Published in final edited form as:

Alcohol Clin Exp Res. 2012 March ; 36(3): 497–508. doi:10.1111/j.1530-0277.2011.01616.x.

Acamprosate for Alcohol Dependence: A Sex-Specific Meta-Analysis Based on Individual Patient Data

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Abstract

Background—It is unknown whether women derive comparable benefits and have a similar safety and tolerability profile as men from acamprosate, a widely prescribed drug for the maintenance of abstinence in alcohol dependence. The objective of this study was to assess sex-specific differences in the efficacy, safety and tolerability of acamprosate in the treatment of women and men with alcohol dependence.

Methods—A sex-specific meta-analysis was conducted based on individual patient data (IPD). Data were obtained from double-blind, randomized controlled trials (RCTs) with quantitative drinking measures in patients with alcohol dependence receiving oral acamprosate or placebo. Sources included PubMed, PsychInfo and Cochrane electronic databases; reference lists from retrieved articles and presentations at professional meetings; and direct access to authors and companies who provided IPD.

Results—Individual records were obtained on 1,317 women and 4,794 men who participated in 22 eligible studies conducted in 18 countries. IPD meta-analyses found a significant beneficial effect of acamprosate relative to placebo across all 4 efficacy endpoints: an incremental gain of 10.4% (95% CI 7.1 to 13.7, $p < .001$) in percent of abstinent days, an incremental gain of 11.0% (7.4 to 14.6, $p < .001$) in percent of no heavy drinking days, an odds ratio of 1.9 (1.6 to 2.2, $p < .001$) for rate of complete abstinence and an odds ratio of 1.9 (1.6 to 2.3, $p < .001$) for rate of no heavy drinking, over the study duration. Acamprosate was also associated with significantly higher rates of treatment completion ($p = 0.004$) and medication compliance ($p < .001$) than placebo. Men and women did not differ on any measure of acamprosate efficacy, safety or tolerability.

Conclusion—This sex-specific IPD meta-analysis provides evidence that acamprosate has a significant effect compared with placebo in improving rates of abstinence and no heavy drinking in both women and men with alcohol dependence. Further, acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo among both women and men, and had a comparable safety and tolerability profile.

Keywords

acamprosate; women; alcoholism treatment; individual patient data; meta-analysis

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Financial Disclosure: Dr. Mason has served as a scientific consultant for several pharmaceutical companies, including Merck Sante and Forest Laboratories. Dr. Leheret has served as a statistical consultant for several pharmaceutical companies, including Merck Sante and Forest Laboratories, Inc.

INTRODUCTION

Alcohol dependence traditionally has been viewed as a man's disease, and much of our understanding of the disorder derives from studies comprised largely of males (Greenfield, 2002). However, recent epidemiological studies suggest a closing gender gap, with women representing approximately one-third of individuals with alcohol dependence (Grant et al., 2004; Keyes et al., 2008). Furthermore, although 2.3% of American women are estimated to meet criteria for current alcohol dependence overall, the prevalence is more than two-fold greater (5.5%) among women in the child-bearing ages of 18–29 years, with associated risk of fetal alcohol symptoms in their children (Grant et al., 2004). In addition, women generally experience liver damage and other health problems after consuming less alcohol than men, in part because of gender differences in total body water and alcohol metabolism (Bradley et al., 1998; Greenfield, 2002). Among women, chronic consumption of more than two drinks per day is associated with increased risk of mortality, breast cancer, hypertension, stroke, and reproductive problems (Bradley et al., 1998). Binge drinking among women, e.g., consuming four or more drinks in a row, may incur increased risk of accident, rape, assault, and unprotected sex (Wechsler et al., 1995). Comorbid depression and anxiety disorders also are more prevalent among alcoholic women than men, with associated increased risk of suicidality (Conway et al., 2006).

Given the significant disease burden of alcohol dependence in women, early intervention and effective treatment options are clearly needed. One emerging area in the treatment of alcohol dependence is pharmacotherapy. Available medications include disulfiram, naltrexone, and acamprosate. However, relatively little is known about the efficacy of these medications for alcohol dependence in women. This lack of knowledge was highlighted in a pivotal multi-center randomized controlled trial (RCT) showing that the newly approved long-acting injectable form of naltrexone (Vivitol®) was efficacious for males but not for females (Garbutt et al., 2005). Similarly, a study of oral naltrexone conducted solely in alcoholic women failed to show efficacy relative to placebo (O'Malley et al., 2007).

Acamprosate is an oral prescription medication for the maintenance of abstinence in individuals with alcohol dependence. Its mechanism of action involves normalizing the dysregulation of *N*-methyl-D-aspartic acid (NMDA)-mediated glutamatergic neurotransmission that occurs in recently abstinent individuals with alcohol dependence, thus attenuating one of the physiological mechanisms that may prompt drinking relapse (Littleton, 2007). Acamprosate generally has been shown to significantly increase the rate of abstinence relative to placebo in non-sex specific trials and to have no known serious adverse events, as demonstrated in more than 6,000 male and female outpatients with alcohol dependence studied in 23 RCTs conducted across 18 countries (See Table 1). Acamprosate is not metabolized in the liver and is not known to interact negatively with alcohol or other illicit or prescribed drugs (Rosenthal et al., 2008). A national audit of retail pharmacies found acamprosate to be the most widely prescribed drug for alcohol dependence in the United States (Market al., 2009).

