Meta-Analyses of Placebo-Controlled Trials of Acamprosate for the Treatment of Alcohol Dependence

Impact of the Combined Pharmacotherapies and Behavior Interventions Study

George Dranitsaris, MPharm, Peter Selby, MD, and Juan Carlos Negrete, MD

Objectives: The Combined Pharmacotherapies and Behavior Interventions Study (COMBINE) reported no significant difference between acamprosate and placebo in the treatment of alcohol dependence. To evaluate the impact of COMBINE, we performed a meta-analysis of acamprosate placebo-controlled trials with the inclusion of data from COMBINE. As a secondary analysis, we added the COMBINE data to a recently published meta-analysis of naltrexone placebo-controlled trials.

Methods: A structured literature search of major databases was performed from January 1990 to August 2007 for acamprosate placebo-controlled randomized trials. Mean differences in cumulative abstinence days (CAD) and abstinence rates (AR) from eligible studies were statistically combined to calculate point estimates and 95% CI for differences in CAD and AR.

Results: Ten and 16 studies evaluating CAD and AR, respectively, were suitable for statistical pooling. The findings revealed that acamprosate was superior to placebo in the mean number of CAD ($P < 0.001$) and AR (pooled AR = 1.58; $P < 0.001$). The pooled AR for naltrexone was also significant indicating a relative benefit over placebo (AR = 1.27; $P < 0.001$). The COMBINE trial results contributed a weight of less than 15% to the final pooled statistical outcomes for both agents.

Conclusions: The current study confirmed that acamprosate and naltrexone are both effective agents for the treatment of patients with alcohol dependence. Systematic reviews with meta-analyses of randomized controlled trials and randomized controlled trials with adequate sample sizes are in the same (highest) level of evidence. Therefore, clinicians should use both these sources of information as their foundation for selecting optimal therapy for patients with alcohol dependence.

Key Words: alcohol dependence, acamprosate, naltrexone, meta-analysis

Alcohol dependence is a global problem. In the United States alone, it has been estimated that over 700,000 people receive treatment for this condition. Alcohol abuse and dependence in the United States accounts for the loss of 100,000 lives per year, and alcohol is implicated in 30% of all traffic fatalities. The misuse of alcohol also has a substantial impact on the economy. In one study from the United States, the economic cost of alcohol abuse and dependence was estimated to be more than $184 billion in 1992 dollars.

In Canada, alcohol abuse accounts for approximately $7.52 billion in costs, including $4.14 billion for lost productivity, $1.36 billion for law enforcement, and $1.30 billion in direct health care costs. Therefore, any intervention that effectively reduces the incidence of alcohol dependence will have a major impact on societal costs.

Psychological counseling and 12-step inspired treatment programs have been the mainstay of alcohol dependence clinical management, whereas pharmacologic agents have mostly played an adjunctive role. However, there is a growing body of evidence supporting a more central role for medications in the treatment of alcohol dependence. To date, 3 medications—disulfiram, naltrexone, and acamprosate—have approved indications for the treatment of alcohol dependence in the United States and Europe. Disulfiram carries the risk of toxicity and is contraindicated in many patients. Naltrexone is an opioid antagonist and therefore cannot be used in patients who require opiate therapy; and may also be contraindicated in some patients with significant liver damage. Acamprosate does not undergo metabolism in the liver and is eliminated unchanged through the kidneys. Therefore, it is contraindicated in cases of severe renal insufficiency. However, in patients with moderate renal impairment (creatinine clearance of 30–50 mL/min), a reduced dose may be safely administered.
The effectiveness of both naltrexone and acamprosate in the treatment of alcohol dependence has been amply demonstrated in a number of randomized placebo-controlled trials. Two separate meta-analyses confirmed that both agents reduce relapse rates and promote continuous abstinence from alcohol. In the meta-analysis by Mann et al., the number of patients that need to be treated (NNT) with acamprosate to maintain abstinence was also estimated. At 6 and 12 months, the pooled difference (vs placebo) in success rates were 12.8% (95% CI: 8.2–16.6%) and 13.3% (95% CI: 7.8–18.7%), respectively. Therefore, the NNT to maintain abstinence at 6 and 12 months was reported to be 7.8 and 7.5. Similarly for naltrexone, the NNT to maintain abstinence at a 3 month evaluation period was reported to be 10.

