Key Words: gabapentin, benzodiazepine, treatment, alcohol withdrawal, inpatient

Impact of Gabapentin Adjunct use with Benzodiazepines for the Treatment of Alcohol Withdrawal in a Psychiatric Hospital

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ABSTRACT ~ ***Introduction:*** *Benzodiazepines are currently the gold standard for treatment of alcohol withdrawal. Gabapentin has growing evidence to support its use in the treatment of alcohol use disorder, however there is limited evidence regarding its role in the treatment of alcohol withdrawal. The purpose of this study was to determine if adjunctive gabapentin reduces the need for benzodiazepine (BZD) administration during alcohol withdrawal.* ***Methods:*** *This was a retrospective single-center cohort study. Patients were included if they were 18–89 years old, had an underlying alcohol use disorder, and were initiated on the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) protocol with or without scheduled gabapentin. They were excluded if they had a BZD use disorder, were on concomitant anti-epileptics, as-needed gabapentin, or BZDs outside the CIWA-Ar protocol.* ***Results:*** *A total of 129 patients met inclusion criteria (n = 63 gabapentin group and 66 non-gabapentin group). There was a significant difference in as-needed BZD requirements, with the gabapentin group requiring a higher number of as-needed BZDs in the initial 72 hours of treatment (gabapentin 6 [IQR 0.5–10] non-gabapentin 2 [IQR 0–4]; p = 0.01) and overall (gabapentin 6 [IQR 0.5–10] vs. non-gabapentin 2 [IQR 0–5.5]; p = 0.01). The gabapentin group also had higher maximum CIWA-Ar scores in the initial 72 hours of treatment, and higher anxiety item scores in the initial 48 hours.* ***Conclusion:*** *Gabapentin was not shown to reduce as-needed BZD requirements in patients with a diagnosis of alcohol use disorder admitted for alcohol withdrawal.* Psychopharmacology Bulletin. *2019;49(1):17–27.*

Introduction

Benzodiazepines have the largest and best evidence in the treatment of alcohol withdrawal and as a result are considered the gold standard for treatment.[1,2]

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However, there are several limitations associated with their use. Not only is it a class of medications with high abuse potential, studies have suggested they may increase alcohol cravings and relapse to alcohol use.[3–5] Additionally, they can cause cognitive impairments and respiratory depression when used in higher doses or in patients with liver impairment.[6–10] While other treatment options have been studied, they lack enough data to support use as monotherapy.[10–15]

Gabapentin is an anticonvulsant with anxiolytic properties shown to have beneficial effects in a multitude of areas pertaining to optimal treatment of alcohol withdrawal, as well as alcohol dependence.[10,12,16,17] It can be used in hepatic impairment, with fewer drug-drug interactions than previously studied anticonvulsants (carbamazepine, oxcarbazepine, valproate, phenytoin, phenobarbital, topiramate).[10,18] Previous outpatient studies have demonstrated gabapentin to be superior to benzodiazepines commonly used in alcohol withdrawal in reducing Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) scores, with a lower probability of relapse and less side-effects.[5,19] Mixed study results also suggest that gabapentin may reduce the need for rescue medication during detoxification.[20,21] It should be noted however, that the majority of these studies have either been done in patients with mild to moderate alcohol withdrawal severity, or in the outpatient setting. Few studies exist in patients with moderate or severe alcohol withdrawal in the inpatient setting, and the ones that do possess several limitations.[22–24]

Ultimately, the pharmacotherapy goals for treating alcohol withdrawal are to use an oral medication that will effectively prevent withdrawal seizures, have a low-incidence of side-effects, have a low potential for abuse and overdose, and ideally help decrease alcohol craving and prevent relapse.[25] Gabapentin achieves most of these, though there is no evidence it is effective at preventing withdrawal seizures. While benzodiazepines do prevent withdrawal-related seizures and delirium tremens, they are habit-forming, have a high potential for abuse, have a higher incidence of side-effects, and may put patients at increased risk of relapse associated with heavier drinking.[3–9]

Gabapentin is an appealing option for the treatment of alcohol withdrawal, especially in alcohol dependent patients who will benefit from its ability to reduce the risk of relapse. However, it has previously been mentioned that gabapentin should not be used for the treatment of severe alcohol withdrawal, and should only be considered in cases of mild-to-moderate severity.[26] Since benzodiazepines possess many treatment risks in alcohol-dependent patients but remain the gold standard of treatment, it has also been mentioned that future research should explore if gabapentin in moderate to severe alcohol withdrawal

syndrome can safely reduce cumulative benzodiazepine exposure, which is reported to be a current clinical trend.[27] This study evaluated whether gabapentin use resulted in reduced benzodiazepine administration during alcohol withdrawal in the inpatient setting.

