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Gabapentin Treatment for Alcohol Dependence: A Randomized Controlled Trial

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Abstract

Importance—Approved medications for alcohol dependence are prescribed for fewer than 9% of US alcoholics.

Objective—To determine if gabapentin, a widely-prescribed generic calcium channel/GABA modulating medication, increases rates of sustained abstinence and no heavy drinking, and decreases alcohol-related insomnia, dysphoria and craving, in a dose-dependent manner.

Design, Participants and Setting—A 12-week, double-blind, placebo-controlled, randomized dose-ranging trial of 150 men and women over 18 years of age with current alcohol dependence, conducted 2004–2010 at a single-site outpatient clinical research facility adjoining a general medical hospital.

Interventions—Oral gabapentin (0, 900, 1800 mg/d) and concomitant manual-guided counseling.

Main Outcome Measures—Rates of complete abstinence and no heavy drinking (co-primary) and changes in mood, sleep and craving (secondary) over the 12-week study.

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Results—Gabapentin significantly improved the rates of abstinence and no heavy drinking. The abstinence rate was 4.1% (95% CI, 1.1 to 13.7) in the placebo group, 11.1% (95% CI, 5.2 to 22.2) in the 900 mg group, and 17.0% (95% CI, 8.9 to 30.1) in the 1800 mg group (p = 0.04 for linear dose effect, NNT = 8 for 1800 mg). The no heavy drinking rate was 22.5% (95% CI, 13.6 to 37.2) in the placebo group, 29.6% (95% CI, 19.1 to 42.8) in the 900 mg group, and 44.7% (95% CI, 31.4 to 58.8) in the 1800 mg group (p = 0.02 for linear dose effect, NNT = 5 for 1800 mg). Similar linear dose effects were obtained with measures of mood (F=7.37, df=2, p=0.001), sleep (F=136, df=2, p<0.001), and craving (F=3.56, df=2, p=0.029). There were no serious drug-related adverse events, and terminations from adverse-events (9 of 150 participants), time on study (9.1 [3.8] weeks) and rate of study completion (85 of 150 participants) did not differ between groups.

Conclusions and Relevance—Gabapentin (particularly the 1800 mg dosage) was effective in treating alcohol dependence and relapse-related symptoms of insomnia, dysphoria and craving, with a favorable safety profile. Increased implementation of pharmacological treatment of alcohol dependence in primary care may be a major benefit of gabapentin as a treatment option for alcohol dependence.

INTRODUCTION

An estimated 3.8% of all deaths and 4.6% of disability-adjusted life-years globally are attributable to pathological alcohol use.[1] Such alcohol-attributable costs exceed 1% of the gross national product of high-and middle-income countries, making pathological alcohol use one of the largest avoidable risk factors for the worldwide burden of disease. Alcohol use disorders are present across medical specialties, with alcohol-related deaths particularly prevalent in the categories of injury, cancer, cardiovascular disease, and liver cirrhosis. Nonetheless, implementation of alcohol-specific medications remains limited across most medical specialties. Of the estimated 8,450,000 Americans with current alcohol dependence[2] only 720,000 prescriptions were filled in 2007 for Federal Food and Drug Administration (FDA) approved medications for alcohol dependence; those prescriptions were provided primarily by psychiatrists.[3]

Alcohol dependence,[4] also referred to as alcohol use disorder,[5] is a chronic, relapsing disorder marked by compulsive alcohol use, an inability to stop drinking despite harmful consequences, and the emergence of a withdrawal syndrome upon cessation of use. Early abstinence is associated with activation of brain stress systems in the extended amygdala.[6] Clinically, protracted abstinence involves symptoms of craving, mood and sleep disturbance,[7] all of which have been identified as risk factors for relapse.[8–10]

