mhc
MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Alcohol withdrawal-related outcomes associated with gabapentin use in an inpatient psychiatric facility

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How to cite: Nichols TA, Robert S, Taber DJ, Cluver J. Alcohol withdrawal-related outcomes associated with gabapentin use in an inpatient psychiatric facility. Ment Health Clin [Internet]. 2019;9(1):1-5. DOI: 10.9740/mhc.2019.01.001.

Abstract

Introduction: Limited evidence exists evaluating the impact of gabapentin in conjunction with benzodiazepines for the management of alcohol withdrawal. A review of outcomes associated with combination gabapentin and benzodiazepine therapy may illuminate new therapeutic uses in clinical practice.

Methods: This retrospective study evaluated the impact of gabapentin on as-needed use of benzodiazepines in inpatients being treated for acute alcohol withdrawal. The treatment cohort consisted of patients prescribed gabapentin while on a symptom-triggered alcohol withdrawal protocol. The control cohort consisted of patients on symptom-triggered alcohol withdrawal protocol without concurrent gabapentin use. Secondary objectives included length of hospital stay, duration on alcohol withdrawal protocol, frequency of complicated withdrawal, and use of additionally prescribed as-needed or scheduled benzodiazepines.

Results: The gabapentin cohort was on the alcohol withdrawal protocol for a similar duration, compared with the control cohort (median of 4 [interquartile range: 2,6] days vs 3 [2,4] days, $P=.09$, respectively). Similarly, the gabapentin cohort required a median of 1 [1,2] benzodiazepine dose for alcohol withdrawal symptoms compared with a median of 1 [1,2] dose in the control cohort, $P=.89$. No significant difference was found between cohorts for as-needed and scheduled benzodiazepine use. Length of stay in hospital was similar between groups.

Discussion: These results suggest that gabapentin use, in conjunction with benzodiazepines, impacts neither the time on alcohol withdrawal protocol or the number of benzodiazepine doses required for withdrawal. Larger, prospective studies are needed to detect if gabapentin alters benzodiazepine usage and to better elucidate gabapentin's role in acute alcohol withdrawal.

Keywords: gabapentin, benzodiazepine, alcohol withdrawal, alcohol, ethanol, inpatient, anticonvulsant, detoxification

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Disclosures: The authors have no conflicts of interest to report.

Introduction

Gabapentin is indicated for the management of epilepsy and postherpetic neuralgia by the US Food and Drug Administration.[1] Clinically, gabapentin is used for a variety of other disease states in an off-label manner. Current

literature[2-4] identifies gabapentin for alcohol use disorder management; however, gabapentin's role in alcohol withdrawal requires further study.

Gabapentin's impact on alcohol withdrawal has been primarily evaluated in patients with mild to moderate withdrawal symptoms.[5-8] Both inpatient and outpatient settings were studied. One randomized, double-blind, placebo-controlled trial, conducted by Bonnet and colleagues,[5] examined whether a gabapentin fixed-taper affected the amount of clomethiazole administered using the symptom-triggered method in inpatients. The authors found no difference in clomethiazole administration in patients experiencing moderate withdrawal. Another randomized, controlled trial[6] in 61 inpatients compared a gabapentin fixed-taper and phenobarbital effects on withdrawal symptoms and cravings. This trial also included patients with moderate withdrawal symptoms. No statistically significant difference was found. Notably, supplementary doses of phenobarbital were permitted if patients experienced significant withdrawal symptoms, and patients in the gabapentin group did receive numerically more phenobarbital doses.

