Gabapentin in Alcohol Dependence

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Abstract

Objective: To review the literature related to the use of gabapentin in alcohol dependence following acute alcohol withdrawal. **Data Sources:** Searches of MEDLINE (1946-January 2015) and Cochrane Database (2005-January 2015) were performed using *gabapentin*, *alcohol*, and *alcoholism* as MeSH terms and keywords. Results were limited to human trials in English-language journals. **Study Selection and Data Extraction:** Inclusion criteria included randomized controlled trials with a minimum 4 weeks of gabapentin therapy and at least one alcohol dependence related outcome measure (ie, cravings, abstinence, percent days abstinent, or heavy drinking days). Six randomized clinical trials were identified. **Data Synthesis:** Four trials identified beneficial effects of gabapentin on at least one alcohol-related outcome measure. Two smaller studies, which enrolled patients with minimal withdrawal symptoms, failed to demonstrate beneficial effects on primary outcomes related to heavy drinking or abstinence. Gabapentin at doses up to 1800 mg daily was well tolerated with no serious adverse drug reactions being reported. **Conclusions:** Clinical trials have shown gabapentin is a well-tolerated adjunctive therapy in the management of alcohol dependence. The strongest efficacy evidence occurred in patients experiencing moderate to severe withdrawal when gabapentin was administered early in or concurrently during acute withdrawal and continued for up to 12 weeks.

Keywords

gabapentin, alcohol dependence, craving, abstinence, alcoholism

Background

Alcoholism is a major public health concern and is responsible for 4% of total worldwide mortality.¹ Globally, unsafe alcohol use is responsible for 3.3 million deaths annually.² Alcohol dependence is estimated to affect 7% to 16% of the US adult population.³ In 2006, excessive alcohol ingestion–related expenses, health care, workplace productivity, and crime was estimated to cost \$223.5 billion in the United States.⁴

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, utilized by all reviewed studies, defines alcohol dependence as having 3 or more of the following criteria occurring in the same year: needing increased amounts of alcohol for intoxication, withdrawal on cessation, increased amounts of drinking over longer times, inability to reduce drinking, increased time needed to recover from drinking, or continuing to consciously drink knowing physical and emotional problems may worsen.⁵ Alcohol dependence criteria and definitions have since been modified with the introduction of the fifth edition of the *DSM*. Treatment of alcohol dependence generally involves 2 phases. Patients acutely discontinuing alcohol ingestion may develop alcohol withdrawal syndrome and require treatment to manage symptoms ranging

from anxiety, tremor, and insomnia to more severe cases presenting with delirium tremens.³ Once through initial withdrawal, patients generally need counseling and often pharmacological support to maintain abstinence. Less than 20% of patients will be abstinent a year later and up to 25% remain classified as alcohol dependent.⁶

It is estimated that 2% to 9% of all patients seen in a family physician's office are dependent on alcohol.³ Thus, there is the need for an effective medication that can be used in the outpatient setting to maintain alcohol abstinence. Gabapentin is a Food and Drug Administration–approved anticonvulsant commonly prescribed off-label for indications such as neuropathic pain or fibromyalgia.⁷ The exact pharmacological mechanism of gabapentin is unknown but

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it is thought to augment γ -aminobutyric acid (GABA) synthesis in the brain, inhibit neuronal calcium channels, and inhibit glutamate synthesis.^{8,9} Alcohol-dependent patients experience GABA downregulation following prolonged alcohol exposure. Gabapentin's potentiation of GABA levels may be particularly beneficial in reducing cravings following acute alcohol cessation when patients experience low GABA and high glutamate activity.⁹ Gabapentin's safety in combination with alcohol has been demonstrated.⁹ In addition, gabapentin is renally eliminated, making it advantageous in patients with hepatic dysfunction.⁸ Gabapentin was previously demonstrated to be beneficial during acute withdrawal.¹⁰⁻¹⁴ Additionally, case reports suggested a potential benefit for continuing gabapentin after the acute withdrawal phase.^{15,16} This review will analyze the literature related to the use of gabapentin in the reduction of alcohol dependence symptoms and consumption after the acute withdrawal phase.

Literature Search

A search was conducted using MEDLINE (1946-January 2015) and Cochrane Database (2005-January 2015) using *gabapentin*, *alcohol*, and *alcoholism* as MeSH terms and keywords. Results were limited to human trials in English-language journals. The references of identified articles were reviewed to identify other relevant articles. Inclusion criteria included a minimum 4 weeks of gabapentin therapy and at least one abstinence-related outcome measure. Examples of abstinence-related outcomes include cravings, abstinence, percent days abstinent, time to heavy drinking, or heavy drinking days. Six randomized clinical trials evaluating postacute withdrawal abstinence-related outcomes were identified.