Gabapentin (Neurontin® and multiple generic formulations) is FDA-approved for the management of epileptic seizures and neuropathic pain. It is believed to act by blocking a specific alpha-2d subunit of the voltage-gated calcium channel at selective presynaptic sites and, as a result, to indirectly modulate gamma butyric acid (GABA) neurotransmission.[11] Pre-clinical findings indicate that gabapentin normalizes the stress-induced GABA activation in the amygdala that is associated with alcohol dependence, and provide an excellent pre-clinical rationale for evaluating gabapentin as a treatment for alcohol dependence.[12] A human laboratory study found gabapentin reduced alcohol-cued craving and sleep disturbance in alcohol dependent participants,[13] and clinical studies of various disorders report gabapentin reduced craving and disturbances in sleep and mood.[14–19] Earlier studies of gabapentin in alcohol dependent subjects, attempting to abstain following withdrawal support the safety and potential efficacy of gabapentin in alcohol dependent patients, but definitive conclusions were limited by either small sample size, methodological, or dosing issues.[14,17, 20, 21] The present study was therefore designed to provide a more definitive evaluation of the efficacy and safety of gabapentin at the highest

(1800 mg/d) and lowest (900mg/d) FDA-approved doses vs. placebo in a 3-arm, parallel groups, double blind, randomized clinical trial involving recently abstinent outpatient volunteers with alcohol dependence. We hypothesized that gabapentin would be associated with significant linear dose-related increases in rates of sustained abstinence and no heavy drinking, and decreases in abstinence-related symptoms involving sleep, mood, and craving, over the 12-week treatment course.

METHODS

Setting and Participants

Our single-site outpatient study was conducted at The Scripps Research Institute, La Jolla, CA. Our study physicians also practice internal and hospital medicine at the adjacent Scripps Green Hospital and Clinics; these facilities provide a broad range of medical services to the greater community of San Diego. The study protocol was approved by the Scripps Institutional Review Board (Scripps-IRB); written informed consent was obtained from all participants.

Treatment-seeking volunteers with alcohol dependence were recruited primarily via IRB-approved print and internet advertisements. The first participant was randomized April 2004 and the last follow-up visit was completed February 2010. To be eligible, men and women had to be over 18 years of age; meet the Diagnostic and Statistical Manual-Fourth Edition (DSM-IV)[4] criteria for current alcohol dependence; and be abstinent from alcohol at least 3 days prior to randomization. Exclusion criteria were risk for significant withdrawal based on a Clinical Institute Withdrawal Assessment-Alcohol, Revised (CIWA-AR) score >9;[22] more than one month of abstinence; dependence on substances other than alcohol or nicotine; a urine drug screen positive for benzodiazepines, cocaine, methamphetamine, tetrahydrocannabinol, methadone or opiates; clinically significant medical or psychiatric disorders; treatment with medications that could affect study outcomes; and treatment mandated by a legal authority.

Assessments

Medical clearance for randomization was provided by study physicians (AB, MK, and FS) and included an electrocardiogram, pregnancy test, complete blood count with differential, urinalysis, blood chemistry, and physical exam. The Structured Clinical Interview for DSM IV (SCID)[23] was conducted by study clinicians to establish diagnostic admission criteria. Study visits took place weekly throughout the 12-week double-blind phase, at Weeks 13 and 24 post-treatment, and included standardized assessments of alcohol use, craving, mood, sleep, and safety evaluations.

Alcohol use was assessed with the daily record of standard drinks obtained by the Timeline Followback Interview[24] with a drinking diary as a memory guide, and validated by weekly breathalyzer determinations, monthly GGT values and collateral informant reports. A standard drink was defined as 14g of absolute ethanol content, which is equivalent to 12 ounces of beer, 1.5 ounces of hard liquor, or 5 ounces of wine.[25] A heavy drinking day was defined as four or more drinks per day for women and five or more drinks per day for men.[25] Drinking data were collected by experienced research personnel.

Drinking urges were assessed by self-report using the Alcohol Craving Questionnaire-Short Form.[26] Mood was evaluated by self-report with the Beck Depression Inventory II.[27] Multiple components of sleep disturbance were assessed by self-report using the Pittsburgh Sleep Quality Index, modified for weekly administration.[28]

Safety evaluations included weekly vital signs, the Systematic Assessment for Treatment Emergent Events – General Inquiry (SAFTEE-GI),[29] and urine screening for drugs of abuse; specimens for blood chemistry and urinalysis were obtained monthly and analyzed by LabCorp.