One of the most important double blind placebo-controlled trials conducted to date was the study by Anton et al (2006), which compared acamprosate (3 g daily), naltrexone (100 mg daily), combined behavioral therapy (CBT), various combinations of the former 3 and CBT alone to placebo [The Combined Pharmacotherapies and Behavior Interventions Study (COMBINE) trial]. There were a total of 9 groups in the study with approximately 150 patients per group and all patients received standard medical management for alcohol dependence. The primary endpoints were percent days abstinent and time to the first heavy drinking episode (ie, ≥4 drinks/d for women and ≥5 drinks/d for men). The study duration was 16 weeks with a 1 year follow up. Logistic regression models with planned interaction effects were used to compare each treatment (alone or in combination) to placebo. At the 16-week time point, the overall effect size for percent days abstinent and the hazard ratio for return to heavy drinking (relative to placebo) was statistically significant only for the naltrexone alone group. The findings from patients randomized to CBT or acamprosate groups were not statistically significant.

The negative findings for these treatments from the COMBINE trial are intriguing. In an accompanying editorial to the study publication, it was suggested that patients were highly selected and all were provided with incentives (not routinely done in practice) such as taxi reimbursement, baby sitting arrangements, and weekend or holiday appointments to remain in the study. This resulted in uncharacteristically high treatment compliance rates (ie, 84%) and patient retention rates by the end of the trial (eg, 94% at 16 weeks and 82% at 1 year). Therefore, it was suggested that the findings may not be generalizable to the routine clinical setting. Furthermore, the intense nature of patient follow up in all groups may also have contributed to a “ceiling effect” in treatment efficacy with placebo. Last and most importantly, the COMBINE trial may not have been designed to favor acamprosate from the outset; patients had to be abstinent from alcohol for up to at least 4 days and no more than 21 days before entry. Evidence from clinical trials suggests that acamprosate “works best” when given as soon as possible after withdrawal from alcohol.

Notwithstanding these issues, it is important to evaluate the impact of the COMBINE trial results on the overall pooled efficacy data for pharmacotherapy. The primary objective of the current study was to perform a meta-analysis of acamprosate placebo-controlled trials with the inclusion of data from COMBINE. To provide a balanced perspective, the secondary objective was to assess the impact of the COMBINE trial on published pooled efficacy data for naltrexone. The final objective was to undertake a meta-analysis of randomized trials that directly compared acamprosate to naltrexone for the treatment of alcohol dependence.

METHODS

Literature Review and Meta-Analysis of Randomized Trials

A computer literature search of PubMed, Embase, the Cochrane Database, and Google Scholar was conducted from January 1990 to September 2007 for published randomized studies comparing acamprosate to placebo. Eligibility criteria were used to identify relevant acamprosate trials. To be included, studies must have used a randomized design, been published in a peer-reviewed journal and subjects must have been patients diagnosed with alcohol dependence or abuse according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders—III or IV. A second literature search was performed for randomized trials that directly compared acamprosate to naltrexone. Care was taken to avoid inclusion of duplicate publications.

The following data were extracted from accepted studies: drug, dose, administration frequency, data collection methods, definition of primary and secondary study outcomes, duration of therapy, compliance to treatment, number of withdrawals caused by adverse drug reactions, and all relevant clinical outcomes. The outcomes of primary interest for statistical pooling were the cumulative number of days abstaining from alcohol, abstinence rates (AR), relapsing to heavy drinking, and mean days to first relapse to heavy drinking. In the COMBINE trial, the primary endpoint (ie, percent days abstinent) was converted into cumulative abstinence days over the treatment and follow-up period.

