Gabapentin Enacarbil Extended-Release for Alcohol Use Disorder: A Randomized, Double-Blind, Placebo-Controlled, Multisite Trial Assessing Efficacy and Safety

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Background: Several single-site alcohol treatment clinical trials have demonstrated efficacy for immediate-release (IR) gabapentin in reducing drinking outcomes among individuals with alcohol dependence. The purpose of this study was to conduct a large, multisite clinical trial of gabapentin enacarbil extended-release (GE-XR) (HORIZANT®), a gabapentin prodrug formulation, to determine its safety and efficacy in treating alcohol use disorder (AUD).

Methods: Men and women (n = 346) who met DSM-5 criteria for at least moderate AUD were recruited across 10 U.S. clinical sites. Participants received double-blind GE-XR (600 mg twice a day) or placebo and a computerized behavioral intervention (Take Control) for 6 months. Efficacy analyses were prespecified for the last 4 weeks of the treatment period.

Results: The GE-XR and placebo groups did not differ significantly on the primary outcome measure, percentage of subjects with no heavy drinking days (28.3 vs. 21.5, respectively, p = 0.157). Similarly, no clinical benefit was found for other drinking measures (percent subjects abstinent, percent days abstinent, percent heavy drinking days, drinks per week, drinks per drinking day), alcohol craving, alcohol-related consequences, sleep problems, smoking, and depression/anxiety symptoms. Common side-effects were fatigue, dizziness, and somnolence. A population pharmacokinetics analysis revealed that patients had lower gabapentin exposure levels compared with those in other studies using a similar dose but for other indications.

Conclusions: Overall, GE-XR at 600 mg twice a day did not reduce alcohol consumption or craving in individuals with AUD. It is possible that, unlike the IR formulation of gabapentin, which showed efficacy in smaller Phase 2 trials at a higher dose, GE-XR is not effective in treating AUD, at least not at doses approved by the U.S. Food and Drug Administration for treating other medical conditions.

Key Words: Alcohol Use Disorder, Gabapentin Enacarbil Extended-Release, HORIZANT, Randomized Placebo-Controlled Clinical Trial.

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ALCOHOL USE DISORDER (AUD) is a highly prevalent, highly comorbid disorder, affecting more than 15 million adults in the United States (https://pubs.niaaa.nih.gov/publications/AlcoholFacts&Stats/AlcoholFacts&Stats.htm). Advances have been made in medications to treat AUD, highlighted by U.S. Food and Drug Administration (FDA) approval of 3 medications to treat alcohol dependence, specifically disulfiram, oral and long-acting injectable naltrexone, and acamprosate. Nonetheless, many people do not respond to these medications. Thus, efforts have been made to develop and evaluate new medications (Litten et al., 2015).

One promising agent being investigated for AUD treatment is gabapentin immediate-release (G-IR). G-IR currently is approved by the FDA for the treatment of epileptic seizures, neuropathic pain, and restless leg syndrome (http://www.caremark.com/portal/asset/FEP_Rationale_Gabapentin.pdf). The mechanism of action of gabapentin is unclear, though it appears to have multiple cellular effects, including selectively blocking voltage-gated calcium channels with the $\alpha 2\delta$-1 subunit, enhancement of voltage-gated potassium channels, and modulation of GABA activity (Sills, 2006).

The rationale underlying gabapentin as a treatment for AUD is founded on preclinical evidence that G-IR reduced alcohol intake in alcohol-dependent rats and normalized stress-induced GABA activation in the extended amygdala (Roberto et al., 2008), a stress-related brain region activated during early abstinence in alcohol dependence (Koob, 2008). Clinically, G-IR reduced symptoms of acute alcohol withdrawal (Myrick et al., 2009) and improved alcohol-induced sleep disruption in a polysomnography study of normal participants (Bazil et al., 2005). In human laboratory studies, 1,200 mg/d of G-IR diminished symptoms of protracted abstinence, including craving and sleep disturbance (Mason et al., 2009), which have been identified as risk factors for relapse (Brower et al., 1998; Foster and Peters, 1999; Lowman et al., 1996; see also review Mason et al., 2018).

Several single-site, placebo-controlled randomized clinical trials (RCTs) have evaluated the efficacy of G-IR in alcohol-dependent individuals. Mason and colleagues (2014) conducted a 12-week RCT of G-IR (900 mg/d and 1,800 mg/d) in 150 men and women diagnosed with alcohol dependence. Compared with placebo, G-IR significantly increased rates of abstinence and percentage of subjects with no heavy drinking days (PSNHDD) in a dose-dependent fashion. In addition, G-IR improved measures of mood and sleep and reduced alcohol craving. There were no serious adverse effects (AEs), with the most common side-effects being fatigue, insomnia, and headaches. Furieri and Nakamura-Palacios (2007) conducted a 4-week RCT of G-IR (600 mg/d) in 60 alcohol-dependent men and, compared with placebo, found improvement in the number of drinks per day, percentage of heavy drinking days, and percentage of days abstinent. In another RCT, Brower and colleagues (2008) found that G-IR (titrated up to 1,500 mg/d) significantly delayed the onset to heavy drinking in 21 individuals with alcohol dependence and comorbid insomnia. In a small study, Anton and colleagues (2009) found that G-IR (up to 1,200 mg/d for 39 days) combined with flumazenil, a benzodiazepine receptor antagonist (20 mg/d for the first 2 days), was associated with an increase in the percentage of days abstinent and a longer delay to heavy drinking in a subgroup of alcohol-dependent individuals (n = 16) who had relatively high pretreatment alcohol withdrawal symptoms. In another RCT, Anton and colleagues (2011) found that alcohol-dependent individuals (n = 150) treated with G-IR (1,200 mg/d) combined with oral naltrexone (50 mg/d) experienced better outcomes on several measures of drinking, craving, and sleep than the group taking naltrexone alone or those receiving the placebo over the first 6 weeks.

The present study focuses on gabapentin enacarbil extended-release (GE-XR) (HORIZANT®; Arbor Pharmaceuticals, LLC, Atlanta, GA), a relatively new, extended-release, prodrug formulation of gabapentin approved by the FDA for the treatment of postherpetic neuralgia (PHN) and restless legs syndrome (FDA, 2013). This prodrug formulation is actively absorbed by the high capacity nutrient transporters, monocarboxylate transporters type 1 and sodium-dependent multivitamin transporters, located throughout the intestinal tract (Cundy et al., 2008). After absorption, conversion to gabapentin takes place by non-specific esterases, primarily in enterocytes. One advantage of the prodrug, compared with G-IR, is a reduction in interpatient variability in the blood levels and increased bioavailability (Cundy et al., 2008). Furthermore, whereas G-IR is taken 3 times per day, GE-XR only needs to be taken 2 times per day, which may result in better treatment adherence, an important aspect to consider when developing medications for addiction (Weiss, 2004).

The purpose of this study was to provide the first RCT evaluation of the efficacy and safety of GE-XR as a treatment for AUD. This was also the first 6-month, multisite, double-blind, placebo-controlled RCT of a gabapentin formulation that adhered to FDA guidelines for pivotal alcohol pharmacotherapy trials (FDA, 2015a).

MATERIALS AND METHODS

Study Population

Randomized participants (n = 346) were diagnosed with at least moderate AUD (i.e., 4 or more criteria) in the past year according to the DSM-5 (American Psychiatric Association, 2013). Participants were eligible if they were at least 21 years of age; reported drinking an average of at least 21 standard drinks per week for women or 28 standard drinks per week for men and had at least 1 heavy drinking day per week during the 28-day period before consent; and at least 3 consecutive days of abstinence prior to randomization. Participants had not been diagnosed with a current substance use disorder (other than alcohol or nicotine) or major psychiatric disorder (psychotic, bipolar, and eating disorders; major depressive episode). They did not have underlying medical conditions for which gabapentin might be contraindicated or that could be exacerbated during trial participation. Use of most psychiatric medications was exclusionary except for the stable use of antidepressants (see Supplementary Appendices

S1 and S2 for the full inclusion/exclusion criteria and assessment schedule, respectively).

