DRUG & ALCOHOL FINDINGS *Review analysis*

This entry is our analysis of a review or synthesis of research findings considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original review was not published by Findings; click Title to order a copy. Free reprints may be available from the authors – click prepared e-mail. Links to other documents. Hover over for notes. Click to highlight passage referred to. Unfold extra text. The Summary conveys the findings and views expressed in the review. Below is a commentary from Drug and Alcohol Findings.

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The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, Europe versus the rest of the world: a meta-analysis.

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Addiction: 2015, 110(6), p. 920–930.

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Whether differences between the patients mean impacts of the alcohol treatment medications acamprosate and naltrexone vary between Europe and the USA was the issue which motivated this fresh analysis of randomised trials. It confirmed the medications' efficacy and found no evidence that this differed in European trials versus those conducted elsewhere.

SUMMARY Orally administered acamprosate and naltrexone are the most common pharmacological treatments for harmful alcohol use or dependence. Acamprosate ameliorates the negative feelings experienced during alcohol dependence and withdrawal which induce dependent drinking, while naltrexone seems to dampen the rewarding effects of drinking.

WHO's European region: whether effects of acamprosate and naltrexone differ there from elsewhere was investigated by the featured analysis.

Because they work in different ways, responses to these medications may also differ depending on the characteristics of the patients, such as severity of dependence and their treatment goals. In turn, differences in the characteristics of patients who participate in trials of the medications in Europe compared to the United States may affect their relative efficacy in those areas. Participants in European studies are more often recruited via treatment services rather than advertisements and more often require prior medically assisted withdrawal, suggesting that European participants are more severely dependent. Complicating the picture is that most acamprosate evaluations have taken place in Europe, and most of naltrexone in the United States. The nature of the participants in trials in those two areas could give an impression of the efficacy of the medications which does not apply to the other area.

The featured review aimed to determine the efficacy (prevention of lapse or relapse, and treatment completion) of acamprosate and naltrexone in the treatment of alcohol dependence and whether this differs between the World Health Organization's European region and other parts of the world. Studies published up to September 2013 were sought which had randomly allocated adults diagnosed as dependent on or abusing alcohol, or drinking in a harmful manner, to one of these medications versus an alternative procedure, excepting samples selected also to be suffering mental health problems or dependent on illegal drugs. The method used to amalgamate the studies' results in a meta-analysis did not assume there was one true value for the magnitude of impacts, but that these might vary from study to study.

For acamprosate and naltrexone respectively, 22 and 27 such trials were found involving 2649 and 2253 participants allocated to the medications.

Key points

From summary and commentary

'Do the alcohol treatment medications acamprosate and naltrexone have different impacts in the USA versus Europe?' was the issue which motivated this fresh analysis of randomised trials.

Comparison between effects in Europe versus the rest of the world indicated no differences in effects on drinking, but no specific comparison was made with the USA.

Not included was disulfiram, the second most commonly prescribed anti-alcohol medication in England and one which in the right circumstances has an effectiveness record at least as good as acamprosate and naltrexone.

Main findings

Acamprosate

Of the 22 acamprosate trials just five were conducted outside Europe. Compared to elsewhere, European samples were more often medically referred to treatment, had undergone preparatory detoxification, were aiming for abstinence, and were in treatment longer.

Compared to an inactive placebo, the proportion of patients allocated to acamprosate who had lapsed to drinking six months after treatment started was significantly lower. The raw figures were 65% versus 77%. Though all but one of the trials found an advantage for acamprosate, the magnitude varied substantially. Just two of the trials to report relative proportions who lapsed were conducted outside Europe; the aggregate impact of acamprosate in these trials was identical that in European trials.

Of the 18 studies which reported numbers who discontinued treatment, 13 were conducted in Europe. Across all 18 studies, 47% of patients did not complete treatment, a rate which did not significantly differ whether they had been allocated to acamprosate or to a placebo. However, in European trials acamprosate patients were 14% less likely to leave treatment early, but elsewhere, 23% more likely, creating a statistically significant difference between Europe and the rest of the world.