Statistical Analysis

For cumulative abstinence days and mean days to first relapse to heavy drinking (continuous data), standardized mean differences (SMD) between comparators were estimated. Binary outcomes (ie, AR) were combined using a random effects model in cases of significant heterogeneity. Random-effects meta-analysis assumes that the effect of the intervention varies across studies. When significant between study variation is present, the 95% CI for the summary measure tends to be larger with a random-effects model.

Statistical heterogeneity between studies was assessed by both the Q-statistic and the I² test statistic. Briefly, the I² statistic measures the proportion of variance across studies due to heterogeneity. It is considered to be a superior measure of study heterogeneity than the Q-statistic because the latter is often underpowered when evaluating homogeneity in meta-analyses. The P values associated with the Q-statistic (χ² with k – 1 df, where k is the number of studies) were also reported. In situations where the Q-statistic was statistically

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significant and the $I^2$ statistic was greater than 25%, a random effects meta-analysis model was used. Publication bias was assessed through an evaluation of funnel plots and by the method proposed by Egger, which provides a significant $P$ value when publication bias may be present.\textsuperscript{18,19}

After the completion of the acamprosate statistical pooling exercise, a cumulative meta-analysis was performed whereby trial data was sequentially added by year of publication. The advantages of conducting a cumulative meta-analysis includes the ability to assess changes in the summary measure when one suspects differences in the treatment, procedures, or patients over time.\textsuperscript{20} Finally, to identify individual trial characteristics that could have contributed to heterogeneity between studies, a meta-regression analysis was conducted. All of the statistical analyses were performed using Stata, V9.0 (Stata Corp., College Station, TX).

**RESULTS**

**Impact of the COMBINE Trial on Overall Efficacy for Acamprosate**

Overall, 196 citations were reviewed for eligibility and 19 randomized trials published in peer reviewed journals were potentially appropriate. One trial was excluded due to duplication of data. One other trial, even though it met the inclusion criteria, did not provide the necessary point estimates and measures of variance required for the meta-analysis. In addition, a third trial was a head to head comparison between acamprosate and naltrexone but without a placebo-control group. Therefore, a total of 16 randomized placebo controlled trials including COMBINE met the inclusion criteria and provided the required data for statistical pooling (Table 1).

Ten of these trials provided data for estimating the pooled mean difference in cumulative abstinent days (CAD) whereas all 16 provided the data for the pooled AR. The 2 main endpoints were statistically pooled and both were significantly in favor of acamprosate over placebo. The pooled SMD in CAD and AR between acamprosate and placebo was 0.24 ($P < 0.001$) and 1.58, respectively (95% CI = 1.35–1.84; $P < 0.001$). For both of these endpoints, the inclusion of the original data from COMBINE (Anton et al, 2006) had only a marginal effect on the pooled mean difference in CAD and AR (Figs. 1 and 2). Acamprosate remained significantly more effective than placebo in both of these 2 important clinical measures of drug treatment benefit. In the case of AR,