Although acamprosate has relatively widespread use, women represent only 22% of participants in acamprosate RCTs (Table 1) and sex-specific outcome data from RCTs have not been reported. As a result, the differential efficacy and tolerability of this pharmacotherapy in women and men has not been documented through literature-based meta-analysis and it is not known if women derive comparable benefits and have a similar safety and tolerability profile with acamprosate as do men. Our objective was to conduct an individual patient data (IPD) meta-analysis to assess sex-specific differences in acamprosate efficacy, safety and tolerability in a multi-national sample of female and male participants in RCTs of acamprosate treatment of alcohol dependence.

METHODS

Data Sources

PubMed, PsychInfo and Cochrane electronic databases were searched for human studies from inception through February 2011 without date or language restriction to find RCTs using the terms “acamprosate” and “Campral[®]”, crossed with “alcohol dependence”, “alcoholism”, “randomized controlled trial” and “treatment”. The bibliographies of retrieved articles were examined for other relevant studies, and major scientific meetings were monitored for the results of completed trials that were unpublished at the time of the search.

Study Selection

Using the above search criteria, a total of 152 articles were identified (Figure 1). Trials that met the following criteria were included: (1) prospective, placebo-controlled, double-blind parallel groups design, (2) random assignment of patients with current alcohol dependence to either acamprosate or placebo treatment, and (3) at least one quantitative measure of drinking behavior to assess treatment efficacy. One hundred twenty-nine publications were excluded because they were not randomized placebo controlled trials (e.g., review articles or open label studies) or had outcomes other than alcoholism treatment endpoints (endpoints involving biomarkers, cognition, and economic factors). Independent investigators and Liphosphorus, a subsidiary of Merck of Darmstadt, Germany, the developer of acamprosate, were contacted by the authors and asked to provide access to the electronic databases of acamprosate RCTs and an electronic database in the public domain was accessed (<http://www.csc.unc.edu/COMBINE>). Of the 23 identified alcoholism RCTs, one small (N=26) study in adolescents that included only 3 females was excluded because IPD were not available (Niederhofer and Staffen, 2003). Thus a total of 22 studies, representing all acamprosate RCTs conducted in adults to date, were included in this IPD meta-analysis, as summarized in Figure 1.

Data Extraction

The authors independently assessed the methodological quality of selected RCTs using a validated scale that scores multiple aspects of the experimental design of a trial, including sample size, randomization methods, methods to preserve the double-blind, selection and withdrawal criteria, and statistical analysis (Chalmers et al., 1981). Trials were required to attain a mean Chalmers score of at least 50 of a possible 100 points to be retained in the analysis. The mean Chalmers scores of all studies assessed were within an acceptable range (Table 1).

Study Characteristics

The 22 RCTs selected for inclusion were reasonably homogeneous in terms of admission criteria, outcome variables and provision of concomitant alcoholism counseling. Inclusion criteria typically specified males and females over 18 years of age meeting Diagnostic and Statistical Manual – Third Edition Revised or Fourth Edition (DSM-III R, DSM IV; American Psychiatric Association, 1987, 1994) criteria for current alcohol dependence. Exclusion criteria typically specified pregnancy, lactation or refusal to use reliable birth control in women with child bearing potential¹; significant current psychiatric disorders such as depression, anxiety or other substance dependence disorders except nicotine; significant medical disorders such as severe renal failure²; and pharmacological treatments

¹Acamprosate is Category C in pregnancy.

² Acamprosate is not metabolized in the liver and is excreted unchanged via the kidneys thus severe renal failure (creatinine > 35) but not liver disease is contraindicated.

that could confound the results of the medication under study, such as naltrexone. Subjects were required to be abstinent for at least two days prior to randomization in all but three trials (Chick et al., 2000; Mason et al., 2006; Namkoong et al., 2003). Patients generally received the alcoholism counseling offered by the participating site, with manual guided counseling provided in three recent trials (Anton et al., 2006; Mason et al., 2006; Morley et al., 2006). Fourteen trials had durations of at least 6 months, with five studies having duration of one year (Table 1). The earlier trials adjusted dose on the basis of body weight (i.e., 1332 mg/d for subjects weighing <60 kg and 1998 mg/d for ≥ 60 kg). However, dosing by body weight is no longer recommended and 1998 mg per day is the approved standard fixed dose. Two trials (Anton, 2006 and Mason, 2006 in a small experimental group) used a dose of 3,000 mg which represents a 0.5 fold increase over the approved therapeutic dose. In keeping with the standard approach to meta-analysis, treatment conditions are collapsed to active drug versus placebo groups.

