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▶ Opioid antagonists for alcohol dependence.

Rösner S., Hackl-Herrwerth A., Leucht S. et al.
Cochrane Database of Systematic Reviews: 2010, 12, Art. No.: CD001867.

Comprehensive synthesis of results from 50 trials finds that the opiate-blocking drug naltrexone does on average help more detoxified alcohol dependent patients avoid relapse, but effects are generally small and inconsistent. Useful, but not a magic bullet is the verdict.

Summary By blocking the body's own opiate-type chemicals, opioid antagonist drugs are thought to reduce the pleasurable feelings patients gain from drinking which reinforce further drinking. Most researched is oral naltrexone, normally taken by mouth daily. A relatively new extended-release formulation is intended to help overcome the problem of patients failing to take the tablets. As approved in the USA, it takes the form of a long-acting intramuscular injection which blocks the action of opiate-type drugs for a month or possibly longer. Another naltrexone-like antagonist called nalmefene has also been tested for the treatment of alcohol dependence.

The featured review updates the previous Cochrane review, taking in many more studies, including those of the newer opioid antagonist preparations. The analysts searched for studies of the treatment of alcohol dependence which randomly allocated adult patients to the drugs or to a placebo or alternative medication in such a way ('double-blind') that which they were taking was hidden from both patients and researchers. In synthesising the results of these studies, only drinking outcomes and side-effects were investigated.

The analysts found 50 relevant trials of which 47 were concerned with naltrexone (including four of the long-acting injection) and 44 compared it against a placebo. The remaining three studies were of nalmefene. Most were conducted in the USA, involved patients already detoxified from alcohol or who did not need to be detoxified, and nearly all excluded mentally ill patients and those using other drugs except tobacco.

Main findings

The key issue and the subject of the great majority of the studies was whether

naltrexone was better than an inactive placebo, in particular at preventing a return to heavy drinking, its anticipated major role. Across the 28 studies with 4433 patients which investigated this, during treatment, for every 10 patients who returned to heavy drinking given a placebo, just over eight (8.3) did so if given naltrexone. Put another way, nine patients needed to be treated with naltrexone in order to gain one who did not relapse to heavy drinking during treatment. The raw figures were that 61% drank heavily during treatment without the aid of naltrexone, 51% with it. These gains in heavy drinking outcomes were confirmed by small but statistically significant reductions in the number of days on which patients drank heavily (reduced by 3%) and the amount drunk on each day they drank (reduced by 11g alcohol or nearly one and a half UK units). Confirming the patients' own accounts of their drinking, levels of a chemical in the blood indicative of heavy drinking were also lower on naltrexone than placebo. Though just five studies assessed this, across these the impact on heavy drinking was largely sustained three to 12 months after treatment ended; for every 10 patients who returned to heavy drinking after placebo treatment, just under nine (8.6) did so if they had been prescribed naltrexone.

In contrast to uniformly significant impacts on heavy drinking, the small reduction (about 4%) in the proportion of naltrexone patients who drank at all during treatment narrowly missed the conventional '1 in 20 by chance' criterion of significance. However, naltrexone patients did drink on significantly fewer (also about 4%) days. Just two studies assessed return to drinking after treatment had ended, registering no lasting statistically significant gain from having been prescribed naltrexone.

Across the 37 studies which reported this, the proportion of naltrexone patients who dropped out of treatment was 8% lower than among comparison patients. But when they did drop out, they were much more likely to do so because of unpleasant side effects. Still these led just 6% of naltrexone patients to terminate treatment, and side effects were no more likely to be serious among the naltrexone patients. However, side effects of whatever severity were slightly more common, notably gastrointestinal symptoms like nausea and signs of decreased arousal like sleepiness and lethargy.

