Published in final edited form as:

Addict Behav. 2011 March ; 36(3): 217–221. doi:10.1016/j.addbeh.2010.11.003.

A double-blind, placebo-controlled pilot trial of acamprosate for the treatment of cocaine dependence

Kyle M. Kampman, M.D.^a, Charles Dackis, M.D.^a, Helen M Pettinati, Ph.D.^a, Kevin G. Lynch, Ph.D.^a, Thorne Sparkman, M.D.^b, and Charles P. O'Brien, M.D., Ph.D.^{a,c}

^aDepartment of Psychiatry, University of Pennsylvania School of Medicine, 3900 Chestnut Street, Philadelphia, PA, USA, 19104

^bDepartment of Medicine, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia, PA, USA, 19104.

^cVISN 4 Mental Illness, Research, Education and Clinical Center, Department of Veteran Affairs, Philadelphia, PA, USA, 19104

Abstract

Background—Acamprosate is a medication shown to be effective for the treatment of alcohol dependence. Although the exact mechanism of action of acamprosate is unknown, evidence suggests that it decreases excitatory amino acid activity by postsynaptic inhibition of the NMDA subtype of glutamate receptors. It is possible that the activity of acamprosate via modulating glutamatergic activity could also reduce craving for cocaine and impact abstinence in cocaine dependence. Therefore, we conducted a double-blind placebo-controlled pilot trial of acamprosate for the treatment of cocaine dependence.

Methods—Sixty male and female cocaine dependent patients were included in a nine-week double-blind, placebo-controlled trial. After a one-week baseline, patients were randomized to receive acamprosate 666 mg three times daily or identical placebo tablets for eight weeks. The primary outcome measure was cocaine use as determined by twice weekly urine drug screens.

Results—Thirty-six patients (60%) completed the trial, with no significant between-group difference in treatment retention. Percent cocaine positive urine drug screens did not differ between the two groups. Acamprosate was no better than placebo in reducing cocaine craving, reducing cocaine withdrawal symptoms, or improving measures of drug use severity from the Addiction Severity Index. Adverse events in this trial were generally mild and were evenly distributed between the two groups.

© 2010 Elsevier Ltd. All rights reserved.

Corresponding author: Kyle M. Kampman, M.D. University of Pennsylvania Treatment Research Center 3900 Chestnut Street Philadelphia, PA 19104 Phone: 215 222 3200 x 109 Fax: 215 386 6770 kampman_k@mail.trc.upenn.edu.

Contributors Kyle Kampman, Helen Pettinati, Kevin Lynch, and Charles O'Brien designed the study and wrote the protocol. Kyle Kampman, Charles Dackis and Thorne Sprkman conducted the trial. Kevin Lynch conducted statistical analyses. Kyle Kampman and Kevin Lynch wrote the first draft of the manuscript with editing from Helen Pettinati, Charles Dackis, Thorne Sparkman and Charles O'Brien. All authors contributed to and approved the final manuscript.

Conflict of Interest Kyle Kampman received honoraria from Forest Pharmaceuticals. The authors have no conflict of interest.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Discussion—Acamprosate was well tolerated but was no more efficacious than placebo in promoting abstinence from cocaine in cocaine dependent patients. Acamprosate does not appear to be a promising medication for the treatment of cocaine dependence.

Keywords

acamprosate; cocaine; clinical trial; placebo

1. Introduction

Acamprosate is a medication FDA approved for the treatment of alcohol dependence. Although the exact mechanism of action of acamprosate is unknown, one proposed mechanism is reduction of glutamatergic activity in alcohol dependent individuals during early abstinence. This reduction in glutamatergic activity is thought to be the result of antagonism of NMDA receptors, or antagonism of type 5 metabotropic glutamate (mGluR5) receptors. However, the effect of acamprosate on glutamate receptors may be dependent on resting NMDA receptor activity and therefore acamprosate may be better described as an NMDA partial agonist.

