Gabapentin Reduces Alcohol Consumption and Craving: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: This study examined the efficacy of a 28-day gabapentin treatment in reducing alcohol consumption and craving.

Method: A randomized, double-blind, placebo-controlled trial was performed in a Brazilian public outpatient drug treatment center, with 60 male alcohol-dependent subjects with a mean age of 44 years and an average of 27 years of alcohol use, who consumed 17 drinks per day (165–170 g/day) over the past 90 days before baseline and had no other significant medical or psychiatric condition. Subjects were recruited between July 8, 2004, and February 24, 2005. Following screening, 60 subjects were selected and received diazepam and vitamins as treatment for acute withdrawal for at least 7 days. After the detoxification treatment, 30 subjects were randomly assigned to receive gabapentin (300 mg twice daily) for 4 weeks, and 30 subjects, with similar baseline characteristics, were randomly assigned to receive matching placebo tablets for the same period.

Results: After 28 days of treatment, the gabapentin group showed a significant reduction in both number of drinks per day and mean percentage of heavy drinking days ($p = .02$ for both), and an increase in the percentage of days of abstinence ($p = .008$), compared to the placebo group. Additionally, some improvement in obsessive-compulsive symptoms was noted in both groups after the treatment, but it resulted in a more pronounced decrease in automaticity of drinking and aspects of craving in the gabapentin group than in the placebo group.

Conclusion: Gabapentin reduces alcohol consumption and craving, which may help patients to maintain abstinence. These results, together with the virtual absence of side effects and a favorable safety profile, support gabapentin as a potential drug for the treatment of alcohol withdrawal and dependence.

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Alcoholism can be defined as a chronic relapsing disorder characterized by compulsive drinking, alcohol-seeking, loss of control over alcohol consumption, and impaired social and occupational function.[1]

In one perspective, effective social, behavioral, cognitive, and pharmacologic support during the withdrawal period can be particularly important in encouraging alcohol dependents to abstain from alcohol and subsequently to undergo long-term treatment for alcohol dependence.

Long half-life benzodiazepines are the most commonly used drugs in outpatient alcohol detoxification[2,3] and have a well-documented efficacy profile.[3] However, their use is limited due to their abuse liability, pharmacologic interaction with alcohol, and significant cognitive and psychomotor side effects.[4,5] Because of the disadvantages associated with the use of benzodiazepines, there has been a growing interest in the use of alternative treatment options for alcohol withdrawal syndrome.[4]

Recent studies have suggested that anticonvulsants, such as valproate or carbamazepine, may provide safe and effective alternatives to benzodiazepines, especially in patients with moderate to severe alcohol withdrawal symptoms.[4] However, the use of these agents may be limited by their hepatic and hematologic toxicity.[4] Thus, novel agents with rapid onset of action, lower toxicity, fewer side effects, lower interaction with alcohol and other drugs, and lower potential for abuse are needed in the treatment of alcohol withdrawal.

Anticonvulsants are also effective in the treatment of subtle withdrawal symptoms, known as "protracted

withdrawal syndrome," that may persist for weeks to months following the 5- to 7-day period of acute detoxification.[6,7] They may stabilize the main symptoms observed in this long-term syndrome[6,7] such as mood, anxiety, and sleep disturbances,[4,6] which are strongly related to drug-seeking and high risk of relapse to drug use.[4,6]

Gabapentin, 1-(aminomethyl) cyclohexaneacetic acid, is an anticonvulsant drug with analgesic properties that was originally developed for the treatment of spasticity and partial epilepsy and has proved effective in a number of different animal seizure models.[8] It has been found effective in other clinical conditions besides epilepsy, such as anxiety and affective disorders and chronic pain syndromes.[9–11] Gabapentin has also been reported to be effective in the treatment of drug dependence, especially in alcohol withdrawal syndrome.[6]

Preclinical studies have shown that gabapentin reduces alcohol withdrawal hyperexcitability in isolated slices of hippocampus,[12] as well as convulsions and anxiety in mice withdrawn from alcohol without ataxia and sedative effects.[13] In open studies, gabapentin has shown to be more effective than trazodone in the treatment of persistent insomnia in abstinent alcohol-dependent outpatients[14] and in the reduction of alcohol withdrawal symptoms.[15]

In a study in which alcoholic outpatients with persistent insomnia were treated with gabapentin, Karam-Hage and Brower[16] have observed that most of the patients started to improve with 600 mg/day at bedtime, and one of them with 200 mg/day. In another study,[14] the same authors have found that, after at least 4 weeks of abstinence, alcohol-dependent outpatients with persistent insomnia treated with gabapentin reported significant sleep improvement with a mean dose of 888 mg/day at bedtime. These studies have suggested that low doses of gabapentin may be effective in the treatment of some protracted withdrawal symptoms. In the present study, low doses of gabapentin were chosen, with the aim of identifying more effective and less toxic treatments.

When compared with other anticonvulsant drugs, gabapentin has some pharmacokinetic advantages since it is not metabolized by the liver and does not induce hepatic enzymes. Therefore, it does not significantly interact with other drugs that are hepatically metabolized.[4,17] Furthermore, it does not bind to plasma proteins and is eliminated by renal excretion as an unchanged drug.[4,17]

Thus, a trial was undertaken based on these findings and also because gabapentin is generally considered to be a safe drug with a favorable pharmacokinetic profile and no abuse potential and also does not cause cognitive impairment. This randomized, double-blind, placebo-controlled trial was conducted in a Brazilian public outpatient drug treatment center, in 60 male alcohol-dependent subjects, in order to examine the efficacy of 28-day treatment with gabapentin in reducing alcohol consumption and craving.