Materials and Methods

In this retrospective, single-center cohort study, we evaluated patients admitted for alcohol withdrawal and an underlying alcohol use disorder initiated on the CIWA-Ar protocol with or without scheduled gabapentin. The alcohol withdrawal protocol used at this facility possesses three separate detoxification protocols that the physician may choose to initiate; a "lorazepam protocol," a "diazepam protocol," and a "chlordiazepoxide protocol." Each protocol specifies the equivalent dose to be given based on the calculated CIWA-Ar score, with CIWA-Ar scores $\geqslant 9$ requiring benzodiazepine administration (eg. CIWA-Ar score 9–15 give lorazepam 2 mg, CIWA-Ar score > 15 give lorazepam 4 mg). Once CIWA-Ar scores are $\leqslant 8$ for 72 consecutive hours, the protocol is discontinued. While gabapentin is not a part of the admission order set for patients being admitted for alcohol withdrawal, physicians have the option of ordering this separately for off-label treatment of alcohol use disorder. Dosing of gabapentin is left to the discretion of the prescribing physician and does not follow a set protocol. Patients receiving scheduled gabapentin in addition to the CIWA-Ar triggered benzodiazepines were categorized as the "gabapentin" group, and those on the CIWA-Ar protocol alone as "non-gabapentin." The Seton Healthcare Family institutional review board approved the study protocol prior to evaluation of patient data.

Study patients were identified by cross-matching drug utilization reports for lorazepam, diazepam, chlordiazepoxide, and gabapentin with discharge diagnoses of alcohol withdrawal and alcohol use disorder from January 2016 to December 2016. Patients were included if they were between 18 to 89 years old, were initiated on CIWA-Ar protocol, and initiated on gabapentin within 24 hours of admission (for the gabapentin treatment arm). Patients were excluded if they had a benzodiazepine use disorder, were on concomitant anti-epileptics, as-needed gabapentin, or benzodiazepines outside of the CIWA-Ar protocol.

The primary outcome was total benzodiazepine requirements within the initial 72 hours of treatment with the CIWA-Ar protocol. Secondary outcomes were total benzodiazepine requirements over the full course of CIWA-Ar protocol administration, maximum CIWA-Ar score trends over 72 hours, as well as CIWA-Ar anxiety item scores. Safety of gabapentin administration was evaluated by any documented adverse effects related to gabapentin administration.

The number of benzodiazepines administered was reported in lorazepam equivalents where 1 benzodiazepine equivalent is synonymous with 1 mg of lorazepam, 5 mg of diazepam, and 25 mg of chlordiazepoxide.[28] The dose of gabapentin was reported as total daily doses, which were determined after review of the medication administration record. Per our hospital protocol, moderate alcohol withdrawal was defined as having a CIWA-Ar score between 9–14, with severe alcohol withdrawal being a CIWA-Ar score $\geqslant$ 15. Anti-convulsants included any of the following agents: valproic acid, carbamazepine, phenobarbital, phenytoin, topiramate, tiagabine, vigabatrin, lamotrigine. A standard drink was defined as one of the following: twelve ounce beer, eight ounce malt liquor, 1.5 ounce 80-proof, or five ounce of wine.[29]

Categorical data were analyzed via chi-square or Fisher's test. Continuous data were analyzed by using a Shapiro-Wilk test to determine parametric assumptions and a Student *t* test or Wilcoxon rank-sum test to compare parametric and nonparametric means/medians, respectively. Statistical significance was determined based on an a-priori alpha set at 0.05.

Results

Initially 214 patients were identified for inclusion in the study. 85 patients were excluded due to having a benzodiazepine use disorder, being on concomitant valproic acid, or having scheduled benzodiazepine administration outside the CIWA-Ar protocol. Therefore, data were collected on a total of 129 patients who met criteria for inclusion, 63 in the gabapentin group and 66 in the non-gabapentin group.

Baseline demographics and clinical characteristics were similar between groups, except more patients in the gabapentin group had a diagnosis of severe alcohol use disorder and a higher baseline CIWA-Ar score (Table 1). The majority of patients were white, male, and unemployed. The most prevalent comorbid physical illness was hypertension, and the most prevalent comorbid mental disorder was depression. There was no significant difference in the rate of comorbid anxiety disorders. Comorbid substance use was also similar between groups. About a quarter of patients had a reported history of withdrawal related seizures and had received detox treatment at least once in the past. The median duration of abstinence prior to admission was 24 hours, and blood alcohol levels obtained from an outside facility prior to transfer to our detoxification unit were over 200 mg/dL in both groups.

