National PBM Drug Monograph

Acamprosate (Campral®)

April 2005

VETERANS AFFAIRS HEALTHCARE SYSTEM

Executive Summary:

- Acamprosatę is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence. Patients should be abstinent at treatment initiation.
    - The efficacy of Acamprosatę in promoting abstinence has not been demonstrated in subjects who have not undergone detoxification and not achieved alcohol abstinence prior to beginning Acamprosate treatment.
    - The efficacy of Acamprosatę in promoting abstinence from alcohol in polysubstance abusers has not been adequately assessed.
- The mechanism of action of Acamprosate in maintenance of alcohol abstinence is not completely understood.
- Acamprosate is not known to cause alcohol aversion and does not cause a disulfiram-like reaction as a result of ethanol ingestion.
- The absolute bioavailability of Acamprosatę after oral administration is about 11%. Acamprosate does not undergo metabolism. The major route of excretion is via the kidneys. Acamprosate had no inducing potential on the cytochrome CYP1A2 and 3A4 systems, and in vitro inhibition studies suggest that Acamprosate does not inhibit in vivo metabolism mediated by cytochrome CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4.
    - The concomitant intake of alcohol and Acamprosatę does not affect the pharmacokinetics of either alcohol or Acamprosate.
- The efficacy of Acamprosatę in the maintenance of abstinence was supported by three clinical studies involving a total of 998 patients who were administered at least one dose of Acamprosate or placebo as an adjunct to psychosocial therapy. In a fourth unpublished, American study the efficacy of Acamprosatę was evaluated in alcoholics, including patients with a history of polysubstance abuse and patients who had not undergone detoxification and were not required to be abstinent at baseline. This study failed to demonstrate superiority of Acamprosate over placebo.
- Acamprosatę is contraindicated in patients with severe renal impairment (creatinine clearance ≤30 mL/min).
- Acamprosatę did not produce any evidence of withdrawal symptoms in patients in clinical trials at therapeutic doses.
- The recommended dose of Acamprosatę is two 333 mg tablets (each dose should total 666 mg) taken three times daily.
    - Treatment with Acamprosatę should be initiated as soon as possible after the period of alcohol withdrawal, when the patient has achieved abstinence, and should be maintained if the patient relapses.
    - Patients should be advised that Acamprosate has been shown to help maintain abstinence only when used as a part of a treatment program that includes counseling and support.
- Acamprosate delayed-release tablets should be swallowed whole. Tablets are enteric-coated and should not be chewed, crushed or cut.
- Acamprosate is pregnancy category C.
- Due to the lack of available efficacy data in American alcoholics or the VA population, it is recommended that acamprosate not be added to National Formulary.

Introduction

Acamprosate is a synthetic molecule, originally identified by Laboratories Meram (Meram s.a., Paris, France) and subsequently licensed to Lipha s.a. (Lyon, France) for worldwide development. Acamprosate was authorized for marketing in France, for the indication of maintaining abstinence from alcohol post-withdrawal, in 1987 and has been commercially available (as Aotal®) there since 1989, in the 333 mg tablet strength. Lipha also markets the Acamprosate 333 mg tablets (as Campral®) in 38 additional countries. On 6/25/96, Lipha met with the agency in a Pre-IND meeting to discuss plans to seek marketing authorization in the United States. The initial program proposed consisted of a single multi-center efficacy trial using a new (but compositionally proportional) 500 mg tablet, intended to offer a simpler (b.i.d.) regimen with a total daily dose very similar to the labeled dose for the 333 mg tablet (2000 mg as 500 mg, ii p.o. b.i.d. vs. 1998 mg as 333 mg ii p.o. t.i.d.). The single U.S. trial was to support the application as a pivotal safety and efficacy trial; two completed European trials using the 333 mg tablet were to be submitted as confirmatory evidence of efficacy. When the U.S. trial failed to demonstrate superiority of Acamprosate over placebo, further discussions were held and Lipha elected to submit an application for the 333 mg tablet using the European data as pivotal.

Pharmacology/Pharmacokinetics

The mechanism of action of Acamprosate in maintenance of alcohol abstinence is not completely understood. Chronic alcohol exposure is hypothesized to alter the normal balance between neuronal excitation and inhibition. Acamprosate is an analog of homotaurine, a GABA-ergic agonist[1]. The proposed mechanism of action for Acamprosate is that it stimulates inhibitory GABA-ergic neurotransmission in the brain and antagonizes the effects of certain excitatory amino acids, such as glutamate.[1-3] Acamprosate does not affect blood alcohol[4, 5]. Acamprosate is not a sedative, has little or no abuse potential and does not induce dependence[6]. Acamprosate is not known to cause alcohol aversion and does not cause a disulfiram-like reaction as a result of ethanol ingestion.[2]

Formulary Alternatives:

Disulfiram

-Acetaldehyde dehydrogenase (ALDH) inhibitor

-Works as deterrent by causing painful symptoms if alcohol is consumed.

Naltrexone

-Pure opioid receptor antagonist

-Blunts pleasurable effects of alcohol and reduces cravings.

Pharmacokinetics of Alcoholism Treatments

	Acamprosate	Naltrexone	Disulfiram
Metabolism	None	Liver, extensive first-pass metabolism, to **active** metabolite.	Liver to **inactive** metabolites
Elimination	Kidneys: 100% as unchanged Acamprosate	Kidneys: 60% Feces: 2-3%	Kidneys: 70-76% Feces: 20% as unchanged disulfiram
Half-life	20-33 hours	4 hours	12 hours
Protein Binding	0%	21%	96%
Bioavailability	<10%	5-40%	80-90%

FDA Approved Indication(s) and Off-label Uses

Drug	Indication
Acamprosate	- The maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation - Treatment with Acamprosate should be part of a comprehensive management program that includes psychosocial support
Naltrexone	- Alcohol dependence - Narcotic Addiction
Disulfiram	- Alcoholism

Current VA National Formulary Alternatives

Naltrexone (Revia®) – formulary unrestricted
Disulfiram (Antabuse®) – formulary unrestricted

Alcoholism Treatments: Dosage and Administration

Drug	Formulations	Dosage	Comment
Acamprosate	Tablets: 333 mg	Alcoholism: 666 mg TID	-Dosage in renal impairment: ClCr 30-50 mL/min: 333 mg TID ClCr ≤30 mL/min: DO NOT GIVE
Naltrexone	Tablets: 50 mg	Alcohol Dependence: 50 mg daily Narcotic Addiction: Start: 25 mg first day, then 50 mg daily or 100 mg every other day or 150 mg every 3rd day	-Use caution in renal or hepatic impairment. - May cause hepatocellular injury at excessive doses (single doses above 50 mg)[7]
Disulfiram	Tablets: 250, 500 mg	Alcoholism: Start: up to 500 mg daily for 1-2wks, then 250 mg daily (range of 125-500 mg/day) Max: 500 mg/day	-Disulfiram should be used cautiously in patients with hepatic cirrhosis or insufficiency[8]

Efficacy

Efficacy Measures

Acamprosate has been primarily studied as an alcoholism agent. Therefore, in most studies either continuous abstinence or intermittent periods of abstinence was the success measure. Previous European studies didn't have sufficient methodology to allow precise counting of days drinking or not drinking. It is, therefore, difficult to assess abstinence in terms of time. The single, unpublished, U.S. study failed to support the efficacy of Acamprosate.

For further details on the efficacy results of the clinical trials, refer to

Appendix A: Clinical Trials.

