# National PBM Monograph
# Naltrexone (ReVia®) vs. Acamprosate (Campral®)
# Addendum February 2006

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

*The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.*

Refer to the National PBM Drug Monograph Acamprosate (Campral®) at http://vaww.pbm.va.gov/drugmonograph/aer8aw37AcAcamprosate%20NM.pdf or http://www.pbm.va.gov/monograph/aer8aw37AcAcamprosate%20NM.pdf

## Introduction:

Alcohol dependence is a devastating health, social and economic problem. Pharmacotherapeutic strategies including adding naltrexone and acamprosate as adjuncts to alcohol rehabilitation treatment programs have been shown to be effective in the relapse prevention of alcoholism. Please refer to the following links for a further description of the pharmacologic and pharmacokinetic properties of these agents. http://vaww.pbm.va.gov/drugmonograph/aer8aw37AcAcamprosate%20NM.pdf or http://www.pbm.va.gov/monograph/aer8aw37AcAcamprosate%20NM.pdf

An abundance of studies determining the relative effectiveness of naltrexone to placebo in combination with psychosocial treatments is available in the literature. However, a limited number of studies is available that actually evaluate naltrexone vs. acamprosate specifically in the treatment of alcohol dependence. The purpose of this addendum is to review the available comparative studies in the literature on the effectiveness of naltrexone vs. acamprosate as adjunct to psychosocial treatment in attenuating or preventing relapses in alcohol dependence.

## Summary of Meta-Analysis[1] (Refer to Appendix A )

Meta-analysis of data only from RCTs including drug sponsor documents was included in analysis. Subjects with ICD-10 diagnosis for alcohol dependence (but not currently abstinent) using naltrexone (NTX), nalmefene and other opioid antagonists with or without other biological or psychosocial treatments were included.

## NTX vs. acamprosate (short-term outcomes): (1 study) (Refer to Table 1)

No outcome except the discontinuation rate was computed. The reported discontinuation rates were not significantly different between NTX and acamprosate.

Table 1: Short-Term* Outcome of naltrexone (NTX) vs. acamprosate

| Outcome | NTX (n=40) | acamprosate (n=40) | RR, (95% CI) |
|---|---|---|---|
| Number of participants discontinuing therapy, (%) | 18 (45) | 23 (57.5) | 0.78, (0.51-1.21) |

* 12 weeks ≥ 3 months; RR= Relative Risk (Random)

## NTX vs. acamprosate (medium-term outcomes): (1 study) (Refer to Table 2)

NTX was marginally, but not significantly superior in the respect of discontinuation rate. NTX was superior in reducing the risk of relapse, standard drinks (number of drinks consumed at one time) and craving. No significant difference between the groups was found on the outcome of time to first drink.

Table 2: Medium-Term* Outcomes of naltrexone (NTX) vs. acamprosate

| Outcomes | NTX (n=77) | acamprosate (n=80) | Results |
|---|---|---|---|
| Number of participants discontinuing therapy, (%) | 8 (10.4) | 18 (22.5) | RR 0.46, 95% CI 0.21 - 1.00 |
| Number of participants with relapses or return to heavy drinking | 45 | 66 | RR 0.71, 95% CI 0.57 - 0.88 |
| Mean number of drinks consumed at one time, (SD) | 4 (6) | 9 (7) | SMD -0.76, 95% CI -1.09 - -0.44 |
| Mean composite craving severity score,** (SD) | 11.3 (10.1) | 15.3 (12.1) | SMD -0.36, 95% CI -0.67 - -0.04 |
| Mean number of days to first alcohol consumption, (SD) | 44 (36) | 39 (28) | WMD 5, 95% CI -5.11-15.11 |
| Mean duration of adherence to therapy, (SD) | 44 (6) | 35 (6) | WMD 9, 95 CI 7.12-10.88 |

*3 months≥ 12 months; RR= Relative Risk (Random); SMD= Standardized Mean Difference, (Random) ** based on the average of 3 score scales (frequency, duration and intensity); WMD=weighted Mean Difference (Random)

## Summary of Head-to-Head Trials: (Refer to Appendix A)

Table 3 lists the evidence level and strength of recommendation for each of the included studies based on terms used by the VA National Clinical Practice Guideline Council and US Preventive Services Task Force.
See http://vaww.pbm.va.gov/directive/Guidance%20Off%20Label%20Prescribing.pdf.