In the outpatient setting, a large study sought to compare different gabapentin fixed-dose tapers for managing mild to moderate withdrawal symptoms. With a double-blind, active-control design, Myrick et al[7] found gabapentin 1200 mg/d, divided in 3 doses, statistically superior to both gabapentin 900 mg/d, divided in 3 doses, and lorazepam in reducing alcohol withdrawal symptoms. Of note, the authors did state that the clinical significance between gabapentin and lorazepam's effects may be insignificant. All 3 treatment arms were given rescue doses of their assigned medication (gabapentin or lorazepam) to treat subjective symptoms of alcohol withdrawal. There was no difference between groups in the number of rescue doses needed. Both gabapentin doses reduced cravings during the treatment period but not during the follow-up phase. The probability of drinking was lower with gabapentin than lorazepam starting day 2 of the treatment phase through the early follow-up phase, but the advantage appeared to wane during the follow-up phase. Of note, a third gabapentin treatment arm at a lower dose of 600 mg/d was stopped early, after 9 patients were enrolled, because of 3 serious adverse events, including "seizure-like activity" in 2 patients. More recently, Stock and colleagues[8] compared fixed tapers of gabapentin and chlordiazepoxide in veteran outpatients with mild alcohol withdrawal symptoms. Chlordiazepoxide and gabapentin achieved a similar reduction in cravings and withdrawal symptoms, yet gabapentin produced less sedation.

Currently, the majority of evidence exists comparing gabapentin monotherapy with placebo or as an alternative to benzodiazepines or barbiturates. At some institutions, gabapentin is used for the management of alcohol detoxification in an inpatient setting, in addition to scheduled and/or symptom-triggered benzodiazepines. To the authors' knowledge, the practice of combining gabapentin and benzodiazepines has limited evidence to support its use, and it is unknown whether it affects benzodiazepine use or clinical outcomes. The purpose of this article is to evaluate the impact of adding gabapentin to a symptom-triggered alcohol withdrawal protocol to better illuminate gabapentin's role in acute alcohol withdrawal management.

Methods

Study Design

This was a retrospective cohort study conducted at the Institute of Psychiatry, a stand-alone 100-bed psychiatric hospital within the Medical University of South Carolina, a 700-bed academic medical center. The exposure cohort consisted of patients concomitantly prescribed gabapentin and symptom-triggered benzodiazepines per an alcohol withdrawal protocol between January 1, 2012, and January 1, 2013. To be eligible for inclusion, patients were required to receive at least 1 full day of gabapentin therapy defined as $\geq$3 doses within the first 24 hours on an alcohol withdrawal protocol. The control cohort consisted of patients prescribed symptom-triggered benzodiazepines per an alcohol withdrawal protocol between January 1, 2008, and January 1, 2009. Patients within this cohort could not be concomitantly prescribed gabapentin. Because of increasing use of gabapentin for alcohol detoxification at the investigation site, an earlier time period was selected for the control cohort to achieve an adequate number of patients on an alcohol withdrawal protocol without concomitant gabapentin use. Alcohol withdrawal symptoms were evaluated using the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale. The CIWA-Ar scale is a brief, reliable, 10-item scale that assesses alcohol withdrawal severity that is often used to indicate medication administration using specific score cut-offs.[9] For the purposes of this study, a CIWA-Ar score of 8 triggered benzodiazepine administration. Use of any benzodiazepine was permitted in the study; however, lorazepam was primarily prescribed because of pre-built facility protocols. Diazepam was infrequently substituted for lorazepam on a case-by-case basis. Patients in both cohorts were included regardless of age, sex, renal function, or reason for admission. Patients were excluded if they were in benzodiazepine withdrawal. This study was approved by the Medical University of South Carolina Institutional Review Board.

TABLE 1: Baseline patient characteristics during the study period

Baseline Characteristics	Gabapentin Cohort Median [IQR] or n (%) (n = 40)	Control Cohort Median [IQR] or n (%) (n = 43)	*P* Value
Age, y	42 [37.2,51.7]	46 [32,52]	.92
Sex			.48
Male	25 (63)	30 (70)	
Female	15 (38)	13 (30)	
Race			.42
White	32 (80)	31 (72)	
Black	7 (18)	11 (26)	
Hispanic	0 (0)	1 (2)	
Asian	0 (0)	0 (0)	
Other	1 (3)	0 (0)	
Severity of illness on admission			.75
Extreme	1 (2)	1 (2)	
Major	6 (12)	3 (7)	
Moderate	29 (59)	24 (56)	
Minor	13 (27)	15 (35)	
Complicated withdrawal history	9 (23)	9 (21)	.86
Patients on as-needed benzodiazepines	27 (68)	29 (67)	.99
Patients on scheduled benzodiazepines	30 (75)	15 (35)	<.001

IQR = interquartile range.

