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Role of Gabapentin in the Management of Alcohol Withdrawal and Dependence

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Abstract

Objective: To review the literature evaluating gabapentin for alcohol withdrawal and dependence. **Data Sources:** A literature search of MEDLINE (1966 to end of March 2015) and PubMed was performed using the terms *alcohol, gabapentin, withdrawal*, and *dependence*. Additional references were identified from a review of literature citations. **Study Selection and Data Extraction:** English-language prospective studies evaluating gabapentin for alcohol withdrawal and dependence were evaluated. **Data Synthesis:** A total of 10 publications utilizing gabapentin in alcohol withdrawal (n = 5) and alcohol dependence (n = 5) were included in this review. Limited data suggest that gabapentin can provide benefit in managing mild alcohol withdrawal syndrome. There were 5 reported or suspected seizures in the withdrawal studies, suggesting that additional safety data are necessary before gabapentin monotherapy can be routinely considered. Sleep and mood/anxiety-related outcomes were positively influenced by gabapentin, which may result in long-term benefits if continued beyond the withdrawal period for the treatment of alcohol dependence. Studies evaluating gabapentin for alcohol dependence demonstrated dose-dependent benefits for complete abstinence, rates of no heavy drinking, and cravings. Gabapentin used to treat alcohol dependence was well tolerated with no severe adverse reactions reported in the extant literature. **Conclusion:** Gabapentin may have a role in the treatment of mild alcohol withdrawal, but future studies should focus on adequate dosing strategies. Gabapentin should be considered for the treatment of alcohol dependence when barriers prevent the use of traditional agents. Additional studies should be conducted to further validate findings from the research conducted to date, but the current literature is promising for gabapentin in the treatment of alcohol dependence.

Keywords

gabapentin, alcohol, alcohol dependence, alcohol withdrawal, sleep, cravings, anxiety, mood

Introduction

Alcohol-related disorders contribute to significant morbidity and mortality, with the pathological use of alcohol reported as the third leading modifiable cause of death in the United States.[1] With abrupt cessation of alcohol or significant intake reduction, patients physiologically dependent on alcohol can face fatal complications from alcohol withdrawal syndrome (AWS). In the absence of alcohol, after chronic exposure, there is reduced γ-aminobutyric acid (GABA) activity and *N*-methyl-d-aspartate glutamate overactivity.[2] It is this physiological imbalance that results in the clinical signs and symptoms of AWS. The management of AWS can be variable based on the severity and treatment setting (eg, outpatient, psychiatric unit, or critical care unit), but benzodiazepines, which enhance GABA activity, are considered the initial treatment of choice.[3] However, beyond the acute management of AWS, benzodiazepine use in alcohol-dependent persons can pose serious safety concerns because of their addiction potential and possibly fatal interaction with alcohol. For those who desire to maintain abstinence from alcohol, alternative pharmacotherapy strategies play an important role in early and maintained sobriety by deterring use, reducing cravings, and/or improving insomnia, anxiety, and mood disturbances associated with alcohol cessation. Alcohol use disorder (formerly alcohol abuse and alcohol dependence as separate entities), as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), involves the ongoing use of alcohol that causes significant impairment or distress as demonstrated by a minimum 2 of 11 possible

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criteria related to alcohol: (1) large amounts consumed; (2) desire or inability to reduce use; (3) significant time spent obtaining, using, or recovering from use; (4) failing to meet role obligations; (5) continued use despite problems; (6) societal activities reduced/ceased as a result of use; (7) results in physically dangerous situations; (8) cravings exist; (9) continued use despite insight to dangers; (10) tolerance exists; (11) withdrawal occurs.[4] Alcohol use disorder can be characterized as mild, moderate, or severe based on the number of criteria met. Despite the severe consequences of alcohol use disorder, there are limited pharmacological entities approved by the Food and Drug Administration (FDA). These agents include disulfiram, acamprosate, and naltrexone (oral and intramuscular) and are frequently described as underutilized.[5,6] Barriers to the effective use of these agents include decreased access to medications, medical and psychiatric comorbidities, poor medication adherence, and tolerability issues. Further research is under way to establish the safety and efficacy of additional pharmacological agents that reduce cravings and overall alcohol consumption. This includes gabapentin, which has a growing evidence base in support of its use not only in alcohol dependence but also alcohol withdrawal, in both inpatient and outpatient settings.

