**Canadian Agency for Drugs and Technologies in Health**

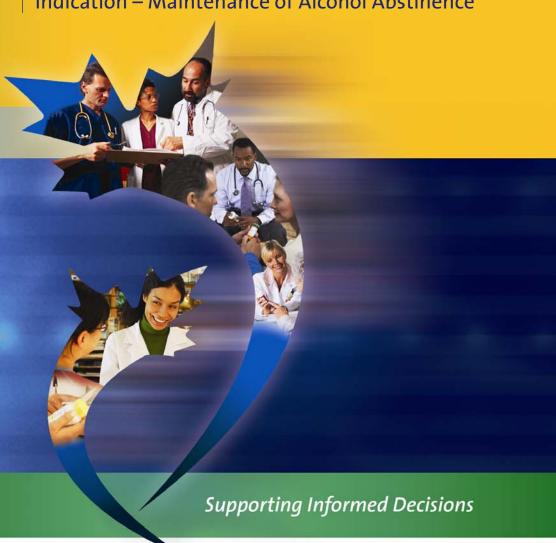**Agence canadienne des médicaments et des technologies de la santé**

## Overview of CDR Clinical and Pharmacoeconomic Reports

*CDR*

August 2008

Acamprosate Calcium
Campral® – Prempharm Inc.
Indication – Maintenance of Alcohol Abstinence

**Supporting Informed Decisions**

*À l'appui des décisions éclairées*

This Overview is a synopsis of the evidence-based reviews prepared by the Common Drug Review (CDR) Directorate at the Canadian Agency for Drugs and Technologies in Health (CADTH) and used by CDR's Canadian Expert Drug Advisory Committee in making formulary listing recommendations to participating public drug plans. The information in this Overview should not be used as a substitute for clinical judgment in the care of a particular patient, nor is it intended to replace professional advice. CADTH is not liable for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

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**COMMON DRUG REVIEW**

Overview of CDR Clinical and Pharmacoeconomic Reports

# Acamprosate Calcium

Campral® — Prempharm Inc.

Indication – Maintenance of Alcohol Abstinence

August 2008

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE** | adverse event |
| **CADP** | cumulative abstinence duration per cent |
| **CDT** | carbohydrate-deficient transferrin |
| **CI** | confidence interval |
| **DB** | double blind |
| **GABA** | gamma-aminobutyric acid |
| **GGT** | gamma-glutamyltransferase |
| **RCT** | randomized controlled trial |
| **SAE** | serious adverse event |
| **WDAE** | withdrawal due to adverse event |

# REVIEW IN BRIEF

*Acamprosate calcium (Campral®) was submitted by the manufacturer to the Common Drug Review (CDR) for consideration for formulary listing by participating public drug plans. This Review in Brief includes the Canadian Expert Drug Advisory Committee's (CEDAC) recommendation and reasons for recommendation, and information used by CEDAC in making its recommendation including: a summary of the best available clinical and pharmacoeconomic evidence identified and reviewed by the CDR, as well as information submitted by the manufacturer.*

## CEDAC Recommendation

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that acamprosate be listed in patients who have been abstinent from alcohol for at least four days and who have contraindications to naltrexone (currently receiving opioids, acute hepatitis or liver failure). The maximum treatment duration should be one year.

## *Reasons for the Recommendation*

1. Acamprosate has been shown to be better than placebo in improving measures of abstinence from alcohol in some randomized controlled trials (RCTs) and in a large meta analysis of clinical trials.
2. Aside from patients with contraindications to naltrexone, there is insufficient evidence for a therapeutic advantage of acamprosate compared to naltrexone. One large RCT reported that acamprosate, with or without combined behavioural intervention, had no evidence of beneficial effect on alcohol drinking outcomes while the same study did report a benefit with naltrexone therapy.
3. Acamprosate costs $4.80 per day which is similar in cost to naltrexone ($5.00 per day). The manufacturer submitted an economic evaluation which assumed that the effectiveness of acamprosate was equivalent to naltrexone. As there was insufficient evidence to support this assumption, the Committee felt that acamprosate should be reserved for use in patients with contraindications to naltrexone.

## Drug

- Acamprosate is approved by Health Canada for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation.
- The recommended dose is 666 mg three times daily.
- Treatment with acamprosate should be part of a comprehensive management program that includes counselling.
- Acamprosate modulates glutamatergic and gamma-aminobutyric acid (GABA)ergic neurotransmission and modifies neuronal excitability; however, the mechanism of action of acamprosate in the maintenance of alcohol abstinence is not well established.

## Condition

Alcoholism is a chronic relapsing condition with associated genetic, psychological, and social factors.

## Clinical Review

- A published systematic review (SR), Mann *et al.* of 17 double-blind, placebo-controlled RCTs of acamprosate in adults with alcohol dependency was reviewed.
- In addition three RCTs not included in the Mann et al. systematic review were reviewed. One trial was included in both the Mann *et al.* systematic review and in the individual trials that were summarized.
- An additional trial using a higher than approved dose was also reviewed and included in supplemental issues.

## *Results*

- No trials reported on the effect of acamprosate on the consequences of alcohol consumption such as alcohol-related mortality, social role functioning, or quality of life.

### *Acamprosate vs. Placebo*

- A meta-analysis of all trials in the Mann *et al.* systematic review showed that acamprosate had a statistically significant improvement in the duration of abstinence and continuous abstinence from alcohol for up to 12 months.

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ii

- There was considerable variability in the treatment results of individual trials and approximately half of the trials in the Mann *et al.* systematic review reported no statistically significant differences.  For example,
  o Three trials reported a relatively large treatment effect with acamprosate.
  o Three trials of mostly outpatients (outside of hospital or treatment centres) reported no differences between acamprosate and placebo.

### *Acamprosate vs. Naltrexone vs. Placebo*

- Two RCTs of 12 weeks duration, using survival analysis approach.
- One trial reported that acamprosate plus naltrexone were associated with statistically significant improvements in time to first drink and time to heavy drinking compared with placebo and with acamprosate alone. There were no significant differences between acamprosate and naltrexone or between acamprosate plus naltrexone and naltrexone.
- The second trial reported no differences between acamprosate, naltrexone and placebo in continuous abstinence at 12 weeks, time to first drink or time to heavy drinking.
- While no differences were shown between acamprosate and naltrexone in abstinence outcomes, the total number of patients (93) exposed to naltrexone was small.

### *Acamprosate and Naltrexone at higher doses*

- One trial evaluated treatment doses (acamprosate 3 g/day, naltrexone 100 mg/day) which are higher than those approved in Canada.
- 16-week trial with up to one year follow-up of 1383 recently abstinent outpatients (6% lost to follow-up).
- Nine treatment groups, receiving acamprosate or naltrexone (or both) or placebo, with or without a combined behavioural intervention, were compared.
- Acamprosate demonstrated no statistically significant effect on drinking outcomes compared to placebo, either by itself or with any combination of naltrexone, combined behavioural intervention, or both.

