

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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▶ **Metaanalysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful?**

Maisel N.C., Blodgett J.C., Wilbourne P.L. et al.
Addiction: 2013, 108(2), p. 275–293.



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Naltrexone and acamprosate both modestly curtail drinking among alcohol-dependent patients, but which is best in which circumstances and for which treatment goals? To find out this review compared the medications' performance when separately benchmarked against a placebo, bringing to bear much more data than is available from the few trials which directly compared the two drugs.

SUMMARY Debates over the use of oral naltrexone and acamprosate to treat alcohol dependence often focus on whether globally they work better than a placebo or one works better than the other. But in practice, clinicians may be most interested in the *circumstances* under which each medication is most effective. For example, if a patient is focused on maintaining abstinence, would naltrexone or acamprosate be most helpful? Whichever is selected, should treatment start only after the patient has detoxified?

Differences in their pharmacological properties suggest naltrexone and acamprosate best target different drinking outcomes. Naltrexone blocks the effects of opiate-type drugs like heroin. It may also block the body's own 'endogenous' opioids which are triggered by alcohol, and dampen activity in neural circuits mediated by the neurotransmitter dopamine. As a result, it is thought to reduce craving and help prevent relapse to heavy drinking by reducing the rewarding effects of alcohol.

Acamprosate is thought to promote abstinence by 're-setting' the balance between two neurotransmitter systems disrupted by regular heavy drinking. Because of these properties, it is believed to be ineffective if the patient starts drinking again. Although sometimes seen as an anti-craving medication, impacts on craving tends to be mixed. Acamprosate is therefore thought most effective at promoting and maintaining abstinence, and least effective at reducing craving or preventing a drinking 'lapse' progressing to a heavy drinking 'relapse'.

Given these expectations, the featured analysis tested whether naltrexone really has been found superior to acamprosate in reducing craving and preventing relapse to heavy drinking, and whether acamprosate really has been found superior to naltrexone in promoting abstinence. Also expected was that acamprosate would be most effective when the treatment programme's goal was abstinence or when patients had been abstinent for a time before treatment started, either because they had detoxified immediately before, or because a period of non-drinking was a requirement of joining the trial.

Findings were amalgamated from trials which had randomly allocated adult patients being treated for an alcohol use disorder to one of the two drugs versus an inactive placebo, the results of which had been published in English between 1970 and 2009. In analysing abstinence and heavy drinking rates, patients who could not be followed up were assumed to have relapsed. When results were expressed as, for example, numbers of drinks or numbers of drinking or heavy drinking days, the analysis was based only on the patients who contributed this data, ignoring study drop-outs. If a trial report presented several measures of abstinence or heavy drinking, these were amalgamated into one composite measure of each, expressed as an [effect size](#).

In all 64 studies were found including 45 of naltrexone versus placebo involving 5434 participants, 16 of acamprosate versus placebo involving 4349 participants, and three studies totalling 1210 participants involving both drugs and a placebo.

Main findings

Assessed at the end of treatment, relative to a placebo acamprosate's impact on abstinence over 15 trials amounted to a small to medium [effect size](#) of about 0.36, greater than the corresponding figure for naltrexone over 36 trials of about 0.12 [▶ chart](#). Each drug on its own generated a statistically significant increase in abstinence. The difference between them was also significant and in line with the expected superiority of acamprosate.

Also assessed at the end of treatment, in respect of heavy drinking the relative superiority of the two drugs was reversed. Compared to a placebo, over 39 trials naltrexone registered a statistically significant but small effect size of about 0.19; over just five trials, acamprosate registered an even smaller and non-significant effect size of about 0.07. Probably because so few acamprosate trials reported usable heavy drinking outcomes, though in the expected direction, the difference between the two drugs was not statistically significant.

Key points
From summary and commentary

The medications naltrexone and acamprosate both modestly curtail drinking among alcohol-dependent patients, but it is unclear which is best in which circumstances and for which treatment goals.

Rather than confining itself to direct comparisons of the drugs, the featured analysis addressed these issues by comparing the two medications' performance when separately benchmarked against a placebo.