Adverse Events (Safety Data)

The adverse event data described below reflect the safety experience in over 7000 patients exposed to Acamprosate for up to one year, including over 2000 Acamprosate exposed patients who participated in placebo-controlled trials.[2]

Common Adverse Events Reported in Controlled Trials:[2]

Events that occurred in acamprosate treatment group at a rate of 3% or greater and greater than the placebo group in controlled clinical trials with spontaneously reported adverse events				
Body System/Preferred Term	**Number of Patients (%) with Events**			
	acamprosate® 1332 mg/day	**acamprosate® 1998 mg/day[1]**	**acamprosate® Pooled[2]**	**Placebo**
Number of Patients in Treatment Group	397	1539	2019	1706
Number (%) with an AE	248 (62%)	910 (59%)	1231 (61%)	955 (56%)
Body as a Whole	**121 (30%)**	**513 (33%)**	**685 (34%)**	**517 (30%)**
Accidental Injury*	17 (4%)	44 (3%)	70 (3%)	52 (3%)
Asthenia	29 (7%)	79 (5%)	114 (6%)	93 (5%)
Pain	6 (2%)	56 (4%)	65 (3%)	55 (3%)
Digestive System	**85 (21%)**	**440 (29%)**	**574 (28%)**	**344 (20%)**
Anorexia	20 (5%)	35 (2%)	57 (3%)	44 (3%)
Diarrhea	39 (10%)	257 (17%)	329 (16%)	166 (10%)
Flatulence	4 (1%)	55 (4%)	63 (3%)	28 (2%)
Nausea	11 (3%)	69 (4%)	87 (4%)	58 (3%)
Nervous System	**150 (38%)**	**418 (27%)**	**598 (30%)**	**500 (29%)**
Anxiety**	32 (8%)	80 (5%)	118 (6%)	98 (6%)
Depression	33 (8%)	63 (4%)	102 (5%)	87(5%)
Dizziness	15 (4%)	49 (3%)	67 (3%)	44 (3%)
Dry Mouth	13 (3%)	23 (1%)	36 (2%)	28 (2%)
Insomnia	34 (9%)	94 (6%)	137 (7%)	121 (7%)
Paresthesia	11 (3%)	29 (2%)	40 (2%)	34 (2%)
Skin and Appendages	**26 (7%)**	**150 (10%)**	**187 (9%)**	**169 (10%)**
Pruritus	12 (3%)	68 (4%)	82 (4%)	58 (3%)
Sweating	11 (3%)	27 (2%)	40 (2%)	39 (2%)

*includes events coded as “fracture” by sponsor; **includes events coded as “nervousness” by sponsor
1 includes 258 patients treated with Acamprosate calcium 2000 mg/day, using a different dosage strength and regimen.
2 includes all patients in the first two columns as well as 83 patients treated with Acamprosate calcium 3000 mg/day, using a different dosage strength and regimen.

Adverse Events Leading to Discontinuation

In placebo-controlled trials of 6 months or less, 8% of Acamprosate treated patients discontinued treatment due to an adverse event, as compared to 6% of patients treated with placebo. In studies longer than 6 months, the discontinuation rate due to adverse events was 7% in both the placebo treated and the Acamprosate-treated patients. Only diarrhea was associated with the discontinuation of more than 1% of patients (2% of Acamprosate-treated vs. 0.7% of placebo-treated patients). Other events, including nausea, depression, and anxiety, while accounting for discontinuation in less than 1% of patients, were nevertheless more commonly cited in association with discontinuation in Acamprosate-treated patients than in placebo-treated patients[2]. For further details on the safety results of the clinical trials, refer to

Appendix A: Clinical Trials.

Precautions/Contraindications

- Use of Acamprosate does not eliminate or diminish withdrawal symptoms.[2]
- **Renal Impairment:** [2] Treatment with Acamprosate in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) requires a dose reduction. Patients with severe renal impairment (creatinine clearance of ≤30 mL/min) should not be given Acamprosate.
- **Suicidality:**[2] In controlled clinical trials of Acamprosate, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in Acamprosate-treated patients than in patients treated with placebo (1.4% vs. 0.5% in studies of 6 months or less; 2.4% vs. 0.8% in year-long studies). Completed suicides occurred in 3 of 2272 (0.13%) patients in the pooled Acamprosate group from all controlled studies and 2 of 1962 patients (0.10%) in the placebo group. Adverse events coded as "depression" were reported at similar rates in Acamprosate-treated and placebo-treated patients. Although many of these events occurred in the context of alcohol relapse, no consistent pattern of relationship between the clinical course of recovery from alcoholism and the emergence of suicidality was identified. The interrelationship between alcohol dependence, depression and suicidality is well-recognized and complex. Alcohol-dependent patients, including those patients being treated with Acamprosate should be monitored for the development of symptoms of depression or suicidal thinking. Families and caregivers of patients being treated with Acamprosate should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's health care provider.

  Acamprosate is contraindicated in patients who previously have exhibited hypersensitivity to Acamprosate calcium or any of its components.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:
LA/SA for generic name *acamprosate*: bacampicillin, acarbose, camptosar, accolate
Potential Severity: Major for camptosar; moderate for acarbose; minor for accolade, bacampicillin
Probability: Remote for camptosar; uncommon for acarbose, accolade, bacampicillin

LA/SA for trade name *Campral*®: camptosar, keppra, captopril
Potential Severity: Major for camptosar; minor-moderate for keppra and captopril
Probability: Remote for camptosar; uncommon for keppra and captopril

Drug Interactions

- NOTE: Acamprosate does not induce CYP1A2 or CYP3A4 isozymes, and in vitro data suggest that Acamprosate does not inhibit in vivo metabolism mediated by the enzymes of the hepatic microsomal CYP450 enzyme system (i.e., CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4).
- The concomitant intake of alcohol and Acamprosate does not affect the pharmacokinetics of either alcohol or Acamprosate.
- Pharmacokinetic studies indicate that administration of disulfiram or diazepam does not affect the pharmacokinetics of Acamprosate.
- Co-administration of naltrexone with Acamprosate produced a 25% increase in AUC and a 33% increase in the Cmax of Acamprosate. No adjustment of dosage is recommended in such patients.
- The pharmacokinetics of naltrexone and its major metabolite 6-beta-naltrexol were unaffected following co-administration with Acamprosate.

Other concomitant therapies: In clinical trials, the safety profile in subjects treated with Acamprosate concomitantly with anxiolytics, hypnotics and sedatives (including benzodiazepines), or non-opioid analgesics was similar to that of subjects taking placebo with these concomitant medications. Patients taking Acamprosate concomitantly with antidepressants more commonly reported both weight gain and weight loss, compared with patients taking either medication alone.

Acquisition Costs

Drug	Dose/tablet	*Cost/day/patient ($)	Cost/year/patient ($)
Acamprosate	333 mg	2.41	879.65
Naltrexone	50 mg	1.21	441.65
Disulfiram	250 mg	1.03	390.37

* Mckesson pricing 2/18/2005

Pharmacoeconomic Analysis

The following cost-analysis is based on information gathered from specialists in the Alcohol and Drug Treatment Program (ADTP) at VA San Diego. The following **assumptions** were made in order to complete the analysis:

- The VA San Diego data may not reflect the exact practice at other VA hospitals or their ADTP.
- Actual reported values are used whenever possible, but in some cases estimates of patient use based on specialist opinion was used.
- The analysis does not incorporate savings that may be seen in reduced ER admissions with successful alcoholism treatment and may underestimate the true cost-benefit to the VA healthcare system.
- The patient population who would most benefit was assumed to be those who are failing traditional outpatient ADTP therapy and are currently at high-risk for inpatient admission. It was estimated, based on the available evidence and specialist opinion, that a 10% reduction in admissions could be achieved if this population (350 pts/year) received acamprosate treatment.

The ADTP at VA San Diego may differ from other programs. In San Diego, the ADTP treats any eligible veteran with substance use disorders. Electronic consults can be ordered by the practitioner or patients can self-refer through the Urgent Care Center. Initial evaluations are carried-out on a walk-in, outpatient basis. Those individuals requiring detoxification are referred to a physician or nurse practitioner for assessment. Following this, veterans are then treated through outpatient visits in the evaluation group.

