

Original Investigation

Gabapentin Treatment for Alcohol Dependence

A Randomized Clinical Trial

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IMPORTANCE Approved medications for alcohol dependence are prescribed for less than 9% of US alcoholics.

OBJECTIVE To determine if gabapentin, a widely prescribed generic calcium channel/ γ -aminobutyric acid-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 older than 18 years with current alcohol dependence, conducted from 2004 through 2010 at a single-site, outpatient clinical research facility adjoining a general medical hospital.

INTERVENTIONS Oral gabapentin (dosages of 0 [placebo], 900 mg, or 1800 mg/d) and concomitant manual-guided counseling.

MAIN OUTCOMES AND MEASURES Rates of complete abstinence and no heavy drinking (coprimary) and changes in mood, sleep, and craving (secondary) over the 12-week study.

RESULTS Gabapentin significantly improved the rates of abstinence and no heavy drinking. The abstinence rate was 4.1% (95% CI, 1.1%-13.7%) in the placebo group, 11.1% (95% CI, 5.2%-22.2%) in the 900-mg group, and 17.0% (95% CI, 8.9%-30.1%) in the 1800-mg group ($P = .04$ for linear dose effect; number needed to treat [NNT] = 8 for 1800 mg). The no heavy drinking rate was 22.5% (95% CI, 13.6%-37.2%) in the placebo group, 29.6% (95% CI, 19.1%-42.8%) in the 900-mg group, and 44.7% (95% CI, 31.4%-58.8%) in the 1800-mg group ($P = .02$ for linear dose effect; NNT = 5 for 1800 mg). Similar linear dose effects were obtained with measures of mood ($F_2 = 7.37$; $P = .001$), sleep ($F_2 = 136$; $P < .001$), and craving ($F_2 = 3.56$; $P = .03$). There were no serious drug-related adverse events, and terminations owing to adverse events (9 of 150 participants), time in the study (mean [SD], 9.1 [3.8] weeks), and rate of study completion (85 of 150 participants) did not differ among 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.

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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 US 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 on 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 treatment of epileptic seizures and neuropathic pain. It is believed to act by blocking a specific α -2d subunit of the voltage-gated calcium channel at selective presynaptic sites and, as a result, to indirectly modulate γ -aminobutyric acid (GABA) neurotransmission.¹¹ Preclinical findings indicate that gabapentin normalizes the stress-induced GABA activation in the amygdala that is associated with alcohol dependence, and it provides an excellent preclinical rationale for evaluating gabapentin as a treatment for alcohol dependence.¹² A human laboratory study found that gabapentin reduced alcohol-cued craving and sleep disturbance in alcohol-dependent participants,¹³ and clinical studies of various disorders report that gabapentin reduced craving and disturbances in sleep and mood.¹⁴⁻¹⁹ Earlier studies of gabapentin in alcohol-dependent participants 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 issues, 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 (900 mg/d) FDA-approved doses vs placebo in a 3-arm, parallel-group, 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, California. 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 (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 in April 2004, and the last follow-up visit was completed February 2010. To be eligible, men and women had to be older than 18 years; meet the *Diagnostic and Statistical Manual of Mental Disorders* (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 of Alcohol Scale, Revised (CIWA-Ar)²² score higher than 9; more than 1 month of abstinence; dependence on substances other than alcohol or nicotine; a urine drug screen that was 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.