Gabapentin dosing and benzodiazepine requirements are reported in Table 2. Cumulative benzodiazepine requirements during the initial 72 hours of treatment were significantly higher in the gabapentin group

TABLE 1

Baseline Demographics and Clinical Characteristics

	GABAPENTIN (N = 63)	NON-GABAPENTIN (N = 66)	P-VALUE
Age, median (IQR)	50 (41–56)	40 (31–52)	0.26
Male, n (%)	39 (62)	47 (71)	0.26
Ethnicity, n (%)			
White	55 (87)	48 (73)	0.04
African American	3 (5)	7 (11)	0.22
Hispanic	2 (3)	7 (11)	0.10
Other	3 (5)	4 (6)	0.75
Comorbid Substance Use, n (%)			
Stimulant	8 (13)	8 (12)	0.92
Cocaine	6 (10)	9 (14)	0.47
Opiate	3 (5)	5 (8)	0.51
MJ	5 (8)	6 (9)	0.84
Comorbid Physical Illness, n (%)			
Cirrhosis	3 (5)	1 (2)	0.29
Hepatitis	9 (14)	10 (15)	0.89
HTN	23 (37)	14 (21)	0.06
Cardiac	2 (3)	0 (0)	0.15
Comorbid Mental Disorder, n (%)			
MDD	38 (60)	33 (50)	0.69
Anxiety	14 (22)	9 (14)	0.20
Psychosis	4 (6)	5 (8)	0.79
Borderline	5 (8)	2 (3)	0.22
Other Personality	1 (2)	1 (2)	0.98
ETOH level prior to admission (mg/dL), median (IQR)	210 (84–306)	222 (96–222)	0.99
Baseline CIWA-Ar score, median (IQR)	8 (5–13)	5.5 (3–8)	0.01
Abstinence Duration (hrs), median (IQR)	24 (12–24)	24 (24–24)	0.11
History Seizures, n (%)	15 (24)	17 (26)	0.84
History Delirium Tremens, n (%)	9 (14)	5 (8)	0.22
Severe Alcohol Use Disorder, n (%)	61 (97)	56 (85)	0.02
# Drinks Per Day, median (IQR)	12 (8–17)	11 (6–17)	0.12
# Prior Detoxification Treatments, median (IQR)	1 (0.5–3)	1 (0–2)	0.16
Homeless, n (%)	20 (32)	16 (24)	0.34
Unemployed, n (%)	42 (67)	37 (56)	0.26

Abbreviations: IQR, interquartile range; MDD, major depressive disorder; HTN, hypertension; ETOH, alcohol; CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised.

(gabapentin 6 [IQR 0.5–10] non-gabapentin 2 [IQR 0–4]; p = 0.01). Total benzodiazepine requirements during the entire course of CIWA-Ar treatment was also higher in the gabapentin group (gabapentin 6 [IQR 0.5–10] vs. non-gabapentin 2 [IQR 0–5.5]; p = 0.01). Total benzodiazepine requirements remained significantly different when excluding patients with minimal withdrawal symptoms as indicated by a maximum CIWA-Ar score of < 9 on day 1 (gabapentin 8 [IQR 6–12] vs. non-gabapentin 4 [IQR 2–10]; p = 0.01). There was no difference in the proportion of patients requiring as-needed benzodiazepines on Day 1 (gabapentin 63% vs. non-gabapentin 50%; p = 0.13) or Day 3 (gabapentin 38% vs. non-gabapentin 22%), though there was a difference on Day 2 (gabapentin 67% vs. non-gabapentin 36%; p = 0.01).

TABLE 2

Benzodiazepine Requirements

	GABAPENTIN (N = 63)	NON-GABAPENTIN (N = 66)	P-VALUE
Day 1			
Patients requiring as-needed BZDs, n (%)	40 (63)	32 (50)	0.13
BZD Requirements (lorazepam equivalents), median (IQR)	2 (0–4)	0 (0–2)	0.10
Gabapentin Dose (mg), median (IQR)	900 (600–1200)	N/A	N/A
Day 2			
Patients requiring as-needed BZDs, n (%)	42 (67)	23 (36)	0.01
BZD Requirements (lorazepam equivalents), median (IQR)	2 (1–4.75)	0 (0–2)	0.01
Gabapentin Dose (mg), median (IQR)	1050 (900–1800)	N/A	N/A
Day 3			
Patients requiring as-needed BZDs, n (%)	24 (38)	14 (22)	0.07
BZD Requirements (lorazepam equivalents), median (IQR)	0 (1–2)	0 (0–2)	0.09
Gabapentin Dose (mg), median (IQR)	1200 (900–1900)	N/A	N/A
Total BZD Requirements Over Initial 72 hours (lorazepam equivalents), median (IQR)	6 (0.5–10)	2 (0–4)	0.01
Total BZD Requirements[£] (lorazepam equivalents), median (IQR)	6 (0.5–10)	2 (0–5.5)	0.01

Note: [£]Total BZD requirements over entire course of CIWA-Ar protocol administration.
Abbreviations: BZD, benzodiazepine; IQR, interquartile range.