The evaluation process goal is to determine the specific needs of each individual and to begin to craft an approach that best meets those requirements. The ADTP places major emphasis on the least restrictive environment of treatment -- that is outpatient whenever possible. Thus, after completion of the evaluation process, some patients are referred to active outpatient care where they participate in group therapy several times a week and are expected to regularly attend 12-step meetings. Those alcohol and drug-dependent veterans who are unable to respond to outpatient treatment may be considered for inpatient care where similar types of groups as used on the outpatient program are established, but now with the individual living in the ADTP for a period usually ranging between ten days and four weeks. After intensive outpatient or inpatient initial interventions, efforts are made for all patients to continue in aftercare on a weekly basis for up to 12 months.

There are several additional aspects of the program that require emphasizing. In order to optimize participation in the treatment program: detoxification is usually on an outpatient basis, there are no direct or immediate admissions to the inpatient program and not all patients warrant or are offered in-patient services.

The following data for alcoholic patients was gathered from the VA San Diego ADTP (2/2005):

ADTP Variables

Avg. Inpt Census (FY04)	21.6 days
Avg. Length of Inpt Stay	22.5 days
Cost/Pt/Day (ADTP)	$474.16
Cost/Outpt Psych Visit	$32.67
Avg. Outpt Visits per month	6.5

- The number of alcoholic patients estimated by ADTP specialists to receive acamprosate per year was 300-400 (350 patients were used for cost calculations). These patients are assessed to be at high-risk of inpatient admission.

- This estimate matches well with the estimates of average bed days of care calculated from the FY04 ATP census for alcoholics. This comparison was done to validate provider estimates with actual previous data.
    - (21.6)(365) = 7884 avg. bed days of care
    - (~350 patients to receive acamprosate)(22.5 days) = 7875 avg. bed days of care.
- Assuming acamprosate would lead to a 10% reduction in avg. bed days of care for those patients who are successfully treated yields the following cost-savings.

Predicted Cost-Savings with Acamprosate

Acamprosate Tx 10% Reduction - Bed Days Saved
788.4
Cost-Savings w/Acamprosate Tx
(788.4 * $474.16)= $373,827.74

- The cost of outpatient psychosocial therapy, however, must also be taken into account as this will be a mandatory component of acamprosate therapy and is associated with significant cost. The length of treatment for high-risk outpatients will significantly impact benefit to cost ratio.

Using the estimated costs and avg. number of visits reported above:

Total Cost of Acamprosate Treatment including Psychosocial Support

	Cost of Psychosocial Support/ Patient (6.5 visits/mo)	Cost of Acamprosate Tx	Total Cost of Treatment
Days			
30	$212.36	$72.30	$284.66
60	$424.71	$144.60	$569.31
90	$637.07	$216.90	$853.97
120	$849.42	$289.20	$1,138.62

Benefit to Cost Ratio for Acamprosate Treatment with Psychosocial Support

Trial Time (days)	Patients	Total Cost of Treatment for Estimated Population	Benefit/Cost Ratio (Total cost-savings w/acamprosate/Total cost of treatment)
30	350	$99,629.25	**3.8**
60	350	$199,258.50	**1.9**
90	350	$298,887.75	**1.3**
120	350	$398,517.00	**0.9**

- As indicated in the table above, the benefit to cost ratio fails to be favorable if responders can't be identified within a 90-day treatment period. In other words, by treating the entire eligible patient population (N~350) with acamprosate you hope to have 10% responders who will not require inpatient admission. After 90 days it would be better, from a cost/benefit perspective, not to continue treatment if non-responders can't be identified.

Sensitivity Analysis

Considering the number of assumptions necessary for cost-benefit calculations a sensitivity analysis was performed utilizing different values for the number of outpatient psychosocial support visits.

If patients were only to require 1 outpatient psychosocial visit per week (**4 visits/month**) instead of 6.5, then the benefit to cost ratios shift as follows:

Acamprosate Sensitivity Analysis – 1 psychosocial visit per week

Trial Time (days)	No. of Patients	Total cost of Treatment for Estimated Population	Benefit/Cost Ratio
30	350	$71,043.00	**5.3**
60	350	$142,086.00	**2.6**
90	350	$213,129.00	**1.8**
120	350	$284,172.00	**1.3**

- In this scenario, treatment of eligible patients over 120 days remains beneficial and could be attempted to identify the responders and reduce inpatient admissions.

Should patient require 2 outpatient psychosocial visits per week (**8 visits/month**), then the benefit to cost ratios shift as follows:

Acamprosate Sensitivity Analysis – 2 psychosocial visits per week

Trial Time (days)	No. of Patients	Total cost of Treatment for Estimated Population	Benefit/Cost Ratio
30	350	$116,781.00	**3.2**
60	350	$233,562.00	**1.6**
90	350	$350,343.00	**1.1**
120	350	$467,124.00	**0.8**

- Despite greater need for psychosocial visits in this scenario, treatment over a 90-day period still results in a benefit/cost ratio <1. As in the original example, after 90 days it would be better, from a cost/benefit perspective, not to continue treatment if non-responders can't be identified.

SUMMARY

Acamprosate is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. The available evidence in three European pivotal efficacy studies does suggest a positive benefit of acamprosate in the treatment of alcoholism versus placebo when accompanied by a psychosocial support program. Although the data support the claim that acamprosate is effective in maintaining abstinence in recently-detoxified alcoholics, it is not possible to quantify the effect in terms of specific duration of abstinence because the method of determining of the number of drinking days in the European studies was insufficiently organized to allow for precise counting of number of days drinking or not drinking. The ascertainment of drinking data in the European studies was essentially retrospective and not diary-based; it was very methodical and rigorous in the U.S. study, using daily drinking diaries and there were tight follow-up provisions in place.

The efficacy of Acamprosate in promoting abstinence has not been demonstrated in subjects who have not undergone detoxification. The efficacy of Acamprosate in promoting abstinence from alcohol in poly-substance abusers has not been adequately assessed. Unfortunately, there is no study to suggest the benefit of acamprosate in American alcoholics or the alcoholic population seen by the VA healthcare system. The one unpublished, American study failed to show benefit versus placebo. The recommended dose of Acamprosate is two 333 mg tablets (each dose should total 666 mg) taken three times daily. Treatment with Acamprosate should be initiated as soon as possible after the period of alcohol withdrawal, when the patient has achieved abstinence, and should be maintained if the patient relapses. Acamprosate is poorly absorbed and not metabolized. In general, it presents a fairly benign safety profile notable only for mild increases in diarrhea. There has been an absence of serious adverse event reports from the post marketing setting in Europe. Acamprosate should not be given to patients with severe renal insufficiency (ClCr ≤30 mL/min).

Conclusion

Treatment with Acamprosate should be initiated as soon as possible after the period of alcohol withdrawal, when the patient has achieved abstinence. The treatment period should not extend past 90 days without documentation of sustained alcohol abstinence.

Recommendations

It is recommended that the National PBM create a registry for acamprosate patients to help track and establish efficacy and safety in the VA population. Prior to establishing success in the VA population it is not recommended that acamprosate therapy extend past 90 days without case-by-case justification through NF consult.

Due to the lack of available efficacy data in American alcoholics or the VA population, it is recommended that acamprosate not be added to National Formulary. Acamprosate may have a role in the following patient population and could be made available through NF consult (both criteria should be met):

1) Adult alcoholic patients who have achieved abstinence and are willing to receive concomitant psychosocial therapy.

Facilities without an established ADTP should not utilize acamprosate as it helps maintain abstinence only when used as a part of a treatment program that includes counseling and support.

AND

2) Patients who also have received and failed traditional outpatient ADTP treatment. These patients should be considered high-risk for re-admission for inpatient services.

References:

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Prepared 4/2005 Monograph prepared by Robert Schoenhaus, PharmD, Primary Care Pharmacy Practice Resident, VA San Diego Healthcare System. Contact person: Anthony Morreale, PharmD, MBA, BCPS; VA San Diego. Reviewed by Janet H. Dailey, PharmD, Clinical Pharmacy Specialist VA PBM-SHG.

Appendix A: Clinical Trials

Despite the availability of oral disulfiram, naltrexone and acamprosate in countries outside the United States, there remains a lack of consistency in how studies have assessed the efficacy of these various agents. As demonstrated in the table by Garbutt et al (1999) below, there are often different efficacy measures, which make comparisons of relative efficacy difficult.