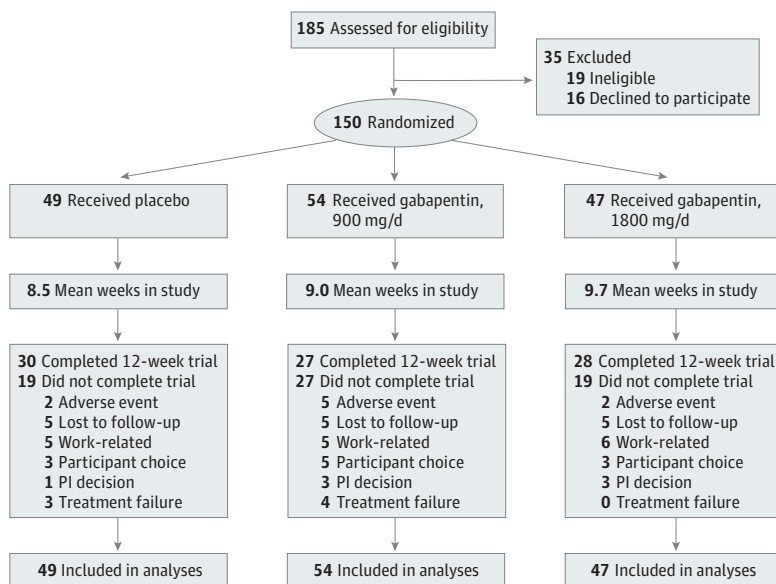
Assessments

Medical clearance for randomization was provided by study physicians (F.S., M.K., and A.B.) and included an electrocardiogram, pregnancy test, complete blood cell count with differential, urinalysis, blood chemistry testing, and physical examination. 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 13 and 24 weeks posttreatment, 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 Interview²⁴ with a drinking diary as a memory guide, and validated by weekly breathalyzer determinations, monthly γ -glutamyltransferase (GGT) values and collateral informant reports. A standard drink was defined as 14 g of absolute ethanol content, which is equivalent to 12 oz of beer, 1.5 oz of hard liquor, or 5 oz of wine.²⁵ A heavy drinking day was defined as 4 or more drinks per day for women and 5 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

Figure 1. Flow of Participants Through the Trial



PI indicates principal investigator.

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 testing 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, 900 mg or 1800 mg (hereinafter, 900-mg and 1800-mg groups), or placebo, in a 1:1:1 ratio, using a computer-generated randomization code provided by our laboratory biostatistician (V.G.). 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 2 identical capsules to be taken 3 times a day. For the gabapentin groups, a placebo capsule was replaced with an identical 300-mg capsule of gabapentin on the evening of day 1, the morning of day 2, the afternoon of day 3, and on a similar schedule each day until the assigned fixed dose of 900 mg was achieved on day 4 or 1800 mg was achieved on day 6 (eTable 1 in Supplement). Participants were maintained on the assigned dose until week 11, and then were titrated off active medication by substituting 1 placebo capsule for 1 capsule of active medication per day, in the reverse order of the initial dose titration, until all participants 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 poststudy analysis by gas chromatography and 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 were 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 coprimary outcome, because 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

Prespecified 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 (OR) of 2.96 for complete absti-

Table. Pretreatment Demographic and Clinical Characteristics by Treatment Group^a

Characteristic	Group		
	Placebo (n = 49)	Gabapentin, 900 mg/d (n = 54)	Gabapentin, 1800 mg/d (n = 47)
Demographic Characteristic			
Age, y	46.8 (11.3)	41.9 (10.1)	45.2 (11.3)
Sex, No. (%)			
Female	28 (57.1)	21 (38.9)	16 (34.0)
Male	21 (42.9)	33 (61.1)	31 (66.0)
White, non-Hispanic ^b , No. (%)	42 (85.7)	40 (74.1)	40 (85.1)
Full-time employment, No. (%)	23 (46.9)	30 (55.6)	17 (36.2)
Clinical Characteristic			
No. 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, No. (%)			
Very mild	1 (2.0)	2 (3.7)	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	1 (2.1)
No. 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, No. (%)	18 (36.7)	26 (49.1)	21 (44.7)
No prior alcoholism treatment, No. (%)	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)
γ-glutamyl transferase level > ULN, No. (%)	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)

Abbreviations: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); ULN, upper level of normal range.

^a Data are given as means (SDs) unless otherwise indicated. Treatment groups did not differ significantly on any pretreatment 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.