Procedures

Simple randomization procedures were followed to randomly assign participants to double-blind treatment with oral gabapentin 900mg, 1800mg or placebo, in a 1:1:1 ratio, using a computer-generated randomization code provided by our laboratory biostatistician. The code was kept by the study pharmacist who provided participants with weekly medication in a blister card package that was consecutively numbered for each participant and prepared according to the randomization schedule. For all groups, each package contained two identical capsules to be taken three times a day. For the gabapentin groups, a placebo capsule was replaced with an identical 300mg capsule of gabapentin on the evening of Day 1, morning of Day 2, afternoon of Day 3 and on a similar schedule each day until the assigned fixed dose of 900mg was achieved on Day 4 or 1800mg was achieved on Day 6 (eTable 1). Participants were maintained on the assigned dose until Week 11, and then were titrated off active medication by substituting one placebo capsule for one capsule of active medication per day, in the reverse order of the initial dose titration, until all subjects received only placebo by the end of Week 12. Participants returned their blister cards at each weekly study visit for drug accountability and compliance review. Correct drug assignment was verified retrospectively by determining gabapentin concentration in plasma samples obtained at Week 2 and frozen for post-study analysis by gas chromatography/mass spectrometry.

Concurrent with study medication, study clinicians provided participants with 20 minutes of weekly manual-guided counseling designed to increase motivation, abstinence, and medication compliance.[30] At study onset, participants were provided with schedules for local self-help groups and encouraged to attend any self-help groups or psychosocial therapies they found beneficial; attendance was not further encouraged but was documented at each study visit.

Outcome measures

Since the time our statistical plan was designed (2003), responder analyses based on definitions that predict clinical benefit have been proposed by the FDA as preferable to analyses of group means.[31–33] The FDA's rationale for this change is that mean differences are difficult to interpret with regard to clinical relevance.[31–33] Thus we modified our original analysis of mean abstinence duration to be a responder analysis based on the rate of complete abstinence over the 12-week study. We also included the rate of no heavy drinking over the 12-week trial as a co-primary outcome, as this has become a standard outcome in alcoholism clinical trials.[32] We used a mixed effect model of drinking quantity (number of drinks per week) and frequency (number of heavy drinking days per week) over the 12-week study period, as supportive primary outcomes.[34] We also report change in GGT, a widely accepted and validated biomarker of drinking reduction, as a supportive primary outcome.[35]

Pre-specified secondary outcomes were standardized measures of alcohol craving, sleep, and mood over the 12-week study period.

Power Calculations and Statistical Analysis Plan

Our sample size estimate was derived from results of a prior trial that found an odds ratio for complete abstinence of 2.96 between drug and placebo,[36] estimating a sample size of 150

would show a medium effect size[37] for the difference between gabapentin and placebo in rate of complete abstinence with 80% power and an alpha level of 0.05.

Baseline demographic and clinical characteristics were compared by χ^2 and ANOVA as appropriate. Outcome analyses were intention-to-treat and involved all subjects who were randomly assigned (*n*=150). All tests were 2-tailed, and an alpha <0.05 was considered statistically significant. Linear dose effects for rates of complete abstinence and no heavy drinking over the 12-week study were assessed using the extended Mantel-Haenszel χ^2 test for linear association.[38, 39] This test uses a single contingency table where both row (0, 900, 1800 mg) and column (responder, non responder) variables are ordinal values and at least one variable has more than 2 levels. It is used to specifically assess dose-effect, with df=1, and multiple comparisons are not required. To facilitate clinical interpretation of primary outcomes, the number needed to treat (NNT) and odds ratio (OR) were calculated as estimates of effect size for each drug group relative to placebo. Reasons for early termination were coded at time of termination under double-blind conditions and served as the basis for the following assumptions: 4 subjects who were verified as abstinent for their entire study participation and as terminating for work-related reasons were classified as responders; one additional drop-out provided drinking data that conflicted with data from their collateral informant and non-response was assumed, which was later corroborated by the subject. Sixty of 65 drop-outs were known to have used alcohol prior to dropping and were known to be non-responders.