Randomized Controlled Trials to Evaluate efficacy of Pharmacotherapies Used for Maintaining Abstinence*[14]

			Efficacy					
Source	**Initial/ Final Sample Size**	**Trial Length, wk**	**Drinking/ Nondrinking Days**	**Return to Drinking**	**Time to First Drink**	**Alcohol Consumed Per Unit of Time**	**Craving**	**Relapse**
Oral Disulfiram								
Fuller and Roth, 1979	128/NA	52	-	-	NM/R	NM/R	NM/R	NM/R
Fuller et al, 1986	605/577	52	+	-	-	NM/R	NM/R	NM/R
Schuckit, 1985	348/348	52	-	NM/R	NM/R	-	NM/R	NM/R
Chick et al, 1992	126/69	24	+	NM/R	NM/R	+	NM/R	NM/R
Naltrexone								
O'Malley et al, 1992	104/68	12	+	+	NM/R	-/+‡	-/+‡	+
Volpicelli et al, 1992	70/44	12	+	-	NM/R	NM/R	+	+
Volpicelli et al, 1997	97/71	12	-/+§	-/+§	NM/R	NM/R	-	-/+§
Acamprosate								
Gerra et al, 1992	28/NA	4	NM/R	NM/R	NM/R	-/+¶	NM/R	NM/R
Ladewig et al, 1993	61/NA	24	+	-	NM/R	NM/R	NM/R	NM/R
Paille et al, 1995	538/NA	52	+	-	+	NM/R	-	NM/R
Roussaux et al, 1996	127/90	12	NM/R	-	NM/R	NM/R	-	NM/R
Sass et al, 1996	272/134	48	+	+	+	NM/R	-	NM/R
Whitworth et al, 1996	448/180	52	+	+	NM/R	NM/R	NM/R	NM/R
Geerlings et al, 1997	262/94	24	+	-	-	NM/R	NM/R	NM/R
Pelc et al, 1997	188/119	12	+	+	+	NM/R	+	NM/R
Poldrulgo, 1997	246/112	26	+	+	+	NM/R	-	NM/R

* NA indicates information not available; NM/R, outcome was not measured or data not reported; plus sign (+), intervention showed efficacy compared with placebo ($P<0.05$); and minus sign (-), intervention did not show efficacy compared to placebo.
‡ Interaction between medication and psychotherapy was significant ($P<0.05$ for amount consumed per unit of time and $P<0.01$ for craving).
§ Compliant subjects showed positive drug effect.
¶ In nonfamilial alcohol-dependent subjects only.

Citation	Paille FM, Guelfi JD, Perkins AC, Royer R, Steru L, Parot P (1995) Double-blind randomized multicentre trial of Acamprosate in maintaining abstinence from alcohol. *Alcohol* 30:239–247[9]
Study Goals	The objectives of the study were to compare the safety and efficacy of 2 dose levels of Acamprosate: 1332 mg/day and 1998 mg/day versus placebo in maintaining abstinence over the 12-month treatment period in alcohol-dependent outpatients withdrawn from alcohol; and to observe the outcome over an additional 6-month period while patients continued on (or were switched to) placebo (single-blind) at the end of the double-blind treatment period.
Methods	• **Study Design** This was a prospective, multicenter (31), randomized, double-blind, placebo-controlled, parallel group (3) study comparing the efficacy and safety of 2 dose levels of Acamprosate and placebo given for 12 months for maintenance of abstinence in alcohol-dependent patients who had been withdrawn from alcohol. This was followed by a single blind 6-month period on placebo. Unlike the Pelc study, patients in this review were permitted under special circumstances to receive the antidepressant maprotiline (at a dose of 75-150 mg/day) and the anxiolytic lorazepam (at a maximum dose of 7.5 mg/day). • **Data Analysis** The protocol did not contain a statistical plan. However, the statistical analysis was conducted in a blinded fashion and may therefore be considered prospective. Assessments were made every month for the first 6 months, then every 2 months for a further 12 months. The principal efficacy variable defined in the statistical analysis was 'continuous abstinence' since the start of treatment. Patients were considered to be continuously abstinent only if they attended all clinic visits and the number of non-abstinent days was recorded as zero. The three pairs of treatment groups were compared using the non-parametric Mann-Whitney U test. Days of controlled drinking (40g or less) were also calculated and compared. Categorical analysis of classification at each visit (abstinent/controlled/uncontrolled/treatment failure, where treatment failure was coded if the subject did not attend or if no data on alcohol consumption were available) was undertaken using Mantel-Hanszel test. Cumulative abstinence duration was also calculated through either day 360 or the date of visit and compared across treatment groups using a one-way ANOVA and Mann-Whitney U tests. CAD was chosen as the primary variable of interest as a common analysis across studies.

Criteria	• **Inclusion criteria** ➢ Age 18-65 ➢ DSM-III (R) diagnosis of alcohol dependence x at least 1 year ➢ Clinical signs of "alcohol impregnation" ("appearance of the face, conjunctivae, or tongue, tremor of the mouth, tongue, or extremities") and/or elevated GGT (>2 xULN) or MCV>98 F[3]. ➢ In outpatient treatment at a specialized center for alcoholics ➢ Abstinent 1 week – 1 month at Day 0 ➢ "Clearly stated desire to maintain abstinence" ➢ "Lifestyle compatible with follow-up" • **Exclusion criteria** ➢ Assessment at "unlikely to comply with treatment over the 18 month period" ➢ More than 3 courses of detox in previous 2 years ➢ Previous treatment with Acamprosate ➢ Recent (past 6 months) participation in clinical trial ➢ Pregnancy, nursing, or "likely to become pregnant" ➢ Severe psychiatric disorder ➢ Significant medical illness (examples included "poorly controlled diabetes, poorly controlled arterial hypertension, septicemia, active TB, cardiac failure, progressive neoplasia") ➢ Epilepsy (not alcoholic withdrawal seizures) ➢ Renal insufficiency (Cr > 14 mg/L) ➢ Hypercalcemia ➢ "Patients whose physical or mental state is incompatible with the trial conditions" ➢ Intellectual limitations or language barrier precluding completion of diaries ➢ Lack of fixed address; residence in "post-cure center" ➢ "Lack of obvious cooperation during the global withdrawal treatment" ➢ Incompatible medication ➢ Recent (past 3 months) institution of chronic medication

Results

A total of 538 subjects were selected for enrollment and randomized to treatment (188 to Acamprosate 1332 mg/day, 173 to Acamprosate 1998 mg/day, and 177 to placebo). There is no indication of how many were screened in order to enroll 538. The majority of patients were male (80%) with a mean age of 43.2 ± 8.6 years.

- At the completion of 12 months' follow-up on treatment, 55.9% of the patients dropped out of the trial, including 13.9% lost to follow-up.

Percentage of patients who were abstinent at each assessment

Assessment	Placebo (N = 177)	Acamp 1.3g/day (N = 188)	Acamp 2g/day (N = 173)	P value
Day 90	39.5	49.5	46.8	0.079
Day 180	29.9	38.8	44.5	<0.001
Day 360	18.6	27.7	34.7	<0.001
Day 540	15.8	21.8	27.7	0.002

The overall analysis confirmed that acamprosate prolonged the initial period of abstinence (P = 0.032). The difference was significant at 6 months (P ≤ 0.02) but not at 12 months (P = 0.096). The mean cumulative abstinence duration (CAD) was as follows:

Cumulative period of abstinence

Efficacy Parameter	Placebo (N=177)	Acamp 1.3g/day (N = 188)	Acamp 2g/day (N = 173)
Mean cumulative abstinence duration (CAD) (days)	173 ± 126	198 ± 133 (P = 0.055)	223.4 ± 134 (P = 0.0005)

- Abstinence figures followed the order high dose > low dose > placebo.
- The low-dose acamprosate group failed to reach statistical significance.

For 60 high-dose acamprosate patients who were abstinent at 12 months, but who had consumed alcohol during the year, 33% had been drinking <10% of the time, in contrast to 24.2% in the placebo group.