METHOD

Subjects

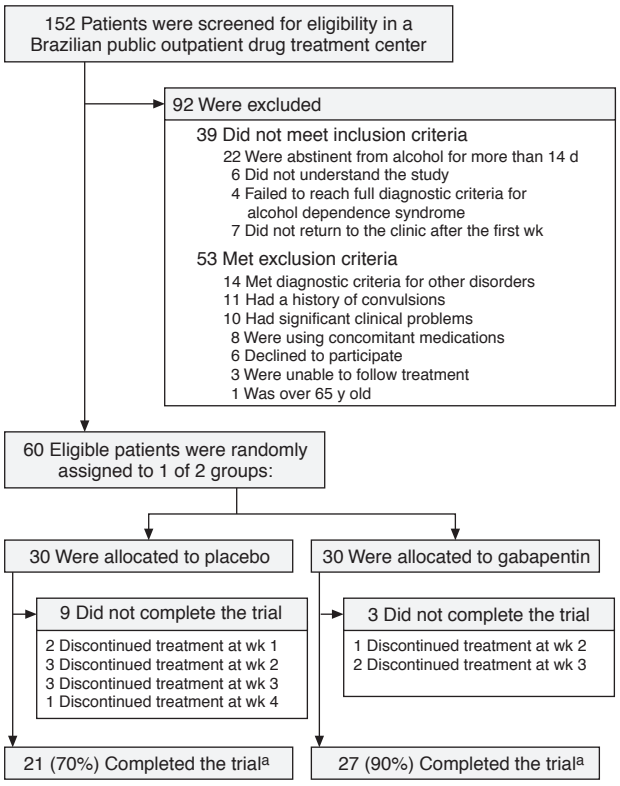
Of 152 alcohol-dependent outpatients consecutively referred to an addiction psychiatrist for alcohol dependence treatment, 60 met the inclusion criteria. After all eligible patients had signed a written informed consent and received a 7-day treatment for acute withdrawal with diazepam (0–30 mg/day) and vitamins, as well as emotional and physical support, they were randomly assigned to receive either gabapentin or placebo (Figures 1 and 2).

The inclusion criteria required the subjects to (1) be aged between 18 and 65 years; (2) have consumed at least an average of 35 drinks per week during the last year and at least an average of 35 drinks per week during the last 90 days before baseline; (3) be abstinent from alcohol for no longer than 14 days before baseline; (4) meet *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria for alcohol dependence, as determined by psychiatric evaluation, and be in stable clinical condition with no need for inpatient care; (5) have normal serum liver transaminases; (6) have a plasma gamma-glutamyl transferase (GGT) level less than 800 U/L; (7) be able to read, write, and speak Portuguese; (8) be diagnosed as nondemented with Mini Mental State Examination (MMSE)[18] scores greater than 20; (9) have no severe withdrawal signs or symptoms, scoring less than 15 in the Clinical Institute Withdrawal Assessment for Alcohol scale, Revised (CIWA-Ar)[19] at baseline; (10) not meet diagnostic criteria for other substance intoxication or withdrawal, or unstable mental or medical disorder other than alcohol dependence, except nicotine and/or caffeine; (11) not have convulsion or delirium tremens during abstinence from alcohol; (12) not have used pharmacologic agents known to reduce the convulsive threshold or to alter alcohol withdrawal or craving during the last 30 days before baseline; and (13) not have a previous history of drug hypersensitivity or adverse reactions to gabapentin, diazepam or other benzodiazepines, and haloperidol.

After having been informed of potential side effects and benefits of each treatment and giving written informed consent, 60 subjects were randomly assigned to 2 groups: (1) placebo group (N = 30) and (2) gabapentin group (N = 30) (Figure 1). Subjects and psychiatrist were blind to the treatment condition. The randomization code was held by a research supervisor, to be broken only in case of emergency. It is important to note that the code was not broken until the study was completed.

Ethics approval was provided by the Brazilian Institutional Review Board at the Federal University of Espírito Santo Health Science Center, Vitória, Espírito Santo, Brazil. Subjects were recruited between July 8, 2004, and February 24, 2005, in a Brazilian public outpatient drug treatment center.

Figure 1. Trial Profile



[a]Trial completers were subjects who completed all 4 weeks (28 days) of double-blind treatment.

Procedures

At baseline (day 0), after providing their written informed consent, all patients (N = 60) underwent a clinical evaluation consisting of a medical history and physical examination; vital signs (blood pressure, pulse, and temperature); hematologic and biochemical tests; a psychiatric evaluation including a structured clinical interview for DSM-IV; age at drinking onset; self-reported drinking over the past 90 days assessed by the timeline follow-back (TLFB) method, which is a widely used objective index of alcohol consumption[20]; measurement of craving by the Obsessive Compulsive Drinking Scale (OCDS)[21]; the CIWA-Ar scale; concomitant medication use; and adverse effects according to the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale[22] (Figure 2).

From the beginning of week 1 to the end of week 4, tablets (gabapentin up to 600 mg/day or placebo) were given to the subjects in a double-blind manner, in combination with a weekly brief behavioral compliance enhancement treatment.

Gabapentin and matching placebo tablets were prepared by a local pharmaceutical company (IMAFAR, Indústria de Manipulação Farmacêutica Ltda., Vitória, Espírito Santo, Brazil). All subjects received an identical number of tablets. Study medication was dispensed in medication containers each labeled with identification of the study performed, subject code number, and date of dispensing.