### *Adverse Events*

- Adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were more common in acamprosate-treated patients than with placebo (1.4% vs. 0.5% in studies of 6 months or less; 2.4% vs. 0.8% in year-long studies).
- There was no statistically significant difference in the rate of death due to suicide.
- The incidence of digestive system adverse events was statistically significantly greater in the acamprosate group compared with placebo.

## Pharmacoeconomic Review

The pharmacoeconomic analysis submitted by the manufacturer was assessed and critiqued.

### *Highlights*

- Acamprosate costs $4.80 per day which is similar to naltrexone at $5.00 per day.
- The manufacturer, in their submitted economic evaluation, reports an annual total cost for acamprosate of $2,384 which is less than the reported annual cost for naltrexone at $2,606 or intensive behavioural therapy at $4,309.
- The submitted economic evaluation assumed that the effectiveness and safety of acamprosate was equivalent to naltrexone and intensive behavioural therapy, based on evidence from clinical trials, including the COMBINE trial. Limited comparative clinical evidence indicates no significant differences in abstinence.

**What is the CDR?**

The CDR conducts objective, rigorous reviews of the clinical and cost-effectiveness of drugs, and provides formulary listing recommendations to the publicly funded drug plans in Canada (except Québec).

# OVERVIEW

## Context

This document is an overview of two Common Drug Review (CDR) reports: the CDR Clinical Review Report (a systematic review of the clinical evidence) and the CDR Pharmacoeconomic Review Report (a critique of the pharmacoeconomic evaluation submitted by the manufacturer). These reports were prepared by the CDR to support the Canadian Expert Drug Advisory Committee (CEDAC) in making a formulary listing recommendation to participating publicly funded drug plans. The reviews are an assessment of the best available evidence that the CDR has identified and compiled, including that submitted by the manufacturer.

This overview report is based on the acamprosate CDR Clinical Review Report, 102 pages in length with 87 references, and the acamprosate CDR Pharmacoeconomic Review Report, 16 pages with nine references. The manufacturer had the opportunity to provide feedback on each of the full reports and on this Overview Report. The CDR has considered the feedback in preparing the final versions of all of these reports. The manufacturer's confidential information as defined in the CDR Confidentiality Guidelines, may have been used in the preparation of these documents and thus, considered by CEDAC in making its recommendation. The manufacturer has reviewed this document and has not requested the deletion of any confidential information.

## Introduction

Acamprosate (Campral), an N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptor antagonist, modulates glutamatergic and GABAergic neurotransmission and modifies neuronal excitability; however, its mechanism of action is not completely understood. Acamprosate, is approved in Canada for the maintenance of abstinence from alcohol in patients who are alcohol dependent and who are abstinent at treatment initiation. Treatment should be part of a comprehensive management program that includes counselling. The recommended adult dose is 666 mg three times daily; dosage should be reduced by one-half in renal impairment (creatinine clearance 30-to-50-mL/min), and is not recommended when creatinine clearance is <30 mL/min.

Alcoholism is a chronic relapsing condition in which genetic, psychological, and social factors all play a role.[1] Based on the most recent Canadian Addiction Survey (CAS) 2005 data,[2] the percentage of drinkers consuming alcohol in excess of low-risk drinking guidelines varies between 21.4% and 27.3%, depending on the province. Amongst former and current drinkers, 24.2% report that their drinking had caused harm to themselves or others. Rates of alcohol-related mortality are substantial in Canada.[3] Younger age, male gender, and a family history of alcoholism are risk factors for alcohol misuse. Illicit drug use and psychiatric co-morbidity are also highly prevalent in persons that misuse alcohol.

In general, treatment of alcohol abuse and dependence can be divided into two phases: abstinence initiation (cessation of heavy drinking and medical detoxification) and relapse prevention (reducing or coping with alcohol cravings). Behavioural and pharmacological treatments can be targeted to one or both treatment phases. Behavioural interventions include participation in self-help groups, such as Alcoholics Anonymous, as well as brief or more intensive clinical motivational interventions with a health care professional. Until recently, the μ-opioid receptor antagonist naltrexone (ReVia®) was the only pharmacologic treatment approved by Health Canada for treatment of alcohol dependence.

## *Clinical Review*

### *Objective*

To evaluate the effect of acamprosate calcium with or without counselling on outcomes as compared with standard therapies or placebo in adults diagnosed with alcohol dependency.

### *Methods*

For information about the methodology employed in the full CDR Clinical Review of acamprosate, refer to Appendix I.

### *Selection Criteria*

Studies were chosen for inclusion in the review based on the criteria listed in Table 1.

| Table 1: Selection Criteria** | | | | |
|---|---|---|---|---|
| **Clinical Trial Design** | **Patient Population** | **Interventions** | **Appropriate Comparators*** | **Outcomes** |
| Published or unpublished DB RCTs of at least 3 months treatment duration<br><br>Systematic Reviews (assessed as high quality)**<br><br>FDA and Heath Canada reports for Harms** | Adult outpatients, with alcohol problems and alcohol dependency, who are newly abstinent | Acamprosate in recommended doses, with or without counselling, alone or in combination with other alcohol deterrents<br><br><br>Potential subgroup analysis by counselling type | • Placebo<br><br>• Naltrexone | **Primary**<br>• All-cause mortality<br>• Traffic-related mortality<br>• QoL<br>• Episodes of impaired driving/family violence<br>• Days of missed work or unable to perform regular daily tasks<br>• SAE<br>• WDAE<br>• Overall withdrawal<br>• Treatment discontinuation<br><br>**Secondary**<br>• Continuous and point-prevalence abstinence<br>• Time to first drink<br>• Cumulative abstinence duration<br>• Biological markers of alcohol use (GGT, CDT, MCV)<br>• Admission for detoxification<br>• Overall AEs |

AE=adverse event; CDT=carbohydrate-deficient transferrin; DB=double blind; GGT=gamma-glutamyltransferase; MCV=mean corpuscular volume; QoL=quality of life; RCT=randomized controlled trial; SAE=serious adverse event; WDAE=withdrawal due to adverse event.

* Standard therapies available in Canada (may include drug or non-drug interventions)
** Protocol was amended November 2, 2007 – see Appendix I.

*Results*

**Findings from the Literature**

**Figure 1:** Included studies (Appendix I contains the flow of trials for the original protocol.)

Based on the protocol amendment, the CDR Systematic Review included:
1 published systematic review and 3 unique individual trials (Kiefer is included in both the published SR and individual trials summarized)

**Mann (systematic review),** 2004[4]

**Lhuintre**, 1990[5]
   Hillemand, 1989[6]

**Baltieri**, 2003[7]
   Baltieri, 2004[8]

**Morley**, 2006[9]
   Richardson, 2006 (abstract)[10]
   Teesson, 2006 (abstract)[11]
   Morley, 2006 (abstract)[12]
   Morley, 2006 (abstract)[13]

**Kiefer**, 2003[14]
   Kiefer, 2004[15]
   Kiefer, 2002(abstract)[16]
   Kiefer, 2003[17]

**Additional Reports**
FDA –Medical Review[18]
FDA –Statistical Review[19]
Manufacturer's Submission Binder[20]
Health Canada Reviewer's Report[21]

**Notes:**
(1) The Combined Pharmacotherapies and Behavioural Interventions for Alcohol Dependence (COMBINE) study,[22] although not meeting inclusion criteria due to its higher than recommended dosing, was summarized in the Supplemental Issues section of the full CDR Clinical Review and can be found in Appendix II of this Overview.