Study Design

The study was a pivotal, randomized, double-blind, placebo-controlled, parallel-group, 26-week treatment clinical trial. Candidates were treatment-seeking volunteers who responded by telephone to advertisements from 10 academic sites in the United States between June 2015 and February 2017. The study (Protocol # NCIG 006) was approved by the local Institutional Review Board at each participating clinical site; all participants in the study provided their voluntary, written informed consent before initiation of any study procedures and were compensated for time and travel. See Appendix S3 for details on clinical sites and study oversight.

Participants completed a screening and baseline visit, during which eligibility was established, as well as 11 in-clinic visits and 17 telephone visits during nonvisit weeks. A follow-up telephone interview was conducted during weeks 28 to 29 (approximately 1 to 2 weeks after the last in-clinic study visit) to assess safety and changes in drinking. Participants were required to have a breath alcohol concentration $\leq$0.02% to complete the in-clinic assessments.

Participants were randomly assigned, in a 1:1 ratio, to receive either GE-XR or matched placebo using a permuted block randomization procedure stratified by clinical site. Clinical site was chosen as the stratification variable because both local study populations and the investigative staff influence on the subject's drinking behaviors may differentially influence end points. Randomization was implemented via a centralized, interactive web-based response system. See Appendix S4 for additional details on randomization and blinding.

Investigational Product

GE-XR was dispensed during in-clinic visits for 26 weeks using a double-blind method. GE-XR was supplied in 600 mg tablets with identical matching placebo tablets. A 600 mg tablet of GE-XR contains 313 mg equivalents of gabapentin. For both the GE-XR and placebo groups, the daily dose was titrated from 1 tablet (600 mg or placebo) on days 1 to 3, to a target dose of 2 tablets (600 mg or placebo twice a day, for 1,200 mg total) on days 4 to 7 and weeks 2 to 25, followed by a taper to 1 tablet (600 mg or placebo) during week 26. GE-XR was selected over other oral gabapentin products because it confers more uniform and increased bioavailability, faster titration time to full therapeutic dose, and less fluctuating gabapentin blood levels with twice-daily administration (Cundy et al., 2008). This dose (600 mg twice a day) was selected because it is the highest approved dose of GE-XR for an FDA-approved indication (PHN), and it achieves a similar level of efficacy as higher doses of GE-XR (2,400 or 3,600 mg) on pain outcomes while maintaining a more favorable adverse event profile (Zhang et al., 2013).

Participants who could not tolerate the target dose were permitted to taper their dose to 600 mg once daily. If 600 mg daily was not tolerated, medication was discontinued but those participants were encouraged to remain in the study, participate in study assessments, and continue to receive the behavioral platform (for details, see below). Dosage compliance was verified by comparing the participants' self-report to pill count. Medication compliance was calculated as the total amount of medication taken, divided by the total amount prescribed during the maintenance phase of the study (weeks 2 to 25). To validate adherence and conduct a population pharmacokinetic (Pop PK) analysis, gabapentin plasma levels were determined from blood samples collected at weeks 12, 20, and 24 (predose, 8 and 12 hours postdose) that were analyzed using a liquid chromatography–mass spectrometry/mass spectrometry (LC–MS/MS) method validated for gabapentin in plasma over the range 80 to 10,000 ng/ml. Estimated population Pop PK parameters were used to compare drug exposure with prior studies (FDA, 2013) and to evaluate a dose–response relationship between gabapentin systemic exposure and drinking.

Behavioral Platform

Participants viewed Take Control modules, a computerized bibliotherapy platform (Devine et al., 2016), at each in-clinic visit.

Measures of Efficacy

Alcohol consumption was captured via the Time-Line Follow-Back and Form 90 interview methodology and procedures (Miller, 1992; Sobell and Sobell, 1992). Drinks were converted into standard drink units (1 standard drink = 0.6 oz of pure alcohol) for all subsequent analyses. The a priori primary efficacy end point was PSNHDD (Falk et al., 2010) during the last 4 weeks of the maintenance phase of the study (weeks 22 to 25). A "heavy drinking day" was defined as 4 or more drinks (women) or 5 or more drinks (men) per drinking day.

A priori secondary efficacy end points (weeks 22 to 25) included other drinking measures (percentage of heavy drinking days, percentage of days abstinent, drinks per week, drinks per drinking day, percentage of subjects abstinent, and percentage of subjects with a reduction of at least 1 or 2 levels in World Health Organization [WHO] drinking risk categories) (Hasin et al., 2017) as well as severity of alcohol craving (Alcohol Craving Scale-Short Form) (Singleton, 2000); number of alcohol-related consequences (ImBIBe, a revised and abbreviated form of the Drinker Inventory of Consequences) (Litten et al., 2013; Miller, 1995; Werner et al., 2008); Pittsburg Sleep Quality Index (PSQI) (Buysse et al., 1989) score; mood, as assessed by the Beck Anxiety Inventory (BAI) (Beck et al., 1988), Beck Depression Inventory Scale-II (BDI-II) (Beck et al., 1996), and the Profile of Mood States (POMS) (McNair et al., 1992); and the number of cigarettes smoked per week among smokers. Exploratory end points included the percentage of subjects with a negative blood phosphatidylethanol (PEth) (United States Drug Testing Laboratories, Inc., Des Plaines, IL), an objective biomarker used to confirm self-reported alcohol consumption end points); the number of AUD criteria endorsed, an indicator of AUD severity; and the percentage of subjects abstinent from smoking among smokers.

Prior research shows that drinking during the first several months of treatment is relatively unstable and not highly predictive of long-term outcomes (Kline-Simon et al., 2014). Thus, a 5-month grace period was granted for all efficacy end points. A grace period is an early period in a trial where outcome is not considered in the final analysis because the measured treatment effect is not thought to represent the full potential of the drug (Falk et al., 2010). Based on FDA guidance, a grace period is permitted for Phase 3 clinical trials (FDA, 2015a,b). Sensitivity analyses examined other grace periods, as well as the full maintenance period (weeks 2 to 25).

Safety Assessments

Safety was assessed via vital signs; blood chemistry tests; urine tests for illicit drug use; blood alcohol concentration, as measured by breathalyzer; adverse events; concomitant medication use; cardiac conduction, measured by electrocardiogram; alcohol withdrawal, measured by the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) (Sullivan et al., 1989); and suicidal ideation, measured by the Columbia Suicide Severity Rating Scale (Posner et al., 2011). Adverse events were assessed in the clinic and during telephone interviews using the open-ended question: "How have you been feeling since your last visit?"

Statistical Analysis

Statistical analyses were similar to our previous trial (Ryan et al., 2017). Baseline safety and efficacy analyses (except for the prespecified models examining smoking among smokers) were analyzed on a modified intention-to-treat (mITT) population that included all randomized participants who received at least 1 dose of investigational product (n = 338; GE-XR = 170, placebo = 168). The smoking efficacy models included only participants who were smokers (i.e., smoked at least 1 cigarette in the past week at baseline) (n = 105; GE-XR = 50, placebo = 55). As a sensitivity analysis, efficacy analyses were also analyzed on an evaluable population of participants randomized to the study who took at least 80% of the per-protocol prescribed dose (269 tablets) during the maintenance period (weeks 2 to 25) and who did not have a major protocol violation (n = 232; GE-XR = 115, placebo = 117).

Continuous outcomes were measured at multiple time points and analyzed using a repeated-measures mixed-effects model. Least-square means, standard errors (SEs), and 95% confidence intervals (CIs) are presented for each treatment group and were derived from fully adjusted models on untransformed outcomes (to facilitate clinical interpretation), averaged across the last 4 weeks of the maintenance period (weeks 22 to 25). Cohen's d and p-values were based on the fully adjusted models with the appropriately transformed outcome variables (if skewed).

For dichotomous outcomes, unadjusted prevalence rates were determined during the last 4 weeks of the maintenance period. Odds ratios (ORs) and p-values were derived from fully adjusted logistic regression models; the number of covariates was limited by the number of events for each dichotomous outcome (Peduzzi et al., 1996).

Except for the primary outcome, no imputation was performed for missing data in the tabled model results. However, as a sensitivity analysis, models were re-estimated with imputation for missing data. For dichotomous outcomes (besides the WHO outcomes), participants with any missing outcome data were imputed as treatment failures. For percentage of heavy drinking days and percentage of days abstinent, days with missing drinking data were imputed as heavy drinking days and drinking days, respectively. For other continuous outcomes, and WHO outcomes, missing data were handled by multiple imputation.