Clinical Trials

Six controlled trials have evaluated the utility of gabapentin in alcohol abstinence (Table 1).¹⁷⁻²² Furieri et al conducted the first trial to assess gabapentin's efficacy in reducing alcohol consumption and craving in a Brazilian outpatient center.¹⁷ Patients had abstained from alcohol for less than 2 weeks before trial inclusion, met *DSM-IV* criteria for alcohol dependence, and had a score of <15 on the Clinical Institute Withdrawal Assessment for Alcohol scale, Revised (CIWA-Ar). Patients received diazepam (0-30 mg per day) and vitamins for 7 days to treat acute withdrawal. Subjects were randomized to receive gabapentin 300 to 600 mg per day or placebo for the following 4 weeks of the trial. Patients could continue taking diazepam and received weekly behavioral therapy focused on medication compliance.

After 28 days, the number of drinks per day and the mean percentage of heavy drinking days (≥ 5 standard drinks/day) were lower in the gabapentin than the placebo

group, approximately 5% versus 20% ($P = .02$). The mean percentage of days abstinent and complete abstinence were higher in the gabapentin than placebo group. The Obsessive Compulsive Drinking Scale (OCDS) assessed drinking-related obsession, automaticity, interference, and consumption at weeks 2 and 4. Improvement was seen in both groups but gabapentin significantly reduced the automaticity of drinking in comparison to placebo. Craving was measured using 5 specific OCDS items. A statistically significant improvement with gabapentin was identified at weeks 2 and 4. Overall, 30% of the placebo and 10% of the gabapentin group dropped out (P value not provided). Adverse drug reactions (ADR) were reported by 43.4% of patients and did not differ between groups.

Brower et al conducted a trial evaluating gabapentin for alcohol dependence and comorbid insomnia.¹⁸ Eligible subjects had to abstain from alcohol for 1 to 2 weeks and meet *DSM-IV* criteria for alcohol dependence and insomnia. Twenty-one patients ranging from 30 to 60 years in age were randomized to receive gabapentin 1500 mg or placebo at bedtime. Patients participated in up to six 30-minute behavioral therapy sessions emphasizing medication compliance.

The primary outcomes were days to the first episode of heavy drinking and improvement in the Sleep Problems Questionnaire (SPQ) at weeks 6 and 12. The secondary outcome was complete abstinence during the 6-week trial and 12-week follow-up period. Heavy drinking was defined as ≥ 4 standard drinks/day for females and ≥ 5 standard drinks/day for males. Blood alcohol level of $>0.08\%$ by breath analysis was also considered a heavy drinking day. During the 6-week trial and 12-week follow-up, fewer gabapentin (30%) than placebo patients (83%) relapsed to heavy drinking. Abstinence during the 6-week trial was infrequent but more common in gabapentin than placebo patients. Insomnia-related SPQ scores significantly improved from baseline but were not different between treatment groups.

Trevisan et al compared gabapentin and valproic acid for alcohol detoxification and relapse prevention in a 2-phase trial.¹⁹ Eligible subjects had a diagnosis of alcohol dependence (*DSM-IV*) and were alcohol abstinent for less than 1 week. Subjects could have other comorbid psychiatric conditions and chemical dependencies such as depression, posttraumatic stress disorder, and cocaine use. Patients were randomized into 3 groups: valproic acid 500 mg 3 times daily, gabapentin 400 mg 3 times daily, or placebo 3 times daily. Phase I consisted of taking identical appearing medications in combination with lorazepam 1 mg every 4 hours as needed based on their alcohol withdrawal symptoms for 5 days. In phase II, subjects continued taking valproic acid, gabapentin, or placebo for the remainder of the 4-week trial. Patients received psychosocial care during weekly visits.

Relapse occurred in 26% of subjects with no significant differences between treatment groups for the time to relapse,

Table I. Summary of Clinical Trials.