(2) The Mann *et al.* systematic review did not include information related to safety and harms. To address this shortcoming, safety information for 13 trials from the Health Canada Reviewer's Report and the FDA Medical Review were summarized. Trials that met the CDR inclusion criteria that were not included in the Mann *et al.* systematic review were also reviewed for safety and harms.

**Trial Accounting**
Many of the trials originally identified as meeting the CDR inclusion criteria were included in Mann *et al.* and also submitted to regulatory agencies [Health Canada and the U.S. Food and Drug Administration (FDA)]. Differences between the lists of studies identified by CDR, included in the Mann *et al.* systematic review and submitted to regulatory agencies are outlined in Table A1 of Appendix 1.

**Summary of Evidence**

*Included Studies and Trial Characteristics*

One systematic review (Mann *et al.*: 16 placebo trials and one trial comparing placebo, naltrexone, and acamprosate plus naltrexone) and three additional individual trials (two placebo trials and one trial with naltrexone and placebo) were included in this review. One trial is summarized both in the Mann *et al.* systematic review (placebo arm) and in the individual trials reviewed by CDR (naltrexone, acamprosate plus naltrexone arms). The primary efficacy outcome in Mann *et al.* was continuous abstinence at six months, whereas individually reviewed trials included efficacy outcomes of continuous abstinence at three or six months, cumulative abstinence duration, time to first drink, and time to heavy drinking. Individual trials employed doses of acamprosate of 1,998 mg/day (three trials) or 1,332 mg/day (one trial), while naltrexone dosing was 50 mg/day (two trials). High rates of attrition were observed in individually reviewed trials and those included by Mann *et al.* (range: 23% to 53%).

To assess the comparative harms of acamprosate, the safety and harms information from 13 trials included in the Health Canada Reviewer's Report and the FDA Medical Review were summarized, as well as the additional individual trials.

In total, this review provides data from 20 unique trials (N=4,900). Participants were alcohol-dependent patients who were newly abstinent. Sample sizes ranged from 10 to 581. Participants were mostly male (range 64% to 100%). Treatment durations ranged from two to 12 months, and follow-up ranged from two months to two years. None of the studies were conducted in North America.

**Summary of Results**

Table 2 provides a summary of the outcome (continuous abstinence) included in the Mann *et al.* systematic review and Table 3 provides a summary of continuous abstinence in the three additional individual trials included in the CDR review.

*Efficacy*

Results from Mann *et al.* (17 RCTs)
- The primary outcome of interest was continuous abstinence at six months.
- Treatment with acamprosate resulted in statistically significant higher rates of continuous abstinence than placebo at three, six, and 12 months [six-month relative benefit=1.47; 95% confidence interval (CI) 1.29 -1.69 and 12-month relative benefit=1.95 (95% CI 1.58-2.42)].
- Cumulative abstinence duration per cent (CADP) at three, six, and 12 months was significantly higher among acamprosate-treated participants compared with placebo. At six months, the between-treatment difference was 11.15% (95% CI 6.91-15.38) in favour of acamprosate.

Review of the four individual trials
- One of two trials reporting continuous abstinence reported a significant difference in favour of acamprosate compared with placebo at 24 weeks [43% versus 20% respectively; relative benefit=2.13 (95% CI 1.00 - 4.52)], while the other trial reported no significant difference between acamprosate and placebo at 12 weeks [20% versus 18% respectively; relative benefit=1.11 (95% CI 0.52-2.35)].
- The one trial that studied cumulative days abstinent, reported no significant difference in the mean [standard deviation (SD)] between acamprosate 66.3 (25.2) days, naltrexone 57.8 (29.2) days, and placebo 56.7 (31.4) days.

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- Two of three trials reporting time to first drink indicated that acamprosate significantly prolonged the time to first drink compared with placebo (mean days to first drink and hazard ratios were not provided). One trial reported no significant difference in the mean (SD) time to first drink between acamprosate 24.1 (32.9) days, placebo 24.6 (32.1) days, and naltrexone 24.3 (31.7) days; p=0.81.
- One of two trials reporting time to return to heavy drinking indicated that acamprosate significantly prolonged the time to return to heavy drinking compared with placebo, based on survival analysis (mean days to heavy drinking and hazard ratio not provided), while one trial reported no significant difference in time to return to heavy drinking-mean (SD) between acamprosate 33.6 (34.6) days, naltrexone 39.2 (32.3) days, and placebo 33.4 (34.9) days; p=0.23.
- It is unclear whether treatment with acamprosate reduces the consequences of alcohol consumption regarding alcohol-related mortality, social role functioning, and quality of life, as these outcomes were not measured.

| Table 2: Proportion of participants achieving continuous abstinence at 6 months* in trials included in systematic review by Mann *et al.* | | | |
|---|---|---|---|
| Trial | Continuous abstinence at 6 months (%) | | RB (95% CI) |
| | CAM | PL | |
| Pelc, 1992 | 27.3 | 6.4 | 4.27 (3.04-5.50) |
| Ladewig, 1993 | 34.5 | 9.4 | 3.68 (2.44-4.92) |
| Borg (unpublished) | 40.0 | 40.0 | 1.00 (0.56-2.56) |
| Paille, 1995 | 31.0 | 20.9 | 1.48 (1.00-1.97) |
| Roussaux, 1996[†] | 28.6 | 32.8 | 0.87 (0.24-1.51) |
| Sass, 1996 | 42.6 | 26.5 | 1.61 (1.12-2.11) |
| Whitworth, 1996 | 28.1 | 20.1 | 1.40 (0.91-1.89) |
| Barrias, 1997 | 44.7 | 30.9 | 1.45 (0.98-1.91) |
| Geerlings, 1997 | 22.7 | 11.2 | 2.02 (1.35-2.70) |
| Pelc, 1997[†] | 44.4 | 21.0 | 2.12 (1.49-2.75) |
| Polodrugo, 1997 | 46.7 | 25.8 | 1.81 (1.29-2.34) |
| Besson, 1998 | 34.5 | 7.3 | 4.75 (3.68-5.82) |
| Chick, 2000 | 14.2 | 13.7 | 1.04 (0.50-1.58) |
| Tempesta, 2000 | 48.2 | 34.9 | 1.38 (0.94-1.82) |
| Gual, 2001 | 48.9 | 40.8 | 1.20 (0.76-1.64) |
| Kiefer, 2003[†] | 40.0 | 25.0 | 1.60 (0.84-2.36) |
| Namkoong, 2003[†] | 37.5 | 31.4 | 1.16 (0.56-1.75) |
| **Pooled** | **36.1** | **23.4** | **1.47 (1.29-1.69)** |

CAM=acamprosate; CI=confidence interval; PL=placebo; RB=relative benefit.
* RB for continuous abstinence at 6 months as reported in SR by Mann *et al.*[4]; intention to treat worst case scenario but last observation carried forward in cases where trial duration was less than 6 months
[†] Trial duration less than 6 months

| Table 3: Proportion of participants achieving continuous abstinence in additional individual trials | | | | |
|---|---|---|---|---|
| Trial | Comparator | Continuous abstinence (%) | | RB (95% CI) |
| | | CAM | Comparator | |
| Baltieri, 2003* | PL | 43 | 20 | 2.13 (1.00-4.52) |
| Morley, 2006* | PL | 20 | 18 | 1.11 (0.52-2.35) |
| Morley, 2006* | NAL | 20 | 17 | 1.18 (0.53-2.61) |
| Lhuintre, 1990 | NI | NI | NI | NI |

CAM=acamprosate; CI=confidence interval; NAL=naltrexone; NI=comparison not included in trial; PL=placebo; RB=relative benefit.
* Relative benefit calculated by CDR for continuous abstinence at three months (Morley) and six months (Baltieri).

