The Utilization of Gabapentin in Alcohol Withdrawal Management at a Community Hospital

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Abstract

Objectives: Recent literature suggests that gabapentin may be an alternative treatment to standard management of the alcohol withdrawal syndrome (AWS). At All Saints hospital it was anecdotally observed that the addiction medicine physician managing patients on the Medically Managed Detoxification Unit (MMDU) utilized lower doses of benzodiazepines than did physicians on the General Medical Units (GMU). This was accomplished by using scheduled gabapentin as adjunctive therapy. The objective of this retrospective outcome study was to compare benzodiazepine usage between the MMDU and the GMU to describe if there exists a difference in treatment outcomes.

Methods: A retrospective chart review was conducted in order to describe the use of gabapentin in patients, meeting inclusion criteria, being treated for alcohol withdrawal between the study timeframe of January 1st, 2016 thru October 31st, 2016. The primary outcome of interest was the time it took for patients to reach a Clinical Institute Withdrawal Assessment for Alcohol (CIWA-ar) score of 7 or less for 24 hours. Secondary outcome measures included total average benzodiazepine and gabapentin dosage used during hospitalization and the development of severe complications of withdrawal including seizures or delirium.

Results: The gabapentin protocol utilized in the MMDU was similar to that of the GMU (mean time to the primary outcome of interest between both groups was non-significant with a p-value of 0.87). This was despite a statistically significant difference in total benzodiazepine dosage among the two groups with much lower benzodiazepine doses in the MMDU than in the GMU (P-Value < 0.0001).

Conclusions: The results of this study support further investigation into the use of a scheduled gabapentin protocol to decrease utilization of benzodiazepines during management of AWS in hospitalized patients.

The alcohol withdrawal syndrome is a pathophysiological response to long-term alcohol use, that when severe, is most effectively managed in an inpatient medically managed detoxification setting to ensure adequate symptom control and prevent the worst consequences of alcohol withdrawal: seizures, delirium, or death.[1] Proper management of the alcohol withdrawal syndrome can improve engagement in long-term treatment for addiction to alcohol. Complications associated with alcohol withdrawal, however, are estimated to still occur in approximately 500,000 individuals in the United States annually, making it an important clinical concern.[1] It is known that neurons producing gamma-aminobutyric acid (GABA), which is the primary inhibitory neurotransmitter in the central nervous system, play a crucial role in the development of the alcohol withdrawal syndrome via a host of neuronal adaptations that lead to excessive neuronal excitation with the abrupt cessation of alcohol use. While the following explanation is an oversimplification of the neuroadaptive changes that occur, the long-term ingestion of high amounts of alcohol produces desensitization and downregulation of the GABA receptors. This causes a commensurate upregulation of the excitatory neurotransmitter system via an increase in the number of N-Methyl-D-Aspartate receptors that have an increased affinity and sensitivity to glutamate (what is clinically described as "tolerance.")[2] Abrupt discontinuation of alcohol, therefore, produces a sudden disequilibrium in this adaptive system resulting in an abrupt reduction in GABA activity with increased, and immediately unopposed, glutamatergic action that leads to excessive central nervous system excitation that is observed clinically as AWS.

The current "gold standard" treatment for the AWS has been the use of benzodiazepines, a class of substances that produce their clinical effects by sensitizing and stimulating the GABA A subunit of the GABA receptor in a fashion similar to alcohol. As a result, benzodiazepines

TABLE 1. ICD-10 Diagnostic Codes Used to Generate Patient Lists for the Study

F10.20	Alcohol dependence	F10.129	Alcohol abuse with intoxication
F10.21	Alcohol dependence (remission)	F10.229	Alcohol dependence with intoxication
F10.231	Alcohol dependence with withdrawal delirium	F10.221	Alcohol dependence with intoxication delirium
F10.921	Alcohol use with intoxication delirium	F10.220	Alcohol dependence with intoxication
F10.121	Alcohol abuse with delirium	F10.120	Alcohol abuse with intoxication
F10.221	Alcohol dependence with intoxication delirium	F10.239	Alcohol dependence with withdrawal