Gabapentin is FDA approved for a wide variety of indications, including adjunctive treatment of partial seizures, postherpetic neuralgia, and restless leg syndrome (as gabapentin enacarbil).[7] Currently, there is literature to support the use of gabapentin for both alcohol withdrawal and alcohol use disorder (the term alcohol dependence will be used throughout the remainder of the text because the available literature predates *DSM-5*). Use in alcohol withdrawal stems from preclinical trials reporting the benefits of gabapentin related to convulsive and anxiety-related signs and symptoms of AWS.[8] Additionally, gabapentin has been shown to reduce withdrawal excitability in hippocampal slices.[9,10] Despite its name and being structurally related to GABA, it is not metabolized to GABA and does not interact directly with $GABA_A$ or $GABA_B$ receptors.[7,11] Other mechanisms by which gabapentin may enhance GABA activity includes increasing GABA concentrations via interaction with the α2δ subunit of voltage-dependent calcium channels and by direct synthesis.[12] In clinical practice, gabapentin's mild anxiolytic and sedative effects are exploited to target symptoms of AWS and other symptoms of early sobriety, such as insomnia and cravings, both risk factors for relapse.[13,14] With continued use, gabapentin has demonstrated long-term benefits by reducing relapse and return to heavy drinking. This potential for gabapentin to provide benefit for both alcohol withdrawal and dependence makes it an attractive agent to explore for these indications. The following is an evaluation of the extant literature in which gabapentin has been utilized for the management of alcohol withdrawal and dependence.

Literature Search and Study Selection

Numerous studies have been published evaluating gabapentin in the treatment of alcohol withdrawal and dependence. Limited data are available from well-conducted studies to make firm recommendations regarding gabapentin's role among traditional medications used for these indications. To assess the current evidence base of gabapentin in alcohol withdrawal (Table 1) and alcohol dependence (Table 2), a search of MEDLINE (1966 to end of March 2015) and PubMed using the terms *gabapentin, withdrawal, dependence*, and *alcohol* was undertaken. Articles that met all the following criteria were included: (1) prospective studies evaluating outcomes related to alcohol withdrawal or prospective studies evaluating outcomes related to dependence in treatment-seeking individuals, (2) gabapentin utilized as monotherapy or in combination with other agents, and (3) studies published in the English language. The references of the articles obtained were evaluated to screen for additional publications.

In total, our search revealed 8 publications utilizing monotherapy gabapentin in alcohol withdrawal (n = 5) and alcohol dependence (n = 3). Two publications involving gabapentin used in combination with other agents for the management of alcohol dependence were also included. A manual search of reference lists did not identify any studies that met inclusion criteria; 32 other publications were excluded because they were reviews (n = 18), did not involve a primary outcome related to withdrawal or maintenance treatment (n = 6), involved evaluation of dependence in non–treatment-seeking individuals (n = 2), were case reports or series (n = 4), were retrospective in nature (n = 1), or did not include gabapentin treatment (n = 1).

Gabapentin for the Treatment of Alcohol Withdrawal

Bonnet et al[15] conducted a randomized, double-blind, placebo-controlled trial to determine the effect of gabapentin during moderate to severe AWS, defined as a Mainz Alcohol Withdrawal Scale (MAWS) score of ≥4. A total of 29 and 32 individuals were included in the placebo and gabapentin groups, respectively. All participants received either placebo or gabapentin (400 mg every 6 hours) for 72 hours when their MAWS score was ≥4 and breath alcohol concentration (BAC) ≤0.150%. They could all receive clomethiazole, a $GABA_A$ modulator available in Europe, as determined by a scoring system calculated by signs and symptoms of AWS (4-6 points = 192 mg; 7-9 points = 384 mg). The amount of rescue clomethiazole doses in the first 24 hours did not significantly differ between groups (6.1 ± 5.4 vs 6.2 ± 4.7 doses, $P = 0.96$). The reduction in MAWS at 24 hours also did not differ ($P = 0.4$). There were no severe adverse drug

Table 1. Prospective Studies Evaluating Gabapentin for Alcohol Withdrawal.