For laboratory assessments, mean values revealed no significant difference for any biological marker of drinking, even after log transformation. Statistically significant differences favoring acamprosate were seen at various intervals for blood alcohol level and GGT.

Efficacy Measure

The protocol specified main efficacy parameters were the number of non-abstinent days, the average alcohol consumption on non-abstinent days, and a responder analysis classifying subjects as success/partial success/failure. These were based on "clinical evaluation" and "biological evaluation of the efficacy" (GGT, MCV, transaminases).

Conclusions	➢ The increase in abstinence with the acamprosate treated patients reached statistical significance at 6 months, but not at 12 months. ➢ The mean CAD was significantly higher for acamprosate treated patients. ➢ Analysis of patients who, although abstinent at 12 months, consumed alcohol during the first course of the first year under treatment, indicated that alcohol consumption was reported as being less in the high-dose acamprosate group. ➢ Clinic attendance was significantly better in the Acamprosate groups than in the placebo group at 6 months (P = 0.002) and 12 months (P = 0.005). During the 6-month post-treatment period, no increased relapse rate or residual drug effect was observed. ➢ The side effect profile for Acamprosate was good compared with controls with only diarrhea being reported more frequently (P < 0.01). ➢ Acamprosate should be used as an adjunct to psychotherapy.
Critique	Overall, the data indicated a consistent benefit for acamprosate patients, but not all assessment criteria reached statistical significance. The patient population consisted of those with 'relatively stable family backgrounds, who were mostly employed." It was noted that this inclusion criteria was necessary to prevent patients being lost to follow-up, but the fact remains that the studied population is not representative of the whole population of alcohol-dependent patients. The indirect efficacy measurement of 'clinic attendance' was significantly better for acamprosate patients at both 6 and 12 months. This may suggest that acamprosate helped patients comply with the overall course of therapy, which included psychotherapy. Good clinic attendance among the treatment group also suggests the drug regimen was tolerable and produced few adverse effects (dose-dependant diarrhea was the only side effect reported more frequently with acamprosate). The authors concluded that 'craving' for alcohol was not substantially changed by acamprosate. This is an important finding as there has been suggestion that this agent may dull this effect. Instead, acamprosate appeared to be most useful in the early periods of treatment where the anxiety and depression associated with withdrawal were most pronounced. It should be noted, however, that patients had access to an antidepressant and anxiolytic as concomitant treatment. Although, the need for psychotropics proved to be 'very similar' for all treatment groups, it is impossible to determine from the data provided whether patients benefited from acamprosate or the other agents. Concerns about the validity of the data include the likelihood that both subject and investigator would be biased in reporting and assessment.

Citation	Pelc I, Le Bon O, Verbanck P, Lehert PH, Opsomer L (1992) Calcium acetyl homotaurinate for maintaining abstinence in weaned alcoholic patients: a placebo-controlled double-blind multi-cent re study, in *Novel Pharmacological Interventions for Alcoholism* (Naranjo C, Sellers E eds), pp 348–352. Springer Verlag, New York. Re-published as Efficacy and Safety of Acamprosate in the Treatment of Detoxified Alcohol-Dependent Patients: A 90-day Placebo-Controlled Dose-Finding Study, in *British Journal of Psychiatry* (1997); 171: 73-77[10]
Study Goals	The purpose of the study was to compare the efficacy and safety of 2 dose levels of Acamprosate and placebo in maintaining abstinence in weaned alcohol-dependent outpatients over 90 days of treatment.
Methods	• **Study Design** This was a prospective, multi-center (11), randomized, double-blind, placebo-controlled, parallel group study comparing the efficacy and safety of 2 dose levels of Acamprosate and placebo in alcoholics who had completed inpatient detoxification. • **Data Analysis** Patients were evaluated at selection and at days 1, 8, 15, 30, 45, 60, 75 and 90. General physical examinations occurred on days 1, 30 and 90. Alcohol consumption was assessed by review of patients' diary consumption cards. In addition, ethanol presence in the urine was checked at each visit. Only patients who completed the entire study period and remained abstinent were classified as 'abstinent'; all the others were considered as 'not abstinent'.

<table>
<tr><td></td><td>There is no description of any psychosocial therapy to be delivered at study visits or external to the study</td></tr>
<tr><td>Criteria</td><td>

Inclusion criteria

Age 18-65
Weight > 60 kg
DSM-III diagnosis of alcohol dependence
“The duration of the disruption must be at least one year”
Abstinent for at least 5 days
“Monitored as outpatients”

Exclusion criteria

Pregnancy, or “likely to become pregnant”
“Associated psychiatric pathology involving the induction of a medicinal treatment during the weaning period or during the follow-up period”
Significant medical illness (examples included “decompensated diabetes, poorly compensated arterial hypertension, septicemia, active TB, poorly compensated cardiac decompensation, progressive neoplasms”)
Epilepsy (not alcoholic withdrawal seizures)
Renal insufficiency (Cr > 14 mg/L)
Hypercalcemia
“Patients whose condition is incompatible with the conditions of the study”
“Obvious lack of collaboration with the general weaning treatment”
Prior treatment with Acamprosate

</td></tr>
<tr><td>Results</td><td>
Of the total of 189 patients who were selected to participate, 188 patients were randomized: 125 in the 10 Belgian centers (range 3-37) and 63 in the French center (1 Belgian patient withdrew consent). Sixty-three patients were randomized to Acamprosate 1998 mg/day, 63 to Acamprosate 1332 mg/day, and 62 to placebo. A total of 119 patients completed the study and
<table>
<tr><th>Parameter</th><th>Acamprosate 1332 mg/day N=63</th><th>Acamprosate 1998 mg/day N=63</th><th>Placebo N=62</th></tr>
<tr><td>Mean Cumulative Abstinence Duration (days)</td><td>51.9 (±4.69)</td><td>56.6 (±4.25)</td><td>34.3(±4.29)</td></tr>
</table>
were assessed on day 90. Reasons for discontinuation are detailed below.
<table>
<tr><th>Reason for Discontinuation</th><th>Placebo</th><th>Acamp. 1332</th><th>Acamp. 1998</th></tr>
<tr><td>Severe adverse event</td><td>1 (1.6%)</td><td>2 (3.2%)</td><td>1 (1.6%)</td></tr>
<tr><td>Concurrent illness</td><td>3 (4.8%)</td><td>2 (3.2%)</td><td>1 (1.6%)</td></tr>
<tr><td>Severe Relapse</td><td>10 (16.1%)</td><td>6 (9.5%)</td><td>9 (14.3%)</td></tr>
<tr><td>Lost to follow-up</td><td>15 (24.2%)</td><td>6 (9.5%)</td><td>6 (9.5%)</td></tr>
<tr><td>Protocol violation</td><td></td><td>1 (1.6%)</td><td></td></tr>
<tr><td>Patient refused to continue</td><td>1 (1.6%)</td><td>1 (1.6%)</td><td>1 (1.6%)</td></tr>
<tr><td>Non-compliance</td><td></td><td>1 (1.6%)</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Total</td><td>30 (48.4%)</td><td>19 (30.2%)</td><td>20 (31.7%)</td></tr>
</table>
Efficacy Measure
The main judgment criteria listed in the protocol was “the consumption of alcohol.” No strategy for transforming the data collected into an overall assessment of alcohol consumption was identified. The analysis by the author regarded the calculation of “cumulative abstinence duration (CAD)” as primary.