Table 3: Quality, Grade and Level of Recommendation of Evidence per Individual Trial

| Trials | Quality of Evidence | Overall Quality | Grade of Recommendation |
|---|---|---|---|
| Rubio et al. (2001) | II-1 | Fair | C |
| Kiefer et al. (2003) | I | | |
| Srisurapanont et al. (2005) | I | | |

**Rubio et al.**[2] (2001) conducted a randomized, 12-month single-blind trial in Spain. The 157 males participants were alcohol-dependent (DSM-III-R) with a mean age of 43 years (range: 18-65) and recruited after completing detoxification in the hospital or as an outpatient. Interventions included naltrexone 50 mg/day (n=77) vs. acamprosate at 1665-1998 mg/day (n=80). All participants received supportive group therapy. The primary outcome variables were the following: days of accumulated abstinence and days to first relapse (defined as the consumption of more than 5 drinks of 40 g ethanol per day). Additional outcome variables were number of drinks consumed per week, number of drinks consumed at a time, craving, abandonment of pharmacological treatment, drop-out from the study and 3 monthly serum GGT.

The average period between the last drink and the start of treatment was 16 days (range 10-22). At the end of the treatment year, 41 patients in the naltrexone group were abstinent compared to 22 patients in the acamprosate group; p=0.0002. The mean number of days before the first relapse (≥ 5 drinks per day) was longer for patients taking naltrexone (63 days) than those taking acamprosate 42 days ( p=0.02). The mean number of days to the first alcohol consumption was not significant between the two groups. Fewer patients randomized to naltrexone used disulfiram compared to patients randomized to the acamprosate group.

**Kiefer et al.**[3] (2003) conducted a 12- week randomized, double-blind, placebo-controlled, multi-center study in Germany in 160 patients with alcohol dependence (DSM-IV) with a mean age of 46 years (range: 18-65). Four interventions were studied including: naltrexone 50 mg/day (n = 40) vs. acamprosate 1998 mg/day (n = 40) vs. naltrexone plus acamprosate (n = 40) vs. placebo (n = 40). All participants received group cognitive-behavioral therapy. Outcomes measured included the discontinuation rate, time to first drink, time to relapse, and the cumulative abstinence time. It was determined that the relapse prevention treatment with naltrexone, acamprosate and the combined medication was significantly more effective than placebo. There was no significant difference in time to first drink between naltrexone and acamprosate.

**Future Studies: Combining Medications and Behavioral Interventions (COMBINE) Study**[4]

The Combine Study is a large, national study sponsored by the National Institute on Alcohol Abuse and Alcoholism. It is a multicenter, randomized, double-blind, placebo controlled clinical trial that will examine the effects of naltrexone and acamprosate and two psychosocial therapies, alone and in various combinations during a 12 month period. The primary outcomes will be percent days abstinent and time to relapse to heavy drinking. Secondary outcomes will include duration of abstinence; measures of frequency and intensity; psychological assessments; quality of life; and adverse experiences. The study started in August 1997 with an enrollment of 1,375 participants that had a current DSM-IV diagnosis of alcohol dependence. Of interest, a press release from NIH dated March 8, 2001 (See http://www.nih.gov/news/pr/mar2001/niaaa-08.htm) announced the trial and stated that recruitment would take place over the next 24 months. Publication of this study is pending. Results will provide further information on perhaps which agent along with behavioral intervention will improve treatment outcomes in patients with alcohol dependence.

**Conclusions and Recommendations:**

There is limited evidence available suggesting one agent is superior to the other. There are two RCTS comparing NTX and acamprosate. Of those studies, one was conducted in a single-blind fashion and the other had only 40 subjects in each arm.

