TITLE: Naltrexone in Combination with Acamprosate for the Treatment of Alcohol Dependence: A Review of the Clinical and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES:

Alcohol dependence is one of the most common psychiatric disorders placing many health, social, and economic burdens on society.1,2 In Canada, 24.1% of men and 9.6% of women reported heavy drinking in 2008.3 Treatment of alcohol dependence benefits both the patient and society by improving patient health, productivity, and quality of life, while generating cost-savings for the health care system.1

Pharmacotherapy can reduce the rate of relapse into heavy drinking for patients with alcohol dependence.4 It has been hypothesized that medication combinations may enhance the treatment effects of single medications by affecting different behavioural aspects of alcohol dependence.5 The combination of naltrexone (ReVia™, Duramed Pharmaceuticals) and acamprosate (Campral®, Mylan Pharmaceuticals) has been investigated for additional therapeutic benefit due to different mechanisms of action.5,6 Naltrexone is a pure opioid receptor antagonist that appears to prevent excessive drinking by blunting the rewarding effects of alcohol.7-9 Acamprosate is a gamma-aminobutyric acid (GABA) analog that has been shown to promote abstinence in individuals who have stopped drinking.8-10 Hence, the combination of naltrexone and acamprosate may reduce the risk for heavy drinking and promote long-term abstinence. However, medication combinations create the potential for reduced compliance (due to the need to take additional tablets), heightened or new treatment-related adverse effects, drug interactions, and higher costs.11

This report reviews the evidence for the clinical effectiveness, safety, and cost-effectiveness of naltrexone used in combination with acamprosate for the management of alcohol dependence.

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RESEARCH QUESTIONS:

1. What are the benefits and harms of naltrexone in combination with acamprosate for the treatment of alcohol dependence?

2. What is the cost-effectiveness of naltrexone in combination with acamprosate for the treatment of alcohol dependence?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID Medline and Embase, The Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused internet search. The search was limited to English language articles published between 2004 and September 2009. For the first question, filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, and safety data. A supplemental search for randomized controlled trials (RCTs), controlled clinical trials published between 2003 and September 2009 was also conducted. For the second question, filters were applied to limit retrieval to economic studies. This search was supplemented by hand searching the bibliographies of selected papers to include background information not originally identified in the original search.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by RCTs and economic evaluations.

SUMMARY OF FINDINGS:

Two RCTs\textsuperscript{12,13} and one economic evaluation\textsuperscript{14} were identified assessing the combination of naltrexone and acamprosate for the management of alcohol dependence. No health technology assessments, systematic reviews, or meta-analyses were retrieved.

Randomized controlled trials

In a single-center, placebo-controlled, double-blind RCT, Kiefer et al.\textsuperscript{12} randomized 160 patients (mean age of 46.2 years; 77.8\% male) with alcohol dependence to receive acamprosate (1998 mg per day) or naltrexone (50 mg per day), alone or combination, or placebo. Each of the four treatment arms had a total of 40 participants. Adults aged between 18 and 65 years were recruited from an inpatient detoxification ward following complete abstinence for 12 to 15 days. Exclusion criteria included the presence of psychiatric impairment, any drug dependence with the exception of nicotine, evidence of severe neurologic or physical disorders (e.g. cerebral, renal, thyroid, or cardiac disease), contraindications to naltrexone use (including a history of opioid abuse, cirrhosis, or liver injury), and homelessness. Patients were treated with the study medication for 12 weeks and were also provided with 90 minutes of behavioral group psychotherapy on a weekly basis. Outcomes of interest for the intent-to-treat efficacy analyses included relapse to heavy drinking (defined as \geq five drinks per day for men or \geq 4 drinks per day for women) and the maintenance of abstinence. At the end of the 12 week study period,
patients discontinued medication and entered a 12 week follow-up period, at the end of which the drinking status of all participants was re-assessed.

Baseline demographic and clinical characteristics were similar for all treatment groups. After 12 weeks of treatment, relapse rates for the placebo, acamprosate, naltrexone, and combined naltrexone with acamprosate groups was 75%, 50%, 35.3%, and 27.5%, respectively. Relapse rates were statistically significantly lower when the combined naltrexone plus acamprosate group was compared with either acamprosate or placebo and when either the naltrexone or acamprosate groups were compared with placebo (all comparisons p<0.05). No significant difference was detected between the combined therapy and naltrexone groups or between the acamprosate and naltrexone groups. At the 12 week follow-up, treatment with naltrexone (52.9%), acamprosate (54.3%), or a combination of the two (34.3%) led to statistically significantly lower relapse rates compared with placebo (80%; p<0.05). However, there was no significant difference between the three treatment groups (naltrexone alone, acamprosate alone, or the combination). Using survival curve analyses for time to first drink and time to relapse into heavy drinking, all three active treatment groups were statistically significantly more effective than placebo (p<0.05). Combined naltrexone and acamprosate was statistically significantly more effective than acamprosate (p<0.05) but not naltrexone. There was no significant difference between the naltrexone and acamprosate groups. No serious adverse effects were observed, although the incidence of diarrhea (13.8%) and nausea (5.6%) were higher in the combination treatment group compared with the other groups (statistical significance relative to monotherapies not reported). The authors concluded that combination treatment with naltrexone and acamprosate may be beneficial for the treatment of relapse prevention in alcohol dependent patients. The authors did not report any conflicts of interest for this trial.