**TABLE 1. Randomized Trials Comparing Acamprosate to Placebo in the Treatment of Alcohol-Dependent Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Design</th>
<th>Intervention</th>
<th>Relevant Outcomes</th>
<th>Results (SD)</th>
</tr>
</thead>
</table>
| Ladewig\textsuperscript{34} | A = 29  
$P = 32$ | Double blind  
trial × 6 mo | A 1998 mg (if ≥60 kg) vs P | AR, CAD | A: AR = 12/29, P: AR = 7/32 |
| Paille\textsuperscript{35} | A = 361  
$P = 177$ | Double blind  
trial × 12 mo | A 2 g vs. A  
1.3 g vs. P | AR, CAD, TFD | AR: A = 45/361, P: AR = 16/177 |
| Whitworth\textsuperscript{36} | A = 224  
$P = 224$ | Double blind  
trial × 12 mo | A 1998 mg (if ≥60 kg) vs P | AR, CAD | TFD: A = 230 (259), P: CAD = 183 (235) |
| Sass\textsuperscript{38} | A = 136  
$P = 136$ | Double blind  
trial × 12 mo | A 1998 mg (if ≥60 kg) vs P | AR, CAD | TFD: A = 54/136, P: AR = 23/136 |
| Poldrugo\textsuperscript{37} | A = 122  
$P = 124$ | Double blind  
trial × 6 mo | A 1998 mg (if ≥60 kg) vs P | AR, CAD, TFD | AR: A = 53/122, P: AR = 37/124 |
| Geerling\textsuperscript{32} | A = 122  
$P = 124$ | Double blind  
trial × 6 mo | A 1998 mg (if ≥60 kg) vs P | AR, CAD | TFD: A = 168 (151), P: CAD = 120 (147) |
| Bess\textsuperscript{30} | A = 55  
$P = 55$ | Double blind  
trial × 12 mo | A 1998 mg (if ≥60 kg) vs P | AR, CAD | TFD: A = 44/55, P: AR = 3/55 |
| Chick\textsuperscript{31} | A = 289  
$P = 292$ | Double blind  
trial × 6 mo | A 1998 mg vs P | AR, CAD | TFD: A = 35/289, P: AR = 32/292 |
| Tempesta\textsuperscript{39} | A = 164  
$P = 166$ | Double blind  
trial × 3 mo | A 1998 mg vs P | AR, CAD, TFD | AR: A = 62/164, P: AR = 48/166 |
| Gual\textsuperscript{33} | A = 141  
$P = 147$ | Double blind  
trial × 6 mon | A 1998 mg vs P | AR, CAD | TFD: A = 155 (114), P: CAD = 127 (115) |
| Namkoong\textsuperscript{32} | A = 72  
$P = 70$ | Double blind  
trial × 2 mo | A 1998 mg (if ≥60 kg) vs P | AR, CAD | TFD: A = 48 (32), P: AR = 23 (16) |
| Blatieri\textsuperscript{41} | A = 40  
$P = 35$ | Double blind  
trial × 6 mo | A 1998 mg vs P | AR, CAD | TFD: A = 8/20, P: AR = 7/35 |
| Kiefer\textsuperscript{23} | A = 40  
$P = 40$ | Double blind  
trial over 12 wk | A 1998 mg vs P | AR at 12 wks | P: AR = 10/40 |
| Morley\textsuperscript{22} | A = 55  
$P = 61$ | Double blind  
| Anton\textsuperscript{13} | A = 152  
$P = 153$ | Double blind  
trial × 6 mo | A 3000 mg vs P | AR, CAD | A: A = 29/152, P: AR = 24/153 |

A, acamprosate; P, placebo; AR, abstinence rate; TFD, time to first drink.

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the overall pooled outcome was 1.58 suggesting that when all published trials were considered, patients randomized to acamprosate were 58% more likely to remain abstinent over the study period than those who received placebo. Despite being a fairly large trial (ie, approximate sample size per group was 150), the COMBINE study results contributed a weight of approximately 11% and 7% on the final pooled statistical outcomes for CAD and AR.

The potential for publication bias was then assessed. Asymmetry in the funnel plot was detected (figure not shown) and the $P$ value from the Egger test (ie, $P = 0.026$) indicated the possibility of publication bias. There was also modest heterogeneity between trials in the pooled AR as indicated by the $Q$ and $I^2$ statistic. To identify potential causes of the heterogeneity, a meta-regression analysis was performed. Independent clinical trial variables included in the regression model consisted of geographic region (Europe vs other), study size (≥100 vs <100 patients per arm), and duration (≤3 vs >3 to ≤6 vs >6 months). The 2 trial characteristics that had a statistically significant association with the AR consisted of study size and duration. Acamprosate trials with less than 100 patients in each arm tended to have lower reported AR, by approximately 39% ($\ln(\text{AR}) = -0.49; P = 0.015$) compared with trials with large sample sizes. In addition, trials with durations beyond 6 months tended to report higher ARs, by approximately 1.6-fold ($\ln(\text{AR}) = 0.48; P = 0.017$) compared with those of shorter duration. The affect of geographic region in which the trial was conducted not significantly associated with the reported AR.