Medications active at NMDA or mGluR5 receptors may be effective at reducing cocaine craving and cocaine use in cocaine dependent patients. Antagonism of NMDA or mGluR5 receptors in certain brain regions can attenuate cocaine-seeking behavior in animal models. In mice, acamprosate was found to inhibit the development of cocaine induced conditioned place preference suggesting that acamprosate may reduce the rewarding effects of cocaine. In another trial, the same investigators found that acamprosate reduced cocaine-induced reinstatement of a previously extinguished cocaine induced conditioned place preference (CPP) in mice. Reinstatement of extinguished CPP is a rodent model of relapse-like behavior. In another animal model of relapse-like behavior, acamprosate attenuated cocaine and cue-induced reinstatement of cocaine seeking behavior in rats. The ability of acamprosate to reduce cocaine craving or cocaine relapse in human cocaine addicted individuals has never been tested. Therefore, we conducted a double-blind, placebo-controlled pilot clinical trial of acamprosate for the treatment of cocaine dependence.

2. Methods

2.1. Subjects

The subjects were 60 DSM-IV cocaine dependent men and women drawn from treatment-seeking cocaine users between the ages of 18 and 70. Drug dependence diagnoses were obtained using the Structured Interview for DSM IV (SCID-IV). Other psychiatric diagnoses were obtained using the Mini International Neuropsychiatric Interview (MINI). Subjects were required to have self-reported at least \$200 worth of cocaine use in the month prior to entry. Patients with co-morbid alcohol dependence were included if their alcohol dependence was not severe enough to require medications for alcohol detoxification.

Medical screening included a complete medical history and physical examination conducted by a certified nurse practitioner. Baseline laboratory testing included a chemistry screen, complete blood count, urinalysis, and a 12 lead EKG. Women received urinary pregnancy testing prior to starting medications, and at monthly intervals throughout the study. Chemistry screening, CBC, urinalysis and EKG were repeated at the end of the trial.

Subjects with current dependence (DSM-IV criteria) on any additional drug except nicotine and alcohol were excluded. Psychiatric exclusion criteria included psychosis, dementia, and

the use of other psychotropic medications. Medical exclusion criteria included unstable medical illnesses, impaired renal function, and a history of hypersensitivity to acamprosate.

2.2. Measures

The primary outcome measure for this trial was qualitative urine benzoylecgonine tests (UBT) obtained twice weekly. Urine collection was monitored by temperature checks. Samples less than 90 degrees, or greater than 100 degrees Fahrenheit were considered invalid and were not accepted. Samples were analyzed for benzoylecgonine by fluorescent polarization assay. Samples containing equal to or greater than 300 ng/ml of benzoylecgonine were considered to be positive.

Treatment retention was determined by attendance at research visits. Severity of addiction-related problems was measured by the Addiction Severity Index (ASI) administered at baseline and at the end of the trial. The study nurse practitioner rated overall improvement weekly using the Clinical Global Impression Scale (CGI). Cocaine craving was measured weekly using the Brief Substance Craving Scale (BSCS). Cocaine withdrawal symptoms were measured weekly using the Cocaine Selective Severity Assessment (CSSA). Safety measures included adverse events, which were monitored at each visit.

2.3. Procedures

Subjects were treatment-seeking cocaine users recruited at the University of Pennsylvania Treatment Research Center (TRC). The TRC recruits through advertisement in the local media as well as through professional referrals. Subjects entering the trial were not involved in any other type of addiction treatment elsewhere. All subjects signed informed consent prior to participation in the trial, after an investigator explained to them the study procedures. The study was reviewed and approved by the Institutional Review Board (IRB) of the University of Pennsylvania. Subjects were reimbursed \$5.00 at each visit for completing all research procedures; at the last visit they received \$30.00 because of the greater number of research procedures done at the end of the study. Subjects received an additional \$5.00 each week for returning the previous week's medication package in order to facilitate the pill-count compliance check. If needed, two transit tokens were provided at each visit.

