Acamprosate and naltrexone, individually or in combination, for the treatment of alcohol dependence
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The findings of the COMBINE Study have recently been published (Anton et al 2006). The COMBINE Study is a major, multisite RCT of acamprosate and naltrexone in conjunction with behavioural treatment. As such this study has the potential to significantly influence treatment of alcohol dependence. This brief critical appraisal of the COMBINE Study has been prepared to assess its implications in terms of the overall effectiveness of acamprosate and naltrexone for the treatment of alcohol dependence.

The COMBINE Study
The design of the COMBINE Study is complex. There were 9 study groups in total. Four of these groups received medication (naltrexone, acamprosate, naltrexone-acamprosate combination or placebo) in combination with medical management. Another four groups received medication in combination with medical management plus combined behavioural intervention. The ninth group received only the combined behavioural intervention and was a control for the placebo effect of medication. This complexity of design makes the results difficult to interpret. The authors report results as 2- and 3-factor interactions, adjusting for study site and baseline data, all of which makes it difficult to assess exactly what effect the medications and behavioural interventions are having.

A potential confounding factor is that there was significant contact time with all study participants. The research interviews were extensive – 2-hour research assessments occurred at weeks 8 and 16 during treatment, and the baseline assessment was longer. The medical management intervention delivered in conjunction with medication was itself a significant intervention – it entailed 9 sessions over the 16 weeks of treatment, with the initial session lasting 45 minutes and subsequent sessions 20 minutes each. Sessions reviewed the negative consequences of drinking, developed a medical adherence plan, supported attendance at community groups such as AA, and reviewed drinking and problems with medication. The combined behavioural intervention (CBI) comprised up to 20 sessions of 50 minutes each over the 16 weeks of treatment and integrated cognitive behavioural therapy, 12-step facilitation, and motivational interviewing.

All groups showed improvement over the study period. The group with the worst outcomes received CBI only indicating a placebo effect was present. The conclusion from the study was that medical management (MM) with naltrexone, CBI, or both resulted in better drinking outcomes, whereas acamprosate showed no evidence of efficacy, with or without CBI.

COMBINE findings in relation to other studies
The finding from the COMBINE Study that acamprosate provides no benefit over placebo is unexpected. To try to make sense of the findings, it was considered along with data from previous studies. The existing research evidence of the effectiveness of naltrexone and acamprosate is summarised in DASSA Monograph No 17 (Gowing LR, 2005. Pharmacotherapies for Relapse Prevention in Alcohol Dependence. Available from http://www.dassa.sa.gov.au). The meta-analyses included in this publication have been repeated, with data from the COMBINE Study incorporated to assess the impact of the additional data. It should be noted that these meta-analyses are two-way comparisons of medication and do not take account of the nature of psychosocial support. Data from the MM and MM+CBI groups were combined for incorporation into the meta-analyses.

1. Naltrexone compared with placebo
The meta-analyses show that treatment with an opioid antagonist is associated with a significantly longer time to relapse. The COMBINE Study found this to be the case for those receiving
naltrexone without CBI, but not for those receiving naltrexone with CBI. (Data from the COMBINE Study was reported as hazard ratios – these data were not able to be incorporated into the meta-analyses.)

With the incorporation of the data from the COMBINE Study, there remains no significant difference in the proportion of participants treated with an opioid antagonist or placebo who experience any adverse effect, while specific adverse effects of gastrointestinal symptoms, nausea or vomiting, headache or neuropsychiatric symptoms remain significantly higher with opioid antagonist compared to placebo.

The proportion treated with an opioid antagonist requiring a dose reduction is significantly greater relative to placebo with the COMBINE Study data incorporated. It is interesting to note that naltrexone was used in the COMBINE Study at doses of 100mg/day, whereas most previous studies used 50mg/day. The rationale for the higher dose was that it might provide greater protection against the effects of missed doses. The average dose of naltrexone administered was 88mg/day.

Significantly more people treated with an opioid antagonist withdrew from treatment because of adverse effects, compared to those receiving placebo. With the COMBINE Study data incorporated the difference is equivalent to an NNT of 20, indicating that for every 20 people treated with an opioid antagonist, one can be expected to discontinue treatment prematurely because of adverse effects. However, it appears that in the COMBINE Study, adverse effects were largely managed with dose reductions thereby minimising the rate of withdrawal from treatment due to adverse effects.

In the COMBINE Study 2% of those treated with naltrexone, and none of those receiving placebo, had liver enzymes that were at least 5 times the upper limit of normal during the study.

The most effective form, and intensity, of psychosocial support as an adjunct to naltrexone treatment for alcohol dependence remains very unclear.