Data Synthesis

Efficacy endpoints are: a.) the percent of abstinent days, defined as the total number of abstinent days on study divided by the total potential treatment duration; this outcome evaluates the treatment effect throughout the study duration, as opposed to “time to event” outcomes; b.) the proportion of patients maintaining complete abstinence throughout the treatment duration, which is the outcome most associated with long-term recovery (Dawson et al., 2007); c.) the percent of no heavy drinking days (≥ 4 drinks females, ≥ 5 drinks males), defined as the total number of no heavy drinking days on study divided by the total potential treatment duration, and d.) the proportion of patients with no heavy drinking days throughout the treatment duration, which is an outcome associated with harm reduction. The Timeline Followback Interview (Sobell and Sobell, 2000) typically was used as the quantitative measure of drinking in the more recent studies (Anton et al., 2006; Baltieri and De Andrade, 2004; Chick et al., 2000; Gual and Leher, 2001; Kiefer et al., 2003; Mason et al., 2006; Morley et al. 2006; Namkoong et al., 2003; Paille et al., 1995; Pelc et al., 1997). Other studies used protocol-specific interviews, similar to the Timeline Followback Interview, that typically recorded frequency of drinking, quantity of drinks, and frequency of heavy drinking over rating intervals that ranged from 1 week to 1 month. Thus, the percent of abstinent days, rate of complete abstinence, percent of no heavy drinking days and rate of no heavy drinking could be calculated across studies from these data. All of the included trials documented the reason for patients’ premature termination. Early terminations clearly not related to alcoholism, e.g., the patient moved, were not treated as drinking; outcomes in these cases were calculated based on the subject’s actual time on study. Other reasons for early termination, e.g., the patient was lost to follow up, were conservatively attributed to drinking. No other missing data imputation was applied to efficacy endpoints.

The safety and tolerability of acamprosate in women and men were assessed with the rates of: a.) treatment completion; b.) discontinuation due to adverse events; c.) one or more adverse events of moderate or greater severity; d.) one or more digestive system adverse events; and e.) medication compliance. Gastrointestinal adverse events, typically loose stools or diarrhea, are the only side effect to consistently occur with greater frequency in acamprosate than placebo groups across clinical trials (Rosenthal et al., 2008). Therefore adverse events involving the digestive system were specifically chosen for evaluation. Medication compliance was assessed by returned pill counts with verification typically provided by at least one determination of acamprosate in plasma. Missing data for variables not related to efficacy were considered Missing at Random (Little and Rubin, 1987). This supported the use of the systematic Full Information Maximum Likelihood Technique (Anderson, 1957).

Statistical Analysis

Baseline characteristics were compared between men and women using t-test or chi square statistics, as appropriate. All such tests were 2-tailed, with $P < 0.05$ considered significant. The IPD meta-analysis was conducted using mixed linear and non linear models to test the significance of the main effects of treatment and gender and the interaction of treatment and gender, while accounting for study heterogeneity.

To test the continuous efficacy endpoints of percent of abstinent days and percent of no heavy drinking days, we used a multilevel general linear mixed model (Higgins et al., 2001) with treatment considered a random effect, study considered a fixed effect, gender as a main effect, and with a first order interaction of gender and treatment. Percent of abstinent days and percent of no heavy drinking days were calculated with and without arcsine transformation. Similar P-values were obtained for transformed and untransformed data. Thus results are reported for untransformed data to facilitate clinical interpretation. For the binary endpoints of rates of complete abstinence and no heavy drinking, a non linear model was used based on the same assumptions as above. Additionally, traditional meta-analysis using summary data for each study was used to support IPD results and evaluate treatment efficacy for women and men separately, using forest tree diagrams (DerSimonian and Laird, 1986). Safety and tolerability endpoints were evaluated in the IPD by 2-way ANOVA, to test the significance of treatment and gender as main effects and the first order interaction of treatment and gender. All analyses were performed using the R statistical package (Version 2.10.1).

All methods were undertaken according to the 2009 PRISMA guidelines for the conduct and reporting of systematic reviews (Moher et al., 2009).

Bias and sensitivity

Although classical literature-based meta-analyses of aggregated data typically are used for contrasting and comparing results from different studies, those study-level analyses may lead to biased assessments and have limitations in explaining heterogeneity across trials. IPD meta-analyses offer advantages over traditional meta-analyses, including consistency in handling missing data, defining endpoints and analyzing endpoints across studies (Simmons et al., 2005). In this IPD meta-analysis, bias in individual studies and across studies was reduced by 1) consistent handling of missing data, 2) standardizing outcomes, 3) analyses of outcomes in the intent-to-treat population and 4) re-calculating endpoints across studies using the IPD to eliminate bias introduced by studies using different analytic approaches. In addition, trials included in this meta-analysis were required to meet stringent inclusion criteria based on a validated scale for assessing methodological quality.

RESULTS

Clinical Characteristics of Women and Men with Alcohol Dependence

A total of 1,317 women and 4,794 men participated in the 22 RCTs of acamprosate for alcohol dependence selected for inclusion in the IPD meta-analysis (Table 1).