Short-term treatment of NTX is an acceptable option for short-term treatment for alcoholism. Because psychosocial therapy was provided in almost all included trials, some form of psychosocial therapy should be concomitantly given to all alcohol-dependent patients receiving NTX treatment. Although NTX treatment is more acceptable than placebo, approximately 37% of those taking NTX discontinued their treatment in the first 12 weeks.

If both NTX and acamprosate are available, NTX may be preferred, especially for the medium-term treatment patients although many questions such as the duration of therapy are not known. It was found in a short-term trial that only NTX but not acamprosate was superior to placebo. A medium-term treatment of NTX gave no benefit for the risk of returning to drink although it was superior to acamprosate (based on one study) in reducing the risk of relapse, standard drinks and craving. Additional issues such as side-effect profiles, costs, and patient acceptance need to be considered when selecting drug of choice.

Some major limitations of the available evidence include few number of studies, short study duration, small sample sizes, high drop-out rates in most studies and the lack of data on psychosocial benefits. Minimal information regarding mortality, health-related quality of life, patient satisfaction, or degree of functioning is available comparing differences between these agents.

**References:**

1. EBM Reviews-Srisurapanont: The Cochrane Library, Volume (4).2005.Opioid antagonists for alcohol dependence. Srisurapanont, M; Jarusuraisin, N. http://gateway.ut.ovid.com/gw1/ovidweb.cgi#toc. Assessed 2005 November.
2. Rubio G, Jimenez-Arriero MA, Ponce G et al. Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. Alcohol and Alcoholism 2001. 36: 419-25.
3. Kiefer F,Holger J, Tarnaske T, et al. Comparing and Combining naltrexone and acamprosate in relapse prevention of alcoholism. Arch Gen Psychiatry 2003; 60:92-99.
4. COMBINE: Effect of Combined Pharmacotherapies and Behavioral Interventions. http://clinicaltrials.gov/ct/gui/show/NCT00006206?order=23. Assessed 2005 December.