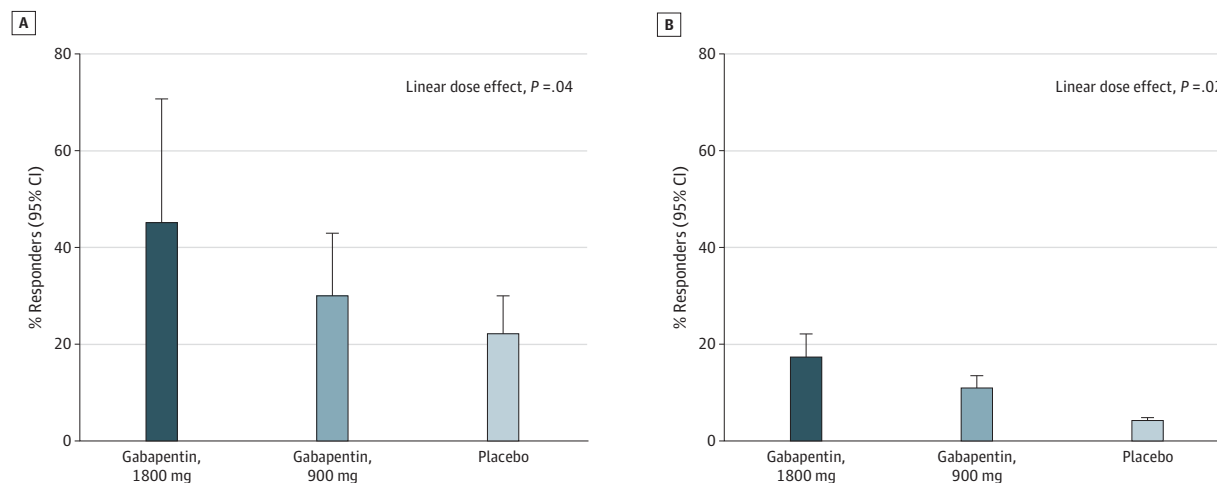
nence between drug and placebo,³⁶ estimating a sample size of 150 would show a medium effect size³⁷ for the difference between gabapentin and placebo in rate of complete abstinence with 80% power and an α level of .05.

Baseline demographic and clinical characteristics were compared by χ^2 and analysis of variance as appropriate. Outcome analyses were intention-to-treat and involved all participants who were randomly assigned ($n = 150$). All tests were 2-tailed, and an $\alpha < .05$ 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 mg, 1800 mg) and column (responder, nonresponder) variables are ordinal values and at least 1 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 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 participants who were verified as abstinent for their entire study participation and as terminating for work-related reasons were classified as responders; 1 additional study dropout provided drinking data that conflicted with the collateral informant's data, and nonresponse was assumed, which was later corroborated by the participant. Sixty of 65 dropouts were known to have used alcohol prior to leaving the study and were known to be nonresponders.

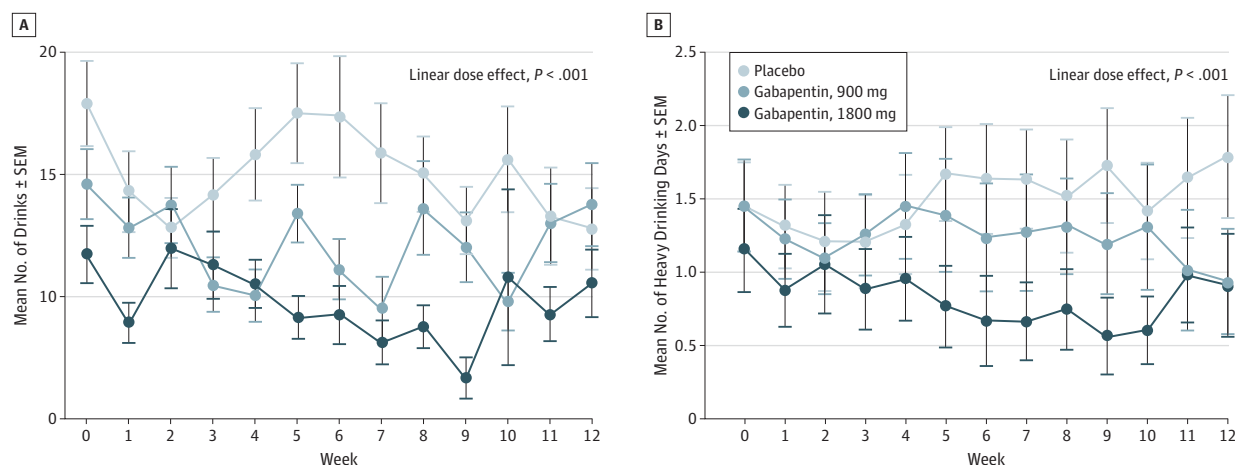
Linear dose effects for supportive and secondary outcomes were determined using the MIXED TEST subcommand for linear trend contrasts and multiple event models (MEMs) using PASW 17.0 software (IBM Corp).^{40,41} All MEMs were repeated measures centered at week 12 and included the baseline value of the dependent variable as a covariate. Week, treatment, and week \times 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 es-