Subjects were instructed to take 2 tablets orally per day, but that the dose could be reduced to 1 tablet daily should any problems arise. Additionally, they were instructed to return weekly to the outpatient center and avoid alcoholic beverages, but to continue treatment even if they had drunk alcohol. In this way, from weeks 1 to 4, subjects were evaluated weekly for vital signs, TLFB, adverse-event profile, concomitant medications, and treatment compliance, which was assessed by counting returned tablets (Figure 2).

Four primary efficacy variables were used to capture self-reported drinking behavior from the start of week 1 to the end of week 4 (total of 28 days) using the TLFB as follows[23]: (1) drinks per day (total number of drinks consumed per number of study days), (2) drinks per drinking day (total number of drinks consumed per number of days of drinking), (3) percentage of heavy drinking days (percentage of days in which the number of drinks consumed was 5 or greater per number of study days), and (4) percentage of days of abstinence (percentage of nondrinking days per number of study days).

The OCDS was applied at baseline (day 0) and at the end of weeks 2 and 4 (Figure 2). Four factors derived empirically by principal component analysis of the OCDS[21,24,25] were analyzed: (1) drinking obsession (obsessional thoughts related to drinking); (2) automaticity of drinking (5 items that assessed the extent to which drinking behavior was controlled or uncontrolled); (3) interference due to drinking (3 items that assessed the extent to which drinking interfered with work and social functioning, and the degree of distress following alcohol deprivation); and (4) alcohol consumption (2 items that assessed the quantity and frequency of alcohol consumption).

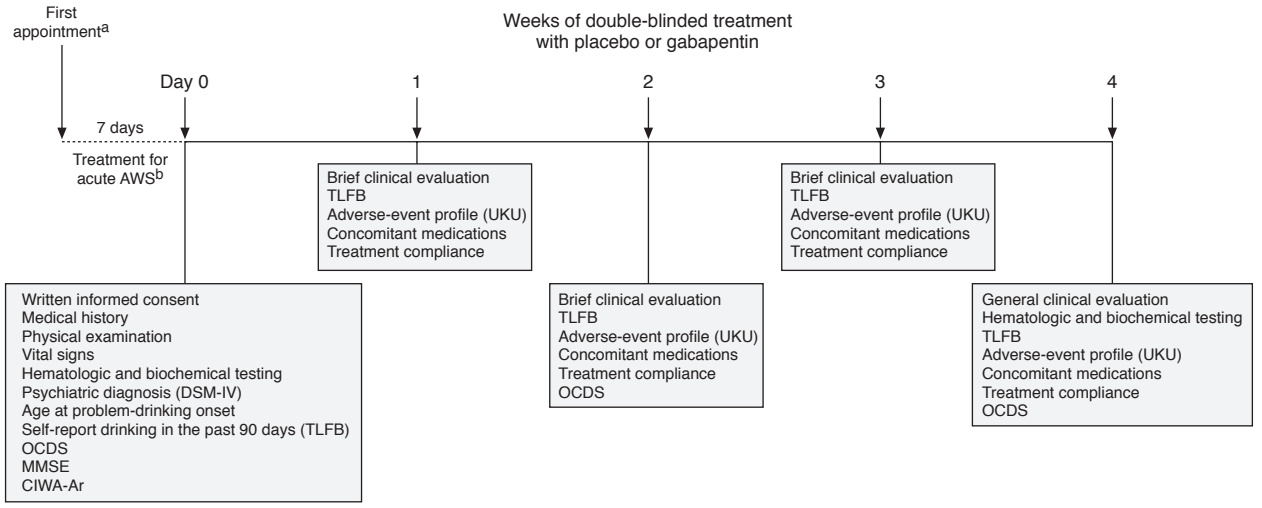
After 28 days of treatment, a comprehensive clinical evaluation and hematologic and biochemical measurements, including transaminases and plasma GGT, were repeated.

Statistical Analysis

Comparisons between the placebo and gabapentin groups (intergroup analysis) were performed using the 2-sample unpaired Student t test. Comparisons between data collected at baseline (day 0) and at the end (day 28) of the study (intra-group analysis) were performed using the 2-sample paired Student t test.

Repeated measures data (weekly measures) were analyzed by the 2-way repeated measures analysis of variance (ANOVA), with differences between placebo and gabapentin groups as between-subjects factors and differences in individual behavior as within-subjects factors.

Figure 2. Outline of the General Procedure



[a]First appointment: first assessment at a Brazilian public outpatient drug treatment center.
[b]Treatment for acute AWS: diazepam and vitamins, as well as emotional and physical support.
Abbreviations: AWS = alcohol withdrawal syndrome; CIWA-Ar = Clinical Institute Withdrawal Assessment for Alcohol scale, Revised; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; MMSE = Mini Mental State Examination; OCDS = Obsessive Compulsive Drinking Scale; TLFB = timeline follow-back; UKU = Udvalg for Kliniske Undersogelser side effect rating scale.