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Acamprosate patients were slightly more likely to leave treatment due to adverse events, but the difference was not statistically significant so may have been due to chance variations. On this comparison these was no significant difference between Europe and elsewhere.

Naltrexone

In contrast to acamprosate, just seven of the 27 naltrexone studies were conducted in Europe; 13 of the remaining 20 studies were accounted for by the USA. Like the acamprosate studies, participants in Europe had more often been medically referred to treatment and abstinence was the treatment goal for all but one European study. However, prior detoxification was no more common in Europe and treatment duration was similar. For acamprosate three rather than six months was the follow-up point chosen for the analysis.

Across the 17 studies to report this, compared to an inactive placebo a smaller proportion of patients allocated to naltrexone had lapsed to drinking three months after treatment started. This advantage for naltrexone was slight but statistically significant, so likely to represent a real effect. The raw figures were 65% versus 71%. On this measure few of the trials found a statistically significant advantage for naltrexone, five reported none at all, and the difference between naltrexone and placebo varied to a statistically significant degree.

In respect of *heavy* drinking three months after treatment started, across the 23 studies to report this, a significantly smaller proportion of patients allocated to naltrexone had relapsed compared to those allocated to an inactive placebo. The raw figures were 50% versus 59%. On this measure, seven of the 27 comparisons made in the 23 studies produced a statistically significant advantage for naltrexone, but the magnitude of the difference between naltrexone and placebo varied substantially.

Of the 25 studies which reported numbers who discontinued treatment, six were conducted in Europe. Across all the studies, a third of patients did not complete treatment, a rate which did not significantly differ whether they had been allocated to naltrexone or to a placebo.

Across the same number of studies, naltrexone patients were however significantly more likely to leave treatment specifically due to an adverse event such as unpleasant side-effects. The raw figures were about 6% versus about 3%.

Neither in drinking nor in treatment completion were there any statistically significant differences between Europe and the rest of the world in naltrexone's impacts relative to a placebo.

The authors' conclusions

Both acamprosate and naltrexone appear to reduce the risk of alcohol-dependent patients returning to drinking (and in respect of naltrexone, heavy drinking) in the first three or six months after treatment started. Across all studies, neither medication was associated with a significantly greater risk of leaving treatment early, though naltrexone was associated with more leaving due to adverse events.

The only comparison to register a statistically significant difference between Europe and the rest of the world was the proportion of acamprosate versus placebo patients who leave treatment early: in Europe, acamprosate seemed to help patients complete treatment; elsewhere, it had the opposite effect. Differences in routes into the trials, prior detoxification, and abstinence goals, suggest that patients in European acamprosate trials had been more engaged with treatment services before starting the trials, perhaps the reason why acamprosate aided treatment completion.

Sometimes these conclusions had to be reached on the basis of very few trials in one of the regions, and there was evidence that smaller trials which had not registered a statistically significant medication effect were less likely to be published and available for inclusion in the analysis.

Whatever the differences between countries, it is the characteristics of the individual patient which should determine the most appropriate pharmacotherapy.

FINDINGS COMMENTARY The results of the featured analysis give some reassurance that trials in other regions are relevant to the results to be expected from naltrexone and acamprosate in Europe, but the comparison between outcomes in Europe versus the USA was blunted by the inclusion of non-US studies among the non-European collection. Just two of the five non-European acamprosate trials were conducted in the USA and 13 of the 20 non-European naltrexone trials, leaving open the question which seems to have prompted the analysis: whether differences between patients in trials in Europe and the USA mean the medications exert different effects in those regions.

Lack of a clear-cut comparison with the USA becomes particularly relevant in respect of naltrexone, where much of the evidence is from the USA – evidence which, despite the featured analysis, remains of questionable relevance to the UK and the rest of Europe. Only one of the European naltrexone trials included in the analysis registered a clear advantage for naltrexone. Among the remainder, the major British study was affected by high drop-out and poor compliance with treatment, and overall recorded no statistically significant difference in drinking among patients randomly allocated to naltrexone versus a placebo. However, the minority of patients who did complete the study and largely complied with treatment drank substantially less on naltrexone than on placebo pills.