Study Outcomes

The primary objective was to assess the impact of gabapentin on the use of as-needed benzodiazepines. Secondary outcomes included duration on alcohol withdrawal protocol, use of additionally prescribed as-needed or scheduled benzodiazepines, length of hospital stay, and frequency of complicated withdrawal. Duration on alcohol withdrawal protocol was determined by the number of days with an active order for the CIWA-Ar protocol. Complicated withdrawal was defined as presence of delirium tremens, seizures, or hallucinations. Baseline demographics and admission severity of illness were collected. Admission severity of illness was provided by an external clinical data management company used by our academic medical center per an algorithm that includes baseline demographics and diagnoses at admission.

Statistical Analysis

Descriptive variables are presented as medians with the interquartile range in brackets. Categorical variables were compared using the Pearson's χ^2 test or Fisher exact test when applicable. All other variables were compared using the Mann-Whitney *U* test. A *P* value less than .05 was considered statistically significant. After identifying a disparity between cohorts in patients taking concomitant scheduled benzodiazepines, a post hoc analysis was performed using ordinal regression analysis. Statistical analysis was performed using SPSS, version 22.0 (IBM, Armonk, NY).

Results

A total of 120 patients were identified for potential inclusion in the analysis based on the pre-specified date ranges. Ultimately, 83 patients were included for analysis. Primary reasons for exclusion included insufficient documentation of either gabapentin use or an alcohol use disorder diagnosis. Both groups had similar baseline demographics; however, there was a statistically significantly greater proportion of patients taking scheduled benzodiazepines in the gabapentin cohort (Table 1). In the gabapentin cohort, the median gabapentin dose was 1200 [1200,1511] mg/d, divided into 3 doses. The median duration of gabapentin therapy was 5 [3.75,7] days.

Effect on Alcohol Withdrawal Protocol

Gabapentin did not significantly impact the time on CIWA-Ar protocol or the number of CIWA-Ar benzodiazepine doses required for withdrawal symptoms. As displayed in Table 2, the gabapentin cohort demonstrated a similar duration on CIWA-Ar protocol as the control cohort, with a median of 4 [2,6] days and 3 [2,4] days (*P* = .09),

TABLE 2: Outcomes associated with gabapentin use in patients on an alcohol withdrawal protocol

Measured Outcomes	Gabapentin Cohort Median [IQR] or n (%) (n = 40)	Control Cohort Median [IQR] or n (%) (n = 43)	*P* Value
Alcohol withdrawal protocol benzodiazepine doses	1 [1,2]	1 [1,2]	.89
Duration on alcohol withdrawal protocol, d	4 [2,6]	3 [2,4]	.09
As-needed benzodiazepine doses	3 [2,6]	3 [1,7]	.83
Duration on as-needed benzodiazepines, d	6 [2,7]	5 [4,6]	.67
Duration on scheduled benzodiazepines, d	4 [3,5]	5 [3,7]	.11
Complicated withdrawal during current hospitalization	5 (13)	2 (5)	.20
Length of stay, d	6 [4,7]	5 [4,7]	.59

IQR = interquartile range.

respectively. Similarly, the gabapentin cohort required a median of 1 [1,2] benzodiazepine dose for alcohol withdrawal symptoms compared with 1 [1,2] dose in the control cohort ($P = .89$).

Effect on Other Benzodiazepine Usage

The gabapentin cohort utilized additionally prescribed as-needed and scheduled benzodiazepines comparably with the control cohort. The 2 groups did not significantly differ in number of doses or duration of benzodiazepines (Table 2).