Table 1. Baseline Sociodemographic and Psychopathological Characteristics of Subjects in Both Placebo and Gabapentin Groups

Characteristics	Placebo (N = 30)	Gabapentin (N = 30)	t Value	p
Demographic variables				
Age, mean (range), y	43.87 (26–60)	44.67 (34–58)	0.404	.69
Years of education, mean (range)	6.53 (1–11)	6.67 (1–13)	0.154	.88
Marital status, N (%)			…	…
Single	6 (20.0)	10 (33.3)		
Married	14 (46.7)	8 (26.7)		
Divorced	7 (23.3)	9 (30.0)		
Employment, N (%)			…	…
Employed	6 (20.0)	4 (13.3)		
Temporary job	6 (20.0)	7 (23.3)		
Insured	8 (26.7)	3 (10.0)		
Unemployed	7 (23.3)	15 (50.0)		
Retired	3 (10.0)	1 (3.3)		
Measures of alcohol drinking behavior				
Age at onset of alcohol use, mean ± SD, y	16.57 ± 4.52	15.87 ± 4.73	0.586	.56
Drinking years, mean ± SD	26.97 ± 8.70	28.67 ± 8.66	0.758	.45
Drinks per day in the last 90 days, mean ± SD	16.47 ± 7.16	17.10 ± 8.04	0.322	.75
Days of abstinence before baseline, mean ± SD	8.23 ± 2.46	8.60 ± 3.36	0.482	.63
Attended the emergency department because of alcohol use at least once, N (%)	18 (60.0)	18 (60.0)	…	…
Received prior treatment for alcohol dependence, N (%)	16 (53.3)	15 (50.0)	…	…
CIWA-Ar score, mean ± SD	7.30 ± 1.73	6.43 ± 1.79	1.907	.06
MMSE score, mean ± SD	24.30 ± 2.90	25.57 ± 2.64	1.770	.08

Abbreviations: CIWA-Ar = Clinical Institute Withdrawal Assessment for Alcohol scale, Revised; MMSE = Mini Mental State Examination test.
Symbol: … = not applicable.

It was followed by the Fisher least significant difference (LSD) (protected t test) as a post hoc test.

A 2-tailed α level of .05 was used to determine statistical significance.[26] GB-Stat Professional Statistics & Graphics version 6.5 (Dynamic Microsystems, Inc., Silver Spring, Md.), GraphPad Prism 4.0 (GraphPad Software, Inc., San Diego, Calif.), and the Statistical Package for Social Sciences (SPSS) software (SPSS, Inc., Chicago, Ill.) were used for statistical analysis and graphic presentation.

RESULTS

Baseline sociodemographic and psychopathological characteristics of subjects (placebo and gabapentin groups) are shown in Table 1. These characteristics (mean

Table 2. Hematologic and Biochemical Measurements[a]

Measurement	Placebo (baseline: N = 30) (28 days: N = 18)	Gabapentin (baseline: N = 30) (28 days: N = 25)	Intergroup Analysis
MCV, mean ± SD, fL			
Baseline	94.28 ± 6.22	94.01 ± 5.81	t = 0.177; p = .86
28 days	93.12 ± 5.31	93.21 ± 4.80	t = 0.061; p = .95
Intragroup analysis	t = 2.112; p = .05*	t = 1.590; p = .12	…
Leukocyte count/μL, mean ± SD			
Baseline	6576.67 ± 1679.02	6966.67 ± 2671.48	t = 0.677; p = .50
28 days	6755.56 ± 1551.17	7216.00 ± 2435.79	t = 0.704; p = .49
Intragroup analysis	t = 0.299; p = .77	t = 1.217; p = .23	…
Platelet count/μL, mean ± SD			
Baseline	260,833.33 ± 70,418.98	258,666.67 ± 74,599.78	t = 0.116; p = .91
28 days	228,944.44 ± 46,500.44	242,160.00 ± 61,900.24	t = 0.763; p = .45
Intragroup analysis	t = 2.019; p = .60	t = 1.100; p = .28	…
SGOT level, mean ± SD, U/L			
Baseline	49.50 ± 37.65	52.23 ± 59.39	t = 0.213; p = .83
28 days	25.28 ± 12.06	26.92 ± 19.66	t = 0.314; p = .76
Intragroup analysis	t = 2.866; p = .01**	t = 2.839; p = .01**	…
SGPT level, mean ± SD, U/L			
Baseline	55.67 ± 57.47	48.17 ± 65.89	t = 0.470; p = .64
28 days	20.00 ± 10.16	27.32 ± 34.19	t = 0.878; p = .39
Intragroup analysis	t = 2.451; p = .03*	t = 2.298; p = .03*	…
GGT level, mean ± SD, U/L			
Baseline	125.87 ± 130.67	122.33 ± 142.26	t = 0.100; p = .92
28 days	69.83 ± 69.02	67.68 ± 61.60	t = 0.108; p = .92
Intragroup analysis	t = 1.831; p = .09	t = 2.724; p = .01**	…

[a]Comparisons between the placebo and gabapentin groups (intergroup analysis) were performed using the 2-sample Student t test for independent measures, and between the data obtained at baseline and after 28 days of treatment (intragroup analysis) using the 2-sample paired Student t test.
*p ≤ .05.
**p ≤ .01.
Abbreviations: GGT = γ-glutamyltransferase, MCV = mean corpuscular volume, SGOT = serum glutamate-oxaloacetate transaminase, SGPT = serum glutamate-pyruvate transaminase.