maintain the neuroadaptive changes produced by long-term use of alcohol and help alleviate the symptoms associated with the AWS.[3] In clinical practice there are several benzodiazepines that are utilized interchangeably, most commonly, chlordiazepoxide, diazepam, and lorazepam. During the past several decades, additional studies have demonstrated that several anticonvulsant medications, including gabapentin, carbamazepine, and valproic acid may also be effective at suppressing the AWS.[4] These medications appear to play a role in inhibitory neurotransmission via direct and indirect effects on the GABA receptor, and perhaps via modulation of the excitatory pathways. Interest in utilizing some of these agents, especially gabapentin, to support treatment during alcohol withdrawal have grown over the past decade. While the primary advantage of utilizing gabapentin now appears to be in outpatient settings for individuals with mild to moderate AWS[5], the literature also demonstrates that the use of gabapentin may be effective in the treatment of seizures associated with AWS[6], a reduction in CIWA scores (in head-to-head trials versus lorazepam)[7], and in the long-term treatment of addiction to alcohol by preventing relapse.[8-10] Gabapentin has been shown to decrease rates of sedation, anxiety, and craving when compared with detoxification using a benzodiazepine.[7] Gabapentin use also increases abstinence rates versus traditional detoxification using only a benzodiazepine. In addition, when used in combination with symptom-triggered benzodiazepine AWS protocols, the anticonvulsants may reduce the overall dosage of benzodiazepines required. While gabapentin is used most often for this purpose (due to its favorable side effect profile), other anticonvulsants including carbamazepine and zonisamide can play an important role in managing the AWS.[4,11,12] In addition to benzodiazepines and anticonvulsants, alpha-2 agonists can play an important role as adjunctive treatment for patients with a significant hyperautonomic response (hypertension, tachycardia, severe diaphoresis) associated with their alcohol withdrawal.[13]

The Ascension Wisconsin All Saints hospital system in Racine, WI has two campuses located within the city of Racine. The Saint Mary's Medical Center facility represents the primary hospital campus and houses most medical specialties including the general medical units, hematology-oncology units, surgical units, intensive care units, cardiovascular services, orthopedic services, an emergency department, and Women's Health (including labor and delivery). The St. Luke's Medical Center facility (approximately 3 miles from the primary hospital campus) houses a Skilled Nursing Facility and the Behavioral Health and Addiction Units (including the state certified MMDU). Both facilities admit and manage patients undergoing alcohol withdrawal symptoms using the same system-wide alcohol withdrawal protocol which permits providers to choose either lorazepam or chlordiazepoxide for symptom-triggered therapy. It was anecdotally noted that higher doses of benzodiazepines were being utilized on the GMU than on the MMDU where scheduled gabapentin was used on a routine basis by the addiction medicine attending. The purpose of this retrospective outcome study was to describe the anecdotal finding that the MMDU was utilizing significantly lower total doses of benzodiazepines (standardized to a milligram dosage equivalent) than the GMU service while not compromising outcomes through augmentation of the alcohol withdrawal protocol by including a scheduled standard dose of gabapentin for all patients admitted for alcohol detoxification. The goal of this study was also to obtain data that will support the standardized application of the scheduled gabapentin protocol utilized by the Addiction Medicine Specialist throughout the Ascension Wisconsin All Saints system (and perhaps throughout Ascension Wisconsin).

Methods

The study utilized a retrospective naturalistic outcome study design to compare differences between alcohol withdrawal management on the GMU

TABLE 2. Baseline Characteristics

	General Medical Unit	Medically Managed Detox Unit	P-value
Age (years)	49.5	48	0.56
Blood alcohol concentration on admit (average)	0.23	0.22	0.71
Seizures pre-admit (# of patients)	9	4	0.02
Initial CIWA-ar score (average)	7.88	6.6	0.17
PAWSS score (average)	5.0	4.3	0.02
Gender	Male: 43, Female: 8	Male:70, Female: 17	

TABLE 3. Summary of Results

	General Medical Unit	Medically Managed Detox Unit	P-value
Against medical advice discharge (# of patients)	4	1	0.06
Length of stay (average days)	2.4	3.1	0.01
Incidence of seizures (# of patients)	0	0	NA
Total chlordiazepoxide equivalent dose used (average)	400 mg	140 mg	<0.0001
Total gabapentin dose used (average)	1565 mg	3890 mg	<0.0001
Average time (hrs) until patients achieved a CIWA-ar score of 7 or less for at least 24 hrs	20.9 hrs	19.8 hrs	0.87
Delirium during treatment (# of patients)	6	2	0.03
Initial CIWA-ar score (average)	7.88	6.6	0.17
Max CIWA-ar score (average)	12	11	0.56

and the addiction medicine service MMDU. The study design was reviewed by the Institutional Review Board (IRB) at Ascension Wisconsin All Saints. The IRB did not feel that the study required formal review because the study did not involve an intervention that would otherwise not have occurred in the routine care of patients at each facility. Also, because the nature of the data being collected did not include any patient-specific identifiers.