Characteristics	Bonnet et al (2003)[15]	Bonnet et al (2010)[16]	Myrick et al (2009)[17]	Mariani et al (2006)[18]	Stock et al (2013)[19]
Setting	2 Inpatient psychiatric centers	Inpatient	Outpatient	Inpatient detoxification service	Outpatient
Design/ Intervention	R-DB-PC	OL-O	R-DB	R-OL	R-DB
Participants	• n = 61 • Age 44.3 ± 7.5 years • 71% Male • 13.5 ± 9.2 drinking years • BAC of 0.360% ± 0.163% prior to study entry	• n = 37 • Ages 18 to 70 years • 73% Male • CIWA-Ar score of ≥15	• n = 100 • Age 39.3 ± 1.1 years[a,b] • 77% ± 12% Male[a,b] • 21.5 ± 3.6 years drinking[a,b] • Baseline drinks/d >in 1200 mg GABA group (P = 0.041) • CIWA-Ar ≥10 (baseline not provided in text; appears to range between groups 11-14 in graph provided)	• n = 27 • Age 44.1 years[a,b] • 57.1%-84.6% Male • 24.7 ± 0.4 drinks/d[a,b] • CIWA-Ar ≥10 (baseline CIWA-Ar 19.4 ± 0.8[a,b])	• n = 26 • Age 53.5 ± 3.3 years[a,b] • 96% Male • 27.8 ± 0.4 drinking years[a,b] • Mild-moderate alcohol withdrawal (baseline CIWA-Ar 8.25 ± 0.8[a,b])
Selected exclusion criteria	• Psychiatric condition requiring medication • Abuse of/ Dependence on other substances • Pregnant/Nursing • Relevant medical condition • Contraindication to study drug • Use of disulfiram, BB, antacids • Positive UDS	• Psychiatric/ Medical instability intervention • Pregnancy • DTs • Severe cognitive deficits • Other substance abuse disorders (except nicotine) • Use of: AP, MS/ ADE, AD, BZD, BB, disulfiram, or non-BZD	• Major psychiatric diagnoses • Substance use disorder (except nicotine/cannabis) • Neurological illness or MMSE <26 • Medical instability, ECG or laboratory abnormalities • Concomitant use of: BZD, BB, CCB, AP	• AWS delirium • Additional psychiatric diagnosis (except substance-related) • Allergy to study drug • Pregnancy • AIDS • Medical instability • Opioids (except maintenance methadone) or sedative hypnotics	• Acute medical or psychiatric care required • Seizure disorder • Abuse of/ Dependence on BZD, opioid, barbiturate • Use of drugs known to affect AWS
Intervention	• GABA 400 mg every 6 hours for 72 hours, with taper over the following 3 days	• GABA 800 mg for all; early-responders received additional GABA 2400 over the next 24 hours	• Four groups: (1) GABA 600 mg, (2) GABA 900 mg, (3) GABA 1200 mg, (4) LOR 6 mg	• Group 1: GABA 2400 mg in divided doses on day 1; tapered by 600 mg daily • Group 2: PHB 240 mg in divided doses on day 1; tapered by 60 mg daily	• Group 1: GABA 1200 mg day 1-3, tapered by 300 mg daily • Group 2: CDPX was initiated at 100 mg orally on days 1 through 3, with subsequent tapering of the medication by 25 mg daily
Outcome measures/ Results	• Difference in rescue CLO doses in the first 24 hours; no difference between groups (P = 0.96)	• Evaluation of CIWA-Ar score reductions in early-responders; 17.3 ± 2.6 vs 8.0 ± 3.6 points (P < 0.001)	• CIWA-Ar scores; GABA 1200 mg group scores decreased >than LOR (P = 0.009)	• Proportion of treatment failures (participants requiring ≥3 breakthrough PHB doses); (P = 0.70)	• Alcohol craving; NS • Daytime sleepiness; no difference between the groups during days 1-4 (P = 0.61) but favored GABA on days 5-7 (P = 0.04)

Abbreviations: AD, antidepressant; AP, antipsychotic; AWS, alcohol withdrawal syndrome; BAC, breath alcohol concentration; BB, β-blocker; BZD, benzodiazepine; CCB, calcium channel blocker; CDPX, chlordiazepoxide; CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; CLO, clomethiazole; DB, double blind; DTs, delirium tremens; ECG, electrocardiogram; GABA, gabapentin; LOR, lorazepam; MMSE, Mini Mental Status Exam; MS/ADE, mood stabilizer/antiepileptic; NS, not significant; non-BZD, nonbenzodiazepine hypnotics; O, observational; OL, open label; PC, placebo controlled; PHB, phenobarbital; R, randomized; UDS, urine drug screen.
[a]No difference between groups.
[b]Calculated mean ± SD of all groups.

events (ADEs) and mild ADEs were similar between groups (vertigo, nausea, dizziness, and ataxia). Gabapentin 400 mg every 6 hours did not reduce clomethiazole use, but the authors concluded that the concomitant use of each medication was safe. Limitations include use of an AWS scale not routinely used in clinical practice and use of clomethiazole.

Table 2. Prospective Studies Evaluating Gabapentin Monotherapy for Alcohol Dependence.