## Appendix A: Naltrexone (NTX) vs. Acamprosate Trials

| TABLE 1. Meta-analysis | Inclusion and Endpoints | Comparisons and Trial Characteristics | Results | Summary |
|---|---|---|---|---|
| Srisurapanont, M; Jarusuraisin, N, 2005 | DATA SOURCES<br><br>Cochrane Group on Drugs and Alcohol (September 2003); Cochrane Controlled Trials Register (Cochrane Library 2001, issue 4), MEDLINE (1966-October 2001), EMBASE (1980-December 2001), CINHAL (1982-December 2001). Du Pont Pharmaceutical and Ivax Corporation were contacted for information regarding unpublished trials. The reference lists of the obtained papers were examined | 29 RCTs were included. All the trials investigated naltrexone (NTX) except 2. Only 2 studies included acamprosate as one of the comparative arms to NTX. The total number of participants assigned to NTX treatment was 1,810 (n=82 with dual alcohol and cocaine dependence; n=6 with alcohol abuse; all others were alcohol-dependent patients.) The sample sizes of most trials were between 0-99 in each arm. Except for 4 trials, all administered NTX daily at 50mg/day. Of the 27 NTX trials:<br>23 had a placebo arm<br>6 provided the details of techniques used for randomization<br>24 applied a double-blinded design<br>9 had duration for longer than 12 weeks | **NTX vs. placebo: (short-term)**<br><br>Risk of Relapse:<br>RR 0.64, 95% CI 0.51-0.82<br><br>Risk of returning to drinking:<br>RR 0.87, 95% CI 0.76-1.00<br><br>Discontinuation Rate:<br>RR 0.82, 95% CI 0.70-0.97<br><br>**NTX vs. Acamprosate (Short-Term)**<br><br>Discontinuation Rate:<br>RR 0.78, 95% CI 0.51-1.21<br><br>**NTX vs. Acamprosate (Medium-Term)**<br><br>Risk of Relapse:<br>RR 0.71, 95% CI 0.57 to 0.88<br><br>Standard Drinks: (Mean Number of drinks consumed at one time)<br>SMD -0.76, 95% CI -1.09 --0.44<br><br>Craving: (Mean composite craving severity score):<br>SMD -0.36, 95% CI -0.67 --0.04<br><br>Discontinuation Rate of Therapy:<br>RR 0.46, 95% CI 0.21 -1.00 | **NTX vs. placebo**<br>NTX treatment can decrease the chance of alcohol relapse by 36% (NNT=7) compared to placebo. In addition, the treatment is likely to reduce the chance of returning to drinking for 13% (NNT=12). Apart from small benefits on time to first dink and craving, no available evidence supports a meaningful benefit of NTX after 12 weeks of treatment. Alcohol-dependent patients taking NTX are more likely to accept the treatment program. According to RR of 0.82 for dropout comparison between NTX and placebo group , the treatment can lower the risk of treatment withdrawal for 18% (NNT=13), however, approximately 37% (319/868) of those taking NTX may discontinue their treatment in the first 12 weeks. Four trials reported that NTX was significantly superior to placebo in decreasing the relapse, 2 RCTS did not find the difference. Three trials reported conflicted results relevant to returning to drinking.<br><br>**NTX vs. acamprosate (short-term)**<br>The reported discontinuation rates were not significantly different between groups. It one short-term trial, NTX, but not acamprosate was superior to placebo. Because the differential benefits were not much, the sample size of 40 in each arm of that study was not large enough to detect that modest difference. NTX may be meaningfully superior to acamprosate in reducing the risk of alcohol relapse.<br><br>**NTX vs. acamprosate (medium-term)**<br>NTX seems to be meaningfully superior to acamprosate in decreasing the risk of relapse for 29% (NNT = 5). However, NTX may not be more beneficial on the risk of returning to drinking. These findings may suggest that the superiority of NTX in comparison to acamprosate would be observed only if the treatment lasts long enough (e.g., more than 12 weeks) and the relapse but not the return to drinking is of concern. In addition, NTX may have a small benefit in reducing the number of drinks consumed at one time. |
| Limitations of the Evidence: Short study duration (9/29 trials were longer than 12 weeks); small sample size (3/29 trials had at least 87 subjects in each arm); Psychosocial benefits including patient satisfaction , quality of life, cost and mortality are not measured consistently, minimal amount of evidence using NTX or other pharmacologic agents for that matter in alcohol-dependent patients with comorbidities or alcohol abuse, high-drop out rates in most studies; minimal evidence in different ethnic groups of people. Other limitations include inconclusive definitions and measures used for assessing alcohol treatment outcomes such as alcohol relapse or heavy drinking. Scales used for assessment of craving also vary. | | | | |

RR-Relative Risk; NTX= Naltrexone; Short-term= 12 weeks ≥3 months; RR= Relative Risk ;Medium term= 3 months≥ 12 months