Potential patient date for inclusion into the study was identified via an electronic medical record search of The International Classification of Diseases (ICD-10) diagnostic codes (See Table 1) for alcohol use disorders, alcohol abuse, or alcohol withdrawal syndrome for all patients admitted to either the GMU or the MMDS.

Inclusion criteria were as follows: all patients 18 years of age or older with a diagnosis of a moderate to severe alcohol use disorder who were primarily being admitted for the treatment of the (AWS). The data was collected and de-identified following chart review of all patient admitted for alcohol detoxification meeting inclusion criteria from Jan 1, 2016 thru Oct 31, 2016.

Datum for patients was excluded if they met any of the following criteria: 1) A diagnosis of end stage liver disease as defined by a Model for End-stage Liver Disease score of 30 or greater, 2) A diagnosis of end stage renal disease, 3) Post organ transplant patients, 4) Patients admitted for treatment of a primary diagnosis other than an alcohol use disorder yet still needing alcohol withdrawal management, and 5) Patients who were initially admitted directly to the intensive care unit.

The study assessed treatment regimens in a naturalistic setting to compare outcomes between a moderate-intensity gabapentin dose schedule (300 mg capsules four times per day with rapid titration to 600 mg three to four times per day as necessary) in conjunction with an alcohol withdrawal protocol utilizing a symptom-triggered benzodiazepine, versus management with lower dose (or no dose) gabapentin in conjunction with an alcohol withdrawal protocol utilizing symptom-triggered benzodiazepines in order to demonstrate the feasibility and efficacy of using gabapentin to reduce overall benzodiazepine dose without affecting primary outcomes.

The primary endpoints included: total dosage of benzodiazepine used (calculated as a chlordiazepoxide dose equivalent); total dosage of gabapentin used; development of delirium or seizures during the withdrawal process after treatment was initiated; initial and maximum CIWA-ar scores; and the time (in hours) until the patient achieved a CIWA-ar score of 7 or below maintained for 24 hrs. The secondary endpoints included: actual length of stay and rate of "against medical advice" discharges.

With respect to benzodiazepine dose equivalency all benzodiazepines utilized were converted to the equivalent chlordiazepoxide dose. This was accomplished using the following relationship - 100 mg of oral chlordiazepoxide is equivalent to 4 mg of oral lorazepam.[14] Patients with the highest risk for severe withdrawal are typically admitted to the GMU due to availability of monitoring equipment (such as telemetry, which is not available on the MMDU). In order to capture risk of withdrawal severity patients were risk stratified using the Prediction of Alcohol Withdrawal Severity Score (PAWSS), a predictive tool utilized to predict the severity of alcohol withdrawal.[15,16] In this study, the investigators used the PAWSS scoring system in a retrospective manner to stratify patients to account for any difference in the risk of alcohol withdrawal severity among the two sites. Those individuals who scored a 3 or less were deemed to be at "low risk" for severe alcohol withdrawal and those that scored a 4 or greater were deemed to be at "high risk" for severe alcohol withdrawal. The average PAWSS score for each site was calculated and compared.

In addition to risk stratification using the PAWSS scoring tool, the average initial blood alcohol level, patient age, and the average initial CIWA-ar score were compared between the two treatment sites to ensure that there was not a statistically significant difference in these measurements that could lead to confounding of the results. In regards to the statistical analysis the alpha level was set to 0.05 for the determination of significance.

The gabapentin treatment protocol utilized on the MMDU was as follows: gabapentin started at a scheduled dose of 300 mg every 6 hours and titrated rapidly to 600 mg every 6-8 hours for symptom

control over 24 hours in conjunction with symptom-triggered chlordiazepoxide 25-50 mg per hour based on the patients CIWA-ar score. No medication for CIWA-ar score < 8. Chlordiazepoxide 25 mg for a CIWA-ar score 8-12. Chlordiazepoxide 50 mg for a CIWA-ar score > 12. Clonidine 0.1 mg for systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg, with hold parameters for Heart Rate < 55 bpm. If patients were 65 years of age or older, or had renal insufficiency, then the chlordiazepoxide dosing was lowered to 5-10 mg. The gabapentin was adjusted per renal function by the physician on a case-by-case basis.

Results

Using the ICD-10 Codes in Table 1, 66 patients admitted to the GMU group and 94 patients admitted to the MMDU group initially meet the inclusion criteria. However, 15 out of 66 patients in the GMU group and 7 out of 94 patients in the MMDU group were excluded due to having met one or more of the exclusion criteria. Baseline characteristics are shown in Table 2.