Characteristics	Mason et al (2014)[22]	Furieri and Nakamura-Palascios (2007)[21]	Brower et al (2008)[20]
Setting	• Outpatient clinical research facility	• Outpatient drug treatment center	• Outpatient drug treatment center
Design	• R, DB, PC; 12 weeks	• R, DB, PC; 4 weeks	• R, DB, PC; 12 weeks
Participants	• n = 150 • Age 44.3 ± 3.5 years[a,b] • 55.5% Male[a,b] • 43.9 ± 4.8 drinks/wk[a,b] • 14.5 years drinking[a,b] • 67.6% ± 10.1% with prior alcoholism treatment[a,b] • Alcohol abstinence for ≥3 days required for randomization • Diagnosis of alcohol dependence; treatment seeking	• n = 60 • Age 44 years • 100% Male • 27 years drinking • 17 drinks/d • Diagnosis of alcohol dependence • Alcohol abstinence ≤14 days	• n = 21 • Age 45 years[a,b] • 52% Male • 93.1% ± 1.3% of days drinking in the past 42 days[a,b] • 35.8% ± 26.9% of heavy drinking days in the past 42 days[a,b] • Diagnosis of alcohol dependence; desire to abstain • Met study criteria for insomnia • BAC <0.05% prior to consent
Selected exclusion criteria	• CIWA-Ar score > 9 • Abstinence > 1 month • Other substance dependence (not nicotine) or positive UDS • Significant medical/psychiatric condition • Medications that could affect outcomes	• CIWA-Ar score ≥ 15 • MMSE < 20 • Abnormal LFTs, GGT > 800 U/L • History of AWS seizure or DTs • Medication influences cravings, withdrawal, or seizure threshold • Unstable medical/mental illness or intoxication/withdrawal from other substances (not caffeine/nicotine)	• MMSE < 27 • Pregnant, nursing • Concomitant medications that affect sleep, alcohol outcomes, sleep apnea, periodic leg movement disorder, or insomnia caused by a medical/psychiatric condition • Significant psychiatric illness • Impaired renal function • Allergy to gabapentin
Intervention	• Titration of GABA 900 or 1800 mg daily over 4-6 days; tapered at week 11 over 1 week • Weekly visits with 20-minute manual-guided counseling	• GABA 300 mg twice daily • Weekly brief behavioral compliance enhancement treatment	• Titration of GABA over 10 days (maximum of 1500 mg at bedtime); tapered at week 6 over 4 days • Up to 6, 30-minute behavioral therapy sessions guided by manual to enhance adherence
Alcohol measures/ Results	• Dose effect on complete abstinence rates, $P = 0.04$ • Rates of sustained abstinence by group: placebo (4.1%), GABA 900 mg (11.1%), GABA 1800 mg (17%) • Dose effect on rates of no heavy drinking; $P = 0.02$ • Rate of no heavy drinking by group: placebo (22.5%), GABA 900 mg (29.6%), GABA 1800 mg (44.7%) • Decreases in the average number of days of heavy drinking/wk compared with placebo: GABA 1800 group; −2.0 ($P < 0.001$) • Decreased number of drinks consumed per week compared with placebo: GABA 1800 mg group: −6.7 ($P < 0.001$)	• Drinks/d: decreased in the GABA group ($P = 0.02$) • Drinks/drinking day: decreased in the GABA group (NS) • Percentage of heavy drinking days: decreased in the GABA group ($P = 0.02$) • Percentage of days abstinent: was greater for the GABA group ($P = 0.008$)	• Return to heavy drinking: favored GABA group at week 6 ($P = 0.03$) and week 12 ($P = 0.04$) • Time to first heavy drinking day: favored GABA group at week 6 ($P = 0.03$) and week 12 ($P = 0.003$) • Complete abstinence: NS between groups at week 6 or 12 but occurred more frequently in the GABA group • Positive association between improved sleep during the first 6 weeks and drinking outcomes ($P = 0.019$)

Abbreviations: AWS, alcohol withdrawal syndrome; BAC, breath alcohol concentration; CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; DB, double blind; DTs, delirium tremens; GABA, gabapentin; GGT, γ-glutamyl transferase; LFTs, liver function tests; MMSE, Mini Mental Status Exam; NS; not significant; PC, placebo controlled; R, randomized; UDS, urine drug screen.

[a]No difference between groups.

[b]Calculated mean ± SD of all groups.

In a prospective, open-label, observational study, the effects of gabapentin loading were assessed in severe AWS, defined as a Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) score ≥15.[16] Gabapentin 800 mg was given to all enrolled individuals (n = 37) when their BAC became ≤0.2%. In all, 27 patients had significant reductions in CIWA-Ar scores (17.3 ± 2.6 to 8.0 ± 3.6 points, $P < 0.001$) and were categorized by authors as early responders, whereas the remaining patients were categorized as nonresponders. Based on this categorization, early responders received additional gabapentin (3200 mg on day 1, 2400 mg on day 2, 1600 mg on day 3, and reduced further by 400 mg each subsequent day). The nonresponders received usual care with clomethiazole or clonazepam. Both groups had statistically significant reductions in both Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale scores from baseline; however, nonresponders had greater anxiety/depressive complaints ($P < 0.001$). Compared with early responders, nonresponders had more severe AWS at baseline ($P = 0.026$). The authors concluded that gabapentin nonresponse was predicted by severe AWS (CIWA-Ar scores >20) and greater depressive/anxiety symptoms. Although gabapentin was reported as well tolerated, 2 individuals classified as early responders suffered a seizure, and 1 developed worsening AWS, resulting in the need for usual care. In addition to the small sample size, limitations of this study include limited description of CIWA-Ar scores within or between groups and differences between groups in demographic data as well as alcohol-related histories. Although the authors suggested that gabapentin loading is a viable option for moderate AWS, the incidence of seizure or worsening AWS highlights the need for additional safety and efficacy data.