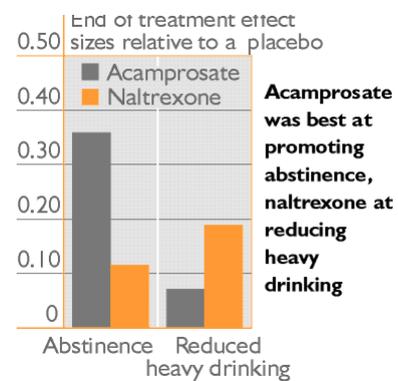
Findings suggested naltrexone is best for patients who want to control their heavy drinking, acamprosate for those seeking abstinence. Both seem more effective when patients have detoxified and/or stopped drinking in the run-up to treatment.

direction, the difference between the two drugs was not statistically significant, so a chance finding could not be ruled out.

For naltrexone, 26 trials had also reported whether at the end of treatment patients felt less craving for alcohol. On average they did, amounting to a small effect size of about 0.14, just failing to significantly better the 0.03 registered across nine acamprosate studies. As expected, naltrexone seemed more effective at dampening craving. To draw more studies into the analysis, the researchers also combined craving and heavy drinking outcomes. On this composite measure, as expected naltrexone had a greater impact relative to a placebo, and this time the difference between the drugs was statistically significant. Over 42 trials naltrexone registered a small effect size of 0.18; over nine trials the corresponding figure for acamprosate was about 0.04.

The above findings were essentially unaffected by selecting out the more unusual studies, including nine naltrexone trials in which patients were also diagnosed with cocaine use or mental health problems. Also tested was whether effects changed when the analyses were restricted to the roughly 8 in 10 studies in which psychosocial 'talking' therapies accompanied the medications. Though impacts on abstinence and heavy drinking/craving were less than among the full set of studies, the differences were very slight and non-significant, and the relative superiorities of the two medications remained unchanged.

Only seven studies for each drug provided usable data indicating effects up to a year after treatment had ended. Findings relative to a placebo were amalgamated for each study's final follow-up. As during treatment, with a small to medium effect size of about 0.40 versus 0.15 for naltrexone, acamprosate was superior (but not quite to a statistically significant degree) at sustaining abstinence. Too few acamprosate studies reported heavy drinking or craving to compare the drugs. Within naltrexone trials, final post-treatment follow-up effects on drinking were slightly less than at the end of treatment (effect sizes of about 0.14 and 0.19 respectively), and across only two studies to report this, there was a near zero impact on craving.



Under what circumstances did the medications have their greatest effects?

Next the analysts tested expectations of the circumstances in which the two medications would be most effective. In respect of naltrexone, the longer patients had been required to be abstinent before treatment started, the greater the effect relative to a placebo. Of the factors tested, this was the only one to bear a statistically significant relationship with abstinence outcomes, and it remained significant after overlaps between the factors had been taken into account. For heavy-drinking outcomes, once overlaps between the factors had been taken into account, having to have been abstinent before treatment started and a programme which did not explicitly aim for abstinence were associated with greater effects.

For acamprosate too, among other factors the longer patients had been required to be abstinent before treatment started the greater the impact on treatment-end abstinence. However, once overlaps between the factors had been taken into account, having undergone detoxification immediately before treatment started was left as the only factor significantly associated with higher levels of abstinence relative to a placebo.

The authors' conclusions

The findings suggest naltrexone should be considered for patients who want less often to drink heavily, while acamprosate is better for those who seek abstinence. Both seem more effective when participants are detoxified and abstinent when treatment begins. Derived from studies which separately compared each drug to a placebo, these findings may seem at odds with the three studies which compared them directly within the same trial, but there are possible reasons for the discrepancy ([unfold supplementary text](#)), and with many more studies, the featured analysis had a greater chance of revealing real differences between the medications.

The featured analysis showed that simply amalgamating all drinking outcomes would have given a misleading impression of the relative effectiveness of the two medications. Due to the preponderance of abstinence outcomes in acamprosate studies, such an analysis would have found this drug twice as effective as naltrexone (effect size of about 0.33 versus 0.16). But when outcomes were separated, acamprosate was only superior at promoting abstinence, not at reducing heavy drinking or craving.

Contrary to earlier theories that naltrexone works best in patients who are still drinking, required abstinence before treatment was associated with greater abstinence during treatment and greater reductions in heavy drinking. In addition, treatment programmes which did not explicitly aim for abstinence were associated with greater effects on heavy drinking. Possibly these programmes were more likely to include help in preventing lapses progressing to heavy drinking.