Women were significantly more likely to be divorced or widowed than men, and had significantly higher rates of suicide attempts, drug abuse, anxiety, depression and non-specific psychiatric problems than men (Table 2). Furthermore, despite having alcoholism of significantly briefer duration than men and lower quantity and frequency of drinking, women showed significantly greater impairment on tests of liver functioning. Women were also more likely to have attended one or more meetings of Alcoholics Anonymous (AA) and to have had prior psychotherapy.

Efficacy Outcomes

The IPD meta-analysis found a significant treatment effect for percent of abstinent days, with acamprosate showing an incremental gain of 10.38% (95% CI 7.1 to 13.7, $p<0.001$) relative to placebo (Table 3). The percent of abstinent days did not vary between women (48.02%) and men (47.08%), nor was there an interaction between treatment and gender. Results from traditional meta-analyses, conducted separately for men and women, confirm the significant effect of acamprosate on increase in percent of abstinent days among both women (+10.68%, 5.7 to 15.5, $p<0.001$) and men (+9.97%, 6.5 to 13.5, $p<0.001$) relative to placebo, as shown in Figure 2.

The IPD meta-analysis found a significant effect of acamprosate on the rate of complete abstinence relative to placebo (OR=1.87, 1.6 to 2.2, $p<0.001$; Table 3). The rate of complete abstinence did not differ significantly between men (24.6%) and women (21.3%) and there was no evidence of an interaction between treatment and gender. Traditional meta-analysis and forest diagrams confirm the significant effect of acamprosate for both women (OR=1.47, 1.2 to 1.8, $p<0.001$) and men (OR=1.51, 1.3 to 1.7, $p<0.001$) on rate of complete abstinence relative to placebo (Figure 3).

The IPD meta-analysis revealed a significant treatment effect for percent of no heavy drinking days, with acamprosate showing an incremental gain of +11.03% (7.5 to 14.6, $p<0.001$) relative to placebo (Table 3). Results did not vary between women and men, nor was there an interaction between gender and treatment. Results from traditional meta-analyses, conducted separately for men and women, confirmed a significant increase with acamprosate in percent of no heavy drinking days among both women (+10.86%, 6.1 to 15.6, $P=0.000$) and men (+10.80%, 7.1 to 14.5, $P=0.000$) relative to placebo (illustrated in Figure 4).

IPD meta-analysis revealed a significant effect of acamprosate on the rate of no heavy drinking relative to placebo (OR=1.93, 1.6 to 2.3, $p<0.001$). The rate of no heavy drinking did not vary between women (33.8%) and men (34.3%), nor was there evidence of an interaction between treatment and gender (Table 3). Traditional meta-analysis and forest diagrams (Figure 5) confirmed a significant effect of acamprosate relative to placebo for rate of no heavy drinking among both women (OR=1.53, 1.2 to 1.9, $p<0.001$) and men (OR=1.39, 1.2 to 1.6, $p<0.001$).

The IPD and traditional meta-analyses and forest diagrams indicate heterogeneity across studies, such that the treatment effect is greater in some studies and smaller in others, particularly among men with regard to the percent of abstinent days (Figure 2), percent of no heavy drinking days (Figure 4), and rate of no heavy drinking (Figure 5).

Safety and Tolerability

Acamprosate was associated with significantly higher rates of treatment completion ($A=56.3\%$, $P=52.1\%$, $p=0.004$) and medication compliance ($A=76\%$, $P=72\%$, $p<0.001$) than placebo, among both men and women (Table 4). Treatment groups did not differ in the rate of discontinuation due to adverse events, the rate of one or more adverse events at a moderate level of severity or greater, or the rate of one or more digestive system adverse events. However, women complained of significantly more adverse events of at least a moderate level of severity or greater than did men (27.6% vs. 19.8%, $p<0.001$), regardless of treatment assignment. There were no interactions between gender and treatment on any of the safety and tolerability measures.

DISCUSSION

Statement of Principal Findings

This IPD meta-analysis is the first comprehensive sex-specific evaluation of acamprosate efficacy and safety and tolerability in a multi-national sample of women and men with alcohol dependence. IPD from 1,317 women and 4,794 men participating in 22 multi-national RCTs of acamprosate showed a significant benefit of acamprosate on all four efficacy endpoints relative to placebo, including the percent of abstinent days, rate of complete abstinence, percent of no heavy drinking days, and rate of no heavy drinking, over the study duration. The effect size of acamprosate in women was comparable to that of men, and comparable to or better than effect sizes reported in non sex-specific literature-based meta-analyses (Mann et al., 2004), thus supporting the efficacy of acamprosate in the treatment of women with alcohol dependence. Furthermore, despite a history of significantly more anxiety, depression, suicide attempts, drug abuse, interpersonal loss and greater liver impairment at baseline than men, women responded comparably well to alcoholism treatment. The side effect and tolerability profile of acamprosate was comparable between women and men. Importantly, acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo among both women and men.