Figure 2. Gabapentin Effects on Rates of No Heavy Drinking and Complete Abstinence During the 12-Week Study in the Intention-to-Treat Population



A, No heavy drinking; B, complete abstinence. Error bars indicate 95% confidence intervals. (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



A, Number of drinks per week; B, number of heavy drinking days per week. Error bars indicate SEM. (N = 150.)

estimates of drug effects (regression coefficients) with associated 95% confidence intervals. Outcomes involving craving, mood, and sleep, and log-transformed GGT values were reported as *F* values from type III tests of fixed effects.

Results

Participants

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

The mean (SD) time in study (9.1 [3.8] weeks; *P* = .52) and rate of study completion (85 of 150 participants; *P* = .46) did not differ among treatment groups, nor did the reasons for ter-

mination (Figure 1) (*P* = .83). The 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* = .79). Groups were similar in their ability to correctly guess the identity of their medication when asked to do so on study completion (59% for participants receiving gabapentin and 45% for participants receiving placebo; *P* = .21).

Outcomes

Gabapentin had a significant linear dose effect in increasing the rates of complete abstinence ($\chi^2_1 = 4.19$; *P* = .04) and no heavy drinking ($\chi^2_1 = 5.39$; *P* = .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%-13.7%) in the placebo group, 11.1% (95% CI, 5.2%-22.2%) in the 900-mg group,

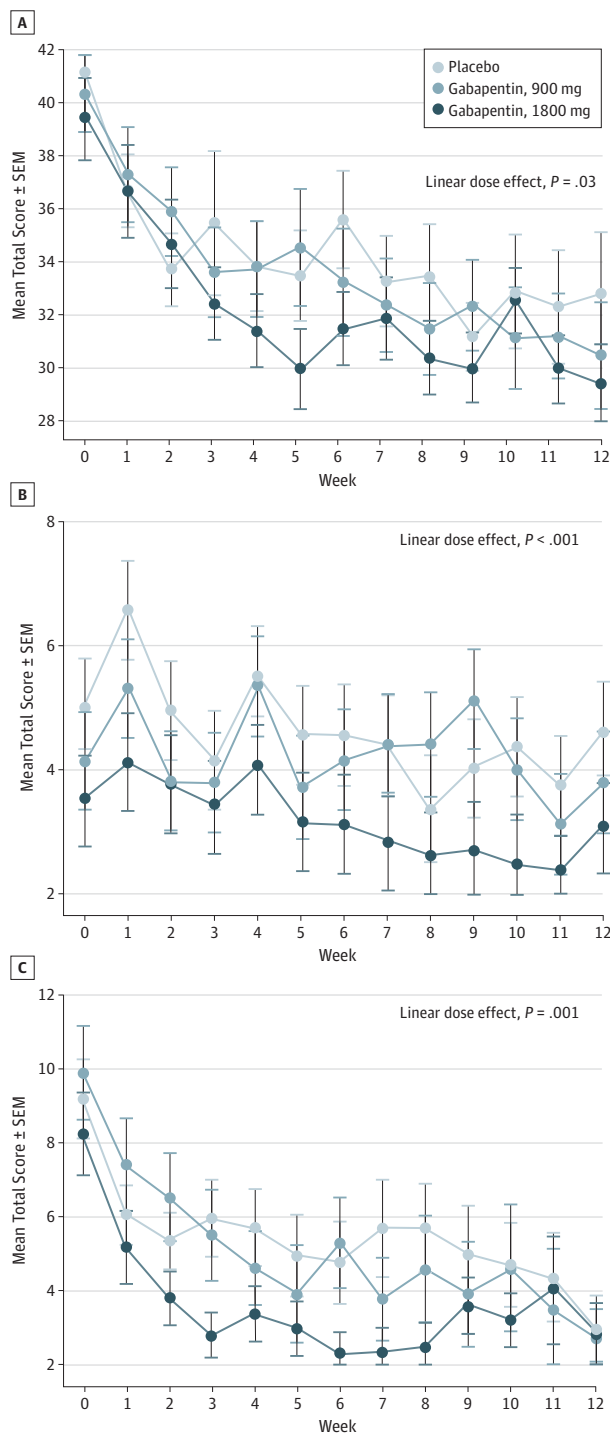
and 17.0% (95% CI, 8.9%-30.1%) in the 1800-mg group. Gabapentin, 1800 mg, had the greatest treatment effect, with an NNT of 8 (95% CI, 6 to ∞) and an OR = 4.8 (95% CI, 0.9-35.0), indicating a large effect size for abstinence.³⁷ The rate of no heavy drinking was 22.5% (95% CI, 13.6%-37.2%) in the placebo group, 29.6% (95% CI, 19.1%-42.8%) in the 900-mg group, and 44.7% (95% CI, 31.4%-58.8%) in the 1800-mg group. The 1800-mg group had an NNT of 5 (95% CI, 3-78) and OR = 2.8 (95% CI, 1.1-7.5), indicating a medium effect size for no heavy drinking.³⁷ Compared with placebo, gabapentin also showed significant linear decreases in the average number of days of heavy drinking per week ($t = -13.12$; $P < .001$ [Figure 3A]; 900-mg group: -1.8 [95% CI, -2.2 to -1.3]; $t = -7.22$; $P < .001$; 1800-mg group: -2.0 [95% CI, -2.5 to -1.5]; $t = -8.14$; $P < .001$) and the number of drinks consumed per week ($t = -5.32$; $P < .001$ [Figure 3B]; 900-mg group: -2.2 [95% CI, -5.3 to 1.0]; $t = -1.30$; $P = .20$; 1800-mg group: -6.7 [95% CI, -9.8 to -3.5]; $t = -4.13$; $P < .001$). Gabapentin also had a significant linear dose effect on reduction in log-transformed GGT values ($F_2 = 4.41$; $P = .02$). 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 ($\chi^2_1 = 4.73$; $P = .02$), number of drinks per week ($t = -2.01$; $P = .04$), and number of heavy drinking days per week ($t = -3.09$; $P = .002$), with a nonsignificant trend for rate of no heavy drinking ($\chi^2_1 = 6.43$; $P = .06$).