As a final evaluation, a cumulative meta-analysis was conducted to assess changes in the pooled AR over time. The findings suggested that the effectiveness of acamprosate was evident from the initial trials and by the year 2000, the relative benefit over placebo in maintaining abstinence was established at approximately 50% (Fig. 3).

**Impact of the COMBINE Trial on the Overall Efficacy Data for Naltrexone**

Srisurapanont and Jarusuraisin recently published a meta-analysis of 7 randomized trials comparing naltrexone to placebo.\textsuperscript{10} For the endpoint relapse to drinking, which included heavy drinking, naltrexone was associated with a 36% relative risk (RR) reduction compared with placebo ($\text{RR} =$...
At the 12-month follow-up period in the COMBINE trial, Anton and colleagues reported that 121 of 154 patients (78.6%) in the naltrexone alone arm returned to heavy drinking compared with 129 of 153 patients (84.3%) in the placebo control group ($P < 0.001$). These data were then added to the original data reported by Srisurapanont and Jarusuraisin and a statistical pooling exercise was undertaken. To be consistent with the earlier analyses for acamprosate, the outcome that was statistically pooled was AR. Despite its considerable sample size relative to previous naltrexone trials, COMBINE contributed a weight of only 9.3% to the overall pooled variance. The overall pooled AR for naltrexone remained significant indicating a relative benefit over placebo (AR = 1.27; $P < 0.001$). Stated differently, patients randomized to naltrexone were 27% more likely to remain abstinent, including reversions to heavy drinking than patients randomized to placebo. These results were consistent with the original report by Srisurapanont and Jarusuraisin. As in the case of acamprosate, the COMBINE trial had only a modest impact on the overall pooled efficacy data for naltrexone.

Meta-Analysis of Acamprosate Versus Naltrexone

A total of 4 randomized trials directly comparing acamprosate to naltrexone met the inclusion criteria for the meta-analysis (Table 2). Three of 4 trials evaluated drug efficacy in terms of the cumulative number of days abstaining from alcohol as a key study endpoint. The statistical pooling of the 3 trials revealed no statistically significant difference between acamprosate and naltrexone in the number of cumulative days abstaining from alcohol (SMD = 0.14; $P = 0.51$). Two of the 4 trials also reported the proportion of patients who returned to heavy drinking at a 12-week evaluation period. The statistically pooled RR of relapse from these trials was also unable to detect a significant difference between acamprosate and naltrexone (RR = 1.12; $P = 0.64$). The final efficacy parameter evaluated between acamprosate and naltrexone was days to first relapse to heavy drinking. There was a trend in favor of naltrexone, but the difference in days to heavy drinking (evaluated as SMD) did not reach statistical significance, which supported the hypothesis of clinical equivalence between the 2 drugs (SMD = -0.40; $P = 0.067$).

FIGURE 2. Inclusion of the COMBINE trial (Anton et al., 2006) into the meta-analysis of pooled abstinence rates with acamprosate versus placebo. Pooled abstinence rates were significantly different between acamprosate and placebo; $P < 0.001$. Test for heterogeneity: $\chi^2 = 21.56$, df = 15, $P = 0.12$, $I^2 = 30.4\%$. © 2009 American Society of Addiction Medicine
DISCUSSION

The COMBINE trial by Anton et al (2006) was one of the most important and complex studies conducted in the field of alcohol-dependence treatment. The investigators reported that relative to placebo, naltrexone demonstrated an improvement in percent days abstinent and time to first heavy...
drinking day at the 16-week evaluation period. In contrast, there were no statistical differences between acamprosate and placebo in the primary and secondary endpoints. Even though these findings raise some concerns related to the efficacy of acamprosate, clinicians making treatment decisions must also consider data from multiple sources to determine if the findings are generalizable to their patient population. Systematic reviews (or meta-analyses) of randomized controlled trials (RCTs) and RCTs with adequate sample sizes are in the same (highest) level of evidence. Therefore, medical decision making should be based on both the results from well-designed randomized trials and meta-analyses of comparable multiple RCTs.