Linear dose effects for supportive and secondary outcomes were determined using the MIXED TEST subcommand for Linear Trend Contrasts and Multiple Event Models (MEMs) using PASW 17.0 software (IBM Corp., Armonk, NY).[40,41] All MEMs were repeated measures centered at Week 12 and included the baseline value of the dependent variable as a covariate. Week, treatment and week x treatment were evaluated as fixed effects in each model. Missing values were assumed missing at random and treatment effects were estimated by the restricted maximum likelihood method. Supportive primary outcomes of drinking quantity and frequency were reported as estimates of drug effects (regression coefficients) with associated 95% confidence intervals (95% CI). Outcomes involving craving, mood and sleep, and log-transformed GGT values were reported as F values from Type III tests of fixed effects.

RESULTS

Subjects

Following recruitment, 185 evaluations yielded the desired sample size of 150 randomized participants (Figure 1). Treatment groups did not differ on pre-treatment demographic and clinical variables, as shown in Table 1.

Time on study (9.1 [3.8] weeks, p=0.52) and rate of study completion (85 of 150 subjects, p=0.46) did not differ among treatment groups, nor did the reasons for termination (shown in Figure 1, p=0.83). Mean rate of medication compliance, defined as number of pills taken divided by number prescribed during study participation, was 96.2% and did not differ among groups (p=0.79). Groups were similar in their ability to correctly guess the identity of their medication when asked to do so upon study completion (59% gabapentin, 45% placebo, p=0.21).

Outcomes

Gabapentin had a significant linear dose effect in increasing the rates of complete abstinence (χ^2=4.19, df=1, p=0.04) and no heavy drinking (χ^2=5.39, df=1, p=0.02) over the 12-week

course of treatment, relative to placebo (Figure 2). The rate of sustained 12-week abstinence was 4.1% (95% CI, 1.1 to 13.7) in the placebo group, 11.1% (95% CI, 5.2 to 22.2) in the 900 mg group and 17.0% (95% CI, 8.9 to 30.1) in the 1800 mg group. Gabapentin 1800mg had the greatest treatment effect, with a NNT of 8 (95% CI, 6 to ∞) and an OR=4.8 (95% CI, 0.9 to 35), indicating a large effect size for abstinence.[37] The rate of no heavy drinking was 22.5% (95% CI, 13.6 to 37.2) in the placebo group, 29.6% (95% CI, 19.1 to 42.8) in the 900 mg group, and 44.7% (95% CI, 31.4 to 58.8) in the 1800 mg group. The gabapentin 1800mg group had a NNT of 5 (95% CI, 3 to 78) and OR=2.8 (95% CI, 1.1 to 7.5), indicating a medium effect size for no heavy drinking.[37] Compared to placebo, gabapentin also showed significant linear decreases in the average number of days of heavy drinking per week ($t=13.12$, $p<0.001$; Figure 3a; 900mg: −1.76 [95% CI, −2.2 to −1.3], $t=-7.22$, $p<0.001$; 1800mg: −2.02 [95% CI, −2.5 to −1.5], $t=-8.14$, $p<0.001$) and the number of drinks consumed per week ($t=5.32$, $p<0.001$; Figure 3b; 900mg: −2.16 [95% CI, −5.3 to 1.0], $t=-1.30$, $p=0.195$; 1800mg: −6.66 [95% CI, −9.8 to −3.5, $t=-4.13$, $p<0.001$). Gabapentin also had a significant linear dose effect on reduction in log transformed GGT values ($F=4.41$, $df=2$, $p=0.015$). On an exploratory basis, drinking outcomes were evaluated for the 65 participants who completed both the 12-week trial and the Week 24 follow-up visit. Significant linear dose effects were sustained at Week 24 for rate of complete abstinence ($\chi^2=4.73$, $df=1$, $p=0.022$), number of drinks per week ($t=2.01$, $p=0.044$), and number of heavy drinking days per week ($t=3.09$, $p=0.002$), with a non-significant trend for rate of no heavy drinking ($\chi^2=6.43$, $df=1$, $p=0.058$).