Mean Cumulative Abstinence Duration (CAD)

Statistical analysis by the sponsor yielded p values <0.05 for the comparisons of Acamprosate 1332 mg/day vs. placebo and Acamprosate 1998 mg/day vs. placebo (Student-Newman-Keuls test), and an overall p-value (one-way ANOVA) of p = 0.001.
In addition, the protocol called for evaluation of “clinical signs linked to alcoholism,” “biological signs” (GGT, AST/ALT, urine alcohol), and “tolerance to the treatment.”
</td></tr>
<tr><td>Conclusions</td><td>There were statistically significant differences seen in the primary efficacy variable (cumulative abstinence days) between acamprosate and placebo. There was no statistically significant</td></tr>
</table>

	difference seen with the high-dose acamprosate (1998 mg) vs. the lower-dose (1332 mg). This study confirms that Acamprosate could be an acceptable adjuvant for maintaining abstinence in detoxified alcoholics.
Critique	This study, although short-term, provides evidence that recently-detoxified alcoholic subjects treated with acamprosate were more frequently assessed as abstinent by the treating physician than were subjects treated with placebo. There was also a sizeable discontinuation rate amongst the placebo group (48.4%), which may suggest that acamprosate patients were receiving some additional benefit.

Citation	Sass H, Soyka M, Mann K, Zieglgansberger W (1996) Relapse prevention by Acamprosate: Results from a placebo controlled study on alcohol dependence. (PRAMA) Arch Gen Psychiatry 53:673–680[11]
Study Goals	The objective of the study was to compare the efficacy and safety of Acamprosate and placebo on maintaining abstinence in weaned alcohol-dependent outpatients, over a 48 week treatment period.
Methods	• **Study Design** ➢ The study was designed as a 48-week, randomized, double-blind, placebo-controlled, outpatient multi-center study to take place in Germany. In addition, there was a 48-week post-treatment follow-up phase. All centers were psychiatric outpatient clinics. At least 6 centers were planned, with each contributing 24-48 subjects. Subjects were required to be recently detoxified, abstinent from alcohol for at least 14 days (but no longer than 4 weeks), and to have no symptoms of alcohol withdrawal. Acamprosate therapy was to be offered in addition to "any psychotherapy usually carried out by the individual center." Counseling and psychotherapy were not standardized between centers. ➢ The use of concomitant psychotropic medication (antidepressants, neruoleptics, benzodiazepines, barbiturates) was not permitted. • **Data Analysis** The statistical evaluation methods included in the protocol specified that: ➢ The evaluation of the study would be according to the intent-to-treat principle; wherever possible, all patients were to be fully documented during the entire planned therapy and follow-up observation phase. ➢ The primary variable for the evaluation was to be the point in time when a relapse occurred; to be evaluated in the form of an event analysis using a log-rank test, whereby a patient enters the statistics as an event at the time of his first relapse. A GGT level of twice the upper limit of normal was considered as suggestive of a relapse. ➢ Patients who were lost to observation and for whom further information could be obtained were to be evaluated up to the point of the last available information. ➢ The total incidence of relapses in both groups was to be evaluated as a secondary variable using a comparison of incidence. ➢ Interim evaluation was called for when the last patient recruited to the study had completed the 24-week evaluation. ➢ A global evaluation of the study was to be carried out after the completion of the 48-week follow-up phase.
Criteria	• **Inclusion criteria** ➢ Age 18 to 65 years ➢ DSM-III-R diagnosis of alcohol (5 of 9 criteria) ➢ History of at least 3 years of alcohol dependence in males and at least 2 years of alcohol dependence in females ➢ Munich Alcoholism Test (MALT) test score of at least 11 points ➢ A minimum of 14 consecutive days abstinence following detoxification that included pharmacotherapy (mainly clomethiazole or benzodiazpeines) ➢ Intelligence level of at least 13 points on the MWT-B questionnaire • **Exclusion criteria**

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“Controlled abstinence” of more than 4 weeks;
Existing withdrawal symptoms;
Existing mental disease necessitating the start of psychotropic drug therapy during the study;
Epilepsy not due to alcoholism, severe general changes in the EEG and/or epileptic foci;
Severe hepatic damage, particularly alcoholic hepatitis and alcoholic cirrhosis, plasma cholinesterase less than the normal;
Hypercalcemia of all etiologies;
A planned stay of more than 3 weeks at a specialist residential clinic for addicts or at a psychiatric clinic;
Lack of fixed address;
Severe drug addiction or drug dependence in the past 3 years;
Known excretory pancreatic failure;
Pregnancy/nursing/inadequate contraception
Severe systemic disease (e.g., poorly controlled diabetes mellitus, noncompensated hypertension, decompensated heart failure);
ECG-confirmed cardiac arrhythmias requiring treatment, ventricular extrasystoles;
Creatinine >120 μmol/L or >1.4 mg/dL;
Malignancies;
“Pronounced organic psychological syndrome which prevented an understanding of the nature of the trial and of the questionnaires”; and
History of gastrointestinal surgery resulting in GI narrowing
Subjects with a body weight >60 kg were to receive 1998 mg of Acamprosate or placebo per day, taken as 2 tablets of 333 mg Acamprosate (or matching placebo) in the morning, at mid-day, and in the evening.
Subjects with a body weight <60 kg were to receive 1332 mg of Acamprosate or placebo per day, taken as 2 tablets of 333 mg Acamprosate (or placebo) in the morning, and 1 tablet of 333 mg Acamprosate (or placebo) at mid-day and in the evening.

</td></tr>
<tr><td>Results</td><td>
A total of 272 subjects were selected for enrollment. There is no indication of how many were screened in order to enroll 272. Of these, 163 were randomized to placebo and 163 were randomized to Acamprosate. Acamprosate dose was based on weight, with subjects >60 kg receiving 1998 mg/day and smaller subjects receiving 1332 mg/day. Only 44 subjects (28 of 61 women and 16 of 211 men) weighed 60 kg or less. Of these, 13 women and 11 men were randomized to Acamprosate. Thus, only 24 subjects in the study received the 1332 mg/day dose
A total of 134 of 272 patients (49.3%) remained in the study after 1 year. 57 patients who were being treated with acamprosate (41.9%) and 81 patients who were receiving placebo (59.6%) were withdrawn (p= 0.01). 134 patients entered the 48-week follow-up period: 79 acamprosate-treated patients and 55 placebo-treated patients. 104 patients completed the entire 96-week period (66 acamprosate and 33 placebo).
The protocol-specified primary analysis was time to relapse. However, for the purpose of this application, the author analyzed all the pivotal trials according to a common outcome measure, cumulative abstinence duration (CAD).
Using a complex method to transform a yes/no assessment into a continuous variable (number of days abstinent), and dividing the number of abstinent days by 360 (duration of the treatment portion of the study) to generate the “corrected cumulative abstinence duration), the author reported the following results (statistically significant by their analysis):
CAD and CCAD – 48 week treatment period
<table>
<tr><td></td><td>Acamprosate
N = 136</td><td>Placebo
N = 136</td></tr>
<tr><td>Mean Cumulative Abstinence Duration (CAD), days</td><td>224.62 ± 136.61</td><td>162.03 ± 132.19</td></tr>
<tr><td>Mean Corrected Cumulative Abstinence Duration (CCAD) (% days abstinent)</td><td>62.4%</td><td>45.3%</td></tr>
</table>
Differences in the markers of alcohol intake (GGT and MCV values) failed to reach statistical significance in the data. This was, in part, due to the variation in GGT seen between patients at baseline and the lack of data points later in the study (after significant patient withdrawal).
The differences seen in abstinence rates remained significant during the 48-week follow-up period (P<0.001), with a drop of 5% to 6% in both groups, and no rebound phenomenon was noted.
</td></tr>
</table>