A double-blind, controlled trial conducted in an outpatient setting compared multiple gabapentin dosing strategies with lorazepam for the treatment of acute AWS.[17] A total of 100 individuals were randomized to 1 of 4 groups when they had a BAC ≤0.1% and a CIWA-Ar ≥10 to assess the effects of gabapentin and lorazepam on CIWA-Ar scores. Also assessed was the intervention's effect on drinking abstinence, craving, anxiety, depression, sleepiness, and the ability to perform work. Groups were defined by the medication received daily: 600 mg gabapentin, 900 mg gabapentin, 1200 mg gabapentin, and 6 mg lorazepam. Medication tapers began on day 4 with access to rescue medication (gabapentin groups had access to gabapentin 400 mg on day 1 and 300 mg on days 2 through 4; the lorazepam group had access to lorazepam 4 mg on day 1 and 3 mg on days 2 through 4). On days 5, 7, and 12, there were also posttreatment evaluations. A total of 68 patients completed the study, with no difference in drop-out rate between groups. Despite no difference between groups in the use of rescue medication, the 600-mg gabapentin was halted after 3 significant adverse events occurred (2 unwitnessed seizure-like episodes, 1 episode of syncope). Overall, the authors noted that CIWA-Ar scores were statistically different between the 1200-mg gabapentin and lorazepam groups, favoring the gabapentin group($P = 0.009$); however, this was not true for the the 900-mg group ($P = 0.62$). There was a significant difference between the gabapentin groups favoring the 1200-mg group ($P = 0.019$). Early benefits of gabapentin on cravings and insomnia were seen, but significance was lost during the posttreatment period. The lorazepam group was more likely to return to drinking after intervention discontinuation ($P = 0.009$). The authors concluded that gabapentin 1200 mg was superior to lorazepam in a fixed-dosed schema to reduce alcohol withdrawal symptoms in an outpatient setting. The use of gabapentin as a rescue medication may have contributed to researchers needing to halt evaluation of the 600-mg group because of seizure concerns. Until additional safety and efficacy data are available, it may be prudent for future studies to utilize benzodiazepines as rescue medication. Because of the inclusion criteria, these findings may not translate to individuals needing hospitalization or those with more severe AWS. Additionally, because participants were randomized to 1 of 4 treatment arms, the overall sample size in each group was small.

Mariani et al[18] compared the effects of gabapentin and phenobarbital in mild AWS in a randomized, open-label controlled study (n = 27). All participants received a 4-day detoxification schedule using phenobarbital (60 mg 4 times daily, decreased by 60 mg daily) or gabapentin (2400 mg on day 1, reduced by 600 mg daily). In the event of breakthrough AWS symptoms, all participants could receive 60 mg phenobarbital, as needed. The primary outcome was the proportion of treatment failures, defined as requiring 3 or more as-needed phenobarbital doses. Treatment completion was similar between groups, with 71% of those on gabapentin and 62% of those on phenobarbital completing detoxification ($P = 0.70$). Use of breakthrough phenobarbital did not differ between groups ($P = 0.45$), but the authors noted that those treated with gabapentin requiring as-needed phenobarbital had significantly greater baseline CIWA-Ar scores than those who did not require rescue medication (24 ± 8.1 vs 14.3 ± 2.6; $P = 0.02$). Other daily assessments of symptom severity included mood states, alcohol craving, irritability, anxiety, dysphoria, and sleep disturbance; no differences were detected between the 2 groups in any measure. The sample size may have diminished the ability to detect differences between groups. Another limitation is the inclusion of individuals using cannabis, cocaine, and maintenance methadone. This may have introduced confounders when assessing AWS and treatment response to the pharmacological agent utilized. However, the study suggests that gabapentin may be equivalent to a fixed-dosed phenobarbital regimen for mild or moderate forms of AWS, whereas those with higher baseline CIWA-Ar scores may not be adequately treated with gabapentin monotherapy.

A randomized, double-blind study conducted in an ambulatory setting compared the level of sedation, ataxia, alcohol craving, and withdrawal symptoms when individuals were treated with chlordiazepoxide versus gabapentin.[19] Participants with AWS were randomized to receive a 7-day medication schedule of either gabapentin (n = 17) or chlordiazepoxide (n = 9). Gabapentin 1200 mg was administered for the first 3 days, with 300-mg daily dose reductions thereafter. Chlordiazepoxide was initiated at 100 mg orally on days 1 through 3, and subsequently tapered by 25 mg daily thereafter. Authors reported that there were no significant differences in adjusted follow-up scores measuring alcohol withdrawal symptoms between the 2 groups. Three individuals in the gabapentin group had worsening withdrawal, with 1 reported unwitnessed seizure, and 3 individuals in the chlordiazepoxide arm did not complete the study because of worsening withdrawal (n = 1) or being lost to follow-up (n = 2). Adjusted mean daytime sleepiness did not differ significantly between the groups during days 1 through 4 ($P = 0.61$), but daytime sleepiness scores were significantly lower with gabapentin treatment compared with chlordiazepoxide on days 5 through 7 ($P = 0.04$). Adjusted scores for alcohol craving did not differ significantly between the groups during the early or late stages of treatment. However, there was an observable nonsignificant trend toward diminished alcohol craving in the gabapentin group compared with the chlordiazepoxide group during days 5 through 7. Overall, the study findings provide limited data that gabapentin is comparable to benzodiazepines in the outpatient setting to treat mild to moderate AWS with less sedation. Limitations include a small sample size that required revision of the power analysis and statistical plan following study completion. The small sample size may have obscured the ability to detect a significant difference in withdrawal symptoms or alcohol craving between the 2 groups. There was also an unequal preponderance of individuals randomized to the gabapentin treatment group, which may have affected results.

