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Off-label use of gabapentin for management of alcohol use disorders

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Abstract

Despite multiple studies evaluating various therapeutic agents, few have emerged as superior agents for the management of alcohol use disorders. As a result, off-label agents, including gabapentin, are being utilized more frequently in clinical practice. Gabapentin has gained popularity as one of the more commonly studied off-label agents. Gabapentin's relatively low abuse potential, side effect profile, and limited hepatic metabolism make it an attractive option compared with benzodiazepines and other anticonvulsants. Several randomized, placebo- and active-controlled trials have evaluated off-label use of gabapentin for the treatment of alcohol detoxification and dependence. Study results and interpretation from the more robust available data are summarized within this article.

Keywords: gabapentin, alcohol use disorder, alcohol, detox, detoxification, dependence

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Introduction

Gabapentin is utilized for a variety of disease states that extend beyond its US Food and Drug Administration–approved indications for epilepsy and postherpetic neuralgia.[1] These disease states include neuropathic pain, fibromyalgia, and restless leg syndrome. Growing evidence supports gabapentin as a promising option for the management of alcohol detoxification and dependence.

Although its exact mechanism of action is unknown, it is widely accepted that gabapentin modulates both gamma-aminobutyric acid (GABA) and glutamate tone.[1-4] Modulation of these neurotransmitters is desirable to target the GABA deficit and glutamate excess that are prominent during alcohol withdrawal.[2,3] Several additional characteristics make gabapentin an attractive option for the management of alcohol use disorders. With its relatively low abuse potential, gabapentin use can avoid concerns regarding prescribing controlled substances, such as benzodiazepines, on an outpatient basis. Additionally, gabapentin causes considerably less sedation and psychomotor impairment compared with benzodiazepines,[1-4] which again may be of particular concern in the outpatient setting. Lastly, gabapentin does not undergo any appreciable hepatic metabolism.[1] Patients with alcohol-related hepatic impairment may experience increased adverse effects related to poor metabolism of therapies traditionally used in treatment of alcohol detoxification or dependence.[2-4] These features have led to further study in animals and humans, which have shown promising results.

Alcohol Detoxification

Various studies have evaluated gabapentin's effect on withdrawal symptoms and cravings in the acute alcohol detoxification stage (Table 1).[2,5-8] Two studies specifically evaluated the use of gabapentin for detoxification in the outpatient setting. Myrick and colleagues conducted the largest (n = 68) double-blind, active-controlled, dose comparison trial evaluating gabapentin's impact on withdrawal symptoms in outpatients.[2] The authors found that gabapentin 1200 mg/day, divided in 3 doses, significantly reduced alcohol withdrawal symptoms compared with gabapentin 900 mg/day and lorazepam.

TABLE 1: Studies evaluating gabapentin use for alcohol detoxification management[2,5-7]

Study	Bonnet et al, 2003	Mariani et al, 2006	Myrick et al, 2009	Stock et al, 2013
Study design	Double-blind RCT	Open-label RCT	Double-blind RCT	Double-blind RCT
Population	Inpatient (n = 61) • MAWS ≥ 4 • Significant history of alcohol abuse permitted • No psychiatric comorbidities	Inpatient (n = 27) • CIWA-Ar ≥ 10 • Significant history of alcohol abuse • History of alcohol withdrawal seizures permitted • No psychiatric comorbidities	Outpatient (n = 68) • CIWA-Ar ≥ 10 • Significant history of alcohol abuse • History of alcohol withdrawal seizures permitted • No psychiatric comorbidities	Outpatient (n = 26) • Mild-moderate alcohol withdrawal • Significant history of alcohol abuse • History of alcohol withdrawal seizures permitted • No acutely decompensated, psychiatric comorbidities
Duration	7 days	5 days	14 days	7 days
Intervention	7-day fixed taper: GABA 400 mg QID → TID → BID → daily versus placebo	4-day fixed taper: GABA 1200/600/600 mg → 600 mg TID → BID → daily versus phenobarbital 60 mg QID → TID → BID → 30 mg BID	4-day fixed taper: GABA 400 mg TID → BID versus GABA 300 mg TID → BID versus GABA 200 mg TID → BID versus lorazepam 2 mg TID → BID	7-day fixed taper: GABA 300 mg QID → TID → BID → daily versus chlordiazepoxide 25 mg QID → TID → BID → daily
Outcomes	Primary Amount of clomethiazole required in first 24 hours Secondary Change in MAWS	Primary Proportion of treatment failures Secondary Alcohol cravings Mean CIWA-Ar score	Primary Mean CIWA-Ar score Secondary Alcohol cravings Probability of drinking	Primary Alcohol cravings Secondary Mean CIWA-Ar score
Results	Primary Amount of clomethiazole required in first 24 hours: NS Secondary Change in MAWS: NS	Primary Proportion of treatment failures: NS Secondary Alcohol cravings: NS Mean CIWA-Ar score: NS	Primary Mean CIWA-Ar score: GABA 400 mg TID superior to GABA 300 mg TID and lorazepam Secondary Alcohol cravings: GABA 400 mg TID superior to lorazepam. Similar to GABA 300 mg TID Probability of drinking: similar among groups	Primary Alcohol cravings: NS Secondary Mean CIWA-Ar score: NS
Comments	• Low power possibly led to nonsignificant outcomes	• Rescue phenobarbital doses in gabapentin group may have masked gabapentin effects	• GABA 200 mg TID group discontinued early due to seizures in 2 participants • Superiority of GABA versus lorazepam of questionable clinical significance	• Sample size too small to detect potential difference on CIWA-Ar end point