Reference, Design	Patients, Mean Age, Sex	Duration	Treatment	Comments	Outcomes	Safety	Strengths/Weaknesses
Furiert et al ¹⁷ (2007), prospective, randomized, double-blind	N = 60, 44 years, 60 males	5 weeks	Week 1: Diazepam 0-30 mg/day and vitamins Weeks 2-5: Gabapentin 300-600 mg/day or placebo	Diazepam was permitted as needed throughout the entire study	Number of drinks per day: 1 gabapentin vs 3 placebo ($P = .02$) Mean heavy drinking days: 5% gabapentin vs 20% placebo ($P = .02$) Mean of days abstinent: 85% gabapentin vs 70% placebo ($P = .008$) Complete abstinence: 20 gabapentin vs 13 placebo (P value not reported) OCDS score: Weeks 2—6 gabapentin vs 9 placebo ($P < .01$); Week 4—5 gabapentin vs 8 placebo ($P < .01$) Relapse to heavy drinking: Week 6—30% gabapentin vs 83% placebo ($P = .03$); Week 12—60% gabapentin vs 100% placebo ($P = .04$) Abstinence: Week 6—3 patients gabapentin vs 1 placebo ($P = .31$) Relapse: Occurred in 26% of patients at an average of 23.6 ± 8 days, no difference between groups ($P > .05$)	43.4% of patients reported ADRs, ADRs did not differ between groups, insomnia was the most common ADR	Study design, multiple standardized assessment tools/single-site, small sample, male only, short treatment duration, race not provided
Brower et al ¹⁸ (2008), prospective, randomized, double-blind	N = 21, 45 years, 11 males	6 week treatment, 6 week follow-up	Gabapentin 1500 mg at nighttime or placebo	Gabapentin and placebo were titrated over a 10-day period as tolerated	Relapse to heavy drinking: Week 6—30% gabapentin vs 83% placebo ($P = .03$); Week 12—60% gabapentin vs 100% placebo ($P = .04$) Abstinence: Week 6—3 patients gabapentin vs 1 placebo ($P = .31$) Relapse: Occurred in 26% of patients at an average of 23.6 ± 8 days, no difference between groups ($P > .05$)	38 ADRs were reported, 18 in placebo vs 20 events in gabapentin; headache, dizziness, somnolence, and nerve of muscle pain were the most common ADRs	Study design, intention-to-treat analysis/single-site, small sample, 33% attrition rate, paid participants, no medication adherence data
Trevisan et al ¹⁹ (2008), prospective, randomized, double-blind	N = 57, 48 years, 57 males	4 weeks	Valproic acid 500 mg TID, or gabapentin 400 mg TID, or placebo TID	Lorazepam 1 mg every 4 hours as needed was available during the initial 5 days	Relapse: Occurred in 26% of patients at an average of 23.6 ± 8 days, no difference between groups ($P > .05$)	100% of patients reported ADRs, ADRs did not differ between groups; depression and anxiety symptoms, poor appetite, diarrhea, restlessness, sleep disturbances, drowsiness, and irritability were the most common ADRs	Study design, documented medication adherence/single site, small sample, short duration, All subjects had low CIWA-Ar scores (mild-moderate withdrawal symptoms)
Anton et al ²⁰ (2009), prospective, randomized, double-blind	N = 60, 47 years, 46 males	41 days	Flumazenil 2 mg IV over 2 days and gabapentin 1200 mg nightly for 39 days or double placebo	Hydroxyzine administered 1 hour prior to active and placebo flumazenil infusions, 7 hydroxyzine 50 mg tablets were provided during the first week for as needed use	OCDS score: Subjects in all groups reported lower scores, with no difference between groups ($P > .05$) Percent days abstinent: No significant difference between groups ($P = .21$). Subanalysis: High pretreatment AW group (CIWA-Ar score ≥ 7)—Higher in flumazenil/gabapentin vs placebo ($P = .0155$); Low pretreatment AW group (CIWA-Ar score < 7)—Lower in flumazenil/gabapentin vs placebo ($P = .0051$) Abstinence: High pretreatment AW group (CIWA-Ar score ≥ 7)—71% flumazenil/gabapentin vs 33% placebo ($P = .14$); Low pretreatment AW group (CIWA-Ar score < 7)—19% flumazenil/gabapentin vs 44% placebo ($P = .08$)	ADRs did not differ between groups, ADRs including muscle twitching, nervousness, memory, and concentration complaints were more frequent among high AW vs low AW patients in both groups	Study design, subanalysis based on AW/single site, small sample, large number of low AW patients (73%)

(continued)

Table 1. (continued)