Eligible subjects entered a 9-week trial that included a 1-week baseline phase during which all pretreatment measures were obtained and subjects began psychosocial treatment. Eligible subjects were randomized to receive either acamprosate or placebo. An urn randomization procedure was used to equally assign subjects to the two groups based on four characteristics: gender, recent cocaine use (determined by UBT at visit 1), cocaine withdrawal symptom severity measured by the Cocaine Selective Severity Assessment (CSSA) (Kampman et al., 1998) score on visit 1 (subjects divided into those with scores greater than 22 or those with scores of 22 or lower), and amount of alcohol use (alcohol use of less than or equal to 68% days drinking vs. more than 68% days drinking in 30 days prior to the study, as determined by the drug-use adapted Timeline Followback). Subjects were started on acamprosate 666 mg three times daily or identical placebo tablets on the first day of week 2 and that dose was continued until the end of week 9 when the medication was discontinued. The dose of acamprosate chosen for this trial was the dose used most commonly for the treatment of alcohol dependence. It was a dose known to be safe to use in addicted patients, and a dose that showed efficacy for the treatment of alcohol dependence. Therefore it was thought to be the most appropriate dose for an early pilot trial of acamprosate for cocaine dependence. An eight week medication phase was selected in order to give subjects exposure to acamprosate for a period long enough to see any potential difference in abstinence rates between the acamprosate and placebo groups.

Forest Pharmaceuticals supplied Acamprosate and identical placebo tablets. Study medication was placed in blister packs with each day's dose clearly marked. Medications were dispensed by a nurse practitioner each week and the previous week's blister pack was collected. Compliance was measured by pill count. Subjects were instructed to take their medication three times daily.

In addition to medication or placebo, subjects received weekly individual cognitive-behavioral relapse prevention therapy utilizing a Cognitive-Behavioral Coping Skills Therapy (CBT) manual. The CBT therapy manual and supporting materials were developed for the National Institute on Alcohol Abuse and Alcoholism Project MATCH. The basic format was accepted, although specific procedures were adapted for treatment of cocaine dependence by our group. Master's level therapists with additional training in CBT provided therapy

2.4. Statistical analysis

Baseline measures between the acamprosate and placebo groups were compared using t tests for continuous variables and chi square tests for dichotomous variables. Measures were transformed when necessary to reduce skew. Treatment retention was analyzed using survival analysis. Urine toxicology results were compared by the generalized estimating equations (GEE). Urines were collected twice a week per subject. In the GEE model, the pre-treatment level of the response was included as a covariate, together with the treatment group indicator, and a linear time effect. The two-way interactions between these covariates were considered for inclusion by examining the P-values of regression coefficients for the GEE models. For the GEE model for the urine test results, a compound symmetry structure was used for the working correlation matrix.

To assess the sensitivity of our inference to assumptions on missing data, we also performed a mixed effects analysis, and a pattern mixture analysis, of the UDS data.

3. Results

3.1. Baseline demographic and drug use

On the whole, the two medication groups, acamprosate and placebo, were very similar in demographics and baseline drug use characteristics (see Table 1). The average age of the subjects was about 45. Most were African American men and most smoked crack cocaine. On average, subjects had used cocaine about 16-18 days in the month prior to treatment (range 2-30 days) and spent around \$700 on drugs in the month prior to treatment. There were no significant differences between the two groups in any baseline demographic or drug use variable.

3.2. Treatment retention

Sixty percent of the subjects completed the trial, 18/26 (69%) in the placebo group and 18/34 (53%) in the acamprosate group. Survival analysis showed no significant differences between groups (Log rank test = 2.0, $p = .158$). Treatment retention, measured by the number of visits attended favored the placebo group. On average, acamprosate-treated subjects attended 27 visits and placebo-treated subjects attended 34 visits (Man-Whitney $U = 338$, $p = .12$).

There were a number of missed visits resulting in missing data. The UBT data were most affected. 363/960 of the urine samples were missing. For the Urine Test results, there was no significant difference between the two groups during the study period of the trial, neither time by medication group interaction effects were significantly different from zero. But the

subjects were more likely to drop out ($F=16.04$, $P<.001$) significantly over time. The Acamprosate -treated subjects were more likely to skip the later visits, but there was no significant difference compared with placebo group. The time to last visit was not significantly different between groups ($F=2.46$, $p=0.11$).

3.3. Urine Benzoyllecgonine Test Results

Overall, out of 17 UBT collected while the patients were receiving study medication, 23% of the UBT submitted by the placebo treated subjects were benzoyllecgonine negative vs. 22% for the acamprosate treated subjects. There was no significant difference between the two groups ($GEE \chi^2=0.61$, $df=1$, $p=0.44$) during the study period of the trial. Neither time effect nor time by medication group interaction effects was significantly different from zero. Analyses using mixed effects models ($F(1,589)=0.58$, $p=0.53$) and pattern mixture models ($GEE \chi^2=0.20$, $df=1$, $p=0.53$) gave very similar results for the test of medication effect, suggesting that missing data has very little influence on the test for medication effect.