*Harms*

The following harms data are based on 13 placebo-controlled trials submitted to Health Canada and the FDA. Findings from the four individual trials reviewed by CDR were not statistically different between acamprosate and placebo and were consistent with the pooled data.

*Mortality:* The treatment emergent mortality rate in acamprosate-treated patients was 0.55% versus 0.46% (no statistical significance) in the placebo-treated patients.

*Serious adverse event (SAE):* There was a numerically greater incidence of treatment-emergent SAEs in acamprosate treatment groups compared with the placebo group. The most common SAEs were alcohol consumption/relapse, depression, procedures (not described), and suicide attempts. There was no significant difference in any specific SAE between treatment groups.
*Suicidality:* There was a statistically significantly greater incidence of an adverse event of a suicidal nature (1.62% versus 0.59%, p=0.006) and suicide ideation (0.59% versus 0.12%, p=0.04), and numerically greater incidence of suicide attempts and intentional overdoses for the acamprosate group compared with the placebo group. There was no statistically significant difference in the number of deaths between the groups suggesting that the incidence of completed suicides was not significantly different between the two groups.

*Adverse event (AE):* There was no significant difference in the overall incidence of AEs, but there was a significantly greater incidence of digestive system AEs in the acamprosate 1998/2000 mg per day group [RR=1.42 (1.25, 1.60), p<0.0001] compared with the placebo group. Overall, the most commonly reported AEs were diarrhea, headache, insomnia, abdominal pain, asthenia, infection, and depression. There was a significantly greater incidence of diarrhea [RR=1.72 (1.43, 2.06), p<0.0001] and flatulence [RR=2.18 (1.39, 3.41), p=0.0007] in the acamprosate group compared with the placebo group.

*Withdrawal due to adverse event (WDAE):* There was no statistically significant difference in WDAEs between the acamprosate and placebo groups. Gastrointestinal events, specifically diarrhea, were the predominant reason for treatment discontinuation.

### Discussion

Within the trials, abstinence was most commonly defined as continuous abstinence, or as the per cent of abstinent days (cumulative abstinence duration). Treatment settings and the intensity of behavioural interventions (Appendix IV) varied between studies, possibly affecting treatment efficacy. None of the trials measured efficacy with respect to reduced consequences

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of alcohol consumption, such as alcohol-related mortality, social role functioning, and quality of life. There were no statistically significant differences in mortality and SAE between the acamprosate and placebo groups.  The greatest concern is the statistically significant greater incidences of an AE of a suicide nature and suicide ideation associated with acamprosate treatment. However, the numbers of death caused by completed suicide were not statistically different between the two groups.

*Efficacy*

- The balance of evidence from Mann *et al.* indicated that acamprosate results in a significantly higher cumulative abstinence duration and continuous abstinence up to 12 months compared with placebo. However, all trials had significant attrition (range 23% to 53%), which was often different between treatments. Further, approximately half of trials reported negative results, and three trials reported relatively large treatment effects versus placebo (relative benefit >3). There was considerable heterogeneity between trials with respect to treatment site, patient population, and behavioural intervention; however, the effects of these variables on study results were often unclear.
- The majority of trials that recruited outpatients reported no differences between acamprosate and placebo; however, one trial recruiting outpatients did report a higher rate of abstinence for acamprosate.
- Trials with both high- and low-intensity behavioural interventions produced positive and negative results.
- High rates of attrition were common in the reviewed trials, although infrequently differential between treatment arms. Those who did not complete the trial were assumed non-abstinent. Documented relapse was often cited as the reason for study withdrawal in CDR-reviewed trials. In contrast, the COMBINE trial (Appendix II), which did not meet inclusion criteria for review due to its higher than recommended doses of both acamprosate and naltrexone, had comparatively low attrition (6%) and reported no significant differences between acamprosate and placebo. This trial was conducted in North America.
- Additional limitations of the included trials include short duration (majority six months or less), frequent reliance on self-report of abstinence (Appendix IV), and the lack of data regarding important clinical outcomes (mortality, social-role functioning, and quality of life).
- While a number of trials, and the results of the meta-analysis by Mann *et al.*, indicate acamprosate is more efficacious than placebo for maintaining abstinence, not all trials report this finding. In addition, no double-blind (DB) RCTs comparing acamprosate with naltrexone provide evidence of superiority of one treatment compared with another in maintaining abstinence.
- The Mason et al. trial[23] which did not meet CDR inclusion criteria because participants were not abstinent at the beginning of the trial but which was conducted in North America, showed no advantage of acamprosate over placebo.

*Harms*

- Harms data was derived predominantly from Health Canada and FDA reports, which included data from 13 short- and long-term DB RCTs, representing the experience of 2,280 acamprosate-treated participants. The incidence of SAEs among acamprosate-treated participants was low, not significantly different from placebo, and included events expected in this patient population (e.g., relapse, depression).
- The higher incidence of suicide ideation, attempt, and intentional overdose among acamprosate-treated individuals is of concern, and the product monograph includes a precaution regarding this possibility. There is limited data regarding the potential to increase

suicide ideation in patients suffering from depression or receiving psychiatric medications, since such individuals were commonly excluded from trials.

*Other Considerations*

- Treatment efficacy and effectiveness may vary by treatment setting and/or the intensity of the behavioural intervention; however, the effect of these variables has received little study.
- There is a wide variation in the effect size among trials included in the Mann *et al.*. systematic review, varying from non-significant to highly significant. The reason for this variability is unclear.

## *Pharmacoeconomic Review*

### *Context*

The CDR assesses and critiques the economic evaluation, submitted by the manufacturer, with respect to its quality and validity, including the appropriateness of the methods, assumptions and inputs, and results. The CDR may provide additional information on the cost-effectiveness of the submitted drug, where relevant, from other sources or by using the economic model to consider other scenarios.

### Objective of the Manufacturer's Submitted Economic Evaluation

To provide health economic data on acamprosate for provincial formulary committees and the CDR, a cost minimization analysis was conducted.

### Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost minimization analysis comparing three alternatives for the treatment of alcohol dependence — acamprosate, naltrexone, and intensive behavioural therapy alone — during a 12-month timeframe. The basis for conducting a cost-minimization analysis is that the clinical effects between the treatment and comparators are equivalent, such that only costs are relevant for consideration when evaluating cost-effectiveness. The authors of the pharmacoeconomic evaluation undertook a meta-analysis of clinical trials to support the claims of similar safety and efficacy between acamprosate and naltrexone. When comparing acamprosate with intensive behavioural therapy, they considered the results of the COMBINE study,[22] in addition to a published meta-analysis.[24]  Based on their review of the clinical literature, the authors concluded that acamprosate had similar safety and efficacy as the comparators.

### Cost Comparison

CDR produced Table 4 to provide a comparison of the cost of treatment of the submitted drug with comparator treatments deemed appropriate by clinical experts. Comparators may reflect recommended or actual practice. Comparators are not restricted to drugs and may include devices or procedures where appropriate. Costs are manufacturer list prices, unless otherwise specified**.**

| Table 4: Cost Comparison of Acamprosate versus Naltrexone | | | | | |
|---|---|---|---|---|---|
| **Drug / Comparator** | **Strength** | **Dosage Form** | **Price ($)** | **Average Daily Treatment** | **Average Cost Per Day ($)** |
| Acamprosate calcium (Campral)* | 333 mg | Tablet | 0.8000 | 666 mg three times daily | $4.80 |
| Naltrexone HCl (ReVia) | 50 mg | Tablet | 5.0000 | 50 mg daily | $5.00 |

Source: Ontario Drug Benefit / Comparative Drug Index (effective from September 4, 2007)
* Manufacturer's (Prempharm Inc.) submission binder
Note: Topiramate (Topamax and generics) is being used off-label for maintenance from alcohol in patients who are alcohol dependent. It is available in 25 mg ($0.5250, generic price), 100 mg ($0.9950), and 200 mg ($1.5750) tablets. At a typical dose range of 25 mg to 300 mg daily,[25] the daily price of treatment ranges from $0.53 to $2.57.

### Results (as submitted by the manufacturer)

From a health care payer perspective:
- The author reports that acamprosate, naltrexone, and intensive behavioural therapy are similar in terms of clinical effects and safety.

| The annual total cost is $2,384 for acamprosate, $2,606 for naltrexone, and $4,039 for intensive behavioural therapy (Table 5).**Table 5:** Cost-minimization analysis (12-month time horizon) | | | |
|---|---|---|---|
| **Resource Item** | **Acamprosate** | **Naltrexone** | **Intensive Behavioural Therapy** |
| Monthly prescriptions | $1,900.80 | $2,123.88 | $0 |
| Pharmacy dispensing fees | $132.88 | $131.88 | $0 |
| Fee for physicians | $350.40 | $350.40 | $350.40 |
| Visits to a licensed behavioural therapist | $0 | $0 | $3,689.28 |
| **Total cost per patient** | **$2,384.08** | **$2,606.16** | **$4,039.68** |

Source: Taken in part from Manufacturer's (Prempharm Inc.) submission binder (Pharmacoeconomic Evaluation)

### Pharmacoeconomic Analysis Discussion Points

In reviewing the manufacturer's submission, the reviewers noted the following:
- *Assumption of similar efficacy and safety — acamprosate versus naltrexone.* The authors have based their review of the clinical information on three clinical trials for the comparison of acamprosate and naltrexone.[9,15,26] The three studies consider different platforms of adjunctive behavioural therapy (four to six brief intervention sessions, weekly supportive group therapy of varying duration and intensity) and assess different treatment outcomes. This complicates the pooling of the results. The pooled results show no statistical difference for the outcomes selected; however, it should be noted that two of the studies support benefits with naltrexone when considering a subgroup analysis by depression and dependence levels,[9,26] although this was a secondary analysis. A cost minimization analysis requires that clinical outcomes between acamprosate and naltrexone are equivalent.

- *Assumption of similar efficacy and safety — acamprosate versus intensive behaviour therapy.* For the comparison with intensive behavioural therapy, the authors considered the COMBINE study[22] in addition to the systematic review by Bouza.[24] The daily treatment doses used in the COMBINE study are greater than those in the product monographs: 3,000

mg of acamprosate (versus 1,998 mg) and 100 mg of naltrexone (versus 50 mg). This could favour the drug treatments. The COMBINE study, however, appears to be a negative trial for acamprosate; this was not discussed by the author. Given that the manufacturer submitted a cost-minimization analysis, the results of the COMBINE trial, which suggest similar effects of acamprosate and placebo, could not be further investigated for the impact on estimates of cost-effectiveness.

- *Dosing.* Based on the product monograph for naltrexone,[27] it appears that the recommended course of naltrexone is for three months, in contrast to a one-year course of acamprosate.[28] In the manufacturer's analysis, the authors have assumed the use of both acamprosate and naltrexone during the course of the year of the analysis, resulting in similar drug (and total) costs – a difference of about $200. Where naltrexone is not taken for the entire year, it will result in a lower annual cost (~$900) compared with acamprosate ($2,384). Dosing was not varied in the manufacturer's sensitivity analyses.

- *Definition of intensive behavioural therapy.* The manufacturer defines intensive behaviour therapy as: weekly 50-minute therapy visits; one hour of paid "prep time" for a therapist, in addition to the appointment time; and lost wages due to attendance of each session. This drives the annual cost of intensive behavioural therapy to be more expensive than the drug therapies, by about $1,700. The COMBINE study is cited as the primary source to justify the use of the cost-minimization model (i.e., that all alternatives are equivalent). However, the results of the COMBINE study show that clinical effects of behavioural therapy are equivalent to the two drugs, and similar to placebo (which was defined as physician visits alone). Consequently, regular physician visits alone should be considered in the cost-minimization model, which in this case would be the least costly option. This study does not adequately address the costs of different types of behavioural interventions that may be beneficial in treating alcohol dependence.

- *Behavioural therapy as part of treatment regimens.* It should also be noted that it is recommended that acamprosate be used as part of a comprehensive management program that includes counselling. Moreover, all studies employing drug therapy have embedded in them some sort of behavioural therapy platform in addition to drug therapy; therefore, they are not mutually exclusive options. Visits to a licensed therapist were not included in the calculation of costs, only monthly physician visits. Where counselling is added to the treatment regimen, this would reduce the cost difference between drug treatments and behavioural therapy. This was not considered in the sensitivity analyses.

## Summary of the Clinical and Pharmacoeconomic Reviews

**Acamprosate versus Placebo**
- The clinical evidence suggests that, compared with placebo, acamprosate results in higher rates of alcohol abstinence for up to 12 months.
- The cumulative abstinence duration per cent was higher for acamprosate compared with placebo at three, six, and 12 months.
- There was considerable variability in the treatment results of individual trials
  o Approximately half of the trials reported no statistically significant differences
  o Three trials reported a relatively large treatment effect with acamprosate

    o   Three trials of mostly outpatients (outside of hospital or treatment centres) reported no differences between acamprosate and placebo

**Acamprosate versus Naltrexone**

- No significant differences in abstinence outcomes between acamprosate and naltrexone were seen in the two included trials, this was based on a small sample size of 93 patients who received naltrexone.