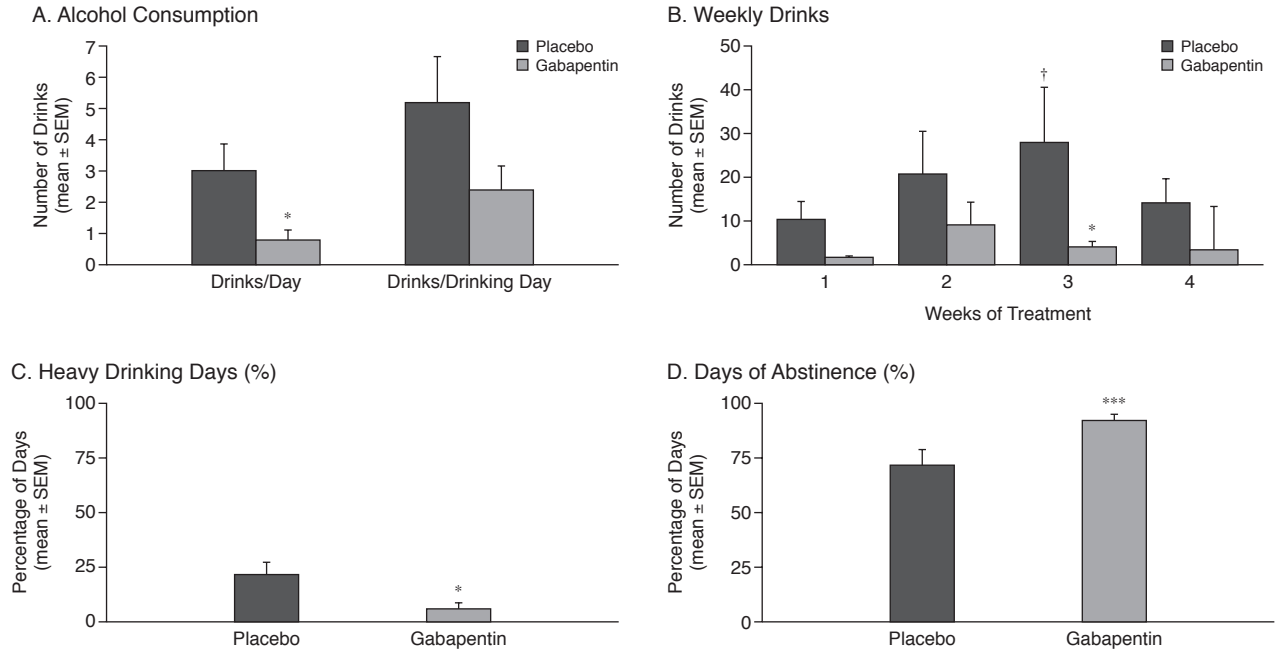
age, years of education, and marital and employment status) were very similar between both groups. All subjects also had very similar profiles of alcohol use (age at onset of alcohol use, drinking years, drinks per day in the last 90 days, and days of abstinence before baseline). Sixty percent of all subjects (N = 36) had already been treated in an emergency department at least once because of alcohol use, and about 50% (N = 31) had been treated for alcohol dependence before. Withdrawal severity and mental state were not significantly different between placebo and gabapentin groups (Table 1).

From 60 subjects selected for this trial, 23 (76.7%) from the placebo group and 16 (53.3%) from the gabapentin group had used diazepam during the treatment for alcohol withdrawal for 7 days before baseline. The mean ± SD total doses of diazepam taken by the placebo and gabapentin groups over the 7 days of treatment before baseline were 78.7 ± 39.6 mg and 90.0 ± 31.4 mg, respectively. Fifteen subjects (50%) in the placebo group and 13 (43.3%) in the gabapentin group continued to use diazepam in mean ± SD total doses of 140.7 ± 146.9 mg and 65.4 ± 39.5 mg, respectively, during the 28 days of the study. No statistically significant difference was observed between treatment groups in the use of diazepam. However, it should be noted that a lower percentage of subjects used diazepam during the 7-day period before baseline in the gabapentin group, but the mean dose used was a little higher in this group than in the placebo group. During the period of study, a slightly lower percentage of subjects in the gabapentin group used diazepam in lower doses than the subjects in the placebo group but not to a statistically significant extent.

Hematologic and biochemical measurements are shown in Table 2. Placebo and gabapentin groups were not significantly different regarding these parameters at baseline. In both groups, the levels of serum glutamate-oxaloacetate transaminase (SGOT) and serum glutamate-pyruvate transaminase (SGPT) decreased significantly after 28 days of treatment compared to baseline (Table 2). GGT levels also decreased after 28 days of treatment in both groups, but to a statistically significant extent only in the gabapentin group (Table 2). After 28 days of treatment, the mean corpuscular volume (MCV) also decreased in both groups compared to baseline, but in a statistically significant manner only in the placebo group (Table 2).

Data on drinking behavior obtained from the subjects in the placebo and gabapentin groups, using TLFB reports from the beginning to the end of the treatment (28 days), are shown in Figure 3. The number of drinks per day de-

Figure 3. (A) Drinks per Day and Drinks per Drinking Day (mean ± SEM), (B) Weekly Drinks (mean ± SEM), (C) Percentage of Heavy Drinking Days (mean ± SEM), and (D) Percentage of Days of Abstinence (mean ± SEM) in 28 Days (or 4 weeks) of Treatment With Placebo or Gabapentin



*p = .02, **p < .01, and ***p = .008 compared to the placebo group (Student t test or Fisher LSD protected t test following the 2-way repeated measures ANOVA).
†p < .01 compared to the placebo group at week 1 (Fisher LSD protected t test following the 2-way repeated measures ANOVA).
Abbreviations: ANOVA = analysis of variance, LSD = least significant difference, SEM = standard error of the mean.

creased significantly more in the gabapentin group than in the placebo group (t = 2.31, p = .02) at the end of the 28-day treatment (Figure 3A). The number of drinks per drinking day also decreased more in the gabapentin group, but not to a statistically significant extent (Figure 3A).