	CAD and CCAD – 48 week follow-up period (no medication) Acamprosate N = 79 / Placebo N = 55 Mean Cumulative Abstinence Duration (CAD), days: 387.14 ± 280.52 / 250.95 ± 244.63 Mean Corrected Cumulative Abstinence Duration (CCAD) (% days abstinent): 54% / 35% **Efficacy Measure** The protocol-specified outcome measure was "abstinence in the patient, evaluated by the trial physician under consideration of clinical and laboratory variables (reports by the patient and his family, clinical impression, GGT and MCV)." The planned primary variable was time to first relapse. Any consumption of alcohol defined a relapse. A relapse was "short-term" if alcohol was consumed up to 24 hours and "long-term" if it continued for a period longer than 24 hours. "Constant" alcohol consumption was termed a "continuous relapse." The protocol specified that, "the point in time when a relapse occurs will be defined as the day on which alcohol consumption starts again."
Conclusions	Acamprosate proved to be a safe and effective aid in treating alcohol-dependent patients and in maintaining the abstinence of patients during 2 years. The present data during 2 years show better relapse control and retention in the study in detoxified alcohol-dependent patients who received acamprosate from the early post-weaning phase. Acamprosate appeared to be well tolerated and without signs of psychotropic side effects or potential for abuse or dependence.
Critique	Although acamprosate patients had consistently superior outcomes, the lack of standardization of counseling and psychotherapy may have contributed in unpredictable ways. Laboratory studies failed to show much difference in markers of alcohol intake between acamprosate and placebo patients, but this must be partially attributed to patient dropout and missing lab values. Patients weren't allowed access to psychotropic agents during the treatment period, but they were given clomethiazole and/or benzodiazepines during the detoxification period. Since acamprosate has reportedly had its greatest benefit in the early periods of treatment, it is unfortunate that patients were likely exposed to anti-anxiety medications just prior to entering the study. Medications like benzodiazepines, clomethiazole, and acamprosate likely have some overlap in their mechanism of action, as they all seem to enhance the effect of GABA. GABA is a major inhibitory transmitter in the CNS. Due to the high dropout rates, sample sizes were much smaller after the 48-week treatment period. It should be noted, however, that acamprosate patients had a significantly higher retention rate. Unlike other studies, patients were observed for an additional 48 weeks after discontinuing medication. This follow-up period revealed that patients were able to sustain abstinence significantly better if they had received acamprosate versus placebo. It is uncertain whether this reflects better patient 'stabilization' with acamprosate or if patients' physiology was better able to adapt to abstinence after exposure to acamprosate.

Citation	Mann K, Lehert P, Morgan MY The Efficacy of Acamprosate in the Maintenance of Abstinence in Alcohol-Dependent Individuals: *Results of a Meta-Analysis* *Alcohol Clin Exp Res*, Vol 28, No 1, 2004: pp 51–63[13]
Study Goals	To undertake a more extensive meta-analysis of the efficacy of Acamprosate in alcohol dependent individuals by using the studies published to date, supplemented, where possible, by data obtained from the manufacturer's in-house reports.
Methods	• **Study Design** ➢ A language unrestricted search of 10 databases, covering the period from January 1, 1985, to April 30, 2003, was undertaken based on a number of key words, including "alcohol drinking," "clinical trials" and "Acamprosate" (Table 1). The references retrieved from CINHAL, PsycINFO, and MEDLINE were manually deduplicated; the references retrieved from EMBASE and the EMBASE databases were initially deduplicated by using the OVID deduplication facility but were also manually rechecked. Finally, the combined lists were manually deduplicated; MEDLINE-retrieved references were given preference because they included key words. The

	printouts from the electronic searches were scrutinized, and all treatment trials were highlighted. ➢ An additional manual search was conducted of relevant journals, symposia, and conference proceedings, and relevant trials retrieved; all identified publications were cross-referenced. Personal contact was made with the authors of the published studies, if necessary, to request additional data. Finally, access was provided by the manufacturer of Acamprosate (Merck-Santé) to the internal trial reports of all their European studies, irrespective of publication status. All the identified publications and internal trial reports, status, were retrieved and reviewed. Trials were selected for further assessment if they were randomized and placebo-controlled and used at least one quantitative measure of drinking behavior to assess treatment efficacy. ➢ The primary outcome measure chosen was continuous abstinence at 6 months. • **Data Analysis** ➢ For ease of interpretation, authors chose to combine the contributing studies in terms of the correlation coefficient *r*. ➢ *r* may be understood as the simple percentage difference in success rates between the experimental and control groups in a standard table. ➢ Independent, composite *r* measures easily can be compared statistically by using Fisher's *Z* transformation. However, unlike the odds ratio, *r* does not account for the rate of non-response. As such, comparisons of *r* across disorders must be viewed in relation to overall rates of treatment response. ➢ Three outcomes were included for the analysis of Acamprosate effects: cumulative abstinent days (CAD), percentage of subjects reporting abstinence for the entire study period, and percentage of subjects remaining in treatment at the end of the study. ➢ For each weighted mean effect size (*Rw*), we report standard deviation, statistical significance, and a 95% confidence interval. The *p* value is calculated by the use of a *z.* The confidence interval allows an inference of the variability of *Rw*, after accounting for sampling error. Between-medication effect sizes were compared by using Fisher's *Z* transformation of *r*.
Criteria	• **Inclusion criteria** ➢ Only randomized, placebo-controlled trials were considered, and only data from intention-to-treat samples were used ➢ The number of Acamprosate studies was reduced to 11 by methodological concerns: Lhuintre et al. (1985) reported data only on completers, and Lhuintre et al. (1990) used only _-glutamyl transferase (GGT) as an outcome measure. ➢ To provide a comparator for the effects of the antidipsotropics, we examined 10 studies of SSRIs for treatment of major depression ➢ These studies were all double-blind, placebo-controlled trials, which were chosen primarily for their methodological comparability to the naltrexone and Acamprosate studies. • **Exclusion criteria** ➢ Non-randomized, non-placebo-controlled trials were excluded from analysis

Results

First Author	Date	Continuous Abstinence Rate (%)		Relative benefit, mean (SEM) (95% CI)
		Acamprosate	Placebo	
Pelc	1992	27.3	6.4	4.27 (0.63) 3.04-5.50
Ladewig	1993	34.5	9.4	3.68 (0.63) 2.44-4.92
Borg	1994	40.0	40.0	1.00 (0.80) -0.56 -2.56
Paille	1995	31.0	20.9	1.48 (0.25) 1.00-1.97
Roussaux	1996	28.6	32.8	0.87 (0.32) 0.24-1.51
Sass	1996	42.6	26.5	1.61 (0.25) 1.12-2.11
Whitworth	1996	28.1	20.1	1.40(0.25) 0.91-1.89
Barrias	1997	44.7	30.9	1.45(0.24) 0.91-1.91
Geerlings	1997	22.7	11.2	2.02(0.35) 1.35-2.70
Pelc	1997	44.4	21.0	2.12(0.32) 1.49-2.75
Poldrulgo	1997	46.7	25.8	1.81(0.27) 1.29-2.34
Besson	1998	34.5	7.3	4.75(0.55) 3.68-5.82
Chick	2000	14.2	13.7	1.04(0.29) 0.50-1.58
Tempesta	2000	48.2	34.9	1.38(0.23) 0.94-1.82
Gual	2001	48.9	40.8	1.20(0.23) 0.76-1.64
Kiefer	2003	40.0	25.0	1.16(0.39) 0.84-2.36
Namkoong	2003	37.5	31.4	1.16(0.31) 0.56-1.75
TOTAL		**36.1**	**23.4**	**1.47 (0.09) 1.29-1.69**

A total of 19 published 1 unpublished RCTs were identified that fulfilled the selection criteria; 3 were excluded because the documentation available was insufficient to allow adequate assessment. The remaining 17 studies, which included 4087 individuals, 53% of whom received active drug, were of good quality and were otherwise reasonably comparable. The mean number of patients included in the studies selected for this meta-analysis was 165 (range, 10–581); only 3 studies included fewer than 100 patients (Borg S, unpublished data, 1994; Ladewig et al., 1993; Namkoong et al., 2003). There was no evidence of publication bias. Continuous abstinence rates at 6 months were significantly higher in the acamprosate-treated patients (acamprosate, 36.1%; placebo, 23.4%; RB, 1.47; [95% confidence intervals (CI): 1.29 –1.69]; $p < 0.001$). This effect was observed independently of the method used for assigning missing data. The effect sizes in abstinent rates at 3, 6, and 12 months were 1.33, 1.50, and 1.95, respectively. At 12 months, the overall pooled difference in success rates between acamprosate and placebo was 13.3% (95% CI, 7.8–18.7%; NNT, 7.5). Acamprosate also had a modest but significant beneficial effect on retention (6.01%; [95% CI, 2.90–8.82]; $p < 0.0106$).