Effect on Hospitalization

As depicted in Table 2, patients in the gabapentin-cohort experienced a similar length of hospital stay (median of 6 [4,7] days vs 5 [4,7] days in the control group, $P = .59$). During hospitalization, a numerically greater proportion of patients in the gabapentin cohort suffered from signs of complicated withdrawal, 13% (n = 5) compared with 5% (n = 2) in the control cohort, although this difference did not reach statistical significance ($P = .20$). Of those patients taking gabapentin that experienced complicated withdrawal, 8% (n = 3) had delirium tremens and 5% (n = 2) had seizures. In the control group, 2% (n = 1) experienced delirium tremens, 2% (n = 1) experienced alcoholic hallucinosis, and none suffered from seizures.

Effect Modification Analysis

In the gabapentin cohort, 75% of patients were taking concomitant scheduled benzodiazepines compared with 35% in the control cohort ($P < .001$). A post hoc analysis identified an interaction between gabapentin use and concomitant scheduled benzodiazepines for the outcome of duration on CIWA-Ar. To better elucidate the impact of this interaction, cohorts were stratified by scheduled benzodiazepine use. Within the group on scheduled benzodiazepines, the gabapentin cohort was on CIWA-Ar for a duration of 4 [2,7] days versus 3 [2,4] days in patients not taking gabapentin ($P = .13$). Within those not on scheduled benzodiazepines, the gabapentin cohort was on CIWA-Ar for 2.5 [1.75,4] days versus 3 [2,4] days patients not taking gabapentin ($P = .92$). Neither cohort demonstrated any statistically significant difference, though the comparison was not powered to detect such a difference.

Discussion

To help clarify gabapentin's role in acute alcohol withdrawal, this analysis evaluated the impact of gabapentin on outcomes related to withdrawal management in an inpatient setting. Gabapentin failed to impact the number of doses or duration of benzodiazepines needed for alcohol withdrawal symptoms. Additionally, no statistically significant difference was found for as-needed or scheduled benzodiazepine use. Bonnet and colleagues[5] found similar results with gabapentin not affecting use of as-needed clomethiazole for alcohol withdrawal. While the concomitant drug was different, the similar results indicate that gabapentin may not offer any additional benefit regarding withdrawal symptoms or hospitalization, though our small sample size may have impacted the ability to detect a difference in outcomes.

At baseline, a statistically significantly greater proportion of patients were on scheduled benzodiazepines in the gabapentin cohort compared with the control cohort. This baseline difference did not demonstrate a statistically significant impact on the selected outcomes; however, a larger sample size may have detected a difference. No reason was identified for the higher number of patients on concomitant scheduled benzodiazepines in the gabapentin cohort. History of complicated alcohol withdrawal episodes (eg, seizures, alcohol withdrawal delirium, autonomic instability) typically necessitates the use of scheduled benzodiazepines; however, in our study, both groups had similar rates of complicated histories. Of note,

13% of patients taking gabapentin experienced complicated withdrawal symptoms during hospitalization, compared with 5% of patients not taking gabapentin. This difference did not reach statistical significance. To date, gabapentin has not been studied as an adjunctive treatment to benzodiazepines in the management of alcohol withdrawal, or as sole treatment for severe alcohol withdrawal. Additionally, there are insufficient data to determine its impact on mitigation of complicated withdrawal. Reports of possible alcohol withdrawal seizures at low studied doses (600 mg/d) raise concern for a lack of efficacy on this important outcome.[7] A larger study is recommended to adequately evaluate this outcome given the clinical implications.

The retrospective design of this study is subject to several limitations. Data collection relied on the accuracy of prior documentation in the medical record. Several variables were unable to be captured including gabapentin indication, gabapentin adverse effects, and CIWA-Ar scores. It was assumed that patients were taking gabapentin for alcohol detoxification or dependence as they were all concomitantly placed on an alcohol withdrawal protocol. In addition, the retrospective design prevented control for confounding variables such as use of other medications or comorbid medical conditions. Comparison of patients from different time periods may have also introduced potential confounders given some baseline characteristics did differ. While the CIWA-Ar scale demonstrates high inter-rater reliability, it is possible that the subjective nature of the scale allowed for some variability in medication administration based on scoring differences. Lastly, the authors recognize that, though not collected, the total benzodiazepine dosage used may have been an additional outcome of interest.