The COMBINE (Combined Pharmacotherapies and Behavioral Interventions) study was a multi-center, double-blind RCT sponsored by the National Institute on Alcohol Abuse and Alcoholism to determine if improvement in treatment outcomes for alcohol dependence could be achieved by combining pharmacotherapy and behavioral interventions. Adults with alcohol dependence were recruited via advertisement and from clinical referrals at 11 academic sites. Exclusion criteria included the presence of psychological disorders (e.g., bipolar disorder, dementia, schizophrenia), a history of substance abuse (with the exception of nicotine and cannabis), and contraindications to naltrexone use including a history of opioid abuse, cirrhosis, or liver injury. A total of 1,383 participants (median age of 44 years; 70% male) who were abstinent for four to 21 days were randomized to one of nine treatment arms (Table 1). Participants were randomized to receive either placebo, acamprosate (3,000 mg per day), naltrexone (100 mg per day), or acamprosate combined with naltrexone. These four treatment groups were combined with or without cognitive behavioral intervention (CBI) consisting of up to 20 counseling sessions of 50 minute duration delivered by alcoholism treatment specialists. All eight groups (n=1226) received medical management (MM), consisting of nine sessions focusing on enhancing medication adherence and abstinence. The ninth treatment group (n=157) received CBI only (no MM, either drug, or placebo pills) and was included to assess placebo effects.
Table 1: COMBINE Study Intervention Groups

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Placebo</th>
<th>Naltrexone</th>
<th>Placebo</th>
<th>Acamprosate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>156</td>
<td>155</td>
<td>151</td>
<td>157</td>
<td>619</td>
</tr>
<tr>
<td>CBI + MM</td>
<td>153</td>
<td>154</td>
<td>152</td>
<td>148</td>
<td>607</td>
</tr>
<tr>
<td>CBI only</td>
<td>157</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>157</td>
</tr>
<tr>
<td>Total</td>
<td>466</td>
<td>309</td>
<td>303</td>
<td>305</td>
<td>1,383</td>
</tr>
</tbody>
</table>

CBI = cognitive behavioural intervention; MM = medical management

A 2 x 2 x 2 factorial design (acamprosate/placebo x naltrexone/placebo x CBI/no CBI) was used to test the effects of each of the interventions as monotherapies, as well as the effects of each combination of two or three therapies combined. Instead of using pair-wise statistical comparisons, the study used analysis of variance (ANOVA) to analyze the effects of two or three interventions simultaneously. Co-primary outcomes for the intent-to-treat efficacy analyses were percent days abstinent and time to first heavy drinking day (defined as ≥ five drinks per day for men or ≥ 4 drinks per day for women). Outcomes were assessed at end of 16 week treatment period and at one-year follow-up.

Baseline demographic and clinical characteristics were similar for all treatment groups. After 16 weeks, there was no significant difference for mean adjusted percent days abstinent when the groups receiving placebo plus MM (77%), naltrexone plus MM (78.2%), acamprosate plus MM (77.3%) and MM with naltrexone and acamprosate (79.5%) were compared (p=0.74). This indicated that combining naltrexone with acamprosate did not increase the number of days the patient was abstinent when compared with placebo or either drug alone in patients receiving MM. Similarly, the mean percent days abstinent did not differ significantly when the group receiving CBI in addition to naltrexone, acamprosate and MM was compared with other the groups receiving only one drug or placebo (actual rates not reported). The combination of naltrexone with acamprosate did not significantly affect the relapse rate to heavy drinking when compared with either drug alone (hazard ratio [HR] 0.90; 97.5% confidence interval [CI] 0.72-1.11). However, naltrexone monotherapy statistically significantly reduced the risk of a heavy drinking day over time when compared to placebo (HR 0.72; 97.5% CI 0.53 to 0.98; p=0.02). There were no significant differences between the nine groups in any of the outcomes at one year post-treatment. Frequency of hospitalization (11%), emergency department treatment for alcohol problems (6%), use of medication for drinking (11%), emotional problems (17%), and detoxification (6%) were not significantly different between the nine treatment groups. Furthermore, the rates of serious adverse events were similar across groups as were adverse events leading to treatment dropout. However, the rates of nausea (42%), vomiting (18%), and decreased appetite (25%) were the highest in the combination therapy group (statistical significance relative to monotherapy not reported). Several of the study authors declared conflicts of interest with regards to funding through pharmaceutical companies.