2. Acamprosate compared with placebo

The COMBINE Study found no significant difference between acamprosate and placebo in terms of the risk of relapse to heavy drinking and the percent days of abstinence during the treatment. However, with data from the COMBINE Study entered into meta-analyses, there remains a significant differences favouring acamprosate. For relapse to heavy drinking the NNT is 17, indicating that for every 17 people treated with acamprosate, one less person will relapse during treatment. For cumulative abstinence the combined result is now 13.37% days, indicating that those treated with acamprosate will be abstinent on 13% more days of treatment than those receiving placebo.

There are now three studies, including the COMBINE Study, reporting dose reductions to manage adverse effects. There are significantly more dose reductions with acamprosate than placebo. The COMBINE Study data also confirms that diarrhoea or other gastrointestinal effects are significantly more likely with acamprosate than placebo (NNT=10), and those treated with acamprosate are significantly more likely to withdraw from treatment because of adverse effects. However, this latter difference is not clinically significant (NNT=50) suggesting that the adverse effects are generally able to be managed with dose reductions or other strategies. Again the COMBINE Study used higher doses of acamprosate (3g/day whereas previous studies generally used 2g/day). The average dose actually administered was 2537mg/day.

Other studies have suggested that the type of psychosocial program provided in conjunction with acamprosate does not influence the outcome. It has been suggested that acamprosate may be more
effective in people with non-familial alcohol dependence. The proportion of participants with non-familial dependence was not reported for the COMBINE Study.

3. Acamprosate compared with naltrexone

Data from the COMBINE Study strengthens the conclusion that there is no significant difference between acamprosate and naltrexone in terms of rates of completion of treatment.

There are now three studies comparing rates of relapse to heavy drinking for acamprosate compared with naltrexone. In one of these studies (Rubio et al 2001) relapse is significantly more likely with acamprosate. The combined result marginally favours naltrexone but is not statistically significant.

Compared to naltrexone, those treated with acamprosate experience significantly less nausea but significantly more diarrhoea (NNT=4) – this conclusion is strengthened with the inclusion of the COMBINE Study data.

The COMBINE Study (both the pilot and full studies) found no significant difference between acamprosate and naltrexone in the proportion of participants needing a reduction of medication dose to manage adverse effects.

4. Acamprosate-naltrexone combination

The results of the COMBINE Study strengthen the conclusion of no significant difference in rates of completion of treatment for the combination treatment compared with placebo, acamprosate alone, or naltrexone alone.

The one prior study of the acamprosate-naltrexone combination (Kiefer et al 2003) found significantly less relapse to heavy drinking with the combination treatment compared with placebo. However, this positive finding was not reproduced by the COMBINE Study, and when the COMBINE Study data are entered into a meta-analysis there is no significant difference overall between combination therapy and placebo in terms of rates of relapse to heavy drinking.

Similarly the differences between relapse rates for combination treatment and acamprosate alone and combination treatment and naltrexone alone are not significant. This indicates that acamprosate does not add to the effectiveness of naltrexone in prevention of relapse to heavy drinking.

The COMBINE Study findings indicate that relative to placebo:

- significantly higher risk of nausea with combination (NNT=6);
- significantly higher risk of diarrhoea with combination treatment (NNT=5) and
- significantly more participants treated with the drug combination require dose reductions (NNT=8).

In addition, significantly more participants treated with the drug combination withdrew from treatment because of adverse effects, but with an NNT of 33 this difference is not clinically significant – it appears the adverse effects are largely able to be managed with dose reduction.

For the combination treatment relative to acamprosate alone:

- significantly more nausea with the combination (NNT=6);
- significantly less diarrhoea (NNT=13)
- significantly more participants treated with the drug combination require dose reduction (NNT=13)

- but there is no significant difference in the proportion discontinuing treatment because of adverse effects.

For the combination treatment relative to naltrexone alone:
• nausea is somewhat more frequent with the combination treatment, but the difference is not statistically significant;
• significantly more diarrhoea with the combination (NNT=4)
• significantly more participants treated with the drug combination require dose reduction (NNT=11)
• but no significant difference in the proportion discontinuing treatment because of adverse effects.

Summary
The COMBINE Study does not change the conclusion that both acamprosate and naltrexone are effective in the treatment of alcohol dependence. More data is needed to form a view of the relative effectiveness of these two medications.

The COMBINE Study does raise some doubt as to the value of combining naltrexone and acamprosate because of the increase risk of adverse effects and apparent lack of additional benefit. However, given the positive findings of previous studies, there would be value in additional research to confirm this outcome.

Particular areas of research need are the significance of different types and intensities of psychosocial support as adjuncts to medication, and the type and severity of alcohol dependence as factors that might influence the effectiveness of treatment.

References