Gabapentin showed significant linear dose effects on craving, mood, and sleep (Figure 4a–c). Over the course of treatment, significant dose-dependent reductions were obtained on the Alcohol Craving Questionnaire ($F=3.56$, $df=2$, $p=0.029$; gabapentin 1800mg v. placebo: −6.80 [95% CI, −1.50 to −12.1], $t=-2.52$, $p=0.012$) the Beck Depression Inventory II ($F=7.37$, $df=2$, $p=0.001$; gabapentin 1800mg v. placebo: −1.13 [95% CI, −2.0 to −0.27], $t=-2.57$, $p=0.010$), and the Pittsburgh Sleep Quality Index total score ($F=136$, $df=2$, $p<0.001$; gabapentin 1800mg v. placebo: −1.49 [95% CI, −2.14 to −0.83], $t=-4.46$, $p<0.001$).

Safety, Tolerability, and Concomitant Therapy

Gabapentin was well-tolerated with no deaths and no serious drug-related adverse events. Nine subjects discontinued the study due to adverse events. Of these, five were rated as drug-related by blinded study physicians: two complaints of headache (900mg), two complaints of fatigue (one 900mg and one 1800mg) and one complaint of euphoria and speediness (placebo). No differences were found among groups in type of adverse events (eTable 2), with ≥10% of the sample complaining of fatigue (23%), insomnia (18%), and headache (14%). Groups also were similar in the number (1.98 [2.14], $p=0.53$) and severity (1.72 [1.14]; 1=mild, 2=moderate, $p=0.63$) of adverse events reported. Groups did not differ in body weight, vital signs, or on measures from urinalysis and blood chemistry testing that took place over the course of treatment. No evidence was found of drug diversion or substitution; of the 1242 urine drug screens collected in our study 27 (2%) tested positive for other drugs of abuse, primarily marijuana and prescription drugs. Five subjects attended individual therapy and nine attended Alcoholics Anonymous (AA) meetings during the course of the study. Attendance was not associated with drug group or primary outcome measures, with one exception: subjects who were completely abstinent attended fewer AA meetings than those who were not abstinent (41 vs. 89 meetings, $p=0.01$). All drug-related adverse events resolved within 1-week of drug discontinuation. There was no evidence of rebound in alcohol use, craving, insomnia or dysphoria when gabapentin was tapered.

DISCUSSION

Beneficial effects of gabapentin for the treatment of alcohol dependence were found in the intention-to-treat population over the 12-week course of treatment on: 1) the rates of complete abstinence and no heavy drinking, 2) the number of heavy drinking days and the number of drinks consumed per week, and 3) severity of craving, insomnia, and dysphoria. Results followed a linear dose-effect, with greatest efficacy achieved at the 1800 mg dose. Laboratory measures of GGT provided validation of gabapentin's effects on self-reported drinking outcomes. Significant effects were found to persist post-treatment in study completers who participated in the Week 24 follow-up assessment.

Gabapentin had a favorable safety profile and there were no unexpected or serious drug-related adverse events or differences in study discontinuation rates due to adverse events. Of note, somnolence has been a commonly reported adverse event in gabapentin pain and epilepsy trials,[42] but was not a common complaint among our alcohol dependent participants. Conversely, prior to treatment our subjects reported experiencing sleep disturbance and related daytime dysfunction that significantly improved with gabapentin relative to placebo. No evidence of drug substitution or misuse of gabapentin was detected.