Exploratory moderator analyses were conducted on the imputed primary efficacy outcome, percentage of heavy drinking days (weeks 22 to 25), to evaluate whether a differential treatment effect existed as a function of 26 patient characteristics of theoretical and scientific interest. These characteristics included patient demographics; baseline measures of alcohol consumption, smoking, alcohol-related severity, mood, sleep, and impulsivity; and medication exposure. A model similar to the primary efficacy model was used for each moderator tested and included moderator and treatment-by-moderator interaction terms.

To evaluate the possibility that alcohol consumption affected the bioavailability of GE-XR (Bode and Bode, 2003; Cundy et al., 2008; Elamin et al., 2013; FDA, 2013), a post hoc analysis compared the alcohol consumption in the 2 days prior to blood measurement among those with low versus high systemic exposure to gabapentin ($AUC_{24,ss}$).

For all statistical tests, $p < 0.05$ (2-tailed) was considered statistically significant. No adjustment was made for multiple inferential tests. For the primary outcome, an estimated sample size of 346 participants yielded 91% power to detect a treatment effect comparable to that obtained by Mason and colleagues (2014) (OR = 2.5; GE-XR = 27% and placebo = 13%), given a 2-tailed 0.05 significance level and assuming a 15% dropout rate where dropouts were imputed as treatment failures. Data were analyzed with SAS version 9.4 (SAS Institute, Cary, NC). See Appendix S5 for additional details regarding the statistical analysis.

RESULTS

Study Sample

Of the 736 participants consented for the study, 346 were eligible and therefore randomized to receive GE-XR or placebo (n = 173 per group); 390 were excluded because they did not meet eligibility criteria or they chose not to participate (see Fig. 1). The top reasons for exclusion included positive urine toxicology drug screen (20.8%), not meeting drinking criteria (14.9%), unable to participate in-clinic/phone visits (9.0%), and having a clinically relevant complicating medical condition (7.7%). The mITT population excluded 8 randomized participants who never received investigational product resulting in GE-XR (n = 170) and placebo (n = 168). In the mITT population, fewer participants in the GE-XR group withdrew early from the study than in the placebo group (n = 28 [16.5%] vs. n = 40 [23.8%], respectively; p = 0.092); however, more participants in the GE-XR group discontinued medication than in the placebo group (n = 21 [12.4%] vs. n = 13 [7.7], respectively; p = 0.158].

Participants in the GE-XR and placebo groups were not statistically different on any baseline characteristic except gender and the Barratt Impulsivity Scale—second-order Attention factor (BIS-Attention; Table 1) (Patton et al., 1995). Randomized mITT participants were mostly male, white, employed, and middle-aged, with approximately 15 years of education. On average, participants drank heavily, consuming ~56 drinks per week, and met or exceeded 4 drinks (women) or 5 drinks (men) per drinking day on ~77% of the days. With respect to treatment drinking goals, ~9% desired permanent abstinence, whereas the majority sought to drink in a limited manner. About one-third (31%) smoked at least 1 cigarette in the week before the screening visit, averaging 77.7 cigarettes per week. On average, participants had very low levels of alcohol withdrawal (CIWA-Ar = 1.5); nonelevated levels of anxiety, depression, and mood disturbance (BAI = 7.3, BDI-II = 10.5, POMS Total Mood Disturbance = 4.9); and were just above the cutoff for poor sleep quality (PSQI = 6.7).

Medication Compliance and Participation

Overall, medication compliance during the maintenance phase was 92.3% and was similar for both treatment groups (92.6% and 92.0% for GE-XR and placebo groups, respectively; p = 0.699). The median number of pills taken during the maintenance phase was nearly identical in both groups: 318.5 pills in GE-XR group and 320 in the placebo (or ~95% of the possible 336 pills) (p = 0.956). Analyte levels of gabapentin were largely consistent with patient self-reports of medication consumption (concordance rates: 86.8 to 89.0% during weeks 12, 20, and 24). The estimated average peak concentration (C_{max}) and 24-hour AUC at steady-state ($AUC_{24,ss}$) obtained from a Pop PK analysis of GE-XR were 4.21 μg/ml and 83.1 μg.hr/ml, respectively. Overall, 83.4%

Table 1. Baseline Characteristics of Patients (mITT Population)

	Placebo (n = 168)			GE-XR (n = 170)			
	n	Mean or %	SD	n	Mean or %	SD	p-Value[a]
Demographics							
Age		49.4	11.4		50.7	10.3	0.268
Gender							
Male	101	60.1%		122	71.8%		0.029
Female	67	39.9%		48	28.2%		
Employed	122	73.1%		133	78.7%		0.252
Married	168	48.2%		80	47.3%		0.913
Education (years)		15.2	2.8		15.3	2.5	
Race/Ethnicity							
White	116	70.7%		111	67.7%		0.959
Black	26	15.9%		33	20.1%		
Hispanic	18	11.0%		14	8.5%		
Other	4	2.4%		6	3.7%		
Self-reported alcohol consumption[b]							
Drinks per week		56.3	29.4		56.8	28.0	0.878
Drinks per drinking day		9.3	4.5		9.3	4.5	0.979
Percent days abstinent		12.9	16.2		12.0	14.5	0.566
Percent heavy drinking days		76.6	23.3		78.2	20.9	0.499
World Health Organization (WHO) risk level (drinks per day)							
Medium (men: 2.9 to 4.3; women: 1.4 to 2.9)	10	6.0%		8	4.7%		0.314
High (men: 4.3 to 7.1; women: 2.9 to 4.3)	42	25.0%		55	32.4%		
Very high (men: 7.1+; women: 4.3+)	116	69.0%		107	62.9%		
Other substance-related indicators							
Alcohol Craving Questionnaire (ACQ-SF-R)		3.6	1.2		3.6	1.2	0.891
Alcohol-related consequences (ImBIBe)		20.4	9.7		19.5	10.4	0.373
Age onset of regular drinking		20.2	7.0		19.7	7.0	0.490
Alcohol use disorder symptoms (MINI)		7.4	2.0		7.4	2.2	0.975
Alcohol use disorder severity (MINI)							
Moderate (4 to 5 symptoms)	40	23.8%		45	26.5%		0.617
Severe (6+ symptoms)	128	76.2%		125	73.5%		
Abstinence alcohol-related treatment goal[c]	13	7.7%		18	10.6%		0.452
Motivation to reach goal		8.8	1.4		8.9	1.5	0.501
Confidence to reach goal		6.6	2.4		6.9	2.2	0.121
Parental history of alcohol-related problems	85	50.9%		89	53.3%		0.743
Current smoker (any vs. none)	55	32.7%		50	29.4%		0.557
Cigarettes (past week) among smokers		88.4	112		65.8	62.9	0.212
Marijuana use[d]	17	10.1%		14	8.2%		0.577
Psychiatric characteristics							
Pittsburgh Sleep Quality Index (PSQI)		6.6	3.8		6.7	3.8	0.845
Barratt Impulsivity Scale (BIS)							
Attention—second-order factor		17.2	3.2		16.6	2.6	0.037
Motor—second-order factor		22.4	4.2		21.7	4.0	0.124
Nonplanning—second-order factor		28.7	4.6		28.8	4.5	0.855
Beck Anxiety Inventory (BAI)		7.2	7.7		7.3	7.2	0.964
Beck Depression Inventory (BDI-II)		10.8	9.1		10.2	8.3	0.492
Profile of Mood States (POMS)–Total Mood Disturbance		6.5	25.6		3.3	21.9	0.217
Clinical Institute Withdrawal Assessment of Alcohol-Revised (CIWA-Ar)		1.4	2.1		1.6	2.8	0.301

mITT, modified intention-to-treat (took at least 1 dose of investigational product).
Scale, number of questions (range), and interpretive values are as follows:
ACQ-SF-R: 12 questions (1 to 7).
ImBIBe: 15 questions (0 to 60).
PSQI: 19 questions (0 to 21); ≥6 indicative of "poor" sleep quality.
BIS: Attention 8 questions (8 to 32); Motor 11 questions (11 to 44); Nonplanning 11 questions (11 to 44).
BAI: 21 questions (0 to 63); ≥10 indicative of at least "mild" anxiety.
BDI-II: 21 questions (0 to 63); ≥14 indicative of at least "mild" depression.
POMS: 65 questions (−32 to 200); ≥18 greater than "normal" in general population.
CIWA-Ar: 10 questions (0 to 67); ≥10 indicative of alcohol withdrawal symptoms that may require treatment.
Variable (n) missing data: race/ethnicity (GE-XR = 6, placebo = 4), marital status (GE-XR = 1), employment status (GE-XR = 1, placebo = 1), POMS-TMD (placebo = 1), Parental History (GE-XR = 4, placebo = 1), Motivation & Confidence (GE-XR = 1).
[a]Group mean differences were tested for significance via t-tests of independent samples for normally distributed variables or Wilcoxon rank-sum tests for skewed variables. Group prevalence rate differences were tested for significance via chi-square or Fisher's exact tests.
[b]Reflects mean values during the 28-day period before screening.
[c]Abstinence defined as permanent abstinence vs. other. Motivation and confidence are single Likert scales (1 to 10).
[d]Marijuana use based on positive urine drug screen.