Strengths and Weaknesses of the Study

The external validity of this report is supported by similarities between the included trials and clinical practice: all but four trials (Anton et al., 2006; Kiefer et al., 2003; Mason et al., 2006; Morley et al., 2006) used the counseling that was routinely provided on site, instead of a standardized manual-guided therapy for all subjects, which tends to inflate response in studies of substance dependence (Nunes and Levin, 2004); most studies recruited from established practices and not through advertisement and did not pay subjects for participation; admission criteria was relatively liberal and appropriate for acamprosate, but did exclude concomitant use of drugs that could affect outcome. Internal validity is supported by the use of raw IPD to re-calculate pre-treatment and outcome measures uniformly across trials. Additionally, the trials included here met rigorous a priori defined methodological criteria, including adequate sample size, research design, and study duration.

Strengths and Weaknesses in Relation to Other Studies

Our IPD meta-analysis differs from previous analyses in several ways that should increase its scientific value. It is the first sex-specific IPD meta-analysis from acamprosate RCTs in alcohol dependence. Second, it is large and comprehensive: the data comprise 1,317 women and 4,794 men participants in 22 acamprosate RCTs conducted in 18 countries, and is the largest dataset representing women seeking treatment for alcohol dependence studied to date. A limitation of this report relative to that of a RCT is that it is an IPD meta-analysis and not a prospective study. The meta-analyses and forest diagrams indicate considerable heterogeneity in effect sizes across trials. Methodological differences across studies may contribute to heterogeneity in effect sizes. For example, Roussaux et al. 1996 was the only study to show a negative effect of acamprosate across all four efficacy endpoints in women (Figures 2–5). This study had a relatively high proportion of women (30%) and was the only trial to admit patients with either alcohol abuse or dependence. Only with alcohol dependence would the neuroadaptions occur that acamprosate is hypothesized to normalize; in alcohol abuse there would be no neuropharmacological target for acamprosate to treat (Littleton, 2007). Similarly, Chick et al. 2000 was the only trial to show negative effects of acamprosate across three efficacy endpoints in men (Figures 2, 3, 5). This is one of the few trials to begin treatment in non abstinent participants and the negative findings likewise may be related to the mechanism of action of acamprosate, which is believed to normalize

hyperactivity in the glutamate system in the brain after chronic heavy alcohol use and withdrawal (Littleton, 2007). This system theoretically would not become destabilized or hyperactive in an alcoholic who continues to drink. Another source of heterogeneity may be the contribution of a patient's baseline characteristics to treatment outcome. Future analyses may investigate patients' baseline characteristics as predictors of treatment response.

Future Research Considerations

Women were more likely to have side effect complaints of greater severity than men, with either acamprosate or placebo treatment. This greater level of physical discomfort may relate to women's higher rates of emotional distress, as evidenced by higher lifetime rates of suicide attempts, depression, anxiety and non specific psychiatric complaints. Thus, future studies of acamprosate in patients with alcohol dependence and comorbid psychiatric disorders may be especially relevant for women. Recent findings of a beneficial effect of acamprosate on sleep (Staner et al., 2006) may be particularly germane to comorbid disorders in which sleep disruption is a factor, e.g., depression, anxiety and post traumatic stress disorder. Importantly, acamprosate is not metabolized in the liver and has been found to raise no safety concerns when used in combination with drugs prescribed to treat comorbid psychiatric disorders (Rosenthal et al., 2008).

Clinical Implications of the Study

Results from this IPD meta-analysis indicate that acamprosate has a significant effect compared with placebo in improving rates of abstinence and no heavy drinking in both women and men with alcohol dependence. Further, acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo among both women and men. Women and men treated with acamprosate shared similar tolerability profiles in terms of rates of discontinuation due to adverse events, rates of adverse events of moderate severity or greater, and rates of digestive system adverse events, and this profile did not differ from that of men and women treated with placebo. This evidence base suggests that treatment providers may routinely consider acamprosate for treating alcohol dependence in both women and men, taking into account the patient's treatment goals and preferences as well as specific safety considerations.

Acknowledgments

Appreciation is expressed to Falk Kiefer, M.D., Kirsten C. Morley, Ph.D., M.P.H., Kee Namkoong, M.D., the COMBINE study and Merck Sante for providing access to electronic datasets used in this project. We also thank Karyn Coveney, B.A. and Allison Versaggi, A.A. for manuscript preparation and Vivian Goodell, M.P.H., John Light, Ph.D., and Charles Heyser, Ph.D., for their editorial comments.