In summary, there have been several studies evaluating gabapentin monotherapy for AWS. However, gabapentin may not confer benefit for all patients with AWS. Limited evidence suggests that gabapentin may provide most benefit in patients experiencing mild AWS. Myrick et al[17] and Stock et al[19] both showed that gabapentin performed comparatively to benzodiazepines for withdrawal in the ambulatory setting for mild withdrawal. Specifically, Stock et al found that alcohol craving and withdrawal complications were not significantly different between patients treated with chlordiazepoxide and gabapentin. In some cases, gabapentin showed increased advantage over benzodiazepines in reducing daytime sedation and preventing patients' return to alcohol use following medication discontinuation. Gabapentin cannot be recommended for those with severe alcohol withdrawal, history of seizure, or risk of progression to delirium tremens, given the increase in adverse events and need for breakthrough benzodiazepines documented in both inpatient and outpatient studies. The small sample sizes of the studies, methods, and inclusion/exclusion criteria limit the generalizability to patients with significant medical illness and/or psychiatric comorbidity.

Gabapentin for the Treatment of Alcohol Dependence

A randomized, double-blind placebo-controlled trial evaluated the effect of gabapentin treatment on alcohol-dependent individuals, with specific evaluation of cravings and comorbid insomnia.[20] For each individual, the lead-in period lasted a minimum of 7 days and until a CIWA-Ar score was <8 for 7 days. After this first phase, patients who continued to meet the inclusion criteria were then randomized to receive either placebo (n = 11) or gabapentin (n = 10) with a goal dose of 1500 mg daily for 6 weeks, followed by a 6-week posttrial evaluation. Assessments of outcomes were completed at the screening period, baseline, and weeks 1, 2, 3, 4, 6, 7, 9, and 12. The Timeline Followback (TLFB) method, a drinking assessment method to estimate daily drinking, was used to assess drinking quantity and frequency with collateral information obtained at baseline and week 6. The Obsessive Compulsive Drinking Scale was used to assess severity of cravings. During the first 6 weeks, 3 of 10 participants randomized to gabapentin were described as having resumed heavy drinking compared with 9 of 11 who received placebo ($P = 0.03$). Analysis of time to first heavy drinking found a statistically significant difference between groups, favoring the gabapentin treatment group ($P = 0.03$). The same held true in the week-12 analysis of percentage returning to heavy drinking (60% vs 100%, $P = 0.04$). The time to first heavy drinking analysis of all 12 weeks revealed a significant difference between the gabapentin group and the placebo group, again favoring the gabapentin group ($P = 0.003$). Abstinence rates, however, were not different between groups at week 6 ($P = 0.31$). Craving outcomes were not reported, and results from overnight polysomnography did not reveal any clinically meaningful outcomes. However, there was a significant relationship between sleep improvement assessed with the Sleep Problems Questionnaire and positive drinking outcomes during the first 6 weeks for those completing the study ($P = 0.019$). Overall, gabapentin was well tolerated, with only minor events reported, none of which led to treatment discontinuation. Major limitations related to this study include the small sample size and attrition. The numbers lost to follow-up were similar between groups and typical for studies evaluating alcohol dependence. Although non–statistically significant findings should be interpreted cautiously, this study seems to suggest that gabapentin treatment may result in a delay of return to heavy drinking for alcohol-dependent persons.

In a 28-week randomized, double-blind, placebo-controlled trial, gabapentin's effect on alcohol consumption was assessed using the TLFB method. Additionally, the effect gabapentin had on cravings was evaluated.[21] Prior to enrollment, all individuals received a 7-day treatment for potential AWS, with diazepam before the randomization to either placebo (n = 30) or gabapentin 300 mg twice daily (n = 30). Participants in both the placebo group (76.7%) and gabapentin group (53.3%) required initial treatment with diazepam. During the study, diazepam could continue based on CIWA-Ar scores, and there were no statistically significant differences in use between groups. Using the TLFB method, the authors reported that at day 28, the number of drinks per study day decreased in the gabapentin group ($P = 0.02$). Those in the gabapentin group drank fewer drinks weekly as compared with placebo ($P = 0.02$). Additionally, whereas the gabapentin group reported a continued reduction in drinking from baseline at week 3 ($P < 0.01$), the placebo group was found to have an increase in weekly alcohol consumption at week 3 ($P < 0.01$). A significant difference was reported between groups for the mean percentage of heavy drinking days and days abstinent, favoring the gabapentin group: $P = 0.02$ and $P = 0.008$, respectively. In evaluating the 5 items from the Obsessive Compulsive Drinking Scale that correlate to actual craving, there was a significant difference between the placebo and gabapentin groups at both weeks 2 and 4 ($P < 0.01$). Adverse events were reported as mild and related to insomnia or sleepiness; 11 individuals in the placebo group reported initial, episodic, or persistent insomnia versus 9 in the gabapentin group. Limitations of the study include the small sample size of a homogeneous population, use of diazepam prior to and during the treatment phases, and a lack of discussion concerning prohibited medications that may have confounded the results.