Reference, Design	Patients, Mean Age, Sex	Duration	Treatment	Comments	Outcomes	Safety	Strengths/Weaknesses
Anton et al ²¹ (2011), prospective, randomized, blinded	N = 150, 45 years, 119 males	16 weeks	50 subjects in each group: naltrexone 50 mg/day and gabapentin 1200 mg/ day, naltrexone 50 mg/day and placebo gabapentin daily, or double placebo daily	Gabapentin was titrated over 5 days, the active or placebo gabapentin administered only for the first 6 weeks	<i>Time to first heavy drinking day:</i> Naltrexone/ gabapentin had a greater delay vs naltrexone/placebo ($P = .04$), naltrexone/ placebo was not different than double placebo <i>Percentage of heavy drinking days:</i> Naltrexone/ placebo had a higher incidence vs double placebo ($P = .02$), no difference between naltrexone/gabapentin and double placebo ($P = .16$) <i>OCDS score:</i> Naltrexone/gabapentin had lower scores than naltrexone/placebo ($P = .04$), also showed nonsignificant lower scores than the double placebo group ($P = .16$) <i>Rates of no heavy drinking:</i> Week 12—22.5% placebo vs 29.6% gabapentin 900 mg vs 44.7% gabapentin 1800 mg ($P = .04$ for linear dose effect)	ADRs were mild/moderate in severity, the placebo group experienced less dizziness ($P = .006$)	Study design, documentation of alcohol withdrawal/ single-site, investigator blinding not reported, individual event rates not provided
Mason et al ²² (2014), prospective, randomized, double-blind	N = 150, 45 years, 85 males	12 weeks, 24 week follow-up	50 subjects were assigned to each group: gabapentin 900 mg/day, gabapentin 1800 mg/ day, or placebo daily	Gabapentin titrated to 900 mg by day 4 and 1800 mg by day 6	<i>Rate of abstinence:</i> Week 12—4.1% placebo vs 11.1% gabapentin 900 mg vs 17% gabapentin 1800 mg ($P = .02$ for linear dose effect) <i>Alcohol Craving Questionnaire score:</i> Week 12—32.9 placebo vs 30.6 gabapentin 900 mg vs 29.5 gabapentin 1800 mg ($P < .001$ for linear dose effect)	No severe side effects reported, ADRs did not differ between groups, >10% experienced fatigue, insomnia, or headache	Study design, longer follow-up period, multiple gabapentin dose studied, no other concurrent medication therapy/single site, 43% dropout rate

Abbreviations: n, number of patients; mg, milligrams; OCDS, Obsessive-Compulsive Drinking Scale; ADRs, adverse drug reactions; T1D, 3 times daily; IV, intravenous; AW, alcohol withdrawal; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol.

number of drinking days, number of heavy drinking days, percentage of drinking days, or abstinence during the trial. Subjects in all groups reported significantly lower measures of craving based on OCDS scores but there were no differences between the individual groups. All participants reported ADRs during the trial with no significant differences between the 3 groups.

Anton et al studied the combination of flumazenil and gabapentin in alcohol-dependent patients (*DSM-IV*), consuming a minimum of 5 drinks/day on 70% of days the month before screening, and abstinent from alcohol ≤ 72 hours before randomization.²⁰ Subjects were stratified based on their baseline CIWA-Ar scores (< 7 or ≥ 7) to flumazenil and gabapentin or double placebo. Subjects also participated in weekly behavioral counseling sessions.

Overall, the percentage of days abstinent (PDA) was not different between the active and placebo groups. However, differences were shown in the flumazenil and gabapentin (F/G) group depending on alcohol withdrawal (AW) status. The high pretreatment AW group (CIWA-Ar score ≥ 7) treated with F/G had significantly higher PDA and abstinence. Conversely, the low pretreatment CIWA-Ar scores had significantly lower PDA and abstinence in the F/G group. Further analysis of secondary outcomes showed similar trends with increased success seen in the high AW group when treated with F/G. ADRs were not significantly different between the treatment groups but were more frequent among subjects in the high AW than the low AW group.

Anton et al conducted a second trial using gabapentin and oral naltrexone.²¹ The trial enrolled patients with alcohol dependence (*DSM-IV*) and consuming a mean of ≥ 5 standard drinks/day for males or ≥ 4 standard drinks/day for females. Patients had to abstain from alcohol 4 days before randomization. Subjects were randomly assigned to naltrexone and gabapentin, naltrexone and placebo gabapentin, or double placebo. The active or placebo naltrexone was administered for 16 weeks while the active or placebo gabapentin was administered only for the first 6 weeks of the trial. Drinking data were provided by 82% to 88% of patients in all 3 groups for the full 16 weeks. Subjects could participate in a maximum of 16 behavioral therapy sessions.