<table>
<tr><th>Study/Design/Purpose</th><th>Inclusion/Exclusion</th><th>Treatment</th><th>Patient Characteristics/Outcomes</th><th>Withdrawals/ Adverse Events/</th></tr>
<tr>
<td>Kiefer et al. (2003)<br>R, DB, PC, MC x 12 weeks in Germany.<br><br>Determine whether both compounds are equally effective and superior to placebo. The combination of both drugs was studied whether it was more effective than a single therapy or placebo.</td>
<td>Inclusions:<br>• At least 5 DSM-4 criteria of alcohol dependence<br>• Between 18-65 years<br>• Body weight of 60-90 Kg<br>• Complete abstinence for 12-15 days<br>• Free of any withdrawal symptoms<br>• Drug screening tests were negative for benzodiazepines, cannabinoids, barbiturates, opiates, cocaine and amphetamines<br>Exclusions:<br>• A current DSM-IV diagnosis of dependence or abuse on other substances except nicotine assessed by the structured clinical interview for DSM-IV<br>• A current mental or psychiatric impairment or disease that required psychotropic medication or inpatient tx on a psychiatric ward<br>• History of opioid or cocaine abuse<br>• A history of psychosis<br>• Current use of any psychotropic medication<br>• Evidence of severe neurology or physical disorders (cerebral, renal, thyroid, or cardiac disease)<br>• History of cirrhosis or laboratory evidence of significant hepatocellular injury<br>• Homelessness<br>• pregnancy, nursing, or refusal to use a reliable method of birth control in women</td>
<td>NTX at 50 mg/day vs. acamprosate at 1998 mg/day vs. NTX plus acamprosate () vs. placebo.<br><br>All participants received weekly group cognitive-beha vioral therapy. Groups had between 8-14 participants, and sessions lasted 90 minutes.<br><br>Medication was given in a double-dummy design.<br><br>Patients were assessed weekly by interview, self-report, questionnaires, and laboratory screening.<br>Study was conducted from November 1, 1998 to November 30, 2000.<br><br>All patients recruited had been admitted to an inpatient alcohol withdrawal program.<br><br>Patients started taking the medication a mean ± SD of 5 ±1 days before discharge from inpatient treatment.</td>
<td>Table 1: Patient Characteristics at Baseline
<table>
<tr><th>Parameter</th><th>Placebo n=40</th><th>NTX n=40</th><th>A n=40</th><th>A + NTX n=40</th></tr>
<tr><td>Age, (mean yrs± SD) †</td><td>45 ± 9..3</td><td>46.1 ± 11.1</td><td>46.3± 7.7</td><td>46.8 ± 10.3</td></tr>
<tr><td>Sex, M/F†</td><td>27/13</td><td>31/9</td><td>30/10</td><td>30/10</td></tr>
<tr><td>Married ,% ¶</td><td>30</td><td>25</td><td>23</td><td>33</td></tr>
<tr><td>Unemployed,% ±</td><td>43</td><td>53</td><td>35</td><td>28</td></tr>
<tr><td>Professional training ,% ¶</td><td>70</td><td>750</td><td>80</td><td>88</td></tr>
<tr><td>Average Alcohol intake before inpatient treatment, ( g/d ± SD) †</td><td>244.79 ±143.65</td><td>257.56 ± 132.83</td><td>275.31 ± 145.70</td><td>242.81 ± 82.53</td></tr>
<tr><td>Mean Intensity of withdrawal on a scale of 1-4 (± SD) ¶</td><td>1.5 ± 1.1</td><td>1.7 ± 2.0</td><td>1.7 ± 1.2</td><td>1.6 ± 0.8</td></tr>
<tr><td>Mean number. of inpatient detoxifications (± SD) ¶</td><td>2.85 ± 3.91</td><td>3.88 ± 5.86</td><td>2.18 ± 2.50</td><td>1.79 ± 2.63</td></tr>
<tr><td>Attendance of self-help groups during the last month ¶</td><td>22.5</td><td>27.5</td><td>27.5</td><td>17.5</td></tr>
</table>
NTX= Naltrexone; A= acamprosate; ¶ Variables without significant differences among groups, † variables that were included as covariates in the multivariate analyses of covariance including years since first alcohol-related problems occurred and GGT.<br><br>Note: Curves of survival probabilities were provided but not the exact data.<br><br>For the outcomes:<br><u>Nonrelapse rates to heavy drinking</u>, using Breslow test, significant differences emerged between:<br>Naltrexone vs. placebo, p=.02<br>Acamprosate vs. placebo, p=.05<br>Combined medication vs. placebo, p=.008<br><br>No significant difference in the course of nonrelapse rates between NTX and acamprosate. However, the combined medication was more effective than acamprosate (p=.04) but not with naltrexone.<br><u>First alcohol intake (Breslow test)</u><br>Naltrexone vs. placebo, p=.03<br>Acamprosate vs. placebo, p=.04<br>Combined medications vs. placebo, p=.002<br><br>No significant difference in time to first drink between naltrexone and acamprosate. The combined medication was significantly more effective than acamprosate (Breslow test, p=.04) but not with naltrexone.</td>
<td>782 patients were aware of the study/ 196 were willing to learn details of the study/ 160 randomized/85 completed study<br><br># Pts. withdrawn because of relapse (%):<br>Placebo: 30<br>NTX: 12<br>Acamprosate: 17<br>NTX + Acamprosate:9<br><br># Pts withdrawn due to adverse effects: relapse (%):<br>NTX: 4<br>Acamprosate: 3<br>NTX + Acamprosate: 4<br><br>1 fatigue, 1 rash, 1 itching, 2 abdominal bloating, 1 diarrhea, 2 pruritus, 3 nausea<br><br># Pts withdrawn due to medical illness<br>Placebo:2<br><br># Pts withdrawn due to changed into psychotherapy<br>Acamprosate: 2<br>NTX + acamprosate: 1<br><br># Pts withdrawn to due rejected participation:<br>Acamprosate: 1</td>
</tr>
<tr>
<td colspan="5">Study Conclusions/Efficacy: 75/160 (46.9%) completed study, 17 (10.6%) were abstinent at the time they dropped, and 68 (42.5%) relapsed of which 61 discontinued participation. No significant differences in the course of nonrelapse rates to heavy drinking between NTX and acamprosate. Relapse prevention with both agents was superior to placebo, with a tendency for a better outcome in the naltrexone group compared with the acamprosate group in maintenance of abstinence. No significant difference in time to first drink was seen between naltrexone and acamprosate. No significant differences across treatment groups for final GGT values at 12 weeks. No difference in attendance among groups. Medication compliance was similar across treatment groups, with an overall mean rate of 81.1% based on returned capsule or table count.<br>Safety: No reasonable differences between the single evaluated adverse effects with the exception of diarrhea (placebo 6.7%, naltrexone, 0.6%; acamprosate, 6.7%; combined medication, 13.8%) and nausea (placebo, 0.4%; naltrexone, 2.5%; acamprosate, 0.6%; combined medication, 5.6%).</td>
</tr>
<tr>
<td colspan="5">Limitations: limited duration of treatment, specific data not provided<br>Quality Assessment: IC: Allocation concealment: A (low risk of bias)</td>
</tr>
</table>