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Figure 1.
Flow Diagram of the Study Selection Process

Figure 2.
Percent of Abstinent Days

Women

Study, year	Placebo			Acamprosate			Odds Ratio	95% CI	
	Freq	N	Prop	Freq	N	Prop			
Uhintre, 1985	1	2	0.50	3	6	0.50	1.00	0.20	4.96
Uhintre, 1990	7	52	0.13	15	51	0.29	2.18	0.97	4.91
Pelc, 1992	0	15	0.03	3	18	0.17	5.00	0.27	92.26
Ladewig, 1993	1	10	0.10	0	5	0.10	1.00	0.04	25.06
Paille, 1995	2	30	0.07	8	78	0.10	1.54	0.35	6.84
Roussaux, 1996	13	24	0.54	6	14	0.43	0.79	0.39	1.61
Sass, 1996	2	27	0.07	14	34	0.41	5.56	1.38	22.39
Whitworth, 1996	2	39	0.05	12	56	0.21	4.18	0.99	17.64
Barrias, 1997	1	13	0.08	5	11	0.45	5.91	0.81	43.3
Geerlings, 1997	4	32	0.12	4	31	0.13	1.03	0.28	3.77
Pelc, 1997	0	8	0.06	4	21	0.19	3.05	0.18	51.42
Poldrugo, 1997	9	29	0.31	21	38	0.55	1.78	0.96	3.29
Besson, 1998	0	14	0.04	1	9	0.11	3.11	0.12	83.57
Chick, 2000	9	59	0.15	10	37	0.27	1.77	0.79	3.95
Tempesta, 2000	13	32	0.41	13	25	0.52	1.28	0.73	2.25
Gual, 2001	10	31	0.32	13	28	0.46	1.44	0.75	2.75
Kiefer, 2003	0	14	0.04	3	10	0.30	8.40	0.47	150.02
Namkoong, 2003	0	4	0.12	1	3	0.33	2.67	0.13	56.17
Anton, 2006	15	96	0.16	14	91	0.15	0.98	0.50	1.92
Mason, 2006	3	91	0.03	8	100	0.08	2.43	0.66	8.87
Morley, 2006	12	22	0.55	8	13	0.62	1.13	0.63	2.00
TOTAL		644	0.17		679	0.25	1.47	1.19	1.82

Men

Study, year	Placebo			Acamprosate			Odds ratio	95% CI	
	Freq	N	Prop	Freq	N	Prop			
Uhintre, 1985	11	35	0.31	17	27	0.63	2.00	1.13	3.54
Uhintre, 1990	39	238	0.16	73	228	0.32	1.95	1.39	2.76
Pelc, 1992	3	33	0.09	13	37	0.35	3.86	1.21	12.39
Ladewig, 1993	2	22	0.09	10	25	0.4	4.40	1.08	17.96
Paille, 1995	14	147	0.10	49	283	0.17	1.82	1.04	3.18
Roussaux, 1996	9	40	0.22	15	49	0.31	1.36	0.67	2.78
Sass, 1996	15	109	0.14	24	102	0.24	1.71	0.95	3.07
Whitworth, 1996	30	185	0.16	38	168	0.23	1.39	0.91	2.15
Barrias, 1997	31	139	0.22	50	139	0.36	1.61	1.10	2.36
Geerlings, 1997	13	102	0.13	25	97	0.26	2.02	1.10	3.72
Pelc, 1997	8	55	0.15	46	105	0.44	3.01	1.53	5.92
Poldrugo, 1997	33	95	0.35	41	84	0.49	1.41	0.99	2.00
Besson, 1998	5	42	0.12	14	46	0.30	2.56	1.01	6.49
Chick, 2000	33	233	0.14	33	252	0.13	0.92	0.59	1.45
Tempesta, 2000	45	134	0.34	66	139	0.47	1.41	1.05	1.90
Gual, 2001	52	116	0.45	56	113	0.50	1.11	0.84	1.45
Kiefer, 2003	4	27	0.15	8	30	0.27	1.80	0.61	5.31
Namkoong, 2003	22	67	0.33	25	69	0.36	1.10	0.69	1.76
Anton, 2006	36	213	0.17	45	212	0.21	1.26	0.85	1.86
Mason, 2006	6	166	0.04	12	235	0.05	1.41	0.54	3.69
Morley, 2006	16	39	0.41	21	42	0.50	1.22	0.75	1.98
TOTAL		2272	0.19		2522	0.28	1.51	1.33	1.71