This study has several limitations to consider. First, the drop-out rate is significant, as is often the case in clinical trials in substance dependence. However, to put our results in context, the treatment completion rates reported in a meta-analysis of randomized controlled trials involving 6,111 outpatients with alcohol dependence were 52.7% for placebo and 57.8% for acamprosate, which is directly comparable to our treatment completion rate of 56%.[43] Furthermore, our mean duration of study participation was 9.1 weeks of a 12-week study, which is a clinically relevant period of drug exposure for assessing treatment effects. Concerns about potential bias introduced by drop-outs are mitigated by a lack of differential drop-out between groups, and by consistency across outcomes that include the assumption of missing at random and response variables derived from data collected on study without assumption for 96.7% of participants. The validity of results is supported by pre-clinical[12] and human laboratory studies[13] of gabapentin effects on models of protracted abstinence and by clinical proof-of-concept studies from different groups.[14, 17, 20, 21]

Another limitation is that results from a single-site study may not generalize to all treatment settings and alcohol dependent populations. Nevertheless, generalizability is supported by the absence of associations between demographic variables with any outcome variable, the high rate of randomized (150) to evaluated (185) volunteers, and the broad range of alcoholism severity included in our sample. However, none of our community-dwelling volunteers required detoxification.[44] Indeed, our participants typically drank 5 days per week and were able to achieve the required 3 days of abstinence prior to randomization simply with monitoring and advice to taper drinking to further reduce risk.

Rates of alcohol dependence exceed those of all illicit drug dependence disorders combined[2] and there is a great unmet need for medications to treat alcohol dependence, per se. Thus, co-occurring illicit substance dependence disorders were excluded from the present study. Future studies are warranted to assess gabapentin efficacy in substance use disorders, alone and in combination, that have protracted abstinence symptoms involving craving, mood and sleep. Indeed, a recent randomized controlled trial of gabapentin in cannabis dependence, the most prevalent illicit drug dependence disorder,[2] found significant reductions in marijuana use, craving, mood and sleep disturbance with gabapentin relative to placebo.[45] Of note, gabapentin is not appreciably metabolized in the liver, an advantage for patients with alcohol-related liver dysfunction, and is not known to interfere with the metabolism of

commonly used illicit or prescribed drugs.[42] To facilitate replication in future studies, our counseling materials can be accessed online (www.alcoholfree.info).

In summary, gabapentin (particularly the 1800 mg dose) effectively treated alcohol dependence and relapse-associated symptoms involving craving, mood and sleep, and had a favorable safety profile. A sustained post treatment effect on drinking outcomes was found in those who responded well to gabapentin on study. Larger studies in more diverse populations of patients with alcohol dependence are needed to replicate and extend these findings. Gabapentin has been used ubiquitously by primary care physicians for many other indications, resulting in familiarity with its pharmacology, pharmacokinetics and side effects. Thus, unlike other approved treatments for alcohol dependence which are prescribed by a small number of specialists, gabapentin may be more readily utilized by primary care physicians. Increased implementation of effective pharmacological treatment for alcohol dependence in primary care may be a major benefit of gabapentin as a treatment option for alcohol dependence.

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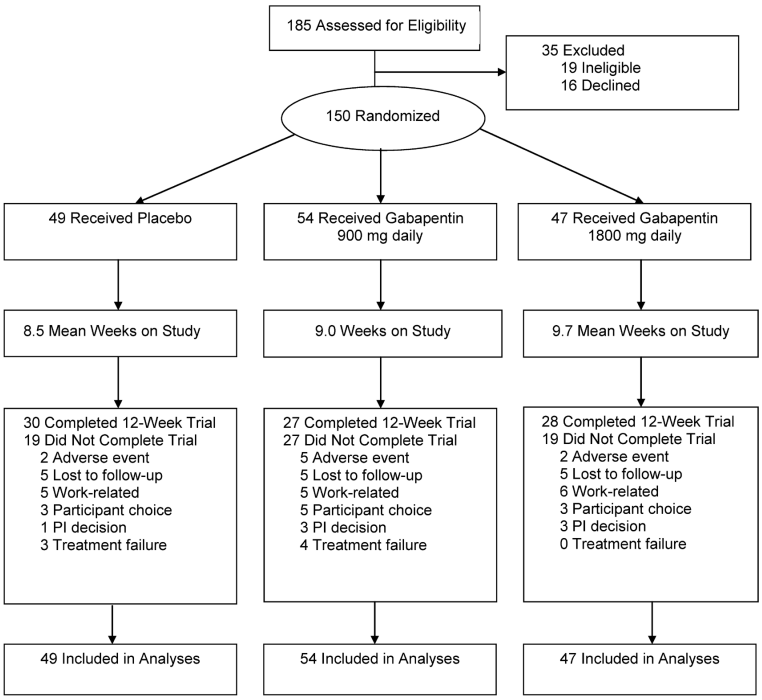

Figure 1.
Flow of participants through the trial.