While its impact on alcohol withdrawal is still emerging, gabapentin's use in alcohol dependence appears clearer. Larger, more robust studies have been performed in this setting. Several randomized, double-blind, placebo-controlled trials[2-4] described gabapentin's ability to increase days of abstinence and to reduce the number of drinking days, heavy drinking days, and cravings. Though the study described within this article found no difference in outcomes for patients using gabapentin, positive findings for alcohol dependence may encourage facilities to initiate gabapentin in preparation for hospital discharge in patients seeking to remain abstinent. Patients' substance use history should be carefully assessed prior to prescribing gabapentin though given that gabapentin misuse, abuse and diversion is on the rise.[10,11] While rates of gabapentin abuse in the general population are low, rates of 15% to 22% have been reported in patients with opioid use disorder.[10] Additionally, diversion rates similar to those of brand name oxycodone have been reported.[11]

Larger, prospective studies are recommended to delineate gabapentin's role in the management of alcohol withdrawal, particularly its impact on benzodiazepine requirements, and to systematically assess its potential for misuse in high-risk patient populations.

References

1. DailyMed [Internet]. Bethesda (MD): National Library of Medicine; c2013 [updated 2014 Mar 3; cited 2018 Jul 1]. LABEL: GABAPENTIN - gabapentin capsule. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0936a88f-b569-49c4-951b-14e8f6273b53
2. Furieri FA, Nakamura-Palacios EM. Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2007;68(11):1691-700. PubMed PMID: 18052562.
3. Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA Intern Med. 2014;174(1):70-7. DOI: 10.1001/jamainternmed.2013.11950. PubMed PMID: 24190578; PubMed Central PMCID: PMC3920987.
4. Anton RF, Myrick H, Wright TM, Latham PK, Baros AM, Waid LR, et al. Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry. 2011;168(7):709-17. DOI: 10.1176/appi.ajp.2011.10101436. PubMed PMID: 21454917; PubMed Central PMCID: PMC3204582.
5. Bonnet U, Banger M, Leweke FM, Specka M, Müller BW, Hashemi T, et al. Treatment of acute alcohol withdrawal with gabapentin: results from a controlled two-center trial. J Clin Psychopharmacol. 2003;23(5):514-9. DOI: 10.1097/01.jcp.0000088905.24613.ad. PubMed PMID: 14520131.
6. Mariani JJ, Rosenthal RN, Tross S, Singh P, Anand OP. A randomized, open-label, controlled trial of gabapentin and phenobarbital in the treatment of alcohol withdrawal. Am J Addict. 2006;15(1):76-84. DOI: 10.1080/10550490500419110. PubMed PMID: 16449096.
7. Myrick H, Malcolm R, Randall PK, Boyle E, Anton RF, Becker HC, et al. A double-blind trial of gabapentin versus lorazepam in the treatment of alcohol withdrawal. Alcohol Clin Exp Res. 2009;33(9):1582-8. DOI: 10.1111/j.1530-0277.2009.00986.x. PubMed PMID: 19485969; PubMed Central PMCID: PMC2769515.
8. Stock CJ, Carpenter L, Ying J, Greene T. Gabapentin versus chlordiazepoxide for outpatient alcohol detoxification treatment. Ann Pharmacother. 2013;47(7-8):961-9. DOI: 10.1345/aph.1R751. PubMed PMID: 23780805.
9. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Addiction. 1989;84(11):1353-7. DOI: 10.1111/j.1360-0443.1989.tb00737.x.
10. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. Drugs. 2017;77(4):403-26. DOI: 10.1007/s40265-017-0700-x. PubMed PMID: 28144823.
11. Buttram ME, Kurtz SP, Dart RC, Margolin ZR. Law enforcement-derived data on gabapentin diversion and misuse, 2002-2015: diversion rates and qualitative research findings. Pharmacoepidemiol Drug Saf. 2017;26(9):1083-6. DOI: 10.1002/pds.4230. PubMed PMID: 28493425.