3.4. Results from the Addiction Severity Index

Days of alcohol use, days of cocaine use, dollars spent on alcohol, dollars spent on drugs, the ASI composite alcohol scores, drug scores, legal scores, family/social scores, and psychiatric scores tended to decline in both groups in the trial, but we found no medication effects. Days of cocaine use ($F=13.02$, $P=.003$), dollars spent on drugs ($F=8.04$, $P=0.05$), ASI composite drug scores ($F=12.69$, $P=.004$), and ASI composite Psychiatric scores ($F=7.14$, $P=.0075$) declined significantly during the trial.

3.5. Results from BSCS

The BSCS composite measure combines three cocaine craving domains: intensity, duration and frequency. Cocaine craving showed a significant decline over the trial in both groups ($F=19.89$, $P<.001$). And there was significant interaction between baseline scores and time, subjects with higher craving at baseline showed a greater reduction in craving during the trial ($F=9.51$, $P=.002$). But no significant difference was found between the two groups for BSCS composite scores.

3.6 Results for the Clinical Global Impression Scale

Improvement was rated by the nurse practitioner weekly using the CGI. Improvement was rated on a scale from very much improved (0) to much worse (6). The improvement scores from CGI were evaluated as continuous variables and as dichotomized variables (very much improved and much improved vs. all other scores). There was no group difference for these two different analyses. When treated as continuous variables, CGI improvement scores ($F=13.41$, $P<.001$) declined significantly in both groups over time, showing an overall improvement in patients' clinical state. However, there was no significant time by treatment interaction. If we dichotomize improvement scores there is a significant trend toward improved / very much improved over time ($F=7.60$, $P=.006$), but no significant time by treatment group interaction.

3.7. Results from CSSA

The CSSA composite measures overall cocaine withdrawal symptoms. CSSA composite score showed a significant decline over the trial in both groups ($F=21.45$, $P<.001$). There was no significant difference found between the two groups for CSSA composite scores.

3.8. Medication adherence

Medication adherence was measured by pill count. The percentage of pills taken was calculated by subtracting the number of pills returned each week from the number of pills

dispensed. Both groups showed good adherence. On average, patients in the placebo group took their pills as prescribed on 90% of trial days, and patients in the acamprosate group took their pills on 86% of trial days ($t = .898$, $df = 58$, $p = .373$).

3.9. Safety analyses

Adverse events were assessed at each visit. Acamprosate was well tolerated. Adverse events were mainly mild and evenly distributed between the acamprosate and placebo groups. The most commonly reported adverse events included aches and pains, upper respiratory tract infections, headache ($n=6$), diarrhea, insomnia, flatulence, nausea, and skin infections. There were no significant differences noted in the occurrence of any adverse event between the two medication groups.

4. Discussion

In this trial, acamprosate did not appear to provide any benefit over placebo for the treatment of cocaine dependence. Neither placebo nor acamprosate treated patients significantly reduced their cocaine use during the trial, as measured by twice weekly UBT. Acamprosate was not associated with better treatment retention than placebo. Acamprosate was no better than placebo in reducing cocaine craving or cocaine withdrawal symptoms during this trial. Nurse practitioners did not rate acamprosate treated patients as more improved compared to placebo treated patients. Acamprosate was well tolerated and safe.

Acamprosate has been shown to be effective for the treatment of alcohol dependence. Its efficacy for the treatment of alcohol dependence is thought to be based primarily on its ability to reduce glutamatergic activity, which is increased in alcoholics during early abstinence. Chronic cocaine use has been shown to be associated with diminished baseline glutamatergic activity in the mesocorticolimbic dopamine reward pathways. Therefore cocaine dependent patients may not benefit from further reductions in glutamatergic activity. It is also possible that the effects of acamprosate on glutamatergic activity might have been different in chronic cocaine users based on acamprosate's partial agonist effects on glutamatergic function. The fact that acamprosate showed potential efficacy in several animal models of cocaine relapse while failing to show efficacy in a clinical trial may simply reflect the multifaceted and complex nature of cocaine dependence in humans.