Selected other findings

All the above analyses combined studies of the oral version of the drug with the few which tested the long-acting injection. When these were separated out, across the two each which assessed these outcomes, the injection slightly and non-significantly reduced the proportion of patients who resumed drinking after detoxification, and significantly reduced by about 9% the number of days on which drinking occurred. Across the three studies which reported relapse to heavy drinking, this was also slightly and non-significantly less common among naltrexone patients. Compared to placebo, excess side effects similar to those experienced with the oral form of the drug were also more common with the injectable form. Again these led more patients to drop out of treatment, but drop out overall was no more common than when the patients had been injected with an inactive placebo.

Apart from disulfiram, whose mechanism of action (an aversive physical reaction when alcohol is drunk) is very different, the main alternative to naltrexone is acamprosate. Three studies tested whether this was more effective than naltrexone. Across these there was no clear advantage for either drug. Except for the number of days on which patients

drank, naltrexone tended to produce slightly better drinking outcomes. Though overall fewer naltrexone patients dropped out of treatment, when they did, it was more likely to be due to adverse possible side effects. The side effect profiles differed; nausea and somnolence more common with naltrexone, diarrhoea with acamprosate. In the two studies which tested a combination of both drugs against a placebo, drinking and heavy drinking were substantially but not significantly reduced, at the cost of more frequent side effects.

The other opioid antagonist used to treatment alcohol dependence is nalmefene. Across the three trials which tested this against a placebo, during treatment the medication reduced the proportion of patients who returned to heavy drinking by 15% and also slightly reduced the number of heavy drinking days and the amount drank on those days. Though overall fewer nalmefene patients dropped out of treatment, when they did, it was more likely to be due to adverse possible side effects. Compared to placebo, nalmefene patients more often experienced nausea, insomnia and dizziness. None of the outcome or drop-out differences were statistically significant.

The authors' conclusions

Based on comprehensive evidence from 50 randomised controlled trials with 7793 patients, the review demonstrates the effectiveness and safety of naltrexone for the treatment of alcohol dependence. Compared to a placebo, the opioid antagonist reduced the risk of return to heavy drinking by 17%, drinking days by about 4%, and heavy drinking days by about 3%, meaning that the drug on average avoids one additional heavy drinking day per month. On days when alcohol is drunk, patients treated with naltrexone manage to refrain from about one more drink than they would have done prescribed a placebo. Naltrexone can be expected to prevent heavy drinking in one out of nine patients who would otherwise have returned to a heavy drinking pattern.

Among patients who take their naltrexone regularly, benefits are likely to exceed those demonstrated in these clinical trials. It should also be kept in mind that in most trials naltrexone supplemented psychosocial interventions, so the results reflect the *extra* benefit associated with the medication.

Though not a 'magic bullet', naltrexone appears a helpful and effective way to reduce drinking in alcohol dependent patients, one which should be brought to their attention and made available as a possible treatment.

FINDINGS Modest impacts on drinking which varied substantially across the trials included in the analysis indicate that naltrexone's average advantage is inconsistently realised in different treatment contexts and even more inconsistently among different individual patients. Sometimes it helps, often it does not. As the authors comment, the same could be said of alcohol treatment and psychiatric treatments in general. Allied with troubling if rarely serious side effects, the analysts' conclusion that it should be 'on the table' as a treatment option but subject to patient preference seems balanced.

Naltrexone's safety and the fact that it does not itself cause dependence, mean that a trial and error approach can be applied, seeing if patients who do not do well with psychosocial therapy only and are not suitable for disulfiram respond well, and discontinuing the medication if treatment cannot be well implemented or side effects outweigh any benefits. Because it generally has a modest impact, naltrexone (and other

medications) are supplements to, not replacements for, psychosocial therapies. Its reward-dampening effect does need to accumulate, so the drug can be taken 'as needed' to cope with what the patient anticipates might be a relapse-precipitating situation, with no apparent reduction in effectiveness (1 2 3).