After the first 6 weeks, naltrexone/gabapentin patients had fewer relapses to heavy drinking than the naltrexone/placebo group. There was no difference between the naltrexone/placebo versus the placebo/placebo group. No outcomes or treatment differences were found during the 10 weeks after gabapentin was discontinued. Subjects treated with naltrexone/placebo had a higher percentage of heavy drinking days compared to both the placebo/placebo and naltrexone/gabapentin groups.²¹

Craving was assessed using the OCDS. Significant differences between the 3 groups were only clear during the

first 6 weeks of the trial. The naltrexone/gabapentin group showed lower scores than the naltrexone/placebo group and nonsignificantly lower scores than the placebo/placebo group. Individual scores were not provided. Patients with a history of alcohol withdrawal in the naltrexone/gabapentin group showed less relapse to heavy drinking than the placebo/placebo group. Subjects with no previous alcohol withdrawal episodes showed no significant differences among the 3 groups. All ADRs reported in the trial were of mild to moderate severity with the placebo group experiencing significantly less dizziness.

Mason et al conducted a placebo-controlled trial evaluating 2 gabapentin doses, 900 mg and 1800 mg, in alcohol-dependent patients (*DSM-IV*) with a CIWA-Ar score < 9 who were abstinent from alcohol 3 days prior to randomization.²² Patients received 20 minutes of weekly counseling and were given schedules for local self-help groups.

Only 57% of subjects completed the trial, with dropouts and terminations not differing between the 3 groups. Rate of abstinence during the 12-week trial increased in a dose-dependent manner. The mean number of days of heavy drinking per week significantly decreased in both gabapentin groups compared to placebo. Cravings at week 12 were significantly improved in the gabapentin 1800 mg group versus placebo. No severe side effects were reported and no difference was found in the types of ADRs reported among the different groups. At 24 weeks significant linear gabapentin dose effects were found for complete abstinence, number of drinks per week, and number of heavy drinking days per week. A nonsignificant trend was found for the rate of non-heavy drinking in the gabapentin groups.

Discussion

The current studies describing gabapentin use in alcohol-dependent patients after acute withdrawal are limited to a patient population consisting of primarily Caucasian, middle-aged, males. A total of 498 patients were enrolled in clinical trials ranging from 3 to 12 weeks in treatment duration. Each trial enrolled subjects utilizing *DSM-IV* to diagnosis alcohol dependence and additional criteria based on alcoholism severity, such as CIWA-Ar score, mean number of drinks per day, and time of abstinence. While outcome measures were not identical, most of the trials evaluated abstinence, craving, and amount of heavy drinking. Every trial included some component of concurrent behavioral therapy or counseling. All studies were prospective randomized clinical trials, relatively small in size, and performed at single sites.

Each trial handled the acute withdrawal phase differently, some administered benzodiazepines and others nothing at all, which further confounds the ability to compare outcomes across trials. Gabapentin doses used in the studies ranged from 300 to 1800 mg, with 1200 mg being the most

studied dose. In the only trial that used multiple doses of gabapentin, 900 mg or 1800 mg daily, a positive dose-response relationship was identified.²² Some trials administered additional medications such as valproic acid, naltrexone, and flumazenil, significantly limiting interpretation of potential benefits of gabapentin treatment.¹⁹⁻²¹

The amount of heavy drinking showed no significant difference between gabapentin and placebo in 2 trials.^{19,21} Two trials demonstrated substantial decreases in heavy drinking.^{17,22} Abstinence was measure in all 6 clinical trials. Four studies showed increased abstinence compared to placebo and 2 showed no difference.¹⁷⁻²² The trials that found no difference both included concurrent therapy with either flumazenil/hydroxyzine or valproic acid.^{19,20} Gabapentin plus naltrexone was the only co-administered therapy that had a positive impact by prolonging the time to relapse longer than naltrexone alone.²¹ Trials showing no beneficial effect on heavy drinking or abstinence enrolled patients with lower CIWA-Ar scores and minimal withdrawal symptoms. This group may have a lower potential for gabapentin improvement of abstinence. Subgroup analysis showed subjects with higher baseline CIWA-Ar scores responded better to gabapentin than placebo.^{19,20} In addition to positive effects on drinking outcomes, 3 of the 6 studies showed reductions in cravings.^{17,21,22} The best designed gabapentin trial was conducted by Mason et al, in which they limited pharmacologic intervention to gabapentin at 1 of 2 doses and included the longest treatment and follow-up monitoring. However, the extended follow-up period may have contributed to the trials' higher dropout rate. No serious adverse drug reactions were reported in any of the reviewed trials.

Summary

Gabapentin appears to be a well-tolerated adjunctive therapy for the management of alcohol abstinence. None of the studies reported serious ADRs or safety issues with gabapentin use in combination with alcohol. Available data support gabapentin at 1200 to 1800 mg/day can be administered during or early after the acute withdrawal phase and continued for up to 12 weeks to support alcohol abstinence.

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