This trial has several weaknesses. The number of subjects was relatively small and thus the results should be considered preliminary. The drop out rate was relatively high, though not much higher than most pharmacotherapy trials involving cocaine dependent patients. The patients included in this trial had relatively severe cocaine dependence symptoms and were mainly lower SES residents of a large city (Philadelphia). Therefore, the results of this trial may not generalize to other populations of cocaine dependent patients. Finally, most of the patients included in this trial entered the trial with a cocaine positive UBT. It is possible that acamprosate may be more effective in patients who started the medication after a period of cocaine abstinence.

5. Conclusion

In this trial, acamprosate was not superior to placebo in any outcome measure. The results of this trial do not support the use of acamprosate combined with cognitive behavioral therapy for the treatment of cocaine dependence. However, this was a small preliminary trial with a high dropout rate and thus the conclusions must be considered preliminary. It is possible that in a different patient population, or under different conditions, acamprosate might be efficacious for the treatment of cocaine dependence.

Acknowledgments

Role of Funding Source Forest Pharmaceuticals provided Acamprosate and placebo. Grant support was provided by from the National Institute on Drug Abuse P60-DA-05186-17 and P50 DA012756. The funding sources had no role in the study design, collection of data, analysis or interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

References

- Allgaier C, Franke H, Sobottka H, Scheibler P. Acamprosate inhibits Ca²⁺ influx mediated by NMDA receptors and voltage-sensitive Ca²⁺ channels in cultured rat mesencephalic neurones. *Naunyn-Schmiedeberg's Archives of Pharmacology* 2000;362(4-5):440–443.
- Backstrom P, Hyttia P. Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology* 2006;31(4):778–786. [PubMed: 16123768]
- Backstrom P, Hyttia P. Involvement of AMPA/kainate, NMDA, and mGlu5 receptors in the nucleus accumbens core in cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology* 2007;192(4):571–580. [PubMed: 17347848]
- Bell K, Duffy P, Kalivas PW. Context-specific enhancement of glutamate transmission by cocaine. [Research Support, U.S. Gov't, P.H.S.]. *Neuropsychopharmacology* 2000;23(3):335–344. [PubMed: 10942857]
- Bowers MS, Chen BT, Chou JK, Osborne MPH, Gass JT, See RE, et al. Acamprosate attenuates cocaine- and cue-induced reinstatement of cocaine-seeking behavior in rats. *Psychopharmacology* 2007;195(3):397–406. [PubMed: 17764007]
- Dahchour A, De Witte P. Ethanol and amino acids in the central nervous system: assessment of the pharmacological actions of acamprosate. *Progress in Neurobiology* 2000;60(4):343–362. [PubMed: 10670704]
- Dahchour A, De Witte P, Bolo N, Nedelec JF, Muzet M, Durbin P, et al. Central effects of acamprosate: part 1. Acamprosate blocks the glutamate increase in the nucleus accumbens microdialysate in ethanol withdrawn rats. *Psychiatry Research* 1998;82(2):107–114. [PubMed: 9754453]
- De Witte P, Littleton J, Parot P, Koob G, De Witte P, Littleton J, et al. Neuroprotective and abstinence-promoting effects of acamprosate: elucidating the mechanism of action. [Research Support, Non-U.S. Gov't Review]. *CNS Drugs* 2005;19(6):517–537. [PubMed: 15963001]
- Diggle PJ, Kenward MG. Informative dropout in longitudinal data analysis (with Discussion). *Applied Statistics* 1994;43:43–93.
- First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). Biometrics Research, New York State Psychiatric Institute; New York: 2002.
- Guy, W., editor. *Assessment Manual for Psychopharmacology*: Publication ADM 76-338. Washington, DC: US Department of Health Education and Welfare; 1976.
- Kadden, R.; Carroll, KM.; Donovan, D.; Cooney, N.; Monti, P.; Abrams, D.; Litt, M.; Hester, R. *Cognitive Behavioral Coping Skills Manual*. Washington, DC: U.S. Government Printing Office; 1992.
- Kampman KM, Volpicelli JR, McGinnis DE, Alterman AI, Weinrieb RM, D'Angelo L, et al. Reliability and validity of the Cocaine Selective Severity Assessment. *Addictive Behaviors* 1998;23(4):449–461. [PubMed: 9698974]
- Lee B, Platt DM, Rowlett JK, Adewale AS, Spealman RD. Attenuation of behavioral effects of cocaine by the Metabotropic Glutamate Receptor 5 Antagonist 2-Methyl-6-(phenylethynyl)-pyridine in squirrel monkeys: comparison with dizocilpine. *Journal of Pharmacology & Experimental Therapeutics* 2005;312(3):1232–1240. [PubMed: 15550570]
- McGeehan AJ, Olive MF. The anti-relapse compound acamprosate inhibits the development of a conditioned place preference to ethanol and cocaine but not morphine. *British Journal of Pharmacology* 2003;138(1):9–12. [PubMed: 12522067]