UK guidance

While in the UK acamprosate is licensed for the treatment of alcohol dependence, naltrexone is not, though because it is licensed for treating opiate dependence it is readily available. Some centres are using it, on the basis of the physician's own responsibility. Britain's National Institute for Health and Clinical Excellence (NICE) recommended that both drugs be considered as supplements to psychological interventions for patients with at least moderately severe dependence who have completed their initial withdrawal from alcohol. A review published by England's National Treatment Agency for Substance Misuse (NTA) concluded that naltrexone and acamprosate show minor positive effects when combined with psychosocial interventions, that naltrexone is most clearly indicated for patients who have lapsed or 'slipped', and acamprosate for supporting abstinence among patients who fear craving will lead to a lapse. NTA guidance partly based on this review stressed that drugs should be seen as adjuncts to psychosocial therapies, not treatments in their own right. Scottish alcohol treatment guidelines published in 2003 were more cautious. While acknowledging evidence of naltrexone's effectiveness, they recommended against routine use in the Scottish health service because it has yet to be licensed for this purpose.

British studies

Without being conclusive either way, two major British studies have provided greater support for naltrexone than for acamprosate. Both studies were plagued by high drop-out rates and poor compliance with treatment, but in the naltrexone study, those patients who did complete the study and largely complied with treatment drank substantially less on naltrexone than on placebo pills. One lesson from both studies seems to be that among typical British alcohol clinic caseloads, the support available from the staff and/or from families and friends is often insufficient to enable patients to sustain their commitment to treatment. For details see background notes to an earlier Findings analysis.

Compared to other medications

The analysts responsible for the featured review have also reviewed studies of the effectiveness of acamprosate for alcohol dependence, reaching conclusions similar to those reached for naltrexone.

A US review and clinical guidelines drawn up by a panel of experts convened by the US health department have usefully compared the pros and cons of all four US-approved medications for alcohol dependence: disulfiram (a drug which produces unpleasant reactions in response to even low levels of drinking); acamprosate; oral naltrexone; and once-monthly, injectable, extended-release naltrexone.

They suggest that patients committed to abstinence who have strong home-based or clinical support, especially in the form of someone to supervise consumption, can sustain

disulfiram therapy and remain abstinent as a result, though some will not be suitable due to medical contraindications. The possibility of a severe reaction to drinking means that it would be unacceptable to use the drug in patients who have little chance of sustaining abstinence. In other circumstances, pharmacotherapies like naltrexone and acamprosate – which do not demand total abstinence – are more likely to be adhered to and can cut consumption. Even with these drugs, 'compliance' – the degree to which patients take the pills as intended – is a key issue. It can be improved by counselling designed to motivate compliance and to minimise side effects such as fatigue and nausea, and by engaging family members or other associates to monitor consumption of the pills. Naltrexone may be the better option for people who are not aiming for or find it hard to stop drinking altogether, and for those with a strong desire to drink in order to achieve what they experience as a pleasurable state of intoxication. However, side effects are more common and more severe (though only rarely such that patients have to stop taking the drug) than with acamprosate, and the drug is contraindicated in patients with certain liver problems or who are also dependent on opiates. There is also the complication that in a medical emergency, patients who have recently taken naltrexone will find that opiates fail to control pain, one reason why some prefer not to take the drug. This is a greater problem with the irreversible long-acting naltrexone injection.

Who benefits most?

Though there are the above pointers to which *types* of patients might benefit most from which medication, a US review points out that there is no secure way of deciding which medication is preferable for an individual patient. Accepting this, nevertheless in several trials naltrexone proved particularly effective among patients with the worst prognosis, characterised by one or more of the following attributes: early onset (pre-25) alcohol problems; family history of alcoholism; abuse of other drugs; strong urge to drink even in the absence of withdrawal symptoms; unable to initiate abstinence at the start of treatment or sustain it during treatment. Among these patients the drug's effect is to counter an otherwise poor prognosis, but this can only happen if they have sufficient social stability and support to stay in treatment and take the pills.

To see all Findings analyses on naltrexone treatment for alcohol dependence, run this search.

Thanks for their comments on this entry in draft to Duncan Raistrick of the Leeds Addiction Unit. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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