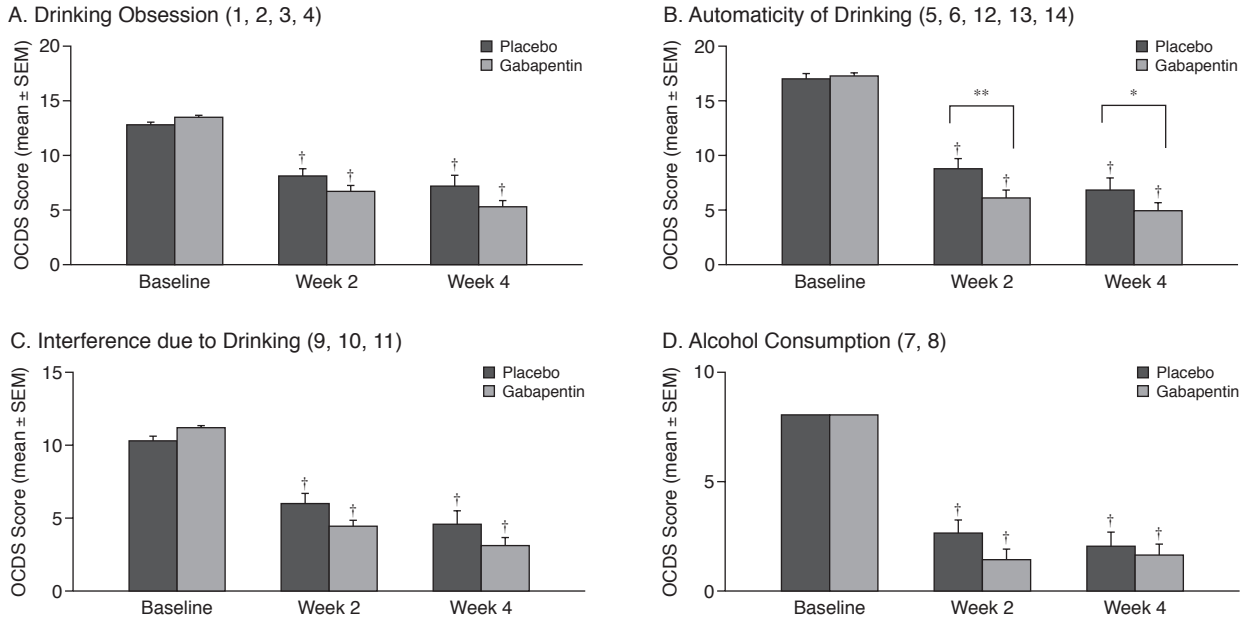
There are also statistically significant differences between groups in the number of weekly drinks (F = 5.71, df = 1,58; p = .02) and in the alcohol consumption during the 4 weeks of treatment (F = 2.69, df = 3,174; p = .05) (Figure 3B). Subjects in the gabapentin group consistently reduced their alcohol consumption over all 4 weeks of treatment more than the placebo group, achieving statistical significance (p < .01) at week 3 (Figure 3B). Besides the higher level of alcohol consumption reported by the placebo group compared to the gabapentin group, this group also reported a progressive increase in alcohol consumption during treatment with a significant increase (p < .01) at week 3 compared to the first week (Figure 3B). In the placebo group, the alcohol consumption dropped at week 4 (Figure 3B).

The mean percentage of heavy drinking days was significantly lower (t = 2.352, p = .02) in the gabapentin group compared to the placebo group (Figure 3C). Additionally, the mean percentage of days of abstinence was significantly higher (t = 2.750, p = .008) in the gabapentin group compared to the placebo group (Figure 3D). Twenty subjects in the gabapentin group and 13 in the placebo group maintained complete abstinence during the 28 days of study.

Figure 4 shows the 4 factors derived empirically from principal component analysis of the OCDS. Two-way repeated measures ANOVA showed statistically significant differences for all within-subjects factors over the weeks: drinking obsession (F = 149.99, df = 2,116; p < .0001), automaticity of drinking (F = 211.14, df = 2,116; p < .0001), interference due to drinking (F = 148.04, df = 2,116; p < .0001), and alcohol consumption (F = 222.02, df = 2,116; p < .0001). The post hoc analysis showed that all parameters were significantly reduced (p < .01) at weeks 2 and 4 in both groups compared to baseline (Figure 4). The gabapentin group showed lower mean scores than the placebo group in all 4 factors. However, this difference was statistically significant only for automaticity of drinking (F = 4.098, df = 1,58; p = .0475). In the post hoc analysis, the gabapentin group showed significantly lower mean scores at week 2 (p < .01) and week 4 (p < .05) than the placebo group (Figure 4).

Results for the 5 OCDS items (1, 2, 4, 5, and 13), considered as "actual craving" by de Wildt et al.,[25] are shown

Figure 4. Obsessive Compulsive Drinking Scale (OCDS) Scores (mean ± SEM) in a 4-Factor Model[a] Measured at Baseline and After 2 and 4 Weeks of Treatment With Placebo or Gabapentin



[a]Four-factor model according to Bohn et al.[21]; the numbers in parentheses correspond to the original OCDS items.[24]
*p < .05 and **p < .01 compared to the placebo group.
†p < .01 compared to baseline scores.
Abbreviation: SEM = standard error of the mean.

in Figure 5. Two-way repeated measures ANOVA showed statistically significant differences between groups ($F = 5.175$, $df = 1,58$; $p = .026$) and within groups ($F = 174.17$, $df = 2,116$; $p < .0001$) (Figure 5). The mean scores decreased significantly ($p < .01$) at weeks 2 and 4 in both groups compared to baseline. This decrease was greater for the gabapentin group, since the mean scores were significantly lower ($p < .01$) in this group than in the placebo group at both weeks 2 and 4 (Figure 5).

