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. The summary conveys the findings and views expressed in the review. Below is a commentary from Drug and Alcohol Findings.

▶ Acamprosate for alcohol dependence.

Rösner S., Hackl-Herrwerth A., Leucht S. et al.

Cochrane Database of Systematic Reviews: 2010, 9. Art. No. CD004332.

The first review from the prestigious Cochrane collaboration of the drug acamprosate as a treatment for alcohol dependence finds clear evidence that it offers worthwhile if modest benefits in preventing a return to drinking after detoxification.

SUMMARY Especially in Europe, acamprosate is one of the most widely used medications to prevent relapse to drinking or heavy drinking among alcohol dependent patients. Taken orally three times a day, the drug ameliorates the symptoms of alcohol withdrawal and helps prevent drink-related cues arousing reactions which could leads to relapse. It also makes drinking less pleasurable, potentially helping to prevent lapses becoming relapses. In these ways it might reinforce psychosocial relapse-prevention programmes. To assess its effectiveness and acceptability to patients, this review used meta-analytic techniques to combine results from the most methodologically advanced types of studies which compared acamprosate against either an inactive placebo or against an alternative treatment. The studies had to report drinking-related outcomes, to have allocated patients at random to the treatments being compared, and to have ensured that neither patients nor researchers knew who was being prescribed acamprosate.

The search for these trials was undertaken in January 2009 and included a request to drug manufacturers and researchers for unpublished trials. In all 24 trials were found with 6915 participants. Generally patients had been withdrawn ('detoxified') from alcohol and been abstinent for several days before acamprosate and its comparator treatment started. These treatments lasted for up to a year, though usually for no more than six months. Nineteen of the 24 trials were conducted in Europe and 17 were organised or resourced by pharmaceutical companies which manufactured acamprosate.

Main findings

Across all relevant 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%, both statistically significant advantages which (with some fading) persisted three to 12 months after treatment ended. However, in 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 had been prescribed acamprosate and placebo. 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. Patients on acamprosate were slightly less likely (9% fewer) to drop out of treatment, but 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. All but one outcome differed considerably across the trials, indicating that the impacts of the drug are not uniform but depend on the particular mix of treatments and patients. Whether the study was sponsored by a pharmaceutical company made no difference to the outcomes.

Next the analysts compared acamprosate not to an inactive placebo, but to an alternative anti-relapse medication, naltrexone, normally taken orally once a day. Depending on the outcome being assessed, just one to three trials contributed data to these analyses. There were no statistically significant differences in the proportion of patients who returned to drinking or to heavy drinking, nor in how long on average patients sustained abstinence. Acamprosate was associated with a higher risk of diarrhoea than naltrexone, while patients on naltrexone more often experienced nausea, fatigue, somnolence and vomiting. In line with this greater range of side effects, more patients dropped out early on naltrexone due to adverse effects but the difference with acamprosate was not statistically significant and nor was it in respect of the overall drop-out rate. Across the two trials to look at this, acamprosate combined with naltrexone led about 30% fewer patients to return to drinking or heavy drinking than when prescribed an inactive placebo, but the results were not statistically significant.

The authors' conclusions

Primary outcomes (the proportion returning to drinking and how long before patients did so) clearly support the abstinence-promoting properties of acamprosate compared to placebo when both supplement psychosocial therapies. Even though the magnitude of the added benefits is moderate, they should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options available for its treatment. Variability in impacts across trials indicates that factors as yet to be understood affect the degree of benefit from the drug. In the post-treatment evaluations in 10 trials, impacts were diminished but still statistically significant three to 12 months after the end of treatment. Acamprosate was shown to be safe to use and well tolerated by patients; side effects led no more often to an early termination of treatment than on a placebo. Though impacts on heavy drinking were not statistically significant, abstinence is the main outcome sought by prescribing the drug. Too few studies are available to be definitive about the relative advantages of naltrexone and acamprosate or the combination of the two compared to placebo.

FINDINGS COMMENTARY It is a concern that 70% of the trials might have been influenced by acamprosate's manufacturers. However, the amalgamated magnitude of the effect of the drug on a return to drinking was very similar regardless of the manufacturers' involvement. It was marginally highest when the manufacturer had helped resource the trial but not actually organised it, lowest when they had organised it, while in between were independent trials instigated by the researchers and funded on a non-profit basis.

Drinking patterns differ somewhat between Britain and parts of mainland Europe where most of the acamprosate trials were conducted. Without being conclusive either way, the 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. Details in background notes of an earlier Effectiveness Bank analysis.

The featured review usefully complements clinical guidelines drawn up by a panel of experts convened by the US health department on how the four US-approved medications (including acamprosate and naltrexone) can be incorporated in to medical practice. UK health care professionals have also developed clinical guidance on managing alcohol problems based on a review of British and international official guidance and major systematic reviews and research syntheses. All available medications are best seen as helping to create a relatively intoxication-free space during which patients can be helped to find other ways to cope and to construct lives incompatible with a return to heavy drinking.

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