Maximum CIWA-Ar score and anxiety item score achieved within the first 48 hours of treatment was significantly different (Table 3). No difference was found in length of stay (gabapentin 4 [IQR 3–7]; non-gabapentin 4 [IQR 3–6]; p = 0.09), 30 day readmission rates (gabapentin 19% vs. non-gabapentin 18%; p = 0.90), or documented adverse effects.

Discussion

In contrast to our hypothesis, the gabapentin group required significantly more benzodiazepines within the initial 72 hours of treatment and over the total duration of CIWA-Ar administration. There was a statistically significant difference in maximum CIWA-Ar scores achieved, with the higher scores occurring in the gabapentin group rather than the non-gabapentin group. However, the gabapentin group also had a significantly higher baseline CIWA-Ar score prior to benzodiazepine administration. While there was also a significant difference

TABLE 3

CIWA-Ar Score Trends Over Initial 72 Hours of Hospitalization

	GABAPENTIN (N = 63)	NON-GABAPENTIN (N = 66)	P-VALUE
Day 1			
CIWA-Ar Total Score, median (IQR)			
Min	2 (1–5)	1 (0–3)	0.01
Max	12 (9–14)	9 (5–11)	0.01
Mean	7 (5–10)	5 (3–7)	0.01
Anxiety Item Score, median (IQR)			
Min	1 (0–1)	0 (0–1)	0.07
Max	2.7 (1–3)	2.1 (1–3)	0.01
Day 2			
CIWA-Ar Total Score, median (IQR)			
Min	2 (0–3.5)	1 (0–2)	0.14
Max	9 (5–11)	5 (3–9)	0.01
Mean	5 (3–7)	4 (2–5)	0.01
Anxiety Item Score, median (IQR)			
Min	0 (0–1)	0 (0–1)	0.62
Max	2 (2–3)	2 (1–3)	0.02
Day 3			
CIWA-Ar Total Score, median (IQR)			
Min	1 (0–2)	1 (0–3)	0.20
Max	5 (3–10)	4 (2–6)	0.04
Mean	3 (2–5)	3 (2–4)	0.37
Anxiety Item Score, median (IQR)			
Min	0 (0–1)	0 (0–1)	0.24
Max	2 (1–3)	2 (1–3)	0.55

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; IQR, interquartile range.

in the maximum CIWA-Ar anxiety item score on the first two days of treatment, the clinical relevance of this numerically small difference is unknown. This suggests that gabapentin prescribing was not solely driven by baseline anxiety levels. The gabapentin group also had a higher proportion of patients with a diagnosis of severe alcohol use disorder, which may have influenced gabapentin prescribing.

Previous studies investigating gabapentin use for the treatment of alcohol withdrawal possessed heterogenous study designs and exhibited mixed results.[5,19–24] Each study utilized different dosing strategies, used different comparators, and included patients with differing alcohol withdrawal severity. Of the studies conducted in the inpatient setting,[20–24] the only controlled trial in favor of gabapentin used phenobarbital as a comparator, with a sample size of only 27 patients.[22] Bonnet and colleagues first published a case series demonstrating gabapentin having potential for the treatment of moderate-severe alcohol withdrawal.[20] However, following this, a two-center, double-blind, placebo-controlled trial using the same dosing strategy yielded conflicting results with the conclusion that gabapentin is no better than placebo in reducing the need for rescue medication for treatment of alcohol withdrawal.[21] An additional study utilizing a higher dosing strategy in severe alcohol withdrawal patients demonstrated that patients presenting with a higher severity of alcohol withdrawal were less likely to respond to gabapentin treatment.[23]