### Study/Design/Purpose

Rubio et al (2001)
R, SB, MC* x 12 months

* Unclear how many centers were involved. It appears authors were affiliated with 2 different hospitals. Patients were recruited from in-patient and out-patient rehabilitation programs. (It is unclear whether these programs were affiliated with the same hospital)

Demonstrate the efficacy and treatment compliance of NTX vs. acamprosate in typical treatment conditions

### Inclusion/Exclusion

Inclusions:

- Male gender aged between 18 and 65 years
- DSM-III R criteria for alcohol-dependence
- Have stable family environment

Exclusions:

- Presence of another substance use disorder(with the exception of nicotine)
- Presence of another psychiatric disorder diagnosed by SCID for DSM-III-R
- Medical condition which could hinder treatment compliance
- AST or ALT > 3x N
- Previous treatment with NTX or acamprosate

### Treatment

NTX 50mg/d ay vs.
Acamprosate (1665-1998mg/day)

Patients visited their psychiatrists every 7 days (± 3 days) over the first 3 months, after which they visited every 15 days, till the end of the study. In the event of relapse, the frequency of visits was increased.

Patients were offered supportive group therapy weekly during the study.

Sertraline could be prescribed (100-200mg/day) if anxiety/depression occurred

Hydroxyzine could be prescribed for insomnia. If relapses occurred, which were difficult to control pharmacologically or psychotherapeutically, disulfiram was added to the treatment until the relapse was fully over (2-3 weeks).
Patients completed detoxification, in the hospital or as an outpatient.

Patients would be removed from trial if they did not keep "in touch" with the investigators for more than 15 days (i.e. two consecutive visits).

### Patient Characteristics/Outcomes

Table 1: Patient Characteristics at Baseline*

| Parameter | NTX (n=77) | Acamprosate (n=80) |
|---|---|---|
| Mean Age (yrs) | 43 ± 10 | 44 ± 12 |
| Married (%) | 95 | 92 |
| Full time employed (%) | 75 | 75 |
| Secondary education (%) | 84 | 85 |
| Mean ASI | 0.70 | 0.71 |
| Mean SADS scale | 29 | 28 |
| Mean percentage of days drinking in past 6 months | 87 | 87 |
| Mean number of days between last drink and study initiation | 15 | 16 |

NTX= Naltrexone; ASI= Addiction of Severity Index; SADS= Severity of Alcohol Dependence Scale; *No significant difference between the group in any of these variables. All comparisons were analyzed by t-tests with df=155.