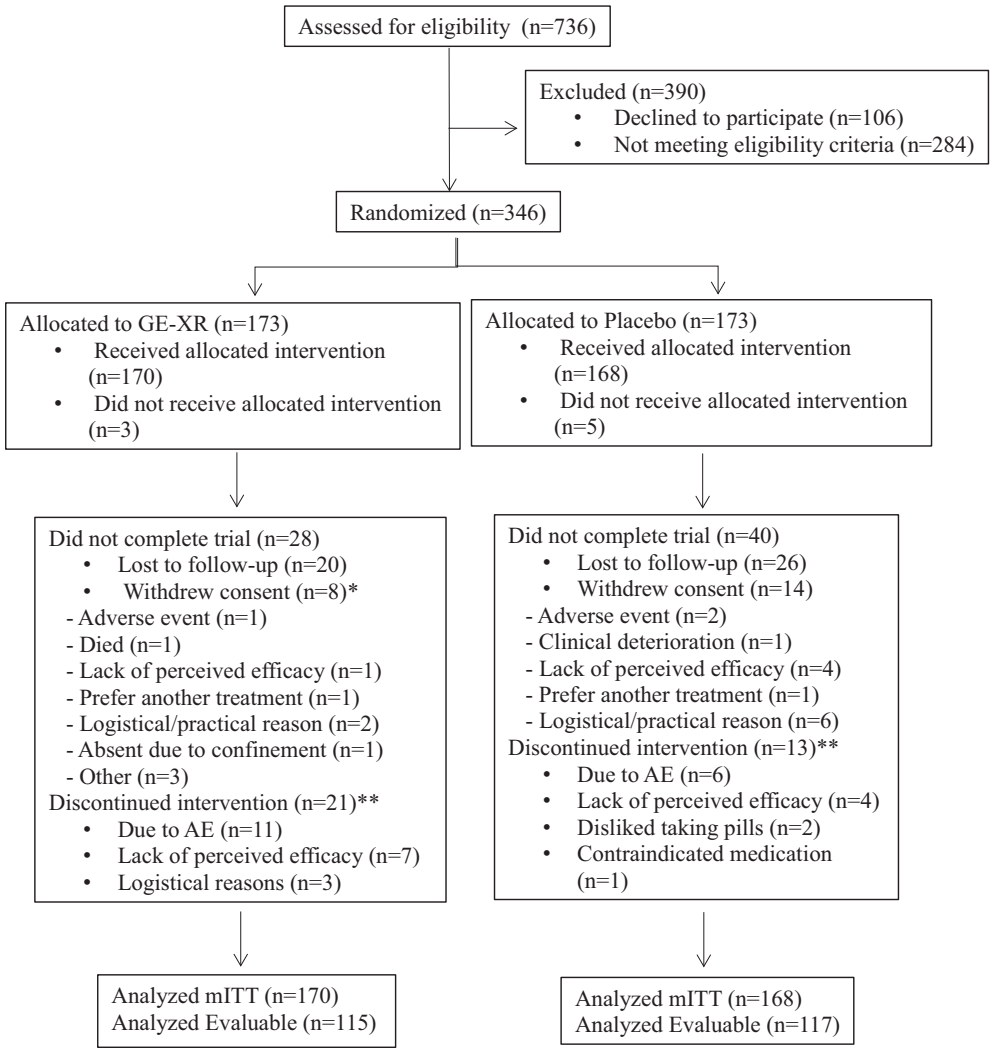

Fig. 1. Study profile (CONSORT). *Subjects may have more than 1 reason for withdrawal of consent. **Subjects who discontinued the intervention may or may not have completed the study.

of mITT participants had complete drinking data during the maintenance phase, with the GE-XR group being slightly higher than the placebo group (86.5% vs. 80.4%, respectively), which was not statistically significant ($p = 0.145$).

Primary Efficacy Outcome

Averaged across the last 4 weeks of the maintenance period (weeks 22 to 25), the GE-XR group had somewhat higher levels of the primary outcome, PSNHDD, than the placebo group (28.3 vs. 21.5, respectively); adjusted odds ratio (aOR) = 1.53 (95% CI = 0.85 to 2.75), although this small effect was not statistically significant ($p = 0.157$) (Table 2). The treatment effect was similar, and also not statistically significant, when participants with missing drinking data were imputed as treatment failures (GE-XR = 24.1 vs. placebo = 17.3, respectively); aOR = 1.50 (95% CI = 0.86 to 2.62; $p = 0.157$) and also for the evaluable subpopulation (GE-XR = 28.6% vs. placebo = 19.8%, respectively); aOR = 1.62 (95% CI = 0.84 to 3.14; $p = 0.153$). Treatment effects were small and nonsignificant for each month of the trial and across the entire maintenance period (all ps > 0.05) (Fig. 2).

Of the 26 moderators evaluated, 2 were statistically significant: treatment drinking goal ($p = 0.016$) and BIS-Attention ($p = 0.044$). Specifically, compared with placebo, the GE-XR group had a significantly higher PSNHDD among the subset of participants whose goal was nonpermanent abstinence (aOR = 2.68, 95% CI = 1.26 to 5.67, $p = 0.010$), yet had nonsignificantly lower PSNHDD among the subset of participants who sought permanent abstinence (aOR = 0.61, 95% CI = 0.24 to 1.55, $p = 0.298$). In addition, compared with placebo, the GE-XR group had a significantly higher PSNHDD among participants with low BIS-Attention scores (aOR = 2.61, 95% CI = 1.17 to 5.81, $p = 0.019$) and nonsignificantly lower PSNHDD among participants with higher BIS-Attention scores (aOR = 0.80, 95% CI = 0.35 to 1.82, $p = 0.599$). Although the treatment-by-moderator

interactions were not statistically significant for the other moderators, GE-XR was significantly more efficacious than placebo in 2 subgroups (elevated PSQI [aOR = 2.24, 95% CI = 1.03 to 4.88, $p = 0.042$]; and nonsmokers [aOR = 2.08, 95% CI = 1.03 to 4.22, $p = 0.043$]); nonstatistical trends (ps < 0.10) were observed for 6 other subgroups (low alcohol consumption, low POMS vigor-activity, high alcohol craving, high reduction in alcohol consumption prior to randomization, no history of alcohol withdrawal, and women). A sensitivity analysis using another outcome, percentage of heavy drinking days, revealed no statistically significant moderator interactions or subgroups (data not shown). See Appendix S6 for further moderator analysis results.

In the Pop PK analysis, participants with higher $AUC_{24,ss}$ (≥83 μg.hr/ml, [$n = 74$]) were significantly more likely to be classified as a nonheavy drinker than participants with lower $AUC_{24,ss}$ (<83 μg.h/ml, [$n = 73$]) (31.1% vs. 17.8%, aOR = 2.53, 95% CI = 1.06 to 6.04, $p = 0.036$), indicating that higher exposure resulted in less alcohol consumption (similar results were obtained for C_{max}, data not shown).