Most of the subjects (56.6%, N = 34) did not report undesirable effects. Symptoms, mostly related to insomnia, were not substantially different between groups. Seven subjects (23.3%) in the placebo group and 3 (10.0%) in the gabapentin group reported persistent insomnia, and 4 (13.3%) subjects from the placebo and 6 (20.0%) from the gabapentin group reported initial or episodic insomnia. Few other symptoms were reported by a very small number of subjects, such as sleepiness reported by 1 subject in the placebo group and 1 in the gabapentin group, headache by 1 subject in the placebo group, and sickness by 1 subject in the gabapentin group.

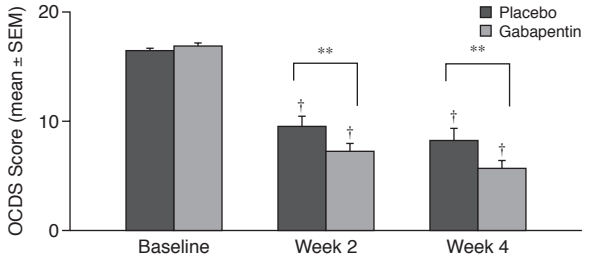
DISCUSSION

Gabapentin significantly decreased the number of drinks and the mean percentage of days of heavy drinking and increased the percentage of days of abstinence over the 28 days of treatment. The greater decrease in GGT levels observed in the gabapentin group when compared to the placebo group is consistent with the lower alcohol consumption in this group. This congruence in turn increases the reliability of the present results.

These results were complemented with weekly assessments of alcohol consumption. In the first week of treatment, alcohol consumption was reduced in both groups, more significantly in the gabapentin group, but not to a statistically significant extent. This decrease in alcohol consumption remained steady over the following weeks for the gabapentin group but not for the placebo group. In the placebo group, there was a significant increase in alcohol consumption at week 3 compared to week 1, reaching the former pattern of alcohol use observed in several subjects at baseline. This pattern of alcohol consumption in the placebo group is consistent with that usually observed in clinical practice when subjects decide to discontinue treatment after 15 to 20 days as they recognize their failure to stop drinking or even to reduce their craving for alcohol.

The mechanism of action of gabapentin is not completely known.[10,27] Although structurally related to γ-aminobutyric acid (GABA), gabapentin does not interact directly with either $GABA_A$ or $GABA_B$ receptors, nor with high affinity Na^+-dependent GABA transporters.[27] Furthermore, gabapentin is functionally different from

Figure 5. Obsessive Compulsive Drinking Scale (OCDS) Scores (mean ± SEM) of 5 Items (1, 2, 4, 5, and 13)[a] Measured at Baseline and After 2 and 4 Weeks of Treatment With Placebo or Gabapentin



[a]The 5 items (1, 2, 4, 5, and 13) are considered as "actual craving" by de Wildt et al.[25]; the numbers in parentheses correspond to the original OCDS items.[24]
**p < .01 compared to the placebo group.
†p < .01 compared to baseline scores.
Abbreviation: SEM = standard error of the mean.

GABA because it crosses the blood-brain barrier readily and is distributed in the central nervous system.[10,27]

Gabapentin does not affect the binding of a wide variety of drugs or neurotransmitters, including GABA.[27] However, it binds itself in a particular binding site in the brain tissue and appears to be the same protein as the Ca^{2+} channel subunit.[27] Actually, gabapentin is the first ligand described that binds to Ca^{2+} channel $\alpha_2\delta$ subunit.[27] Through this mechanism, gabapentin can cause a decrease in calcium influx in presynaptic nerve terminals and inhibit the release of excitatory amino acids[10] and several other neurotransmitters including monoamines such as noradrenaline, dopamine, and serotonin.[27] These actions may directly affect the activity in brain structures involved in the control of tolerance, abstinence, and dependence of alcohol and other drugs, such as the brain reward circuitry constituted by the mesocorticolimbic dopaminergic system.[28–32]

Additionally, gabapentin may act indirectly on the brain reward circuitry, and it is probably mediated by GABAergic inhibitory modulation of dopaminergic transmission in the mesocorticolimbic pathway, since it promotes a nonvesicular release of GABA in the brain by an unknown mechanism.[33] Regardless of the mechanism of action, gabapentin may inhibit the activation of brain reward circuitry by alcohol, decreasing the rewarding effect and, consequently, the motivation to consume alcohol. These findings are supported by decreases in the OCDS scores observed in the present study, especially in automaticity of drinking[21] and craving for alcohol,[24] reported by subjects who were treated with gabapentin.

Bohn et al.,[21] in a study examining the psychometric properties and validity of the OCDS, showed that automaticity of drinking was positively associated with the intensity and salience of drinking and inversely associated with use of active-approach coping, as well as abstinence duration. Based on OCDS scores, Ait-Daoud et al.[34] have shown that the combination of ondansetron and naltrexone effectively reduces automaticity of drinking and alcohol consumption and might reduce craving for alcohol. It is important to note that, in the present study, a similar result (decreased automaticity of drinking and alcohol consumption) was obtained with only 1 medication (gabapentin) in a very short period of treatment (28 days). Furthermore, in agreement with Bohn et al.,[21] subjects who received gabapentin were able to maintain abstinence from alcohol for significantly longer periods of time when compared to those who received placebo.