Conclusions

Acamprosate has a significant beneficial effect in enhancing abstinence in recently detoxified, alcohol-dependent individuals.

Critique	• **Strengths**
	  • Additional data allowed several further calculations and assessments to be undertaken, including (1) the relative benefits of treatment on several alternative study endpoints, including point prevalence estimates; (2) the effects of various missing data imputations on the estimates of relative benefit; (3) the relative benefits of treatment in study completers; and (4) the relative benefits of treatment over time.
	  • Four studies were of 3 months' duration or less (Kiefer et al., 2003; Namkoong et al., 2003; Pelc et al., 1997; Roussaux et al., 1996), so their contribution was estimated by extrapolation using LOCF methodology. In order to exclude potential bias introduced by these extrapolations, these four studies were excluded and the analysis was rerun on the remaining 3550 patients. These exclusions did not substantially affect the overall effect of treatment: estimated RB 1.50 (95% CI, 1.30–1.74, $p<0.001$).
	  • Although the meta-analysis was based on a literature review, the restrictions imposed by this approach were largely overcome because of the access provided to the original trial reports of the 15 European studies, which allowed additional calculations and analyses to be undertaken as necessary (i.e., Relative Benefit).
	  • In a separate analysis, inclusion of the results of the large American multicenter trial (Mason, 2001) did not significantly affect the estimate of the relative benefit of treatment on this primary efficacy variable: estimated RB 1.44 (95% CI, 1.24–1.66; $p<0.001$).
	• **Limitations**
	  • There was evidence of some variability in outcome between studies ($p=0.035$). Thus, no significant drug effect was observed in four studies (Borg S., unpublished data, 1994; Chick et al., 2000; Namkoong et al., 2003; Roussaux et al., 1996), whereas a particularly favorable drug effect was observed in another three (Besson et al., 1998; Ladewig et al., 1993; Pelc et al., 1992).
	  • Four of the published studies reported no effect of treatment with Acamprosate on any of the drinking outcomes.
	  • The large American multicenter trial (Mason, 2001), which has also been reported to show no significant effect of treatment, at least in the intention-to-treat population, could not be included in the main meta-analysis because only limited data are available in the public domain.
	  • The data on the changes in effect size with time, although interesting and evidenced in two separate analyses, must, at this stage, be treated with caution.

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 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: 23 had a placebo arm 6 provided the details of techniques used for randomization 24 applied a double-blinded design 9 had duration for longer than 12 weeks	**NTX vs. placebo: (short-term)** Risk of Relapse: RR 0.64, 95% CI 0.51-0.82 Risk of returning to drinking: RR 0.87, 95% CI 0.76- 1.00 Discontinuation Rate: RR 0.82, 95% CI 0.70-0.97 **NTX vs. Acamprosate (Short-Term)** Discontinuation Rate: RR 0.78, 95% CI 0.51-1.21 **NTX vs. Acamprosate (Medium-Term)** Risk of Relapse: RR 0.71, 95% CI 0.57 to 0.88 Standard Drinks: (Mean Number of drinks consumed at one time) SMD -0.76, 95% CI -1.09 --0.44 Craving: (Mean composite craving severity score): SMD -0.36, 95% CI -0.67 --0.04 Discontinuation Rate of Therapy: RR 0.46, 95% CI 0.21 -1.00	**NTX vs. placebo** 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. **NTX vs. acamprosate (short-term)** 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. **NTX vs. acamprosate (medium-term)** 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

Study/Design/Purpose	Inclusion/Exclusion	Treatment	Patient Characteristics/Outcomes	Withdrawals/ Adverse Events/
Kiefer et al. (2003) R, DB, PC, MC x 12 weeks in Germany. 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.	**Inclusions:** • At least 5 DSM-4 criteria of alcohol dependence • Between 18-65 years • Body weight of 60-90 Kg • Complete abstinence for 12-15 days • Free of any withdrawal symptoms • Drug screening tests were negative for benzodiazepines, cannabinoids, barbiturates, opiates, cocaine and amphetamines **Exclusions:** • A current DSM-IV diagnosis of dependence or abuse on other substances except nicotine assessed by the structured clinical interview for DSM-IV • A current mental or psychiatric impairment or disease that required psychotropic medication or inpatient tx on a psychiatric ward • History of opioid or cocaine abuse • A history of psychosis • Current use of any psychotropic medication • Evidence of severe neurology or physical disorders (cerebral, renal, thyroid, or cardiac disease) • History of cirrhosis or laboratory evidence of significant hepatocellular injury • Homelessness • pregnancy, nursing, or refusal to use a reliable method of birth control in women	NTX at 50 mg/day vs. acamprosate at 1998 mg/day vs. NTX plus acamprosate () vs. placebo. All participants received weekly group cognitive-behavioral therapy. Groups had between 8-14 participants, and sessions lasted 90 minutes. Medication was given in a double-dummy design. Patients were assessed weekly by interview, self-report, questionnaires, and laboratory screening. Study was conducted from November 1, 1998 to November 30, 2000. All patients recruited had been admitted to an inpatient alcohol withdrawal program. Patients started taking the medication a mean ± SD of 5 ±1 days before discharge from inpatient treatment.	Table 1: Patient Characteristics at Baseline **Parameter** / **Placebo n=40** / **NTX n=40** / **A n=40** / **A + NTX n=40** Age, (mean yrs± SD) † / 45 ± 9..3 / 46.1 ± 11.1 / 46.3± 7.7 / 46.8 ± 10.3 Sex, M/F† / 27/13 / 31/9 / 30/10 / 30/10 Married ,% ¶ / 30 / 25 / 23 / 33 Unemployed,% ± / 43 / 53 / 35 / 28 Professional training ,% ¶ / 70 / 750 / 80 / 88 Average Alcohol intake before inpatient treatment, (g/d ± SD) † / 244.79 ±143.65 / 257.56 ± 132.83 / 275.31 ± 145.70 / 242.81 ± 82.53 Mean Intensity of withdrawal on a scale of 1-4 (± SD) ¶ / 1.5 ± 1.1 / 1.7 ± 2.0 / 1.7 ± 1.2 / 1.6 ± 0.8 Mean number. of inpatient detoxifications (± SD) ¶ / 2.85 ± 3.91 / 3.88 ± 5.86 / 2.18 ± 2.50 / 1.79 ± 2.63 Attendance of self-help groups during the last month ¶ / 22.5 / 27.5 / 27.5 / 17.5 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. Note: Curves of survival probabilities were provided but not the exact data. For the outcomes: Nonrelapse rates to heavy drinking, using Breslow test, significant differences emerged between: Naltrexone vs. placebo, p=.02 Acamprosate vs. placebo, p=.05 Combined medication vs. placebo, p=.008 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. First alcohol intake (Breslow test) Naltrexone vs. placebo, p=.03 Acamprosate vs. placebo, p=.04 Combined medications vs. placebo, p=.002 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.	782 patients were aware of the study/ 196 were willing to learn details of the study/ 160 randomized/85 completed study # Pts. withdrawn because of relapse (%): Placebo: 30 NTX: 12 Acamprosate: 17 NTX + Acamprosate:9 # Pts withdrawn due to adverse effects: relapse (%): NTX: 4 Acamprosate: 3 NTX + Acamprosate: 4 1 fatigue, 1 rash, 1 itching, 2 abdominal bloating, 1 diarrhea, 2 pruritus, 3 nausea # Pts withdrawn due to medical illness Placebo:2 # Pts withdrawn due to changed into psychotherapy Acamprosate: 2 NTX + acamprosate: 1 # Pts withdrawn to due rejected participation: Acamprosate: 1
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. **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%).				
Limitations: limited duration of treatment, specific data not provided Quality Assessment: IC: Allocation concealment: A (low risk of bias)				

Study/Design/Purpose	Inclusion/Exclusion	Treatment	Patient Characteristics/Outcomes	Withdrawals/ Adverse Events/
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	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	NTX 50mg/day 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).	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	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 per centage 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