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 ($F_2 = 3.56$; $P = .03$; gabapentin, 1800 mg, vs placebo: -6.8 [95% CI, -1.5 to -12.1]; $t = -2.52$; $P = .01$) the Beck Depression Inventory II ($F_2 = 7.37$; $P = .001$; gabapentin, 1800 mg, vs placebo: -1.1 [95% CI, -2.0 to -0.3]; $t = -2.57$; $P = .01$), and the Pittsburgh Sleep Quality Index total score ($F_2 = 136$; $P < .001$; gabapentin, 1800 mg, vs placebo: -1.5 [95% CI, -2.1 to -0.8]; $t = -4.46$; $P < .001$).

Safety, Tolerability, and Concomitant Therapy

Gabapentin was well tolerated, with no deaths and no serious drug-related adverse events. Nine participants discontinued the study owing to adverse events. Of these, 5 were rated as drug related by blinded study physicians: 2 complaints of headache (900 mg), 2 complaints of fatigue (1 in the 900-mg group and 1 in the 1800-mg group), and 1 complaint of euphoria and feeling “on speed” (placebo group). No differences were found among groups in type of adverse events (eTable 2 in Supplement), with 10% or more of the sample complaining of fatigue (23%), insomnia (18%), and headache (14%). Groups also were similar in the number (mean [SD], 1.98 [2.14]; $P = .53$) and severity (1.72 [1.14]; 1 = mild, 2 = moderate; $P = .63$) of adverse events reported. Groups did not differ in body weight, vital signs, or in 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 screen samples collected in our study, 27 (2%) tested positive for other drugs of abuse, primarily marijuana and prescription drugs. Five participants attended individual therapy,

Figure 4. Gabapentin Effects on Standardized Measures of Craving, Sleep, and Mood During the 12-Week Study in the Intention-to-Treat Population



A, Alcohol Craving Questionnaire; B, Pittsburgh Sleep Quality Index; C, Beck Depression Inventory II. Error bars indicate SEM. (N = 150.)