To evaluate the impact of the COMBINE trial, an updated meta-analysis of acamprosate placebo-controlled trials was undertaken. Despite the negative findings for acamprosate from the COMBINE trial, the meta-analysis of all placebo-controlled randomized trials confirmed that acamprosate is an effective agent for the treatment of alcohol-dependent patients. Similarly, the inclusion of the COMBINE data for naltrexone to the recent meta-analysis of Srisurapanont and Jarusuraisin also had a modest impact on the overall pooled AR. The findings of the meta-regression investigation also provided insight on the clinical performance of acamprosate under the setting of a placebo-controlled randomized trial. The drug tended to perform better in trials of large sample size and of longer duration. The former observation could be related to the increased statistical power in the trials with larger sample sizes. For the latter, patients may require a longer treatment duration to enhance the drug’s effectiveness.

Notwithstanding, the positive results from the current meta-analysis raise the question of acamprosate’s failure in the COMBINE trial, which was conducted in the United States. The non-North American trials are arguably less representative of clinical practice in the United States because they almost universally began following an extended (sometimes 5 weeks) inpatient treatment episode, whereas fewer than 100% of COMBINE patients were admitted in the 30 days before randomization. Thus, the COMBINE patient population is perhaps different and more comparable to United States practice than the other populations included in the meta-analysis (ie, patients of lesser severity). One important placebo-controlled trial of acamprosate by Mason et al was conducted with less intensive research handling than COMBINE and in a more representative population.

In a post-hoc analysis controlling for baseline variables, the investigators reported that patients treated with acamprosate had significantly higher percent days abstinent than placebo. This study did meet our criteria for inclusion into the meta-analysis. Unfortunately, it did not provide the necessary point estimates and measures of variance required by the statistical analysis.

Acamprosate and naltrexone are both active agents for the treatment of alcohol dependence. However, each drug seems to work via unique mechanisms of action. Acamprosate inhibits glutamatergic receptor function and may exert its therapeutic effect by decreasing an alcoholic’s need to drink. In contrast, naltrexone exerts its effect by inhibiting opiate receptors, which are involved in alcohol’s reward effects on the brain. As a result, a patient drinking while on naltrexone would experience less reinforcing euphoria. Therefore, acamprosate may be optimally effective in those patients who tend to consume alcohol for its stress-reducing effects, including the distress caused by withdrawal whereas naltrexone may optimally work in those patients who are motivated by the positive reward effects of alcohol. Additional research is needed to identify which patients would best respond to acamprosate, naltrexone, or even combination therapy.

There are a number of limitations in the current study that must be addressed. Publication bias characterized by a failure to publish negative studies was suggested by the funnel plot analysis. In our study, pooled AR for both acamprosate (AR = 1.58; P < 0.001) and naltrexone (AR = 1.27; P < 0.001) were estimated. Even though the magnitude of effect over placebo seems to be somewhat higher with acamprosate, direct comparisons of these pooled rates are discouraged because one has to be aware of the potential biases associated with cross trial comparisons. Secondary to resource constraints, an unorthodox approach was conducted to assess the impact of the COMBINE results on the pooled efficacy data for naltrexone. We did not conduct a full systematic review of the literature for oral naltrexone, but simply assessed the impact of the COMBINE trial on a meta-analysis that was recently published. Notwithstanding, a full systematic review and meta-analysis would have been the preferred approach for naltrexone.

CONCLUSIONS

The findings of this study suggest that acamprosate and naltrexone are both effective for patients with alcohol dependence. Systematic reviews with meta-analyses of RCTs and well-designed RCTs with adequate sample sizes are both good sources of clinical evidence. Therefore, clinicians should use both these sources of information as their foundation for selecting optimal therapy for patients with alcohol dependence.

REFERENCES