**Adverse Events (Including those of a Suicidal Nature)**

- There were no statistically significant differences in mortality or SAEs between acamprosate and placebo.
- AEs of a suicidal nature and suicide ideation were statistically significantly higher with acamprosate than with placebo. The number of deaths caused by completed suicide was not statistically different between the two groups.
- There was a statistically significant greater incidence of digestive system AEs in the acamprosate group compared with placebo.

**Pharmacoeconomic Evaluation**

- The daily cost of acamprosate ($4.80) is similar to the cost of naltrexone ($5).
- The manufacturer, in the submitted economic evaluation, reports an annual total cost for acamprosate of $2,384 which is less than the reported annual cost for naltrexone at $2,606 or intensive behavioural therapy at $4,309.
- The submitted economic evaluation assumed that the effectiveness and safety of acamprosate was equivalent to naltrexone and intensive behavioural therapy, based on evidence from clinical trials, including the COMBINE trial. Limited comparative clinical evidence indicates no significant differences in abstinence among these interventions.

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## *CEDAC Final Recommendation — Issued March 27, 2008*

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Following careful consideration and deliberation of the information contained within the CDR Clinical and Pharmacoeconomic Review Reports, CEDAC recommended that acamprosate be listed in patients who have been abstinent from alcohol for at least four days and who have contraindications to naltrexone (currently receiving opioids, acute hepatitis or liver failure). The maximum treatment duration should be one year.

# APPENDIX I: METHODOLOGY FOR THE FULL CDR CLINICAL REVIEW

## Methods

## Reviewer Information

- A critical appraisal of a published systematic review of clinical trials was performed by two CDR clinical reviewers.
- The systematic review of clinical trials was prepared by two CDR clinical reviewers in consultation with an external clinical expert specializing in addiction medicine.
- Supplemental Issues were prepared by CDR reviewers.
- Background Information on the Condition (not included in this Overview) was prepared by an external clinical expert specializing in addiction medicine.

## Systematic Review Methods

### Review Protocol

- The review protocol was developed jointly by the two CDR clinical reviewers and the external clinical expert in consultation with the internal and external pharmacoeconomic reviewers. Members of the Canadian Expert Drug Advisory Committee (CEDAC) also provided input and comments.

### Literature Search Methods

- The literature search was performed by an internal CDR information specialist using a standardized search strategy.
- Published literature was identified by searching the following bibliographic databases: BIOSIS Previews, EMBASE, PsycINFO and MedLine through Ovid, and The Cochrane Library (2007, Issue 3) through Wiley InterScience.
- Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. The initial search was completed September 19, 2007. Regular alerts were established to update the search until CEDAC's January 23, 2008 meeting.
- Grey literature was obtained by searching the web sites of regulatory, health technology assessment and near-technology assessment agencies, and clinical trial registries. Google and other Internet search engines were used to search for a variety of web-based information, including conference abstracts.
- In addition, the manufacturer of the drug was contacted for additional information regarding trial data.

### Selection of Studies

- Each CDR clinical reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

**Selection Criteria**

- Studies were chosen for inclusion in the review based on the criteria listed in Table 1, located in the body of this report.
- The protocol was amended on November 2, 2007. Acamprosate has been available for more than 10 years in Europe and was approved for use in the US in 2004. There are numerous clinical trials comparing acamprosate with placebo, the earliest of which dates back to the 1980s. At the time of identification of the 16 unique RCTs, (Figure A1 in this Appendix - QUOROM), it was noted by CDR reviewers that a number of systematic reviews of acamprosate versus placebo had been published. The large number of primary studies of acamprosate, the identification of a number of systematic reviews, and the desire to avoid duplication of work led to the decision to select a published systematic review (Mann *et al.*.) as the basis of the evidence for acamprosate in comparison with placebo for this review.

**Quality Assessment**

- Study bias was critically assessed independently by the two CDR clinical reviewers.

**Data Analysis Methods**

- Data was extracted from published literature and unpublished literature provided by the manufacturer. For binary outcomes, clinical reviewers used Review Manager software v4.2.10 to calculate relative risks and 95% CIs. No pooling of data was conducted.
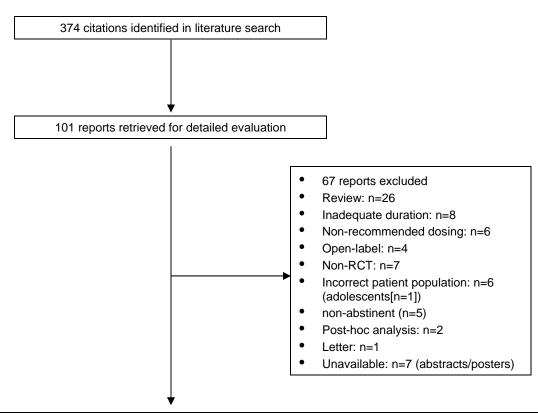
## Methods for Supplemental Issues

In addition to the systematic review, a number of supplemental issues were extensively considered and reported within an 18-page supplemental issue section of the CDR Clinical Review Report.

Supplemental Issues included:
- Additional clinical trials – see Appendix II
- Additional harms information
- Comparator information
- Validity of outcome measures – see Appendix III
- Psychosocial interventions – see Appendix IV.

## Findings from the Literature for the Original CDR Protocol

**Figure A1:** QUOROM Flowchart Detailing Flow of Studies

374 citations identified in literature search

101 reports retrieved for detailed evaluation

- 67 reports excluded
- Review: n=26
- Inadequate duration: n=8
- Non-recommended dosing: n=6
- Open-label: n=4
- Non-RCT: n=7
- Incorrect patient population: n=6 (adolescents[n=1])
- non-abstinent (n=5)
- Post-hoc analysis: n=2
- Letter: n=1
- Unavailable: n=7 (abstracts/posters)

**34 relevant reports for inclusion in systematic review containing 16 unique RCTs**

**Lhuintre, 1990**[5]
Hillemand, 1989[6]

**Ladewig, 1993**[29]

**Paille, 1995**[30]
Sass, 1993(abstract)[31]

**Sass, 1996**[32]
Soyka, 1994[33]
Sass, 1996[34]

**Whitworth, 1996**[35]
Whitworth, 1996(abstract)[36]
Whitworth, 1995(abstract)[37]

**Poldrugo, 1997**[42]

**Barrias, 1997**[38]

**Geerlings, 1997**[39]
Geerlings, 1995[40]

**Pelc, 199**[41]

**Besson, 1998**[43]

**Chick, 2000**[44]

**Tempesta 2000**[45]

**Gual, 2001**[46]

**Kiefer, 2003**[14]
Kiefer, 2004 [15]
Kiefer, 2002(abstract)[16]
Kiefer, 2003 [17]

**Baltieri, 2003**[7]
Baltieri, 2004[8]

**Morley, 2006**[9]
Richardson, 2006 (abstract)[10]
Teesson, 2006 (abstract)[11]
Morley, 2006 (abstract)[12]
Morley, 2006 (abstract)[13]

