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Acamprosate for alcohol dependence: a sex-specific meta-analysis based on individual patient data.

Mason B.J., Lehert P.

Alcoholism: Clinical and Experimental Research: 2012, 36(3), p. 497–508.

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The first comprehensive analysis of whether acamprosate treatment works as well for alcohol-dependent women as for men definitively concludes that across 22 mainly European trials it has had a virtually identical impact. The analysis also reports the drug's overall impact, finding that it helps prevent heavy drinking as well as fostering abstinence.

Summary Traditionally alcohol dependence has been seen as a man's disease, and much of our understanding derives from studies largely of men. In particular, little is known about the efficacy of medications for alcohol dependence in women, including disulfiram, naltrexone, and acamprosate.

The featured analysis addresses this gap in respect of acamprosate, an oral prescription medication for the maintenance of abstinence in individuals with alcohol dependence. Acamprosate normalises neurotransmitter systems disrupted when alcohol-dependent individuals stop drinking, helping prevent this disruption from prompting relapse. In 23 trials in 18 countries which randomly allocated over 6000 patients to placebo or acamprosate, the drug has been shown to significantly increase the rate of abstinence relative to placebo without causing serious adverse effects. It is the most widely prescribed alcohol dependence medication in the United States.

However, only 22% of participants in acamprosate trials have been women, and outcomes have not been reported separately across these trials for men versus women, leaving it unclear whether the drug is equally effective and safe for both sexes.

The featured analysis searched for high quality trials available up to February 2011 which had randomly allocated patients to placebo or acamprosate. They had to have hidden this allocation from both patients and research assessors and reported impacts on some measure of drinking. The search included as yet unpublished trials and a request for trial data from the drug's developers.

Of the 22 such studies of adult patients, 17 had been conducted in Europe including one from the UK. In all, the trials involved 1317 women patients and 4794 men. Typically the trials excluded patients suffering significant psychiatric or medical disorders or dependent on other substances except tobacco. In all but three trials patients had to have stopped drinking for at least two days before being allocated to their medications. As well as medications, generally they received the alcoholism counselling offered at the participating clinics.

Compared to the men, the women in these trials were significantly more likely to be divorced or widowed and to also have suffered from drug abuse, anxiety, depression, and nonspecific psychiatric problems, and 22% versus 13% had attempted suicide. Despite being alcohol dependent for fewer years and drinking less, women exhibited significantly worse signs of impaired liver functioning.

Main findings

Outcomes were amalgamated across the trials using meta-analytic techniques. In analysing drinking outcomes, patients who had left trials early were considered to have been drinking through to the end of the trial unless the reason was clearly unrelated, such as moving out of the area. In general, relative to placebo the results showed acamprosate to have curbed drinking and heavy drinking about equally and to have caused no more adverse effects in women versus men.

Specifically, compared to placebo (average 43% days abstinent) acamprosate led to an extra 10% of days of non-drinking. Across placebo and acamprosate patients, women and men were abstinent on virtually the same proportions of days (48% and 47%), and the extra impact of taking acamprosate was about the same for both sexes (11% for women and 10% for men). Similarly, the 19% of placebo patients who sustained non-drinking throughout the trials was improved to 28% by acamprosate and improved roughly equally among women (from 17% to 25%) and men (from 19% to 28%).

Days when patients had drunk 'heavily' were defined as consuming at least 56g alcohol (seven UK units) for women and at least 70g (about nine UK units) for men. Across the trials placebo patients managed not to drink heavily on 53% of days, a figure improved by 11% by acamprosate. The extra impact of taking acamprosate was about the same among women (increased from 55% to 65%) and men (52% to 62%). Results were similar for the proportions of patients who avoided heavy drinking altogether, increased among women from 15% on placebo to 24% on acamprosate, and among men from 32% to 43%.

Compared to placebo, across both sexes acamprosate was associated with significantly higher rates of treatment completion (56% v. 52%) and compliance with taking medication (76% v. 72%). Acamprosate patients were no more likely than placebo patients to experience adverse events (and in particular, gastrointestinal, the main type associated with acamprosate) or as a result to leave the trials, and this was equally the case for women and men. However, across placebo and acamprosate patients, women reported significantly more at least moderately severe adverse events than men – 28% v. 20%.

Impacts of acamprosate on drinking outcomes varied substantially across the trials, particularly among male patients.

The authors' conclusions

The analysis shows that, compared to a placebo, acamprosate significantly improves rates of abstinence and no heavy drinking in both women and men with alcohol dependence, and also leads to significantly more patients completing treatment and taking their medication as intended. Women and men tolerated the drug equally well. The implication is that treatment providers may routinely consider acamprosate for treating alcohol dependence in both women and men, taking into account the patient's treatment goals and preferences as well as safety considerations specific to that individual.