BID = twice daily dosing; CIWA-Ar = Clinical Institute Withdrawal Assessment for Alcohol Revised; GABA = gabapentin; MAWS = Mainz Alcohol Withdrawal Score; NS = not significant; QID = four times a day dosing; RCT = randomized controlled trial; TID = thrice daily dosing

Despite reaching statistical significance, the authors noted the difference was of minimal clinical significance compared with lorazepam. The higher dose of gabapentin also reduced cravings but did not demonstrate any consistent impact on reduced drinking. Stock et al also compared gabapentin with chlordiazepoxide in the outpatient population but found conflicting results.[5] These authors concluded that gabapentin and chlordiazepoxide produced similar reductions in withdrawal symptoms and cravings; however, the smaller sample size of this study may have contributed to the nonsignificant findings.

Similar results were found in the inpatient setting. Mariani et al compared gabapentin with phenobarbital in 61 inpatients.[6] The authors found no significant difference between the 2 treatments with regards to withdrawal symptoms or cravings although the small sample size might have limited the study's ability to detect significant differences in the measured outcomes. Furthermore, patients in both groups were able to receive additional rescue phenobarbital potentially masking gabapentin's effect on outcomes. Although there was no statistically significant difference between groups, there was a numerical trend toward more rescue phenobarbital use in the gabapentin group that could have potentially reached statistical significance with a larger patient sample. The use of phenobarbital as an active comparator may limit the applicability of the study results as phenobarbital is not frequently utilized to manage patients in acute alcohol withdrawal. Bonnet and colleagues conducted a randomized, double-blind, placebo-controlled trial evaluating the impact of gabapentin on symptom-triggered clomethiazole administration in an inpatient population.[7] Clomethiazole is a sedative hypnotic commonly used in Europe for the treatment of acute alcohol withdrawal.[9] Gabapentin 1600 mg/day, divided in 4 doses, failed to impact the amount of clomethiazole needed by inpatients in acute alcohol withdrawal.[7] The latter study may more closely reflect how gabapentin is used in inpatient populations. Gabapentin is often prescribed to inpatients in conjunction with benzodiazepines administered via the symptom-triggered method. Little evidence exists evaluating this practice, and as demonstrated by the results of the Bonnet et al study, existing evidence does not support it.

Alcohol Dependence

Additional studies have been conducted assessing the impact of gabapentin on drinking-related outcomes in the alcohol-dependence setting (Table 2).[3,4,10] In 2007, Furieri and colleagues conducted a randomized, double-blind, placebo-controlled trial in 60 alcohol-dependent outpatients.[4] The authors found that gabapentin 300 to 600 mg/day reduced the number of drinking days, heavy drinking days, and cravings when compared with placebo. The positive findings were noteworthy considering the relatively low gabapentin doses used. In 2011, Anton et al conducted a randomized, double-blind, active- and placebo-controlled trial using a larger sample size. The study evaluated gabapentin 1200 mg/day plus naltrexone 50 mg/day versus naltrexone 50 mg/day versus placebo.[3] Gabapentin and naltrexone were administered concomitantly for the first 6 weeks and then discontinued. Naltrexone was continued for another 10 weeks. Gabapentin plus naltrexone decreased the percentage of heavy drinking days and number of drinks per day compared to the naltrexone and placebo groups. The difference between groups diminished over time and was no longer statistically significant at 16 weeks. More recently, Mason and colleagues performed a randomized, double-blind, placebo-controlled, dose-comparison study and found gabapentin 1800 mg/day, divided in 3 doses, significantly improved abstinence rates, number of heavy drinking days, and alcohol cravings compared with gabapentin 900 mg/day and placebo.[10] These dose-dependent effects persisted 12 weeks postgabapentin discontinuation. These results directly conflict with the Anton et al study, which found that benefits of gabapentin did not persist after its discontinuation.[3] Differences in study design make it somewhat difficult to compare results from the 2 studies. The dose-dependent effects demonstrated in the study conducted by Mason and colleagues allude to potentially increased benefits when gabapentin is used at higher doses. Similar results were found in the Myrick et al study evaluating gabapentin use for alcohol detoxification management. Although compelling, these results need to be replicated prior to implementation in clinical practice.

