomes Research Study (DTORS): final outcomes report STUDY 2009

Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone STUDY 2009

Heroin maintenance for chronic heroin-dependent individuals REVIEW 2010

Long-acting depot naltrexone extends opiate abstinence STUDY 2006

Opiate antagonist treatment risks overdose STUDY 2004

Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial STUDY 2009

Rapid opiate detox guarantees completion, but abstinence depends on what follows STUDY 2002

Prescription of heroin for the management of heroin dependence: current status REVIEW 2009

High risk of overdose death for opiate detoxification completers STUDY 2008