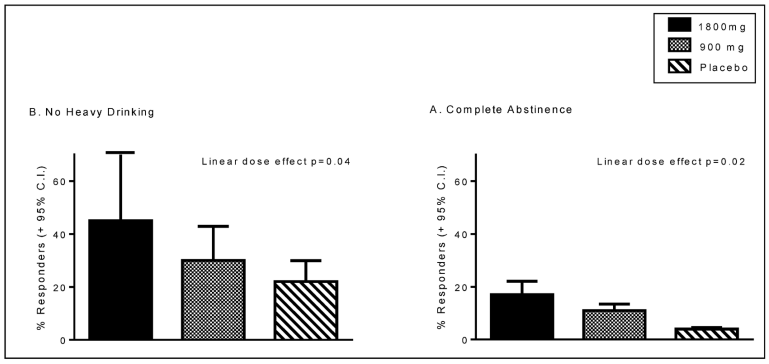

Figure 2.
Gabapentin effects on rates of no heavy drinking and complete abstinence during the 12-week study in the intention-to-treat population (N = 150).

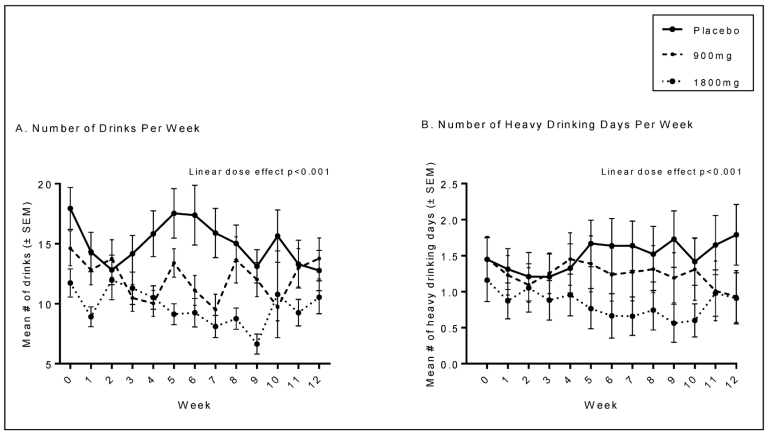

Figure 3.
Gabapentin effects on number of drinks per week and number of heavy drinking days per week during the 12-week study in the intention-to-treat population (N = 150).

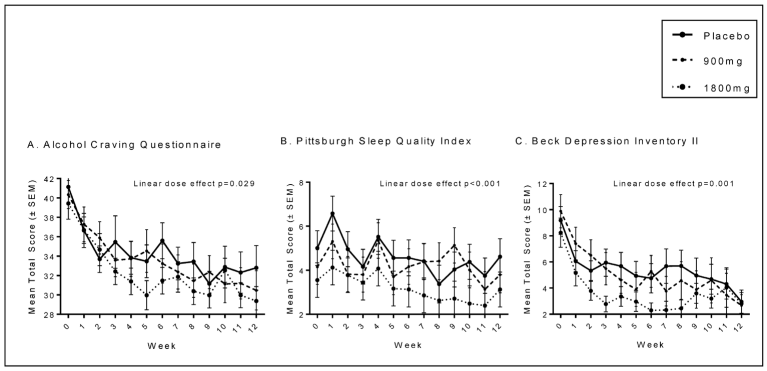

Figure 4.

Gabapentin effects on standardized measures of craving, sleep, and mood during the 12-week study in the intention-to-treat population (N = 150).