Conclusions

Based on available evidence, gabapentin appears to be a viable option for monotherapy in the management of alcohol dependence. Several studies identified positive effects on drinking-related outcomes.[3,4,10] At this time, it is unclear how long beneficial effects may persist. Additionally, the target gabapentin dose is unclear as the doses varied greatly among the studies. Higher doses may be more beneficial, but these results have yet to be replicated. Gabapentin's role in the management of alcohol detoxification has not been fully elucidated. Gabapentin failed to separate from active control in the majority of existing studies.[2,5-7] Small sample sizes may have limited these studies' ability to detect significant findings. Studies comparing gabapentin with placebo may better indicate gabapentin's impact on alcohol withdrawal; however, the ethical considerations of administering

TABLE 2: Studies evaluating gabapentin use for alcohol dependence management[3,4,10]

Study	Anton et al, 2011	Furieri et al, 2007	Mason et al, 2014
Study design	Double-blind RCT	Double-blind RCT	Double-blind RCT
Population	Outpatient (n = 150) • Met DSM-IV criteria for alcohol dependence • No psychiatric comorbidities	Outpatient (n = 60) • Met DSM-IV criteria for alcohol dependence • Consumed average of ≥ 35 drinks per week • No unstable psychiatric comorbidities	Outpatient (n = 150) • Met DSM-IV criteria for alcohol dependence • No psychiatric comorbidities
Duration	16 weeks	4 weeks	12 weeks
Intervention	GABA 300/300/600 + naltrexone 50 mg/day versus naltrexone 50 mg/day versus placebo	GABA 300 to 600 mg/day versus placebo	GABA 600 mg TID versus GABA 300 mg TID versus placebo
Outcomes	Primary Time to first heavy drinking day Percentage heavy drinking days Drinks per drinking day Secondary Alcohol cravings	Primary Drinks per day Drinks per drinking day Percentage heavy drinking days Percentage abstinent days Secondary Alcohol cravings	Primary Rate of abstinence Rate of no heavy drinking days Drinks per week Heavy drinking days per week Secondary Alcohol cravings
Results	Primary[a] Time to first heavy drinking day: GABA + naltrexone superior to naltrexone alone and placebo Percentage heavy drinking days: GABA + naltrexone superior to naltrexone alone. Similar to placebo Drinks per drinking day: GABA + naltrexone superior to naltrexone alone and placebo Secondary Alcohol cravings: NS	Primary Drinks per day: GABA superior to placebo Drinks per drinking day: NS Percentage heavy drinking days: GABA superior to placebo Percentage abstinent days: GABA superior to placebo Secondary Alcohol cravings: GABA superior to placebo	Primary Rate of abstinence: GABA 600 mg TID superior to GABA 300 mg TID and placebo Rate of no heavy drinking days: GABA 600 mg TID superior to GABA 300 mg TID and placebo Drinks per week: GABA 600 mg TID superior to GABA 300 mg TID and placebo Heavy drinking days per week: GABA 600 mg TID superior to GABA 300 mg TID and placebo Secondary Alcohol cravings: GABA 600 mg TID superior to GABA 300 mg TID and placebo
Comments	• GABA given only during first 6 weeks of naltrexone treatment • Positive effects on drinking outcomes did not persist post-GABA discontinuation	• Utilized relatively small doses of gabapentin	• GABA exhibited dose-dependent effects indicating better outcomes at higher dose • Effects on rate of abstinence, drinks per week, and heavy drinking days per week remained significant at 24 weeks

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); GABA = gabapentin; NS = not significant; RCT = randomized controlled trial; TID = thrice daily dosing

[a]Based on measurements at 6 weeks

placebo to patients in active withdrawal likely prevent these studies from being conducted. Larger, active-controlled studies are needed to adequately identify if gabapentin favorably impacts outcomes in the alcohol detoxification setting.

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