For acamprosate, becoming abstinent via pre-trial detoxification and (in the analysis not adjusted for other factors) longer pre-treatment abstinence amplified impacts on treatment-end abstinence, seeming to confirm that like naltrexone, the drug is most effective among patients who are not currently drinking. The drug's pharmacological properties may account for these findings, but it could also be that these requirements filter out less committed and motivated drinkers, leaving a sample more likely to comply with treatment, giving acamprosate a greater chance to exert its effects.

Though the featured analysis focused on differences between the medications, it also established that across all trials each was modestly effective relative to a placebo. Based on the effect sizes found, eight patients would need to be treated with acamprosate to achieve an additional case of abstinence, and nine treated with naltrexone to prevent an additional case of return to heavy drinking. Though few studies addressed this issue, effects tended to stay consistent or decline somewhat after medication treatment ended.

FINDINGS COMMENTARY Reinforced by the featured analysis, it has become accepted (1 2) that acamprosate has a better record at promoting abstinence than naltrexone, while naltrexone has a better record at preventing return to heavy drinking. Neither advantage is large or consistent enough to be decisive for clinical practice, and we could have greater confidence in these conclusions if more acamprosate trials had recorded relapse to heavy drinking. Though the featured analysis focused on acamprosate and naltrexone, disulfiram, which causes aversive reactions if patients drink, has a substantial usage in the UK. For selected patients and in the right circumstances, it has [at least as good](#) a record as the other two medications.

Other than to ease withdrawal, only a minority of alcohol patients in the UK are prescribed alcohol treatment medications of any kind, and reviews such as the featured analysis suggest most would not benefit if they were.

medications of any kind, and reviews such as the featured analysis suggest most would not benefit if they were prescribed them. Relegation of medications to a minority option reflects their generally minor effects relative to other influences, including the patient's impetus to get better, the processes in their life which help them realise and sustain this ambition, and the impact of deciding to enter and get actively engaged in treatment, one manifestation of which is regularly taking medication – even if that is in fact a placebo. Medications may help most when psychosocial therapy is not provided. More on these conclusions below.

Confirmatory analysis

Another synthesis of research came to similar conclusions to the featured analysis. It was based on the [naltrexone](#) and [acamprostate](#) trials found by versions of two reviews conducted for the Cochrane collaboration and published in 2008 and 2010 respectively. Unlike the featured analysis, its methodology enabled it to amalgamate findings from the three trials which had evaluated both drugs, as well as those which had separately evaluated each against a placebo. It concluded that relative to a placebo, both medications exerted a modest but statistically significant effect in preventing a return to drinking – though acamprostate had the edge and also led to more days of abstinence – but only naltrexone had also been found to prevent relapse to heavy drinking.

When the analysis compared the two, naltrexone had a significantly better record at preventing relapse, but acamprostate at promoting days without drinking. The analysts were able to calculate the probabilities of these (and also a placebo and the combination of the two drugs) being the best treatments at achieving different outcomes. There was over an 8 in 10 chance that acamprostate was number one for promoting days without drinking, while naltrexone had a 6 in 10 chance of being best at preventing relapse. The same kind of analysis was done for a composite outcome combining (with equal weights) preventing drinking, preventing relapse, days abstinent, and treatment completion. On this basis, naltrexone was slightly preferable, having a 35% versus 24% chance of being best, though both together (tested however only in two trials) registered a slightly higher 41%. With such small differences, these composite outcome calculations yielded no definitive advantage for either medication or for their combination, but did strongly suggest all would perform better than a placebo.

Most patients not prescribed medications and would not benefit if they were

Such findings suggest that on these grounds treatment choice for patients seeking abstinence might be weighted towards acamprostate, those seeking to control their heavy drinking, towards naltrexone. However, slight 'on average' indications emerging across thousands of patients are a minor consideration in respect of an individual. Beyond medical contraindications, there is [no evidence-based way](#) to tell which drug will work best for an individual patient, or if any will help at all. Even on the drinking outcomes most suited to each of the drugs, the featured analysis estimated that 1 in 7 or 1 in 8 trial participants would not benefit more than when prescribed an inactive placebo. The proportions found in [another review](#) were slightly less favourable: acamprostate prevented 1 patient in 12 and naltrexone 1 in 20 returning to drinking, and naltrexone also prevented 1 in 12 returning to heavy drinking, while health improvements remained unclear. Fortunately, the fact that these medications can safely be prescribed and, in their oral forms, easily terminated, paves the way for a trial error approach to identifying who benefits (if at all) from which medication – not unusual in medical practice.