Table 1

Pre-treatment demographic and clinical characteristics by treatment group.[a]

Demographic characteristic	Placebo (N = 49)	Gabapentin 900 mg/d (N = 54)	Gabapentin 1800 mg/d (N= 47)
Age, y	46.8 (11.3)	41.9 (10.1)	45.2 (11.3)
Sex			
Female	28 (57.1%)	21 (38.9%)	16 (43.3%)
Male	21 (42.9%)	33 (61.1%)	31 (66.0%)
White, non Hispanic [b]	42 (85.7%)	40 (74.1%)	40 (85.1%)
Full-time employment	23 (46.9%)	30 (55.6%)	17 (36.2%)
Clinical Characteristic			
Number of DSM-IV criteria met for alcohol dependence (3 of 7 criteria required for diagnosis)	5.8 (1.2)	6.1 (1.0)	5.5 (1.3)
Alcoholism Clinical Global Impression			
Very Mild	1 (2.0%)	2 (3.7%)	0 (0%)
Mild	9 (18.4%)	10 (18.25%)	12 (25.5%)
Moderate	26 (53.1%)	32 (59.3%)	28 (59.6%)
Marked	10 (20.4%)	8 (14.8%)	5 (10.6%)
Severe	3 (6.1%)	2 (3.7%)	1 (2.1%)
Very severe	0 (0%)	0 (0%)	1 (2.1%)
Number of drinks per week [c]	47.3 (28.7)	40.5 (25.0)	40.9 (23.2)
Drinking days per week [c]	5.2 (2.0)	5.4 (3.1)	5.3 (1.8)
Years of heavy drinking	15.0 (10.4)	14.3 (9.7)	14.0 (9.6)
Parental alcoholism	18 (36.7%)	26 (49.1%)	21 (44.7%)
No prior alcoholism treatment	34 (70.1%)	32 (60.4%)	33 (71.7%)
Consecutive days abstinent prior to randomization	3.2 (4.1)	3.2 (4.0)	2.7 (3.0)
Gamma-glutamyl transferase >ULN	7 (14.3%)	13 (24.1%)	7 (14.9%)
Pittsburgh Sleep Quality Index score [d] (range 0–30)	4.9 (2.7)	3.9 (2.3)	3.5 (2.6)
Beck Depression Inventory II score [d] (range 0–63)	8.6 (6.7)	9.5 (8.0)	8.3 (6.9)
Alcohol Craving Questionnaire score [d] (range 7–84)	42.5 (13.6)	42.5 (12.0)	42.5 (10.6)

[a] Data are given as means (standard deviations) unless otherwise indicated as numbers (percentages). Treatment groups did not differ significantly on any pre-treatment variable.

[b] Race and ethnicity were self reported by the participants.

[c] Mean values are derived from the 90 day period prior to intake.

[d] Higher scores indicate worse condition.

eTable 1

Gabapentin dose titration schedule: Number of 300mg capsules dispensed.

	Morning Dose		Afternoon Dose		Evening Dose		Total Daily Dose	
	900mg Group	1800mg Group	900mg Group	1800mg Group	900mg Group	1800mg Group	900mg Group	1800mg Group
Week 0:								
Day 1	0	0	0	0	1	1	1	1
Day 2	1	1	0	0	1	1	2	2
Day 3	1	1	1	1	1	1	3	3
Day 4	1	1	1	1	1	2	3	4
Day 5	1	2	1	1	1	2	3	5
Day 6–7	1	2	1	2	1	2	3	6
Weeks 1–10:	1	2	1	2	1	2	3	6
Week 11:								
Day 1	1	2	0	1	1	2	2	5
Day 2	0	1	0	1	1	2	1	4
Day 3	0	1	0	1	0	1	0	3
Day 4	0	1	0	0	0	1	0	2
Day 5	0	0	0	0	0	1	0	1
Day 6–7	0	0	0	0	0	0	0	0

The placebo and gabapentin groups received the same number of identical capsules (6 per day).

eTable 2

Adverse events occurring in ≥ 10% of participants (N=150).

Adverse Event	Placebo N=49	Gabapentin 900mg N=54	Gabapentin 1800mg N=47
Fatigue	12 (24%)	13 (24%)	9 (19%)
Insomnia	11 (22%)	10 (19%)	6 (13%)
Headache	8 (16%)	7 (13%)	6 (13%)