FDA – Medical Review[18]
FDA – Statistical Review[19]
CDR Submission Binder[20]

RCTs=randomized controlled trials

| Table A1: Trials Identified by CDR, included in the Mann *et al.*. Systematic Review, and Submitted to Health Canada and the Food and Drug Administration (FDA) | | | |
|---|---|---|---|
| **All Identified Trials** | **Identified by CDR** | **Included in Published Systematic Review** | **Safety Data Submitted to Health Canada and/or the FDA** |
| Lhuintre, 1990 | X | | |
| Pelc, 1992 | | X | |
| Ladewig, 1993 | X | X | X |
| Borg (unpublished) | | X | |
| Paille, 1995 | X | X | X |
| Roussaux, 1996 | | X | |
| Sass, 1996 | X | X | X |
| Whitworth, 1996 | X | X | X |
| Barrias, 1997 | X | X | X |
| Geerlings, 1997 | X | X | X |
| Pelc, 1997 | X | X | X |
| Polodrugo, 1997 | X | X | X |
| Besson, 1998 | X | X | X |
| Chick, 2000 | X | X | X |
| Tempesta, 2000 | X | X | X |
| Gual, 2001 | X | X | X |
| Kiefer, 2003 | X | X | |
| Namkoong | | X | |
| Baltieri, 2003 | X | | |
| Morley, 2006 | X | | |
| Mason, 2006 | | | X |

# APPENDIX II: COMBINE TRIAL

The COMBINE (Combined Pharmacotherapies and Behavioural Interventions for Alcohol Dependence) study[22] was conducted to evaluate the efficacy of medical management (MM), drug therapy (acamprosate, naltrexone), combined behavioural intervention (CBI), and their combinations for the treatment of alcohol dependence and to evaluate the placebo effect on overall outcome. The randomized controlled trial (RCT) included 16 weeks of treatment and up to one year follow-up, post-treatment. This RCT enrolled 1,383 recently abstinent volunteers recruited through advertisement and by clinical referrals.

MM was a nine-session intervention by a licensed health care professional that focused on enhancing medication adherence and abstinence, using a model that could be adapted in primary care settings.
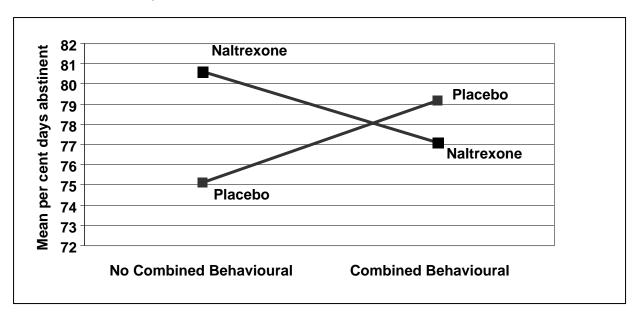
CBI was more intensive counselling delivered by licensed behavioural health specialists integrating aspects of cognitive behavioural therapy, 12-step facilitation, motivational interviewing, and a support system involvement external to the study.

Eight treatment combinations were chosen to form a two (acamprosate/placebo) by two (naltrexone/placebo) by two (CBI/no CBI) factorial design. A ninth group received CBI only (no MM or drugs). Provision of medications was double-blinded using a double-dummy design (as described below), with the exception of the treatment arm, which received CBI only (no MM or drugs). For this reason, we provide data only for the eight-treatment arms, which were double-blinded. There were two co-primary endpoints: per cent days abstinent and time to first heavy drinking day during the 16-week treatment period.

**Summary of Results:** Seventy-six pre-treatment characteristics were compared across groups, and the only significant between-group difference was the number of *Diagnostic and Statistical Manual of Mental Disorders*-IV alcohol dependence symptoms [i.e., $5.4 \pm 1.3$ for the collapsed MM plus CBI groups versus $5.6 \pm 1.3$ for MM without CBI; $P<0.05$]. There were no statistically significant differences in retention between groups, and the average one-year post-treatment drinking data completion rate was 82.3%, with no significant differences between groups. Mean medication adherence through 16 weeks was 86% (median 96%). A total of 6% of participants were lost to follow-up and assumed to have resumed heavy drinking. Ongoing or recurrent dose reductions were 7.8% (placebo), 11.9% (acamprosate), 12.1% (naltrexone), and 20.9% (acamprosate plus naltrexone). Therapist adherence rates were high and considered to be acceptable. Biological verification [% carbohydrate-deficient transferrin (CDT) level] corroborated reports of drinking or abstinence from participants. Rates of SAEs and WDAEs were similar across the groups, although there were significant differences between groups in some AEs (e.g., nausea, vomiting, diarrhea, and somnolence).

**Within-Treatment Drinking Outcomes for Drug-Taking Groups:** For per cent days abstinent, there were no significant differences between acamprosate or naltrexone and placebo, or for CBI and no CBI (main effects). However, a statistically significant effect was observed for naltrexone compared with placebo when stratified by CBI treatment (interaction effect); p=0.009. Specifically, for participants not receiving CBI, the adjusted mean per cent days abstinent were 80.6% versus 75.1% for naltrexone and placebo respectively, while for participants receiving CBI, the adjusted mean per cent days abstinent were 77.1% versus 79.2% for naltrexone and placebo respectively. This interaction is illustrated in the subsequent diagram. Thus, it appears

that naltrexone results in significantly greater mean days abstinent compared with placebo, only for those not receiving CBI; Cohen d=0.22 (97.5% CI 0.03-0.40).



For "time to return to heavy drinking", there were no significant differences between acamprosate and placebo, or CBI and no CBI. A significant p-value is evident for the comparison of naltrexone to placebo; however, because of the significant interaction with CBI, the effect of naltrexone can only be interpreted when considered in conjunction with CBI. Specifically, naltrexone increased the "time to return to heavy drinking" compared with placebo, only in those participants not receiving CBI; harms ratio (HR)=0.78 (97.5% CI 0.63-0.97).

For numbers of participants with $\geq$1 heaving drinking day during treatment, the only significant difference was in the comparison of main effects between naltrexone and placebo; 71.4% versus 68.2% respectively (p=0.02). It should be noted that the naltrexone and CBI interaction was not significant for this endpoint (p=0.15). There were no statistically significant differences for acamprosate alone or with any combination of naltrexone, CBI, or both, for either main effects or interactions. Alternate secondary analyses of drinks per drinking day (p=0.03), drinks per day (p=0.03), or heavy drinking days per month (p=0.006) were consistent with the primary outcomes (i.e., the only statistically significant results were for the naltrexone and CBI interaction). Differential treatment effects were not apparent on gamma-glutamyltransferase (GGT) or %CDT levels.

**Post-treatment Follow-up Outcomes:** There were no differences in hospitalization (11%); emergency department treatment for alcohol problems (6%); use of medication for drinking (11%), or emotional problems (17%); and detoxification (6%) between groups. Overall, per cent days abstinent declined in all groups after treatment ended and although the direction of differences seen during treatment remained, the naltrexone and CBI interaction was no longer significant. Overall, more participants had at least one heavy drinking day during the post-treatment period than during treatment. The direction of effects persisted and only those receiving naltrexone showed nominally less risk when main effects were compared [i.e., HR: 0.77 (97.5% CI: 0.58, 1.02); p=0.04]. There were no significant differences for any interactions.