Secondary Efficacy Outcomes

Averaged across the last 4 weeks of the maintenance period, the GE-XR and placebo groups were statistically similar on all secondary measures of alcohol consumption, alcohol craving, alcohol-related consequences, cigarette smoking, sleep quality, and anxiety (Table 2). The average number of DSM-5 AUD criteria was significantly higher in the GE-XR group than the placebo group (3.4 vs. 2.8, respectively; $p = 0.046$; $d = 0.24$) as was the level of depression symptoms (BDI-II: 6.5 vs. 5.2, respectively; $p = 0.046$; $d = 0.23$). Results were similar when missing data were imputed or for the evaluable subpopulation (data not shown). Moreover, compared with placebo, GE-XR did not show a benefit on any secondary outcome for any of the times evaluated during the entire maintenance period (all treatment × time interactions ps > 0.05) (see Appendix S7 for percentage of heavy drinking days outcome across maintenance period).

Analysis of alcohol affecting bioavailability of GE-XR revealed that, among participants with high GE-XR compliance (269+ pills), those with a relatively low blood levels of GE-XR ($AUC_{24,ss}$ below the median) drank more alcohol in the 2 days prior to blood measurement than those with relatively high blood levels of GE-XR (4.5 vs. 3.0 drinks per day, $p = 0.010$), despite having taken nearly an identical number of pills (321 vs. 323 pills, $p = 0.548$).

Safety

Among participants who took at least 1 dose of study medication, 28 types of AEs were reported in at least 5% of participants from either treatment group (Table 3). Of these, compared with the placebo group, the GE-XR group reported significantly greater rates of fatigue (25.9% vs. 15.5%; $p = 0.022$), somnolence (17.6% vs. 9.5%; $p = 0.038$), and tremor (5.9% vs. 0.6%; $p = 0.010$); a numerical, though not statistically significant, increase was found for dizziness (21.2% vs. 13.7%; $p = 0.085$). Among GE-XR participants who reported at least 1 of these 4 AEs, the majority rated the AE as "mild" (65.0%), relative to "moderate" (33.3%) or "severe" symptoms (1.7%). Significantly lower rates of arthralgia and rash occurred in the GE-XR group compared with the placebo group; pruritus and depressed mood were statistical trends. Regarding AEs that occurred in fewer than 5% of participants, GE-XR produced a numerical, though not statistically significant, increase in suicidal ideation compared with placebo ($n = 7$ [4.1%] vs. $n = 1$ [0.6%]; $p = 0.067$).

As shown in Fig. 1, only 1 patient in the GE-XR group withdrew from the study because of AEs (dizziness, headache, somnolence, feeling abnormal) versus 2 in the placebo group (paranoia, suicidal ideation). However, more participants discontinued investigational product because of AEs in the GE-XR group than in the placebo group ($n = 11$ [6.5%] vs. $n = 6$ [3.6%], respectively).

Among participants reporting dizziness or somnolence, those in the GE-XR group had greater odds of experiencing dizziness and somnolence on drinking than nondrinking days (dizziness: OR = 2.75, 95% CI = 0.79 to 9.78, $p = 0.094$; somnolence: OR = 1.65, 95% CI = 0.38 to 6.03, $p = 0.452$) compared with the placebo group, suggesting that GE-XR may synergistically interact with alcohol to cause dizziness and somnolence; these associations were not statistically significant because of the small AE sample sizes.

Eight participants taking GE-XR experienced 11 events during the treatment phase that were rated as serious AEs: pneumonia ($n = 3$), alcohol withdrawal syndrome ($n = 3$), migraine headache ($n = 1$), back pain ($n = 1$), orbital fracture ($n = 1$), orbital infection ($n = 1$), and acute intoxication resulting in death ($n = 1$). All serious AEs were considered unlikely or unrelated to study medication by the Medical Monitor. Six participants taking placebo experienced 6 serious AEs: bradycardia ($n = 1$), suicidal ideation ($n = 1$), paranoia ($n = 1$), gastric ulcer ($n = 1$), alcoholism (increasing alcohol consumption) ($n = 1$), and humerus fracture ($n = 1$). No additional differences between the GE-XR and placebo groups were rated as being clinically meaningful for any other safety measures.

DISCUSSION

This was the first multisite pivotal trial to evaluate the efficacy and safety of GE-XR in individuals with moderate-to-severe AUD. GE-XR was not effective in reducing any of the a priori-defined alcohol consumption or nonconsumption outcomes. In fact, at the end of treatment, the placebo group reported significantly fewer AUD DSM-5 symptoms and lower depression scores than the GE-XR group (Table 2). The results were unexpected because several prior RCTs reported G-IR improved drinking and nondrinking

Table 2. Treatment Outcomes: Differences Between Placebo and GE-XR During Last Treatment Month (Weeks 22 to 25)

	Placebo (n = 168)			GE-XR (n = 170)						
	LSMEAN[b]	SE	95% CI	LSMEAN	SE	95% CI	LSMEAN Δ	SE	d	p-Value
Drinking outcomes										
Percent heavy drinking days										
No imputation	32.6	3.8	25.1 to 40.0	31.8	3.7	24.4 to 39.1	−0.8	3.6	−0.03	0.826
Missing imputed as heavy drinking days	46.5	4.2	38.2 to 54.9	43.1	4.1	35.0 to 51.1	−3.4	4.1	−0.09	0.397
Percent days abstinent	49.0	3.9	41.3 to 56.7	49.3	3.9	41.7 to 56.9	0.3	3.8	0.09	0.371
Drinks per week	21.4	2.4	16.8 to 26.0	23.1	2.3	18.5 to 27.7	1.7	2.3	0.07	0.545
Drinks per drinking day	3.9	0.4	3.5 to 5.0	4.1	0.4	3.3 to 4.8	0.2	0.4	0.05	0.641

	%	n	denom	%	n	denom	% Δ	aOR (95% CI)	p-Value
Percent subjects with no heavy drinking days[a]									
No imputation	21.5	29	135	28.3	41	145	6.8	1.53 (0.85 to 2.75)	0.157
Missing imputed as heavy drinker	17.3	29	168	24.1	41	170	6.8	1.50 (0.86 to 2.62)	0.157
Percent subjects abstinent	11.8	16	136	11.6	17	146	−0.2	0.86 (0.38 to 1.95)	0.717
WHO 1-shift reduction	79.9	107	134	78.8	115	146	−1.1	0.87 (0.48 to 1.58)	0.642
WHO 2-shift reduction	51.5	69	134	54.8	80	146	3.3	1.11 (0.69 to 1.80)	0.674
Percent subjects negative blood PEth	3.4	4	116	6.1	8	132	2.7	1.35 (0.37 to 4.96)	0.653
Nondrinking outcomes									
Percent subjects abstinent from smoking[b]	17.1	7	41	7.1	3	42	−10.0	0.37 (0.09 to 1.56)	0.178

	LSMEAN	SE	95% CI	LSMEAN	SE	95% CI	LSMEAN Δ	SE	d	p-Value
Cigarettes per week[b]	61.4	8.3	44.9 to 77.9	71.0	8.3	54.4 to 87.6	9.6	11.6	0.31	0.162
Alcohol Craving Questionnaire (ACQ-SF-R) Score	2.5	0.1	2.4 to 2.7	2.5	0.1	2.3 to 2.6	−0.1	0.1	−0.06	0.623
Alcohol-related consequences (ImBIBe) Score	8.3	0.7	6.9 to 9.7	9.6	0.7	8.3 to 10.9	1.3	1.0	0.13	0.239
Alcohol use disorder DSM-5 criteria (#)	2.8	0.2	2.4 to 3.2	3.4	0.2	3.0 to 3.8	0.6	0.3	0.24	0.046
Pittsburg Sleep Quality Inventory (PSQI) Score	4.4	0.2	4.0 to 4.9	4.9	0.2	4.4 to 5.3	0.4	0.3	0.16	0.152
Beck Depression Inventory (BDI-II) Score	5.2	0.5	4.1 to 6.2	6.5	0.5	5.5 to 7.5	1.3	0.7	0.23	0.046
Beck Anxiety Inventory (BAI) Score	3.3	0.5	2.4 to 4.2	4.6	0.4	3.7 to 5.4	1.3	0.6	0.14	0.208
Profile of mood scale (POMS)—Total Mood Disturbance score	0.3	1.8	−3.3 to 3.8	3.9	1.7	0.5 to 7.2	3.6	2.4	0.17	0.139

aOR, adjusted odds ratio; CI, confidence interval; d, Cohen's d (GE-XR-placebo); denom, denominator; GE-XR, gabapentin enacarbil; LSMEANS, least squared means; SE, standard error; Δ, GE-XR—placebo difference.