A 12-week, randomized, placebo-controlled trial evaluated the effect of gabapentin or placebo on rates of complete alcohol abstinence and no heavy drinking days (4 or more drinks per day for women and 5 or more drinks per day for men).[22] Also assessed were the number of drinks per week and number of heavy drinking days per week. During 12 weekly visits as well as at posttreatment visits (13 and 24 weeks), assessment of alcohol use, cravings, mood, sleep, and medication safety occurred. Those who met criteria for enrollment were randomized to receive either placebo (n = 49), gabapentin 900 mg daily (n = 54), or gabapentin 1800 mg daily (n = 47). Of the 150 individuals, 85 completed the study (mean enrollment length = 9.1 ± 3.8 weeks). Alcohol consumption was assessed via the TLFB method, weekly breathalyzer tests, monthly γ-glutamyl transpeptidase assessment, and collateral information. Gabapentin was found to have a significant linear dose effect on complete abstinence rates ($P = 0.04$) and no days of heavy drinking ($P = 0.02$). Sustained rates of abstinence were greatest with the 180-mg dose of gabapentin at 17%; odds ratio = 4.8 (95% CI = 0.9-35), with a number needed to treat of 8. Rates of sustained abstinence were 11.1% in the 900-mg gabapentin group and 4.1% in the placebo group. Similar effects were reported for rate of no heavy drinking per week: 22.5%, 29.6%, and 44.7% in the placebo, 900-mg gabapentin, and 1800-mg gabapentin groups, respectively. There was a linear dose effect on outcomes of number of drinks per week ($P < 0.001$) and number of heavy drinking days per week ($P < 0.001$) with statistically significant differences between each group and placebo. Using self-reported rating scales, the authors found linear dose effects related to cravings, mood, and sleep, with a statistically significant difference between placebo and the 1800-mg group for these outcomes. At 24 weeks, 65 of the individuals returned for follow-up. There was a dose-dependent response reported for rates of complete abstinence ($P = 0.02$), number of drinks per week ($P = 0.04$), and number of heavy drinking days per week ($P = 0.002$). The rates of no heavy drinking were not statistically significant ($P = 0.06$) at 24 weeks. Five individuals withdrew from the study because of mild adverse events: placebo group, euphoria (n = 1); 900-mg group, headache/fatigue (n = 3); 1800-mg group, fatigue (n = 1). In general, gabapentin was well tolerated, with no significant ADEs reported. Whereas the high drop-out rate is comparable to that in other alcohol dependence studies, this is a limitation that should be considered.

In addition to monotherapy studies, several studies evaluated the use of gabapentin combined with other agents for the management of alcohol dependence. A randomized, placebo-controlled trial assessed gabapentin combined with flumazenil in alcohol-dependent persons.[23] Previous studies have demonstrated that long-term alcohol exposure results in a change of specific receptor subunits, leading to a reduction in benzodiazepine response. Flumazenil, in combination with gabapentin, may reverse this change by stabilizing GABA and glutamate systems and was hypothesized to improve outcomes over traditional methods. A total of 60 alcohol-dependent individuals were randomized to receive a 2-mg bolus of flumazenil for 2 consecutive days, with gabapentin (maximum dose of 1200 mg) provided thereafter for 39 days, or placebo. Results showed that those with high pretreatment AWS treated with combination pharmacotherapy had significantly more percentage days abstinent during treatment ($P = 0.0155$), a larger percentage of participants completely abstinent ($P = 0.03$), and higher percentage days abstinent 14 weeks from the start of treatment ($P = 0.021$) when compared with placebo. Surprisingly, results indicated that those with low pretreatment AWS had significantly more percentage days abstinent while taking placebo ($P = 0.0051$) instead of combined pharmacotherapy.

The same authors examined the efficacy of gabapentin combined with naltrexone during the early drinking cessation phase (first 6 weeks) for alcohol-dependent

individuals.[24] The trial was a randomized, double-blind, placebo-controlled trial, wherein alcohol-dependent persons received either naltrexone plus gabapentin (n = 50), naltrexone plus placebo (n = 50), or double placebo (n = 50). Naltrexone was given up to 50 mg/d for 16 weeks, whereas gabapentin was administered up to a maximum dose of 1200 mg/d. Results suggested that during the first 6 weeks, the naltrexone/gabapentin group had a longer time to relapse than the naltrexone/placebo group ($P = 0.04$) and had significantly fewer drinks per drinking day ($P = 0.01$). Additionally, the combination therapy group reported significantly better sleep than placebo/placebo ($P = 0.02$) or naltrexone/placebo ($P = 0.03$) groups. Combination therapy also proved to be more effective than placebo ($P = 0.03$) in preventing relapse to heavy drinking in persons with a history of alcohol withdrawal. Gabapentin was only given for the first 6 weeks of the study, precluding any ability to draw conclusions regarding long-term use of gabapentin plus naltrexone.