A recent retrospective cohort study by Leung and colleagues[24] described the use of a gabapentin protocol for the management of alcohol withdrawal in patients predicted to have a high risk for moderate-severe alcohol withdrawal as determined via the Prediction of Alcohol Withdrawal Severity Scale (PAWSS).[30] By day 2 of admission, significantly fewer patients in the gabapentin protocol group had maximum daily CIWA-Ar scores exceeding that required for benzodiazepine administration, suggesting this type of protocol may be benzodiazepine sparing. However, 32 of the 77 patients included in the gabapentin group received benzodiazepines during the initial 48 hours of admission prior to initiation of the gabapentin protocol, and the amount of benzodiazepines received on these days actually exceeded that of the benzodiazepine group (4.7 $\pm$ 5.0 mg vs. 3.8 $\pm$ 6.5 mg on day 1, 10.8 $\pm$ 15.0 mg vs. 5.9 $\pm$ 11 mg on day 2). A significant number of patients in the gabapentin group also received valproate (36.4%), therefore this and the use of benzodiazepines may explain the lack of treatment complications that occurred in this small cohort. Despite these limitations, a formalized order set utilizing a gabapentin protocol for alcohol withdrawal is currently being utilized at the study institution. Our study was proposed in response to similar requests made by psychiatrists from our institution to create a gabapentin protocol

for alcohol withdrawal treatment. However, due to significant limitations of the studies available, no such protocol was developed.

In previous studies investigating the efficacy of gabapentin in the treatment of alcohol withdrawal, a taper of gabapentin starting with daily doses of 1200–2700 mg on day 1 of treatment showed a benefit in reducing withdrawal symptoms.[5,19,22,24] However, prescribing of gabapentin at our facility occurs differently in this population. A gradual titration of gabapentin is performed in order to prepare patients for treatment of their underlying alcohol use disorder (Table 2), rather than a taper off the gabapentin upon resolution of their withdrawal. Therefore, daily doses in the initial 48 hours of treatment were lower than that of previous studies demonstrating treatment success in moderate alcohol withdrawal. It should be noted however that dosing used in previous studies varied substantially, and occurred both in the outpatient and inpatient setting.[5,19,22,24] It is therefore unknown what the ideal dosing strategy would be for studying the efficacy of gabapentin for alcohol withdrawal.

Similar to previous studies, gabapentin was well-tolerated in this study, with no documentation of any adverse effects. There were no reports of seizure occurrence, or development of delirium tremens. Fifty-nine patients (93%) in the gabapentin group were discharged with a prescription for gabapentin for ongoing treatment of their underlying alcohol use disorder.

There were multiple limitations of this study. First and foremost, there appeared to be some degree of selection bias in regards to which patients were prescribed gabapentin, given the gabapentin group had higher baseline CIWA-Ar scores. There was also an association between being of white ethnicity and being prescribed gabapentin, though it is unknown whether these findings are clinically significant given the small number of non-white patients included in the study. When discussing these results with the physicians at our institution, some felt that the presence of anxiety during the initial psychiatric evaluation may have influenced the decision to initiate gabapentin in some patients. While there were small, statistically significant differences in the CIWA-Ar anxiety item score between groups, there was not a significant difference in the number of patients diagnosed with an underlying anxiety disorder. It should be noted that day 1 of treatment is not necessarily indicative of day 1 of detoxification, which is reflected in patients that were documented as having been abstinent for $\geqslant$ 24 hours, but were admitted with blood alcohol concentrations $>$ 200 mg/dL. Furthermore, given the retrospective nature of this study, the accuracy of the documented abstinence duration in the medical record is unknown. Lastly, the majority of patients never achieved CIWA-Ar scores $>$ 15, and several patients did not require

as-needed benzodiazepines during their admission (Table 3). Therefore, while this study was conducted in the inpatient setting, this population is more reflective of those being treated for mild-moderate alcohol withdrawal. This is interesting considering the majority of studies supporting the use of gabapentin for the treatment of alcohol withdrawal symptoms occurred in populations with mild-to-moderate alcohol withdrawal.[5,19,22] However, as mentioned above, dosing of gabapentin in this study may have been sub-therapeutic. As a result, findings from this study are not generalizable to other institutions that may be utilizing higher gabapentin dosing strategies used for the treatment of alcohol withdrawal.

Conclusion

Gabapentin was not shown to reduce as-needed benzodiazepine requirements in patients admitted for alcohol withdrawal. While gabapentin has evidence for the treatment of alcohol use disorder, no conclusion can be made at this time regarding its role in the treatment of alcohol withdrawal in the inpatient setting. Caution is advised in utilizing gabapentin protocols for the treatment of alcohol withdrawal given larger, prospective, fixed-dose studies are still needed to answer this question. ✤

Conflicts of Interest/Funding

The authors have no conflicts of interest to disclose related to financial or personal relationships for the subject matter of this manuscript.

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