Figure 3.
Rates of Continuous Abstinence

Figure 4.
Percent of No Heavy Drinking Days

Women

Study, year	Placebo			Acamprosate			Odds Ratio	95% CI
	Freq	N	Prop	Freq	N	Prop		
Lhuintre, 1985	1	2	0.50	3	6	0.50	1.00	0.20 4.96
Lhuintre, 1990	7	52	0.13	15	51	0.29	2.18	0.97 4.91
Pelc, 1992	0	15	0.03	3	18	0.17	5.00	0.27 92.26
Ladewig, 1993	1	10	0.10	0	5	0.10	1.00	0.04 25.06
Paille, 1995	2	30	0.07	8	78	0.10	1.54	0.35 6.84
Roussaux, 1996	13	24	0.54	6	14	0.43	0.79	0.39 1.61
Sass, 1996	2	27	0.07	14	34	0.41	5.56	1.38 22.39
Whitworth, 1996	2	39	0.05	12	56	0.21	4.18	0.99 17.64
Barrias, 1997	1	13	0.08	5	11	0.45	5.91	0.81 43.30
Geerlings, 1997	4	32	0.12	4	31	0.13	1.03	0.28 3.77
Pelc, 1997	0	8	0.06	4	21	0.19	3.05	0.18 51.42
Poldrugo, 1997	9	29	0.31	21	38	0.55	1.78	0.96 3.29
Besson, 1998	0	14	0.04	1	9	0.11	3.11	0.12 83.57
Chick, 2000	9	59	0.15	10	37	0.27	1.77	0.79 3.95
Tempesta, 2000	13	32	0.41	13	25	0.52	1.28	0.73 2.25
Gual, 2001	10	31	0.32	13	28	0.46	1.44	0.75 2.75
Kiefer, 2003	0	14	0.04	3	10	0.30	8.40	0.47 150.02
Namkoong, 2003	0	4	0.12	1	3	0.33	2.67	0.13 56.17
Anton, 2006	15	96	0.16	14	91	0.15	0.98	0.50 1.92
Mason, 2006	3	91	0.03	8	100	0.08	2.43	0.66 8.87
TOTAL		622	0.15	666	0.24		1.53	1.22 1.92

Men

Study, year	Placebo			Acamprosate			Odds Ratio	95% CI
	Freq	N	Prop	Freq	N	Prop		
Lhuintre, 1985	18	35	0.51	20	27	0.74	1.44	0.97 2.13
Lhuintre, 1990	74	238	0.31	106	228	0.46	1.50	1.18 1.89
Pelc, 1992	4	33	0.12	17	37	0.46	3.79	1.42 10.13
Ladewig, 1993	8	22	0.36	16	25	0.64	1.76	0.94 3.29
Paille, 1995	31	147	0.21	105	283	0.37	1.76	1.24 2.49
Roussaux, 1996	13	40	0.32	28	49	0.57	1.76	1.06 2.92
Sass, 1996	22	109	0.20	40	102	0.39	1.94	1.25 3.03
Whitworth, 1996	46	185	0.25	57	168	0.34	1.36	0.98 1.89
Barrias, 1997	42	139	0.30	67	139	0.48	1.60	1.17 2.17
Geerlings, 1997	16	102	0.16	34	97	0.35	2.23	1.32 3.78
Pelc, 1997	17	55	0.31	62	105	0.59	1.91	1.25 2.93
Poldrugo, 1997	41	95	0.43	46	84	0.55	1.27	0.94 1.72
Besson, 1998	10	42	0.24	17	46	0.37	1.55	0.80 3.00
Chick, 2000	38	233	0.16	43	252	0.17	1.05	0.70 1.56
Tempesta, 2000	65	134	0.49	84	139	0.60	1.25	1.00 1.55
Gual, 2001	67	116	0.58	73	113	0.65	1.12	0.91 1.38
Kiefer, 2003	4	27	0.15	10	30	0.33	2.25	0.80 6.34
Namkoong, 2003	34	67	0.51	36	69	0.52	1.03	0.74 1.43
Anton, 2006	57	213	0.27	65	212	0.31	1.15	0.85 1.55
Mason, 2006	87	166	0.52	125	235	0.53	1.01	0.84 1.23
TOTAL		2198	.32	2440	43		1.39	1.24 1.55

Figure 5.
Rates of No Heavy Drinking

Table 1

Studies Included in the Individual Participant Data Meta-Analysis

Study, year	Country	Women		Men		X Dose (mg/d)	Study Duration (Months)	Chalmers Scores
		N	(%)	N	(%)			
Lhuinre, 1985	France	8	(11)	62	(89)	1,878	3	51
Lhuinre, 1990	France	103	(18)	466	(82)	1,708	3	70
Pelc, 1992	Belgium	32	(31)	70	(69)	1,842	6	65
Ladewig, 1993	Switzerland	14	(23)	47	(77)	1,838	6	68
Paille, 1995	France	108	(20)	430	(80)	1,765	12	80
Roussaux, 1996	Belgium	38	(30)	89	(70)	1,828	3	65
Sass, 1996	Germany	61	(22)	211	(78)	1,911	12	80
Whitworth, 1996	Austria	95	(21)	353	(79)	1,911	12	74
Barrias, 1997	Portugal	24	(08)	278	(92)	1,828	12	71
Geertings, 1997	Belgium, Luxembourg, Netherlands	63	(24)	199	(76)	1,875	6	73
Pelc, 1997	Belgium, France	28	(15)	160	(85)	1,665	3	74
Poldrugo, 1997	Italy	67	(27)	179	(73)	1,828	6	79
Besson, 1998	Switzerland	22	(20)	88	(80)	1,878	12	70
Chick, 2000	United Kingdom	96	(17)	485	(83)	1,998	6	82
Tempesta, 2000	Italy	57	(17)	273	(83)	1,998	6	75
Gual and Leheret, 2001	Spain	59	(20)	229	(80)	1,998	6	81
Kiefer, 2003	Germany	23	(29)	57	(71)	1,864	3	82
Namkoong, 2003	South Korea	6	(04)	136	(96)	1,642	2	80
Baltieri, 2004	Brazil	0	(00)	75	(100)	1,998	3	78