Economic evaluations

Zarkin et al. evaluated the costs and cost-effectiveness for the interventions used in the COMBINE study. Main outcomes were the incremental cost per percentage point increase in percentage of days abstinent and incremental cost per patient of avoiding heavy drinking. A micro-costing approach was used to calculate the costs of interventions from the perspective of the treatment provider. The cost of each intervention was determined based on the sum of
space, labor, medication, and laboratory costs. Daily costs for acamprosate (US$ 5.76) and naltrexone (US$ 2.74) were obtained from Federal Supply Schedule pricing. Results showed that the total mean cost per patient for MM plus combined naltrexone and acamprosate therapy was US$1,003. This cost was higher than MM with placebo, naltrexone, or acamprosate alone (US$ 409, US$ 671, or US$ 748, respectively). The addition of CBI increased costs. Combination therapy with CBI, MM, naltrexone and acamprosate was the most expensive intervention (US$ 1,313). The incremental cost-effectiveness ratio (ICER) of adding naltrexone to medication management was US$ 42 per percentage point increase in percent days abstinent and US$ 2,847 per patient avoiding heavy drinking. With the addition of acamprosate to medication management and naltrexone, the ICER increased to US$ 664 per percentage point increase in percent days abstinent and US$ 8,095 per patient avoiding heavy drinking. The authors identified three interventions as cost-effective options relative to the other interventions: MM with placebo, MM plus naltrexone, and MM plus combined naltrexone and acamprosate therapy. The authors noted that pair-wise comparisons for the cost-effectiveness analyses may explain this finding despite the results of the COMBINE study regarding combination therapy. Interventions incorporating CBI were not judged to be cost-effective. The authors concluded that MM plus combination therapy with naltrexone and acamprosate therapy may be a cost-effective option depending on the whether the cost is justified by the decision maker.

Limitations

- In the trial conducted by Kiefer et al., monitoring of alcohol intake during the 12 week follow-up period relied of self-report rather than laboratory parameters to estimate relapse and abstinence control. Furthermore, patients who relapsed were withdrawn from the study contributing to a high rate (53.1%) of study discontinuation. In contrast, high study completion (94%) and laboratory verification of self-reports were described in the COMBINE study.

- A significant placebo effect (≥73.8% percent days abstinent across all groups receiving placebo pills compared with 66.6% for CBI only) was reported in the COMBINE study. This may be due to the highly intensive recruitment process and sessions with up to five specialized staff at every visit. This may reflect a highly treatment motivated participant pool and it is possible that the COMBINE results may not be generalizable to patient populations commonly found in clinical practice.

- The exclusion of participants with substantial concurrent psychiatric illness and drug abuse in both trials may limit generalizability of the results to populations in clinical practice.

- The three to four month treatment duration in both trials may have limited clinical effectiveness given the chronicity and relapse potential of alcohol dependent individuals. It is not currently known if increasing treatment duration will increase the long-term clinical effectiveness of combination therapy relative to monotherapy.
Differences between the two trials in terms of statistical methods, patient populations (inpatient versus outpatient setting), required minimum number of days for abstinence, dosing for naltrexone and acamprosate, and intensity of concurrent behavioral interventions make meaningful comparisons for clinical outcomes difficult.

Although one economic evaluation indicated that naltrexone given in combination with acamprosate may be a cost-effective option, clinical and cost estimates were derived from institutions in the US as part of single RCT. These results may not be representative of the patient population and treatment patterns in Canadian medical centers.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Overall, the available evidence indicates that combination therapy with naltrexone and acamprosate for alcohol dependence is well tolerated. Minor adverse effects (e.g. nausea) were observed to occur more frequently with combination therapy relative to monotherapy. However, the evidence to support the clinical effectiveness of combination therapy with naltrexone and acamprosate for the management of alcohol dependence is inconsistent. One RCT showed that combination therapy was significantly better than acamprosate alone, but not naltrexone alone, for the prevention of relapse into heavy drinking and the maintenance of abstinence. However, results from COMBINE demonstrated that combining naltrexone and acamprosate with or without CBI was not more clinically effective than either drug, CBI alone, or placebo in the presence of MM. Differences in statistical analyses, patient populations, study settings, intensity of concurrent behavioral therapies, and dosing may explain this inconsistency. Results from an ongoing RCT assessing if specific patient groups may respond better to combination therapy with naltrexone and acamprosate will be of particular interest. It is not yet known whether long-term combination therapy with naltrexone and acamprosate with or without other behavioral interventions may be beneficial to patients relative to monotherapy. Furthermore, optimal dosing and sequencing of combination therapy remain to be established. There is a lack of information to support the cost-effectiveness of combination therapy with naltrexone and acamprosate in a Canadian setting.

Until further information is available, the limitations of the available evidence for the clinical and cost-effectiveness of combination therapy may be a consideration when treating alcohol dependence in different health care settings and patient populations.

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