**CDR Comments:** Approximately 5,000 potential participants were screened for COMBINE; however, only 1,383 (28%) were randomized to treatment. No explanation was provided for the high rejection rate other than individuals "did not meet eligibility criteria," which resulted in a highly selected cohort, possibly introducing selection bias. The trial was also not completely double blind. All study site personnel (investigators, research staff, evaluators, health care practitioners, CBI therapists) and participants were blinded to medication assignment; however, research assistants who assessed alcohol consumption and craving at the nine MM visits were not blinded to (but were not involved in providing) psychosocial treatment. Based on tolerability, the MM clinician could reduce the acamprosate dose; however, it was not clear if concurrent reductions in naltrexone or placebo dose were also done, although it was indicated that attempts were made to re-establish the full dose. Despite these concerns, the balanced treatment groups (based on baseline variables), high drug and therapy adherence, complete 16-week drinking data for approximately 94% of the sample, and biological verification of self-report support good internal validity. Limitations of the study regarding external validity are the intensive research assessments (up to 12 hours), patient recruitment, treatment in non-primary care academic settings, exclusion of participants with substantial concurrent psychiatric illness and drug abuse, and the limited duration of treatment (16 weeks).

The doses of acamprosate (3 g/day) and naltrexone (100 mg/day) used in COMBINE are higher than the usual recommended doses (i.e., acamprosate 2 g/day and naltrexone 50 mg/day). According to the investigators, higher doses were used because they could be more efficacious and provide better coverage for missed doses; however, this compromises external validity and must be considered in comparison to results with other trials. The investigators commented on their surprise in the lack of acamprosate efficacy, especially in light of the higher dose used. They noted a number of differences between COMBINE and previous positive acamprosate studies, which were the requirement in COMBINE for only four days of abstinence, achieved primarily on an outpatient basis; whereas other acamprosate studies had a longer pre-treatment abstinence period established during inpatient treatment. Other trials used less frequent assessment, non-standardized counselling, and patients recruited from clinical (primarily inpatient) settings. Other commentaries have attributed the lack of acamprosate efficacy to differences in patient populations, study designs, the rigorous retention strategy for COMBINE, and possibly the modest effects of the specific treatments and lack of additive or synergistic effects of combining treatments.[47] Another hypothesis is that previous acamprosate studies included alcohol-dependent patients during medically supervised detoxification (generally inpatients), whereas only 2.3% of the patients in COMBINE required any medication during detoxification, thus implying that 98% of the COMBINE patients did not exhibit significant withdrawal symptoms. This is where the pharmacologic action of acamprosate is thought to act (i.e., attenuation of the hyperglutamatergic state that underlies acute and protracted alcohol withdrawal).[48]

# APPENDIX III: VALIDITY OF OUTCOME MEASURES

## Self-Report

There are many types of self-report measures of alcohol use; however, the two general approaches most widely used are:
- quantity and frequency (Q/F) methods
- retrospective and prospective daily estimation procedures.

Q/F measurement requires respondents to summarize the amount of alcohol they consume and the frequency with which they drink, either for specific timeframes (e.g., a week, past month, past year) or in terms of their "typical" or "usual" drinking patterns. Daily estimation requires individuals to report the amount they drink on each day during a specified time interval.

The validity of self-report as an outcome measure in alcoholism treatment studies is controversial and remains a subject of debate despite its widespread use. Nonetheless, the majority of studies in the literature have concluded that various types of self-report are valid and reliable based on comparisons with collateral reports, alcohol sales or other objective measures of alcohol consumption, blood and/or urine ethanol concentrations, and changes in biological markers. Reasons for lack of accuracy of self-report may be attributed to patient factors (e.g., denial, lack of motivation, cognitive, or memory deficits) and/or methodological problems (e.g., small sample sizes, Q/F of drinking, specificity of validation criteria, and timeframe of reports). A recent review[49] of the reliability, validity, and utility of alcohol self-report measures concluded that self-report has demonstrated reasonable validity and reliability, but cautioned that no single measure of alcohol use is suitable for all research purposes and populations. The authors advise that corroborating data sources should be used in studies because alternative measures may allow investigators to assess whether differential biases are present across conditions, time points, or respondent groups.

# APPENDIX IV: PSYCHOSOCIAL INTERVENTIONS

**Brief Intervention:**  Brief interventions are generally considered to be any therapeutic or preventative consultation of short duration (i.e. one to five sessions) undertaken by a health care professional, general practitioner, or nurse with the goal of reducing alcohol consumption.[50] They may vary in intensity and typically include an initial counselling session of 10 to 15 minutes, incorporating feedback, advice, and goal setting, along with follow-up to assess change and to reinforce goals.[51] Several systematic reviews and meta-analyses[52-55] have concluded that brief intervention is effective in reducing alcohol consumption. A 2007 Cochrane review[53] (21 RCTs, n=7,286) found that alcohol consumption was reduced by -41 g/week (95% CI: -57; -25) in those receiving brief intervention compared with controls, although there was substantial heterogeneity between trials. Subgroup analysis by gender showed a significant benefit in men, but not in women. There appeared to be no significant benefit of extended intervention when compared with brief intervention.

**Motivational Enhancement Therapy:**  Motivational interviewing (MI) is a counselling technique for eliciting behaviour change by helping the patient explore and resolve ambivalence about change.[51] A meta-analysis[50] was conducted of 15 studies (n=2,767, nine studies comparing MI with no treatment and nine studies comparing MI with another treatment; three of the studies compared both). The other treatments included usual, brief advice, standard care; directive-confrontational counselling; educational intervention; skill-based counselling; and cognitive behavioural treatment. The primary outcome measure was the between-groups effect size (a measure of alcohol consumption). Positive values of effect sizes indicate better outcomes for MI. It was found that the aggregate effect size of MI was 0.18 (95% CI: 0.07; 0.29) when compared with no treatment and 0.43 (95% CI: 0.17; 0.70) when compared with another treatment.

**Cognitive Behavioural Therapy:** This intervention is a structured, goal-directed form of psychotherapy in which patients learn how their thought processes contribute to their behaviour.[51]  Increased cognitive awareness is combined with techniques to help patients develop new and adaptive ways of behaving, and to alter their social environment, which in turn leads to change in thoughts and emotions.

**Alcoholics Anonymous and Other 12-Step Programs:** Alcoholics Anonymous (AA) is a self-help group organized through an international organization of recovering alcoholics. The group offers emotional support and a model of abstinence using a 12-step approach.[56] Although AA is the most common program, there are other 12-step approaches available (labelled Twelve Step Facilitation or TSF). A 2006 Cochrane systematic review[56] assessed the effectiveness of AA or TSF compared with other forms of PSI. Eight trials (n=3,417) were included; however, the findings were inconclusive.

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