Table 2: Outcomes after 1 year (Intention-to-Treat)

| Outcomes | NTX n=77 n (%) | Acamprosate n=80 n (%) | P* |
|---|---|---|---|
| Number of subjects who completed study | 69 | 62 | 0.14 |
| Percentage of subjects abstinent since last assessment (6 months) | 41 | 22 | 0.002 |
| # of subjects received disulfiram | 17 | 22 | 0.0002 |
| # of subjects received sertraline | 1 | 1 | 0.9 |
| # of subjects receiving hydroxyzine | 7 | 9 | 0.6 |
| # pts abandoning pharmacological treatment§ | 28 | 37 | 0.21 |

NTX=Naltrexone; * Pairwise $\chi 2$ were used to analyze differences; §provided by a family member accompanying the patient

### Withdrawals/ Adverse Events/

356 considered/197 recruited/160 selected/157 randomized/131 completed

# Pts. withdrawn because of not committing to attend weekly, (%):
NTX: 5 (6.5)
Acamprosate: 5 (6.3)

# Pts withdrawn due to refusing to continue after relapse
NTX: 1 (1.3)
Acamprosate: 13 (16.3)

# Pts withdrawn due to side effects:
NTX: 2 (2.6)
Acamprosate: 0

Table 3: Percentage of patients with side-effects

| Side Effects | NTX n=77 | Acamprosate n=80 | P value |
|---|---|---|---|
| Nausea | 25 | 4 | 0.0001 |
| Abdominal pain | 23 | 4 | 0.0003 |
| Nasal congestion | 23 | 1 | 0.0004 |
| Drowsiness | 35 | 2 | 0.0000 |
| Headache | 13 | 6 | 0.15 |
| Diarrhea | 1 | 4 | 0.3 |
| Epigastric discomfort | 4 | 4 | 0.64 |

Table 3: Additional Outcomes after 1 year (Intention-To-Treat)

| Parameters | NTX n=77 | Acamprosate n=80 | P value |
|---|---|---|---|
| Mean number of days to first alcohol consumption | 44 | 39 | 0.34* |
| Mean number of days to first relapse^ | 63 | 42 | 0.02* |
| Mean number of drinks consumed at one time | 4 | 9 | 0.01** |
| Mean number of days of accumulated abstinence | 243 | 180 | 0.03** |
| Mean composite craving severity score | 11.3 | 15.3 | 0.01** |

^Relapse: consumption of ≥ 5 drinks or 40g ethanol/day,
* Kaplan-Meier survival (log-rank) statistic; **analysis of covariance (ANCOVA)

**Study Conclusion/Efficacy:** No difference between treatments in mean time to first drink (naltrexone, 44 days vs. acamprosate, 39 days). The time to first relapse (≥ 5 or more drinks) was 63 days with naltrexone vs. 42 days with acamprosate; p=0.02. At the end of one year, 41% patients receiving naltrexone and 17% receiving acamprosate had not relapsed; p=0.0009. The cumulative number of days of abstinence was significantly greater, and the number of drinks consumed at one time and severity of craving were significantly less, in the naltrexone group compared to the acamprosate group, as was the percentage of heavy drinking days ; p=0.038. More patients in the acamprosate than the naltrexone group were commenced on disulfiram during the study. There were non-significant trends for the naltrexone group to comply better with medication, to stay in the study longer.
**Safety:** Side-effects were more common in patients taking naltrexone compared to acamprosate. (See Table 3). Authors stated that the side-effects gradually disappeared after the first 2 weeks of the study. There was no significant difference in the rate of drop-out due to the incidence of side-effects.

**Limitations:** Open study design. All participants had moderate alcohol dependence. Compliance was assessed by questionnaires corroborated by information from the family. High level of family support was available. Additional pharmacological agents were available if needed. Multiple ethnic participants were not included.
Quality Assessment: II-1 Allocation concealment: B (Moderate risk of bias) Funding was provided by Fundacion Cerbro y Mente (foundation dedicated to neuroscience research)

R=Randomized, SB=Single blind, MC=Multiple Centers