Study, year	Country	Women		Men		X Dose (mg/d)	Study Duration (Months)	Chalmers Scores
		N	(%)	N	(%)			
Anton, 2006	United States	187	(31)	425	(69)	3,000	4	80
Mason, 2006	United States	191	(32)	401	(68)	2,436	6	85
Morley, 2006	Australia	35	(30)	81	(70)	1,998	3	80
Total		1,317		4,794				

Table 2

Baseline Characteristics of Women and Men Participants in Randomized Controlled Trials of Acamprosate in Alcohol Dependence

	Women	Men	p-value
Demographic Variables	1,317	4,794	
Age (years)	43.3±9.2	42.8±9.2	0.023
Marital Status			
Single	18%	20%	0.003
Married	54%	58%	
Divorced	22%	18%	
Widowed	6%	4%	
Alcohol History			
Days of Abstinence in Prior Year	85±175	106±320	0.071
Drinks per Drinking Day	10.6±4.5	12.8±3.9	<0.001
Drinking Days per Week	5.9±1.7	6.4±1.4	<0.001
Alcoholism Duration (Years)	9.7±5.6	10.4±5.5	0.006
Alcoholism Severity Category			
Mild	28%	31%	0.071
Medium	31%	29%	
Severe	41%	40%	
Prior Detoxifications	61.5%	64.3%	0.26
Prior Anti-alcohol Drug	37.2%	38.1%	0.464
Prior AA Attendance	30.1%	22.9%	0.002
Liver Functioning			
GGT x ULN	2.89±4.7	2.72±3.3	0.018
SGPT x ULN	1.5±7.2	1.3±2.2	0.003
SGOT x ULN	1.2±7.1	1.0±1.0	<0.001
History of Psychosocial Problems			
Legal Problems	45.3%	45.0%	0.576
Anxiety Disorder	45.1%	31.5%	0.012
Mood Disorder	26.3%	17.4%	0.019
Non-Specific Psychiatric Problems	40.0%	32.5%	0.048
Suicide Attempt	21.6%	13.3%	0.004

	Women	Men	p-value
Drug Abuse	9.5%	5.5%	0.044
Psychotherapy	47.1%	37.3%	0.007

Values provided are mean $\pm$ one standard deviation, or percent (number affected/total number).

Abbreviations: AA=Alcoholics Anonymous, GGT=Gamma-glutamyl transpeptidase, ULN=Upper limit of normal, SGPT=Serum glutamic pyruvic transaminase, SGOT=Serum glutamic oxaloacetic transaminase, MCV=mean cell volume

Table 3

Individual Participant Data (IPD) Meta-Analyses: Efficacy Outcomes

Mean Percent of Abstinent Days				
Acamprosate = 51.24 (40.95)				
Placebo = 42.96 (40.31)				
	Incremental Value	95% CI	P-value	
Gender	-0.88	-3.09 1.32	0.55	
Treatment	10.38	7.10 13.65	<.001	
Treatment x Gender	0.12	-4.27 4.12	0.95	
Rate of Continuous Abstinence				
Acamprosate = 28% (45)				
Placebo = 19% (39)				
	Odds Ratio	95% CI	P-value	
Gender	0.83	0.66 1.04	0.11	
Treatment	1.87	1.57 2.23	<.001	
Treatment x Gender	1.14	0.84 1.54	0.41	
Mean Percent of No Heavy Drinking Days				
Acamprosate = 62.78 (39.91)				
Placebo = 52.95 (40.99)				
	Incremental Value	95% CI	P-value	
Gender	-0.16	-3.55 3.24	0.93	
Treatment	11.03	7.45 14.62	<.001	
Treatment x Gender	1.33	-3.36 6.02	0.58	
Rate of No Heavy Drinking				
Acamprosate = 39% (49)				
Placebo = 28% (45)				
	Odds Ratio	95% CI	P-value	
Gender	1.00	0.88 1.14	0.99	
Treatment	1.93	1.62 2.31	<.001	
Treatment x Gender	1.11	0.84 1.34	0.49	

Table 4**Safety and Tolerability of Acamprosate**

	Women		Men		Treatment	Gender	Interaction
	Acamprosate	Placebo	Acamprosate	Placebo			
	N=678	N=639	N=2,522	N=2,272	P-value	P-value	P-value
Treatment completion	57.8%	52.7%	55.9%	51.9%	0.004	0.37	0.72
Discontinuation due to AE	5.2%	4.8%	5.3%	4.8%	0.51	0.99	0.93
≥1 AE of ≥ moderate severity	28.1%	27.1%	20.2%	19.3%	0.16	<.001	0.86
≥1 Digestive AE	5.6%	6.3%	5.7%	4.4%	0.63	0.20	0.14
Medication compliance	77.0%	73.0%	75.0%	72.0%	<.001	0.28	0.78

Abbreviation: AE, adverse event.