and 9 attended Alcoholics Anonymous (AA) meetings during the course of the study. Attendance was not associated with drug group or primary outcome measures, with 1 exception:

participants who were completely abstinent attended fewer AA meetings than those who were not abstinent (41 vs 89 meetings; $P = .01$). 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 posttreatment 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 owing to adverse events. Of note, somnolence has been a commonly reported adverse event in gabapentin pain and epilepsy trials,⁴² but it was not a common complaint among our alcohol-dependent participants. Conversely, prior to treatment our participants 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 dropout 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 6111 outpatients with alcohol dependence were 52.7% for placebo and 57.8% for acamprosate, which is directly comparable with 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 dropouts are mitigated by a lack of differential dropout 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 preclinical¹² and human laboratory

studies¹³ 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 ratio of randomized to evaluated volunteers (150:185), 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 posttreatment effect on drinking outcomes was found in those who responded well to gabapentin in the 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 adverse effects. Thus, unlike other approved treatments for alcohol dependence that 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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take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mason.

Acquisition of data: Quello, Shadan, Kyle, Begovic.

Analysis and interpretation of data: Mason, Goodell.

Drafting of the manuscript: Mason.

Critical revision of the manuscript for important intellectual content: Mason, Quello, Goodell,

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Statistical analysis: Goodell.

Obtained funding: Mason.

Study supervision: Mason, Quello, Shadan, Kyle, Begovic.

Conflict of Interest Disclosures: Dr Mason has served as a consultant for Eli Lilly USA LLC and

Johnson & Johnson Pharmaceutical Research & Development LLC; has served as a scientific advisory board member for Lohocla Research Corp; has served as a scientific advisory board member for and has had equity interest in Addex Pharmaceuticals and in Arkeo Pharmaceuticals Inc; has served as a speaker for Merck KGaA; and has received study drug for a National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded human laboratory study and travel support for an investigators' meeting from Concept Therapeutics Inc. No other conflicts of interest are reported.