Models were based on a mITT population that included subjects who received at least 1 dose of medication. No imputation was used for missing outcome data, unless otherwise specified. For continuous outcomes, LSMEANS were estimated from fully adjusted models on untransformed outcomes (for interpretive purposes); corresponding Cohen's d and p-values were based on the same model but with the appropriately transformed outcome.

[a]A priori primary end point.

[b]Models for smoking outcomes included only participants who were smokers at baseline (i.e., smoked at least 1 cigarette per day in the past week) (GE-XR n = 50, placebo n = 55).

outcomes in AUD patients (Anton et al., 2009, 2011; Brower et al., 1998; Furieri and Nakamura-Palacios, 2007; Mason et al., 2009, 2014).

There are several possible explanations for the lack of efficacy of GE-XR in this trial. First, because this was a new formulation of gabapentin, never studied for the treatment of AUD, it may not have been the optimal dose for showing efficacy in reducing drinking in AUD individuals. The dose used in this study was 1,200 mg per day (600 mg twice a day), which is the dose approved by the FDA to treat PHN. For PHN, higher doses of 2,400 and 3,600 mg per day did not increase efficacy but did increase side-effects (Zhang et al., 2013). The FDA-approved dose of GE-XR for the treatment of restless legs syndrome is even lower, at 600 mg per day (FDA, 2013). In addition, our study target dose was selected because (i) it was as efficacious on pain outcomes as the maximum approved daily dose of G-IR for treating PHN (1,800 mg; 600 mg 3 times per day) (Rice and Maton, 2001; Zhang et al., 2013) and (ii) given doses of G-IR ranging from 600 mg to 1,800 mg per day have demonstrated efficacy in alcohol pharmacotherapy trials, the target dose for this study (1,200 mg GE-XR) produces an intermediate systemic exposure (steady-state $AUC_{24,ss}$) between 900 and 1,800 mg G-IR —approximately 40% lower systemic exposure than 1,800 mg G-IR and 34% higher systemic exposure than 900 mg G-IR (Backonja et al., 2011; Bockbrader, 1995; FDA, 2012). Thus, the dose selected for this study was within the efficacious range for AUD in the literature. Yet it is possible that a higher dose may have been necessary to achieve efficacy for this indication as: (i) 1,800 mg G-IR showed greater efficacy than 900 mg G-IR in a similarly designed clinical trial (Mason et al., 2014); and (ii) our Pop PK analysis indicated

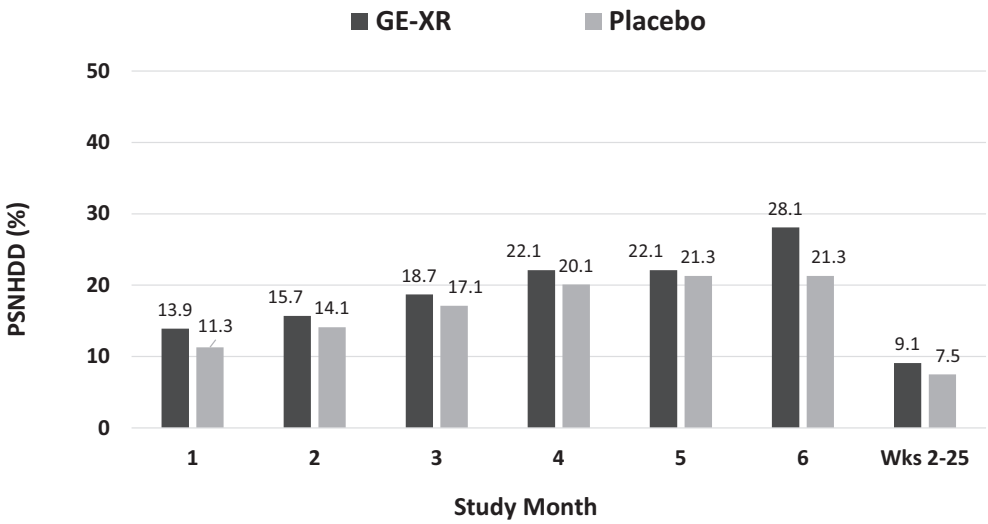

Fig. 2. Percentage of subjects no heavy drinking days (primary outcome) across the treatment period (mITT). Notes: Missing data were not imputed. All *p*s > 0.05. Wks = Weeks. Weeks 2 to 25 were the maintenance period.

Table 3. Number and Percentage of Participants with Adverse Events Occurring in at Least 5% of mITT Population

MedDRA SOC/Preferred term	Placebo (*n* = 168)	GE-XR (*n* = 170)	*p*-Value[a]
Blood pressure diastolic increased	42 (25.0%)	43 (25.3%)	1.000
Headache	47 (28.0%)	38 (22.4%)	0.260
Fatigue	**26 (15.5%)**	**44 (25.9%)**	**0.022**
Blood pressure systolic increased	32 (19.0%)	33 (19.4%)	1.000
Dizziness	23 (13.7%)	36 (21.2%)	0.085
Aspartate aminotransferase increased	26 (15.5%)	24 (14.1%)	0.761
Gamma-glutamyltransferase increased	19 (11.3%)	30 (17.6%)	0.122
Somnolence	**16 (9.5%)**	**30 (17.6%)**	**0.038**
Nasopharyngitis	21 (12.5%)	19 (11.2%)	0.739
Nausea	23 (13.7%)	17 (10.0%)	0.316
Upper respiratory tract infection	17 (10.1%)	22 (12.9%)	0.497
Insomnia	17 (10.1%)	18 (10.6%)	1.000
Alanine aminotransferase increased	19 (11.3%)	14 (8.2%)	0.365
Back pain	19 (11.3%)	11 (6.5%)	0.130
Vomiting	8 (4.8%)	15 (8.8%)	0.194
Blood creatinine increased	8 (4.8%)	14 (8.2%)	0.270
Anxiety	7 (4.2%)	14 (8.2%)	0.175
Diarrhea	10 (6.0%)	11 (6.5%)	1.000
Arthralgia	**14 (8.3%)**	**5 (2.9%)**	**0.035**
Blood bilirubin increased	9 (5.4%)	10 (5.9%)	1.000
Cough	6 (3.6%)	13 (7.6%)	0.155
Paresthesia	6 (3.6%)	11 (6.5%)	0.320
Abnormal dreams	9 (5.4%)	6 (3.5%)	0.442
Rash	**13 (7.7%)**	**2 (1.2%)**	**0.003**
Pruritus	10 (6.0%)	3 (1.8%)	0.052
Agitation	3 (1.8%)	9 (5.3%)	0.139
Depressed mood	9 (5.4%)	3 (1.8%)	0.085
Tremor	**1 (0.6%)**	**10 (5.9%)**	**0.010**

Multiple occurrences of a specific adverse event for a subject were counted once in the frequency for the adverse event. Adverse events with at least 5% of participants occurring in either arm were included in the table, sorted by total prevalence.

[a]Fisher's exact test. Bold: $p < 0.05$.

that higher exposure to gabapentin was associated with lower alcohol consumption. However, with regard to the latter, the possibility of reverse causation cannot be ruled out, that is, for the reasons discussed below, lower alcohol consumption could have resulted in higher exposure to gabapentin.

Second, alcohol may have reduced the bioavailability of gabapentin. It is possible that taking GE-XR in proximity to alcohol consumption may have degraded the extended-release properties, rendering it to be a mixture of extended (GE-XR) and immediate-release gabapentin enacarbil (G-IR), which could have lowered the estimated AUC (Cundy et al., 2008). In vitro studies of GE-XR have demonstrated that alcohol accelerates the release of gabapentin enacarbil (between 43 to 65% of gabapentin enacarbil is released within 1 hour when alcohol is present in concentrations ranging from 5 to 40%) (FDA, 2013). In addition, because this prodrug formulation is actively absorbed by several transporters located throughout the gut (Cundy et al., 2008), it is possible that these transporters may have been negatively altered by alcohol. Alcohol is known to affect the integrity of the gut wall (Bode and Bode, 2003; Elamin et al., 2013), which could have diminished the medication's bioavailability. Interestingly, a post hoc analysis revealed that participants with relatively low blood levels of GE-XR drank more alcohol in the 2 days prior to blood measurement than those with relatively high blood levels of GE-XR. Thus, consuming alcohol during the trial may have reduced the bioavailability of gabapentin.