Despite its equivocal findings, the British naltrexone trial recorded better results than the equivalent trial of acamprosate, which found no impact on drinking, even among patients who took the 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.

Somewhat better results from naltrexone in the UK echo the results of several of the head-to-head trials of naltrexone versus acamprosate within the same study. These studies are particularly significant because they help eliminate the possibility that caseload or regimen differences account for the medications' relative impacts. Such studies conducted in Spain, Germany, the USA, and Australia, consistently favoured naltrexone, but when results from a slightly different set of studies were amalgamated no statistically significant differences were found in return to drinking or heavy drinking or number of days on which alcohol was drunk.

Other syntheses of the research

Another amalgamation of findings on acamprosate found 24 trials and agreed with the featured analysis that it reduced the risk of a return to drinking after detoxification, in this case to 86% of the risk with a placebo. It also increased the average time patients sustained abstinence by 11%, both statistically significant advantages which (with some fading) persisted three to 12 months after treatment ended. The featured analysis was unable to consider relapse to *heavy* drinking, but this earlier analysis did, and the results were less reassuring. Across the six trials which yielded this data,

results were virtually identical for the proportion of patients who returned to heavy drinking, regardless of whether they

results were virtually identical for the proportion of patients who returned to heavy drinking, regardless of whether they had been prescribed acamprosate or a placebo.

A corresponding amalgamation of findings on naltrexone and similar drugs concluded that naltrexone does on average help more detoxified alcohol-dependent patients avoid relapse, but effects are generally small and inconsistent. 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. Though just five studies assessed this, across these the impact on heavy drinking was largely sustained three to 12 months after treatment ended, results similar to those from the featured analysis.

Disulfiram results in aversive physical reactions when alcohol is drunk and is the second most commonly prescribed alcohol treatment medication in England. Positive evidence derives mainly from trials in which consumption has been supervised by families or clinical staff, among which was a UK trial which found the drug's short-term impact on promoting abstinence and reducing consumption was substantial. Patients also have to know they are taking the drug in order for it to have a deterrent effect, and across such trials disulfiram has a strong record in curbing drinking, at least as good as the records of acamprosate and naltrexone.

UK guidance and practice

Acamprosate and naltrexone are two of the three main medications licensed in the UK for the treatment of alcohol dependence and endorsed in national guidance for Scotland and England and Wales, the latter published by the National Institute for Health and Care Excellence (NICE). The other medication is disulfiram. NICE guidance says acamprosate and naltrexone should be considered in cases of moderate and severe alcohol dependence, but only in combination with a psychological intervention targeted at drinking such as cognitive-behavioural therapy. Compared to the other two medications, the guidance envisages a less routine and/or first-line post-detoxification role for disulfiram, cautioning that total abstinence is required to avoid unpleasant and potentially dangerous reactions. It notes that positive evidence derives only from situations where consumption has been supervised.

Other UK expert guidelines drafted by pharmacologists go further than NICE, arguing that medications including acamprosate and naltrexone should be the default treatment response to dependence, and only rejected if in some way contraindicated. This should, they recommend, even be the case for *non*-dependent problem drinkers who have not responded well to 'talking' therapies.

Contrary to this advice, the on average small benefits from these and other medications may be one reason why medications of any kind are prescribed in the UK for a minority of patients. In 2014/15 in England about 23% of the 89,107 patients seen at specialist services solely for problems with alcohol rather than other drugs were prescribed a medication, but this included inpatients prescribed a medication to ease withdrawal rather than to sustain their recovery. The previous year, of all alcohol patients (whether or not also recorded as having other drug problems) treated as outpatients, just 16% were prescribed medications.

However, in England the number of prescriptions for alcohol dependence has been rising sharply from 108,081 in 2004 to 194,706 in 2014, a rise largely accounted for by acamprosate, prescribed 137,596 times in 2014 compared to 55,620 for disulfiram, figures dominated by GP prescribing. Since 2012 disulfiram has been on a downward trajectory while acamprosate has continued upwards. Naltrexone is not recorded in these statistics while its new close pharmacological neighbour nalmefene has yet to generate much of a presence in the statistics.

This draft entry is currently subject to consultation and correction by the study authors and other experts.

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