In this, the largest trial-based dataset of women seeking treatment for alcohol dependence to date, despite a history of significantly more anxiety, depression, suicide attempts, drug abuse, interpersonal loss, and greater liver impairment than men, women responded comparably well to alcoholism treatment.

The results of this analysis are likely to be applicable to routine clinical practice because generally the clinics' routine counselling was provided and patients entered treatment in the normal way. However, some categories of patients were excluded. Selection of only rigorous trials suggests the amalgamated results can be relied on. However, results did vary substantially across the trials. Causes of this variation may include the recruitment of non-dependent patients to one of the trials, among whom acamprosate would not have been able to exert its normalising impact on neural systems because these would not have been disrupted by dependence and withdrawal; this trial was the only to have found acamprosate counterproductive among women. Similarly, results of a British trial which found negative effects of acamprosate among men could have been due to the recruitment of patients who were still drinking when they started treatment, so were yet to experience the neural disruption which acamprosate helps reverse.

FINDINGS The distinctive contribution of the featured analysis is to definitively confirm that on the evidence to date, alcohol-dependent women seeking treatment respond as well to acamprosate as men. In both sexes it typically made a modest but worthwhile contribution to

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sustaining abstinence and avoiding heavy drinking.

The analysis also offers a valuable update on the overall effectiveness of acamprosate across the sexes. With respect to abstinence, the results accord with a review conducted for the Cochrane Collaboration. This found that across all trials acamprosate reduced the risk of a return to drinking after detoxification to 86% of the risk with a placebo and increased the average time patients sustained abstinence by 11%. However, results differed in respect of heavy drinking. In the Cochrane analysis, across the six trials which yielded this data acamprosate made virtually no difference to the proportion of patients who returned to heavy drinking, though across seven trials, a biochemical marker indicative of heavy drinking was lower on acamprosate than on placebo, a finding which just failed to reach statistical significance. In contrast, with many more trials (about 20) to draw on, and a uniform and more precise definition of heavy drinking as excessive consumption on a single day, the featured analysis did find a significant improvement with acamprosate about as large as that found for the abstinence outcomes.

The Cochrane analysis agreed with the featured analysis that patients on acamprosate were slightly less likely (9% fewer) to drop out of treatment, but did find they were much more likely (35% more) to drop out early due to side effects and other adverse events, of which diarrhoea was the only one reported significantly more often on acamprosate. However, the numbers involved were generally few and the great majority of patients on either acamprosate or placebo completed the early phases of treatment.

The featured analysis attributes acamprosate's poor record in the major British trial to patients not having stopped drinking when they started the medication. Indeed, nearly a third of patients did not remain abstinent for the week before being randomised into the study, a requirement in some other studies. Outcomes in the British study may also have suffered from not starting the drug in the immediate post-withdrawal period, when theory suggests its effectiveness should be at its height, the reason why UK guidance stipulates that acamprosate should be started "As soon as possible after assisted withdrawal". Also, many of the patients were episodic heavy drinkers and high drop-out and non-compliance rates meant that just a third of the sample completed the study, and by the end fewer than 30% were taking at least 90% of their tablets.

In contrast, in the major UK naltrexone trial, patients who completed the study and largely complied with treatment drank substantially less on naltrexone than on placebo tablets. One lesson from both trials 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.

UK policy and practice

On the basis of the evidence, acamprosate, disulfiram and naltrexone are all endorsed in national guidance for Scotland and England and Wales. The guidance envisages a more routine and/or first-line post-detoxification role for acamprosate than for disulfiram, the latter coming with the caution that total abstinence is required to avoid unpleasant and potentially dangerous reactions, and that the positive evidence derives from situations where consumption has been supervised. Naltrexone is seen as fulfilling a similar role to acamprosate, but at the time the guidance was drafted it had no UK licence for the treatment of alcohol dependence, so the Scottish advisers felt they could not commend it for use in the NHS.

Statistics for England in 2012 show that doctors in general have forefronted acamprosate, prescribed 117,405 times compared to 60,842 for disulfiram, figures dominated by GP prescribing. However, in hospitals disulfiram is prescribed slightly more often. In these settings patients are likely to be so severely dependent that at least initial abstinence is the preferred objective, and there is the support for patients and the expertise to handle the risks of prescribing disulfiram.

For more on alcohol treatment medications see these Findings analyses of an omnibus review, and of reviews focused on acamprosate and the main alternative, naltrexone. Another review has focused on disulfiram, a different type of medication which aims not to help patients cut back but to enforce abstinence due to the aversive effects of drinking while the drugs is active in the body.

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