In a multinational study, de Wildt et al.[25] have investigated the structure of craving using structural equation modeling in analysis of the OCDS and have compared the results with those of 3 alternative causal models, which are based on modern theories of craving. This study showed that the causal cognitive-behavioral model was superior when compared to an obsessive-compulsive disorder model and an inhibition model. It also showed that the OCDS contains many items that do not represent the core concept of craving but instead are indicators of the consequences of craving. Based on this causal cognitive-behavioral model, the authors selected 5 items from the OCDS that are believed to be reliable to assess craving in a narrow sense.[25]

In the present study, all subjects were assessed using the 5 OCDS items selected by de Wildt et al.,[25] and both groups showed significantly lower scores at weeks 2 and 4 compared to baseline; however, subjects in the gabapentin group reported significantly lower scores on all 5 OCDS items than those in the placebo group for the same time periods. Therefore, this study suggests that gabapentin significantly reduced craving for alcohol, allowing subjects a better control over alcohol use, thus enabling them to be more successful in achieving abstinence.

Myrick et al.[15] were probably the first authors to report on the clinical use of gabapentin in the treatment of alcohol withdrawal. The authors conducted a small study of 6 subjects to whom gabapentin (400 mg 3 times daily for the first 3 days, 400 mg twice on day 4, and 400 mg once on day 5) was administered and found that mean CIWA-Ar scores decreased from 17 on day 1 to 0 on day 4.[15,35]

Previous preclinical studies have shown that gabapentin has a selective action in decreasing both convulsive and anxiety-related aspects of withdrawal behavior after chronic ethanol treatment in mice,[13] and also that, depending on the concentration used, gabapentin significantly reduces the signs of withdrawal hyperexcitability in mouse hippocampal slices.[12]

Few other studies[5] have suggested that, when administered at high doses in the beginning or during the course of the treatment, gabapentin generally protects against withdrawal effects and reduces alcohol craving. Gaba-

pentin appears promising as a safe and effective treatment for alcohol-dependent patients with comorbid insomnia during early recovery.[5] In a randomized, open-label, controlled trial, Mariani et al.[5] showed that gabapentin was as effective as phenobarbital in the treatment of alcohol withdrawal. Moreover, the authors suggested that, given the favorable pharmacokinetic profile of gabapentin, further studies of its effectiveness in treating alcohol withdrawal would be warranted.

In a retrospective study, Voris et al.[36] showed that data from inpatients and outpatients suggested that gabapentin works well for the mild to moderate alcohol withdrawal patient. The authors also suggested the need for controlled studies to differentiate the usefulness of gabapentin for mild to severe withdrawal.[36] However, Bonnet et al.[37] showed in a controlled 2-center trial that gabapentin was no better than placebo in reducing the amount of clomethiazole needed to suppress alcohol withdrawal symptoms or in decreasing Mainz Alcohol Withdrawal Scale scores in comparison with baseline, suggesting that gabapentin is ineffective in the management of acute alcohol withdrawal syndrome.

It should be noted that, in the present study, gabapentin treatment started 7 days after the last alcohol drink, that is, only after the initial 7-day treatment with benzodiazepines for acute alcohol withdrawal syndrome, as the primary purpose of this study was not to investigate the treatment of acute alcohol withdrawal. Considering the study of Bonnet et al.[37] mentioned above, diazepam was given during the course of the study.

Gabapentin was administered for 28 consecutive days after the initial treatment of acute withdrawal. It was intended to suppress withdrawal symptoms that emerge later in the withdrawal process, which may be considered as a protracted withdrawal syndrome. Most importantly, it was particularly directed toward craving and related alcohol consumption, a symptom highly associated with relapse that could also be considered, at least to some extent, as part of the protracted withdrawal syndrome.

It is relevant to note that even if gabapentin was administered in lower doses (300–600 mg/day) compared with those reported in the literature (400–1600 mg/day), it was found to be more effective than placebo in reducing alcohol consumption, salience of drinking, and, most importantly, craving for alcohol and also to have a safe mode of administration and good patient acceptance and be associated with only mild adverse effects.

Frequently, sleep disorders are related to protracted alcohol withdrawal. Insomnia is very frequent and may increase the risk of relapse in treated alcoholics, even after controlling for other clinical variables.[14] In an open pilot study of gabapentin versus trazodone to treat persisting insomnia in alcoholic outpatients, Karam-Hage and Brower[14] showed that both treatment groups improved significantly on the Sleep Problem Questionnaire, but the gabapentin group improved significantly more than the trazodone group.

In the present study, however, the small number of reported cases of insomnia was similar in both gabapentin and placebo groups. It is important to note that in this study a lower dose of gabapentin was used compared to that of the Karam-Hage and Brower study.[14] Thus, it has to be considered that higher doses of gabapentin might be needed in the treatment of protracted withdrawal syndrome.

According to the present results, gabapentin has been shown to be a safe medication to be used as monotherapy or as an add-on pharmacotherapy in outpatient settings in the control of alcohol consumption and craving, helping patients to achieve abstinence. Therefore, gabapentin has shown great potential in the treatment of alcohol dependence and withdrawal syndromes.

Drug names: carbamazepine (Equetro, Carbatrol, and others), diazepam (Valium and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), naltrexone (Vivitrol, Revia, and others), ondansetron (Zofran and others).

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