Beyond relative impacts on different drinking outcomes are practical considerations such as needing to remember to take acamprostate three times a day, and naltrexone's interference with the effects of opiate-type drugs – a bonus perhaps for patients also seeking to end their dependence on these drugs, but not for those who are or may soon be in need of [opioid](#)-based pain relief.

Though medication usage has been increasing, in Britain treatment for alcohol dependence usually consists entirely of advice and psychosocial support. Drugs are almost universally used to ease withdrawal in inpatient units, but in 2013/14 in England, of the 101,782 drinkers treated in non-residential community settings, [just 16% were prescribed](#) a medication, with acamprostate far in the lead. [In England in 2015](#) disulfiram was dispensed 52,466 times but acamprostate 139,193 times. [Among the general population](#) in England in 2014, a quarter of adults whose scores on the [AUDIT screening questionnaire](#) for risky drinking indicated probable dependence were receiving treatment and services for a mental or emotional problem, but treatment for drinking as such was much rarer. Just 6% said they were being prescribed a medication intended to treat substance misuse and about the same proportion said they were receiving substance misuse counselling.

Relegation of medications to a minority option reflects their generally minor effects relative to the other influences which together constitute the 'placebo effect' seen in trials. For this 'disease', medications usually add little (but on average, *do* add a little) to the patient's impetus to get better, the processes in their life which help them realise and sustain this ambition, and the impact of deciding to enter and get actively engaged in treatment, one manifestation of which is regularly taking medication. As a result, across relevant trials, improvements in drinking among patients randomly allocated to an inactive placebo [on average dwarf](#) estimates of the additional effects of medications. Disulfiram, which causes aversive reactions if the patient drinks, is a partial exception; in the special circumstances when doses can be and are effectively supervised to make sure pills are taken, [effects verge](#) on what is conventionally considered large.

With or without psychosocial therapy?

Whether acamprostate and naltrexone are most effective when accompanied by psychosocial therapy as well as medical care was addressed in the featured analysis by excluding the few trials which did not provide therapy. For both drugs, impacts on abstinence and a composite of heavy drinking and craving fell slightly. The implication is that in the remaining trials which did not provide therapy, impacts were greater than in those which did. With so few non-therapy trials, little reliance can be placed on this finding, but it does suggest that neither medication needs therapy to succeed, and that they may have their greatest impacts when not overshadowed by effective psychosocial approaches.

In respect at least of naltrexone, the suggestion that it makes its greatest contribution in the absence of psychosocial therapy emerged from the large-scale US 'COMBINE' study. It tested acamprostate, naltrexone, and both together against a placebo, and at the same time tested whether adding psychological therapy boosted results from medical care. Therapy elevated placebo drinking outcomes to match the most effective medication, but without therapy, naltrexone elevated outcomes to about the same degree. When patients were offered psychosocial therapy, neither medication nor the two together augmented outcomes relative to a placebo. A similar message emerged from [another US study](#) which used the typical 50mg a day dose of naltrexone rather than COMBINE's 100mg. In line with these findings, a [review](#) which confined itself to studies offering minimal psychosocial support recommended both oral naltrexone and acamprostate (and also topiramate and, given supervised consumption and motivated, abstinent patients, disulfiram). Only brief support to promote compliance with treatment was recommended.

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Reviewers generally evaluate only whether therapy raises the performance of medications relative to the same therapy accompanied by a placebo. However, patients and doctors are probably more concerned with whether a patient is doing well in *absolute* terms, rather than whether they are doing better than they would have done if prescribed a placebo. Despite [contrary findings](#) from some trials, it remains possible that in terms of absolute improvements, supplementing medication with therapy will gain the best outcomes for a patient.

Thanks for their comments on this entry in draft to [Jonathan Chick](#), medical director at Castle Craig Hospital in Scotland. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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