In summary, there have been numerous studies that have evaluated gabapentin monotherapy and in combination with other agents for patients with alcohol dependence. Brower et al[20] were able to demonstrate a significant delay in return to heavy drinking with gabapentin treatment. This was echoed by Furieri and Nakamura-Palacios,[21] who found a significant reduction in the number of drinks weekly by patients receiving gabapentin monotherapy. Gabapentin monotherapy was also shown to reduce alcohol craving in 2 of the reviewed studies.[21,22] Mood and sleep were positively affected by gabapentin at 1800 mg, according to the results of Mason et al.[22] Mason et al were also able to show that gabapentin had a linear dose effect on complete abstinence, with the highest rates of abstinence occurring in patients treated with 1800 mg of gabapentin. Neither of the combination studies accounted for the independent effect of gabapentin alone versus a combination; thus, these studies may only suggest the safety of the combinations versus determining efficacy.

Discussion

Gabapentin has a variety of FDA-approved indications and off-label uses, including management of alcohol withdrawal and dependence.[7] Limited data suggest that gabapentin provides benefit for symptoms associated with AWS and early sobriety. Whereas small studies suggested that gabapentin can be used for AWS, larger studies should be conducted to further evaluate safety and optimal dosing. During 3 of the studies evaluating gabapentin for the management of AWS, there were 5 reported events of alcohol withdrawal-related seizures or seizure-like activity. This may have been a result of inadequate gabapentin doses; however, the possibility that some individuals were at higher risk for seizure (eg, discontinued maintenance benzodiazepine therapy prior to enrollment) should be considered. In contrast to benzodiazepines, gabapentin has low abuse potential, is non–habit forming, and has been shown to not enhance alcohol's depressant effects.[25] These characteristics make gabapentin a safe alternative for acute or even prolonged use. Another safety benefit of gabapentin is that it appears to be nonlethal in overdose, an important consideration because many patients with an alcohol-related disorder have comorbid psychiatric illness.[26,27] Whereas future research is needed to determine optimal dosing, gabapentin can be considered only for those with mild AWS, including outpatient settings where benzodiazepine use cannot be safely monitored. Currently, gabapentin cannot be recommended as monotherapy for those admitted to a critical care unit for AWS management, with severe AWS, at high risk for seizures, with complicated AWS history, or known recent benzodiazepine use given the absence of data in these populations. Additionally, it is likely that gabapentin monotherapy is not a sufficient modality in patients with moderate to severe AWS. However, future research should explore if gabapentin in moderate to severe AWS can safely reduce cumulative benzodiazepine exposure, a current trend in clinical practice.

In alcohol-dependent patients who desire to abstain from drinking, the need for benzodiazepine use during AWS management should not preclude the initiation of gabapentin. In fact, after the acute management of AWS and with benzodiazepine discontinuation, there is often rebound insomnia, anxiety, and cravings that increase the risk of a return to drinking.[20,28] Based on preclinical and clinical data, gabapentin may provide a unique bridge therapy from AWS through early sobriety, where there is a high risk of relapse, to sustained alcohol remission. In the alcohol dependence studiesreviewed, gabapentin was well tolerated, with minimal and self-limiting side effects. Although it cannot be concluded that gabapentin is superior or equivalent to naltrexone, acamprosate, and/or disulfiram because of a lack of head-to-head studies, patients with sleep, anxiety, and/or mood symptoms from protracted abstinence may benefit from gabapentin therapy. Further study is also needed to confirm the use of combination therapy versus gabapentin alone in alcohol dependence. The overall safety profile of gabapentin paired with consistent data demonstrating benefits in alcohol dependence make it a viable option when barriers exist to prescribing FDA-approved agents for alcohol dependence. As demonstrated by Mason et al,[22] benefits occur in a dose-dependent manner, and clinicians who wish to initiate gabapentin for alcohol-dependent patients should consider targeting a total daily dose of 1800 mg. It should be noted that cases of gabapentin-related withdrawal seizure, AWS-like symptoms, and the development of delirium tremens exist in the setting of abrupt gabapentin discontinuation.[29] This is likely only relevant with

long-term use of gabapentin, but all patients should be counseled on medication nonadherence. Gabapentin is not metabolized by the liver, and patients with advanced liver disease would be expected to tolerate gabapentin.[30] However, caution is advised when patients have comorbid kidney disease due to the risk of medication accumulation and subsequent side effects. Further studies are needed to define the role of gabapentin in those with advanced medical illness, which were exclusion criteria in available dependence studies.

Conclusion

The current evidence suggests that gabapentin can be utilized in those with mild AWS. Additional studies are required before defining the role of gabapentin for moderate to severe alcohol withdrawal and in patients with a history of alcohol withdrawal seizures or delirium tremens. Gabapentin initiation during early sobriety may reduce the anxiety, insomnia, and cravings associated with this time period when relapse is most likely to occur. Based on the current literature, gabapentin for the treatment of alcohol dependence shows promise. Future dependence studies should be larger, with more diverse populations, and directly compare gabapentin with the traditional agents that are FDA approved. Identifying specific phenotypes of alcohol withdrawal and dependence that may be more responsive to treatment with gabapentin should also be pursued.

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