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REFERENCES

- Rehm J, Mathers C, Popova S, Thavorncha-rensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*. 2009;373(9682):2223-2233.
- Substance Abuse and Mental Health Services Administration. Results from the 2006 national survey on drug use and health: national findings. Rockville, MD: Office of Applied Studies (NSDUH Series H-32, DHHS publication No. SMA 07-4293); 2007. <http://www.samhsa.gov/data/nsduh/2k6nsduh/2k6results.pdf>. Accessed February 10, 2013.
- Mark TL, Kassed CA, Vandivort-Warren R, Levit KR, Kranzler HR. Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. *Drug Alcohol Depend*. 2009;99(1-3):345-349.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Press; 2000.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Press; 2013.
- Koob GF. A role for brain stress systems in addiction. *Neuron*. 2008;59(1):11-34.
- Geller A. Protracted abstinence. In: Miller NS, ed. *Comprehensive Handbook of Drugs and Alcohol Addiction*. New York, NY: Marcel Dekker; 1991:905-913.
- Lowman C, Allen J, Stout RL; Relapse Research Group. Replication and extension of Marlatt's taxonomy of relapse precipitants: overview of procedures and results. *Addiction*. 1996;91(S51)(suppl):S51-S71.
- Brower KJ, Aldrich MS, Hall JM. Polysomnographic and subjective sleep predictors of alcoholic relapse. *Alcohol Clin Exp Res*. 1998;22(8):1864-1871.
- Foster JH, Peters TJ. Impaired sleep in alcohol misusers and dependent alcoholics and the impact upon outcome. *Alcohol Clin Exp Res*. 1999;23(6):1044-1051.
- Sills GJ. The mechanisms of action of gabapentin and pregabalin. *Curr Opin Pharmacol*. 2006;6(1):108-113.
- Roberto M, Gilpin NW, O'Dell LE, et al. Cellular and behavioral interactions of gabapentin with alcohol dependence. *J Neurosci*. 2008;28(22):5762-5771.
- Mason BJ, Light JM, Williams LD, Drobos DJ. Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. *Addict Biol*. 2009;14(1):73-83.
- Furieri FA, Nakamura-Palacios EM. Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2007;68(11):1691-1700.
- Ghaemi SN, Katzow JJ, Desai SP, Goodwin FK. Gabapentin treatment of mood disorders: a preliminary study. *J Clin Psychiatry*. 1998;59(8):426-429.
- Harden CL, Lazar LM, Pick LH, et al. A beneficial effect on mood in partial epilepsy patients treated with gabapentin. *Epilepsia*. 1999;40(8):1129-1134.
- Karam-Hage M, Brower KJ. Gabapentin treatment for insomnia associated with alcohol dependence. *Am J Psychiatry*. 2000;157(1):151.
- Lo HS, Yang CM, Lo HG, Lee CY, Ting H, Tzang BS. Treatment effects of gabapentin for primary insomnia. *Clin Neuropharmacol*. 2010;33(2):84-90.
- Malcolm R, Myrick LH, Veatch LM, Boyle E, Randall PK. Self-reported sleep, sleepiness, and repeated alcohol withdrawals: a randomized, double blind, controlled comparison of lorazepam vs gabapentin. *J Clin Sleep Med*. 2007;3(1):24-32.
- Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. *Alcohol Clin Exp Res*. 2008;32(8):1429-1438.
- Anton RF, Myrick H, Wright TM, et al. Gabapentin combined with naltrexone for the treatment of alcohol dependence. *Am J Psychiatry*. 2011;168(7):709-717.
- Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar). *Br J Addict*. 1989;84(11):1353-1357.
- First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P)*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
- Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, eds. *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods*. Totowa, NJ: Humana Press; 1992:41-72.
- National Institute on Alcohol Abuse and Alcoholism. *The Physicians' Guide to Helping Patients With Alcohol Problems*. Rockville, MD: US Department of Health and Human Services; 1995.
- Singleton EG, Henningfield JE, Tiffany ST. *Alcohol Craving Questionnaire: ACQ-Now: Background and Administration Manual*. Baltimore, MD: NIDA Addiction Research Center; 1994.
- Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. 1996;67(3):588-597.
- Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.
- Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull*. 1986;22(2):343-381.
- Mason BJ, Goodman AM. *Brief Intervention and Medical Compliance Procedures Therapist's Manual*. New York, NY: Liphia Pharmaceuticals Inc; 1997. www.alcoholfree.info.
- Winchell C, Rappaport BA, Roca R, Rosebraugh CJ. Reanalysis of methamphetamine dependence treatment trial. *CNS Neurosci Ther*. 2012;18(5):367-368.
- Falk D, Wang XQ, Liu L, et al. Percentage of subjects with no heavy drinking days: evaluation as an efficacy endpoint for alcohol clinical trials. *Alcohol Clin Exp Res*. 2010;34(12):2022-2034.
- US Food and Drug Administration. *Medical Review of Vivitrol: 21-897*. Rockville, MD: US Government Printing Office; 2006.
- Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the *Archives of General Psychiatry*. *Arch Gen Psychiatry*. 2004;61(3):310-317.
- Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet*. 2003;361(9370):1677-1685.
- Pelc I, Verbanck P, Le Bon O, Gavrilovic M, Lion K, Leher P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients: a 90-day placebo-controlled dose-finding study. *Br J Psychiatry*. 1997;171:73-77.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
- Cochran WG. Some methods for strengthening the common χ^2 tests. *Biometrics*. 1954;10(4):417-451.
- Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22(4):719-748.
- Norusis MJ. *SPSS Statistics 17.0 Advanced Statistical Procedures Companion*. Upper Saddle River, NJ: Prentice Hall Inc; 2008.
- West BT. Analyzing longitudinal data with the linear mixed models procedure in SPSS. *Eval Health Prof*. 2009;32(3):207-228.
- Neurontin (gabapentin) [package insert LAB-0106-9.0]. New York, NY: Pfizer. Revised January, 2007.

43. Mason BJ, Leher P. Acamprosate for alcohol dependence: a sex-specific meta-analysis based on individual patient data. *Alcohol Clin Exp Res*. 2012;36(3):497-508.

44. Sullivan JT, Swift RM, Lewis DC. Benzodiazepine requirements during alcohol

withdrawal syndrome: clinical implications of using a standardized withdrawal scale. *J Clin Psychopharmacol*. 1991;11(5):291-295.

45. Mason BJ, Crean R, Goodell V, et al. A proof-of-concept randomized controlled study of

gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. *Neuropsychopharmacology*. 2012;37(7):1689-1698.