- McGeehan AJ, Olive MF. Attenuation of cocaine-induced reinstatement of cocaine conditioned place preference by acamprosate. *Behavioural Pharmacology* 2006;17(4):363–367. [PubMed: 16914955]
- McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, et al. The Fifth Edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment* 1992;9(3):199–213. [PubMed: 1334156]
- Rammes G, Mahal B, Putzke J, Parsons C, Spielmanns P, Pestel E, et al. The anti-craving compound acamprosate acts as a weak NMDA-receptor antagonist, but modulates NMDA-receptor subunit expression similar to memantine and MK-801. *Neuropharmacology* 2001;40(6):749–760. 749–60,2001. [PubMed: 11369029]
- Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* 1998;59(Suppl 20):22–33. [PubMed: 9881538]
- Somoza, E.; Dyrenforth, S.; Goldsmith, J.; Mesinkis, J.; Cohen, M. In search of a universal drug craving scale. Paper presented at the Annual Meeting of the American Psychiatric Association; 1995.
- Xi ZX, Ramamoorthy S, Baker DA, Shen H, Samuvel DJ, Kalivas PW, et al. Modulation of group II metabotropic glutamate receptor signaling by chronic cocaine. [Research Support, U.S. Gov't, P.H.S.]. *Journal of Pharmacology & Experimental Therapeutics* 2002;303(2):608–615. [PubMed: 12388642]
- Zeise ML, Kasparov S, Capogna M, Zieglgansberger W. Acamprosate (calciumacetylhomotaurinate) decreases postsynaptic potentials in the rat neocortex: possible involvement of excitatory amino acid receptors. *European Journal of Pharmacology* 1993;231(1):47–52. [PubMed: 8444281]

Table 1

Subject characteristics, expressed as percents or means (standard deviation).

Variable	Acamprosate N=34	Placebo N=26
Age	45.3 (8.8)	46.1 (7.7)
% Male	74%	77%
Race		
African American	82%	88%
Caucasian	18%	12%
Years of education	13.2 (1.9)	12.7 (2.1)
Days of alcohol use in past 30 days*	7.4 (8.5)	5.6 (7.3)
Days of cocaine use in past 30 days	16.8 (9.2)	18.5 (9.1)
\$ spent for drugs	\$699 (623)	\$747 (849)
Route of cocaine use		
Intranasal	9%	4%
Smoked	91%	96%
Years of cocaine use, lifetime	13.6 (7.8)	16.1 (8.2)
Number of prior treatments*	3.7 (8.3)	3.8 (4.5)
ASI Composite Drug Score	.264 (.049)	.264 (.068)
ASI Composite Alcohol Score*	.099 (.147)	.070 (.083)
ASI Composite Employment Score	.716 (.242)	.776 (.204)
ASI Composite Legal Score*	.077 (.136)	.097 (.200)
ASI Composite Family/Social Score*	.217 (.230)	.215 (.263)
ASI Composite Psychiatric Score*	.174 (.215)	.153 (.195)
ASI Composite Medical Score*	.211 (.337)	.280 (.391)
Hamilton Depression Rating Scale (24 item)	9.3 (7.8)	10.8 (9.6)
Hamilton Anxiety Rating Scale	5.5 (4.9)	7.2 (5.8)

*
transformed prior to analysis to reduce skew

Table 2

Adverse events reported by more than 10% of patients.

Adverse event	Acamprosate n = 34	Placebo n= 26
Aches and pains	38%	50%
Upper respiratory infection	32%	35%
Headache	31%	23%
Diarrhea	18%	23%
Insomnia	18%	20%
Flatus	12%	12%
Nausea	6%	20%
Skin infection	12%	12%