Third, given the literature showing that bioavailability of GE-XR is greater in the fed than fasted state (particularly with high fat meals) (Cundy et al., 2008; FDA, 2012) and that individuals with high alcohol consumption often have poor dietary habits (Breslow et al., 2010), we conducted a post hoc analysis of the PK data to explore whether bioavailability of gabapentin may have been impacted by food intake (or lack thereof) in the present study. Although diet was not explicitly studied, consistent with the PK literature, we found that AUC (and other PK parameters) was greater among patients whose PK samples were all taken in the fed state

(87.5; 32% of patients) or a mixture of fed and fasted states (88.7; 55% of patients) than in patients whose samples were all taken in the fasted state (68.2; 13% of patients). Because the majority patients (87%) took GE-XR with food (on at least some days), the bioavailability of gabapentin could be considered maximized to some extent. Importantly, however, as we did not assess dietary fat content, it is unknown the degree to which this factor may have impacted gabapentin bioavailability.

Fourth, it is possible that, given the heterogeneity of the AUD population (Litten et al., 2015), average treatment effects do not sufficiently describe the efficacy of GE-XR and that more nuanced moderator analyses are necessary to show efficacy among only certain participant subgroups. However, despite an extensive analysis of 26 participant attributes, we were able to identify only 2 characteristics—treatment drinking goal and attentional impulsiveness—that were statistically significant, independent moderators of the treatment effect (i.e., greater treatment effects among participants with a treatment goal of nonpermanent abstinence and low attention problems). Furthermore, only 2 additional subgroups (nonmoderators) were statistically significant (i.e., those with elevated sleep problems and nonsmokers). Given the variety of these characteristics and the possibility of spurious findings given numerous statistical tests (2 of 26 moderators could be expected to be significant by chance alone), it is not possible to identify a cohesive participant responder profile. Because gabapentin is thought to reduce drinking by relieving aversive symptoms related to protracted withdrawal (Mason et al., 2009, 2014; Roberto et al., 2008), we hypothesized that gabapentin might have greater efficacy among subgroups with a history of withdrawal (endorsement of the AUD [MINI] withdrawal symptom); relatively elevated sleep problems, anger/hostility, fatigue, tension/anxiety, mood disturbance, and depression; and relatively lower vigor-activity. However, GE-XR did not show a consistent pattern of efficacy across these characteristics (except for elevated sleep problems and lower vigor-activity). Similarly, GE-XR did not show differential efficacy as a function of AUD severity (AUD symptoms, alcohol consumption, craving, and alcohol-related consequences). Because GE-XR did not improve outcomes related to protracted withdrawal, it is perhaps not surprising that GE-XR generally had little effect on participants experiencing these symptoms at baseline.

GE-XR was well tolerated in this study with no serious AEs related to the medication. Compared to placebo, medication adherence was similar, and study dropout was relatively lower, suggesting relatively low patient burden for GE-XR and good engagement, although somewhat more GE-XR patients discontinued medication. The most commonly reported side-effects were fatigue, dizziness, and somnolence, consistent with those of G-IR (FDA, 2013). Although there is some evidence from human laboratory studies that G-IR does not interact with alcohol (Bisaga and Evans, 2006; Myrick et al., 2007), consistent with the label for gabapentin, there was some evidence that GE-XR interacted with alcohol to increase rates of dizziness and somnolence, although the small numbers of participants experiencing these AEs preclude definitive conclusions. Additionally, while infrequent (<5% of participants), GE-XR was associated with higher rates of treatment-emergent suicidal ideation than placebo, which is consistent with the increased ideation rates reported for antiepileptic medications (like gabapentin) as indicated in the GE-XR label (FDA, 2013). Thus, suicidal ideation should be monitored in patients taking GE-XR. Gabapentinoids, such as gabapentin and pregabalin, have misuse potential, and there have also been reports that gabapentin is misused, especially among participants with opioid use disorder with some gabapentin-related deaths associated with other substances (Mersfelder and Nichols, 2016; Smith et al., 2016). Although not directly assessed, research staff did not voice any concerns that participants in this study were misusing study tablets.

Study strengths included a relatively large sample size, long treatment period (6 months vs. the 3 months typically used for Phase II trials within the alcohol field), high treatment retention, low rate of missing data, Pop PK evaluation, use of a standardized behavioral platform, and an extensive and rigorous evaluation of possible outcomes and moderators of treatment effect. Moreover, the study benefited from a multisite design which increased the generalizability of results, though presumably at the expense of added site variability which may account for the observation that Phase 2 single-site trials are often not replicated in larger Phase 3 multisite trials (FDA, 2015b). Study limitations included the lack of additional treatment arms to evaluate the efficacy and safety of higher doses of GE-XR in an AUD population and limited power to detect moderator effects. Also, like most AUD pharmacotherapy trials, the study excluded patients with significant psychiatric comorbidities and alcohol withdrawal which may limit generalizability to the subpopulation of severe patients seen in certain specialty treatment settings where these features are more prevalent.

In summary, although previous single-site studies have reported G-IR reduced drinking in patients with AUD, this multisite clinical trial did not observe any benefit of the GE-XR formulation on a variety of alcohol consumption and nonconsumption outcomes in participants with moderate-to-severe AUD. It is possible the target dose was not adequate for this AUD population and/or that the heterogeneity of the population obscured a potential treatment effect. GE-XR was well tolerated in trial participants. Additional studies may be needed to examine GE-XR at higher dosages, compare side-by-side GE-XR versus G-IR within the same RCT, and evaluate the effect of alcohol on the mechanism of action of the prodrug formulation as well as identifying subtypes of patients who might be more likely to benefit from this medication. Given the null efficacy results of the present study, weighed against the potential interaction of GE-XR with alcohol and the potential for misuse of gabapentinoids, GE-XR, at least at the dose tested in this present study, cannot be recommended for the treatment of AUD.

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CONFLICTS OF INTEREST

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REFERENCES

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, 5th edn. American Psychiatric Association, Arlington, VA.

Anton RF, Myrick H, Baros AM, Latham PK, Randall PK, Wright TM, Stewart SH, Waid R, Malcolm R (2009) Efficacy of a combination of flumazenil and gabapentin in the treatment of alcohol dependence: relationship to alcohol withdrawal symptoms. J Clin Psychopharmacol 29:334–342.

Anton RF, Myrick H, Wright TM, Latham PK, Baros A, Waid LR, Randall PK (2011) Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry 168:709–717.

Backonja MM, Canafax DM, Cundy KC (2011) Efficacy of gabapentin enacarbil vs placebo in patients with postherpetic neuralgia and a pharmacokinetic comparison with oral gabapentin. Pain Med 12:1098–1108.

Bazil CW, Battista J, Basner RC (2005) Gabapentin improves sleep in the presence of alcohol. J Clin Sleep Med 1:284–287.

Beck AT, Epstein N, Brown G, Steer RA (1988) An inventory for measuring clinical anxiety: psychometric properties. J Consult Clinical Psych 56:893–897.

Beck AT, Steer RA, Ball R, Ranieri W (1996) Comparison of Beck depression inventories -IA and -II in psychiatric outpatients. J Personality Assess 67:588–597.

Bisaga A, Evans SM (2006) The acute effects of gabapentin in combination with alcohol in heavy drinkers. Drug Alcohol Depend 83:25–32.

Bockbrader HN (1995) Clinical pharmacokinetics of gabapentin. Drugs of Today 31:613–619.

Bode C, Bode JC (2003) Effect of alcohol consumption on the gut. Best Pract Res Clin Gastroenterol 17:575–592.

Breslow RA, Guenther PM, Juan W, Graubard BI (2010) Alcoholic beverage consumption, nutrient intakes, and diet quality in the US adult population, 1999–2006. J Am Diet Assoc 110:551–562.

Brower KJ, Aldrich MS, Hall JM (1998) Polysomnographic and subjective sleep predictors of alcoholic relapse. Alcohol Clin Exp Res 22:1864–1871.

Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA (2008) A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. Alcohol Clin Exp Res 32:1429–1438.

Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213.

Cundy KC, Sastry S, Luo W, Zou J, Moors TL, Canafax DM (2008) Clinical pharmacokinetics of XP13512, a novel transported prodrug of gabapentin. J Clin Pharmacol 48:1378–1388.

Devine EG, Ryan ML, Falk DE, Fertig JB, Litten RZ (2016) An exploratory evaluation of Take Control: a novel computer-delivered behavioral platform for placebo-controlled pharmacotherapy trials for alcohol use disorder. Contemp Clin Trials 50:178–185.

Elamin EE, Masclee AA, Dekker J, Jonkers DM (2013) Ethanol metabolism and its effects on the intestinal epithelial barrier. Nutr Rev 71:483–499.

Falk D, Wang XQ, Liu L, Fertig J, Mattson M, Ryan M, Johnson B, Stout R, Litten RZ (2010) Percentage of subjects with no heavy drinking days: evaluation as an efficacy endpoint for alcohol clinical trials. Alcohol Clin Exp Res 34:2022–2034.

Foster JH, Peters TJ (1999) Impaired sleep in alcohol misusers and dependent alcoholics and the impact upon outcome. Alcohol Clin Exp Res 23:1044–1051.

Furieri FA, Nakamura-Palacios EM (2007) Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 68:1691–1700.

Hasin DS, Wall M, Witkiewitz K, Kranzler HR, Falk D, Litten R, Mann K, O'Malley SS, Scodes J, Robinson RL, Anton R; Alcohol Clinical Trials Initiative (ACTIVE) Workgroup (2017) Change in non-abstinent WHO drinking risk levels and alcohol dependence: a 3 year follow-up study in the US general population. Lancet Psychiatry 4:469–476.

Kline-Simon AH, Weisner CM, Parthasarathy S, Falk DE, Litten RZ, Mertens JR (2014) Five-year healthcare utilization and costs among lower-risk drinkers following alcohol treatment. Alcohol Clin Exp Res 38:579–586.

Koob GF (2008) A role for brain stress systems in addiction. Neuron 59:11–34.

Litten RZ, Falk D, Ryan M, Fertig J (2015) Heterogeneity of alcohol use disorder: understanding mechanisms to advance personalized treatment. Alcohol Clin Exp Res 39:579–584.

Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, Green AI, Pettinati HM, Ciraulo DA, Sarid-Segal O, Kampman K, Brunette MF, Strain EC, Tiouririne NA, Ransom J, Scott C, Stout R (2013) A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. J Addict Med 7:277–286.

Lowman C, Allen J, Stout RL (1996) Replication and extension of Marlatt's taxonomy of relapse precipitants: overview of procedures and results. The Relapse Research Group. Addiction 91(Suppl):S51–S71.

Mason BJ, Light JM, Williams LD, Drobes DJ (2009) Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. Addict Biol 14:73–83.

Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A (2014) Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA Intern Med 174:70–77.

Mason BJ, Quello S, Shadan F (2018) Gabapentin for the treatment of alcohol use disorder. Expert Opin Investig Drugs 27:113–124.

McNair DM, Lorr M, Droppleman LF (1992) EdITs Manual for the Profile of Mood States. EdITs/Educational and Industrial Testing Service, San Diego, CA.

Mersfelder TL, Nichols WH (2016) Gabapentin: abuse, dependence, and withdrawal. Ann Pharmacother 50:229–233.

Miller W (1992) Form 90: A Structured Assessment Interview for Drinking and Related Behaviors (Test Manual). (NIH publication no. 96–4004). National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Miller W (1995) The Drinker Inventory of Consequences (DrInC): an instrument for assessing adverse consequences of alcohol abuse, in *NIAAA Project MATCH Monograph Series*, Vol. 4 (Mattson M, Marshall LA eds), pp 1–94. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Myrick H, Anton R, Voronin K, Wang W, Henderson S (2007) A double-blind evaluation of gabapentin on alcohol effects and drinking in a clinical laboratory paradigm. Alcohol Clin Exp Res 31:221–227.

Myrick H, Malcolm R, Randall PK, Boyle E, Anton RF, Becker HC, Randall CL (2009) A double-blind trial of gabapentin versus lorazepam in the treatment of alcohol withdrawal. Alcohol Clin Exp Res 33:1582–1588.

Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt Impulsiveness Scale. J Clin Psychol 51:768–774.

Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR (1996) A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 49:1373–1379.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ (2011) The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 168:1266–1277.

Rice AS, Maton S; for the Postherpetic Neuralgia Study Group (2001) Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. Pain 94:215–224.

Roberto M, Gilpin NW, O'Dell LE, Cruz MT, Morse AC, Siggins GR, Koob GF (2008) Cellular and behavioral interactions of gabapentin with alcohol dependence. J Neurosci 28:5762–5771.

Ryan ML, Falk DE, Fertig JB, Rendenbach-Mueller B, Katz DA, Tracy KA, Strain EC, Dunn KE, Kampman K, Mahoney E, Ciraulo DA, Sickles-Colaneri L, Ait-Daoud N, Johnson BA, Ransom J, Scott C, Koob GF, Litten RZ (2017) A phase 2, double-blind, placebo-controlled randomized trial assessing the efficacy of ABT-436, a novel V1b receptor antagonist, for alcohol dependence. Neuropsychopharmacology 42:1012–1023.

Sills GJ (2006) The mechanisms of action of gabapentin and pregabalin. Cur Opin Pharmacol 6:108–113.

Singleton EG (2000) A brief version of the Alcohol Craving Questionnaire (ACQ-NOW), in *Proceedings of the 60th Annual Meeting, The College on Problems of Drug Dependence, Inc. Volume II: Abstracts*. NIDA Research Monograph 180. National Institute on Drug Abuse, Rockville, MD, p. 304.

Smith RV, Havens JR, Walsh S (2016) Gabapentin misuse, abuse and diversion: a systematic review. Addiction 111:1160–1174.

Sobell LC, Sobell MB (1992) Timeline follow-back: a technique for assessing self-reported alcohol consumption, in *Measuring Alcohol Consumption: Psychosocial and Biological Methods* (Litten RZ, Allen JP eds), pp 41–72. Humana Press, Totowa, NJ.

Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM (1989) Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict 84:1353–1357.

U.S. Food and Drug Administration (2015a) Alcoholism: developing drugs for treatment, Guidance for Industry (draft guidance). Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM433618.pdf. Accessed May 16, 2018.

U.S. Food and Drug Administration (2015b) 22 case studies where phase 2 and phase 3 trials had divergent results. Available at: https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm535780.pdf. Accessed September 21, 2018.

U.S. Food and Drug Administration (FDA) (2012) Review for NDA 022399 SUPPL-3. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022399Orig1s003.pdf. Accessed June 13, 2018.

U.S. Food and Drug Administration (FDA) (2013) HORIZANT (gabapentin enacarbil) Extended-Release Tablets for oral use label. Revised April 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022399s006,s007lbl.pdf. Accessed May 16, 2018.

Weiss RD (2004) Adherence to pharmacotherapy in patients with alcohol and opioid dependence. Addiction 99:1382–1392.

Werner M, Rentz A, Frank L, Bowman L, Duhig A, Moss H (2008) Participant consequence measures. Presented at the annual meeting of the Research Society on Alcoholism, Washington, DC.

Zhang L, Rainka M, Freeman R, Harden RN, Bell CF, Chen C, Graff O, Harding K, Hunter S, Kavanagh S, Laurijssens B, Schwartzbach C, Warren S, McClung C (2013) A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of gabapentin enacarbil in subjects with neuropathic pain associated with postherpetic neuralgia (PXN110748). J Pain 14:590–603.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Inclusion/exclusion criteria.

Appendix S2. Schedule of visits and assessments.

Appendix S3. Clinical sites and oversight.

Appendix S4. Randomization and blinding details.

Appendix S5. Statistical analysis details.

Appendix S6. Moderators of the GE-XR treatment effect using PSNHDD outcome (weeks 22 to 25).

Appendix S7. Differences between GE-XR and placebo during study maintenance phase (weeks 2 to 25): percentage of heavy drinking days.