Analysis of the data demonstrated that patients admitted to both treatment sites shared some similar characteristics including age (p-value 0.56), initial blood alcohol level (p-value 0.71), and initial CIWA-ar score (p-value 0.17). There was a difference in pre-admit seizures between the two groups with the GMU showing 9 and the MMDU showing 4 (p-value 0.02). The average PAWSS score on admission was also different with a score of 5 for the GMU group and 4.3 for the MMDU group. Both groups scored in the "high risk" category (PAWSS score 4 or greater) for alcohol withdrawal. However, the GMU group (score of 5) had a greater PAWSS score than the MMDU group (score of 4.3) with a p-value of 0.02.

The total chlordiazepoxide equivalent dose used on average was 400 mg in the GMU group and 140 mg in the MMDU group, a difference that was statistically significant with a p-value of < 0.0001. As expected, the total gabapentin dose on average was lower in the GMU group than it was in the MMDU group, a difference that was also statistically significant with a p-value of <0.0001. The difference between average length of time (in hours) until patients achieved a CIWA-ar score of 7 or less that was maintained for 24 hours was statistically non-significant (GMU group 20.9 hours, MMDU group 19.8 hours, p-value 0.87). A total of six patients experienced alcohol withdrawal delirium in the GMU group while only two patients experienced delirium in the MMDU Group, a difference that was statistically significant with a p-value of 0.03. No other medication usage data were collected for this study. A summary of all results are shown in table 3.

Discussion

Alcohol withdrawal is an extremely unpleasant, and potentially life-threatening, experience for patients affected. It is a difficult and challenging acute condition that requires vigilant monitoring and appropriate pharmacologic interventions to prevent complications. The intervention for the MMDU group involved the use of the scheduled gabapentin along with as needed chlordiazepoxide protocol described earlier. The interventions used for the GMU group involved the utilization of lorazepam for symptom control based on physician specified parameters that varied based on the patient's individual needs. The study was carried out to determine if the GMU group was in fact utilizing much higher doses of benzodiazepine than the MMDU group. This was confirmed by the finding that the difference between the two groups in this study was statistically significant favoring much lower average benzodiazepine dose utilization in the MMDU group. The study was also carried out to demonstrate that despite utilizing lower doses of benzodiazepines, the MMDU group's outcome was similar to that of the GMU group. Not only did the study confirm similarity with the addition of scheduled gabapentin, but the rates of delirium were also statistically significantly lower in the MMDU group, a finding that was not expected.

Generalizability of the study results may be limited by the study's design and the presence of confounding variables. These confounding variables largely derive from the different unit locations. Nursing staff on the MMDU are more specialized in handling treatment of AWS compared to those on the GMU and therefore affecting overall benzodiazepine utilization. However due to the fact that both groups use the same scoring tool for assessing CIWA-ar scores, it was felt that this variable was at least somewhat lessened. Due to the absence of any supporting data; however, this remains as a potential confounding variable. Additionally, the patients on the GMU had more medical comorbidities which could have played a role in overall treatment and affected the study results. However, it is not known the extent in which it was affected, which is why good clinical judgment remains important to overall treatment. Despite attempts to address confounding variables the design of the study does not allow one to make clear cause and effect assumptions regarding the use of gabapentin and the decrease in benzodiazepine utilization in the MMDU group. Other factors (including the higher PAWSS score in the GMU group) could have accounted for the difference in benzodiazepine use. While the difference in the PAWSS score between the groups was statistically significant favoring higher risk for severe alcohol withdrawal in the GMU Group, both groups had an average score of over 4 that was felt to be indicative of severe withdrawal risk. Another factor may include greater discrimination in CIWA-ar scoring by the nursing staff on the MMDU versus the GMU. Though this factor seems unlikely given that the average initial CIWA-ar score and the time to CIWA-ar less than 7 are statistically non-significant between the two groups.

Conclusion

Based on the results of this study, it is appropriate to conclude that the use of scheduled gabapentin in conjunction with symptom-triggered chlordiazepoxide may decrease overall benzodiazepine utilization during alcohol withdrawal management without affecting outcomes. This is important because studies have demonstrated that gabapentin may improve rates of abstinence over use of benzodiazepines during detoxification in an outpatient setting. Additionally, further benefits from using gabapentin instead of benzodiazepines is the avoidance of the adverse drug reactions such as respiratory depression, increased fall risk,

and increased confusion/delirium seen with many benzodiazepines. The results of this study do support the utilization of gabapentin for the treatment of more severe alcohol withdrawal. It is yet to be determined whether use of scheduled gabapentin, as is routine on the MMDU, would also lead to improved abstinence rates versus a traditional benzodiazepines-only withdrawal protocol. Future research regarding the use of anticonvulsants, particularly gabapentin, should focus attention on this important question. In addition, this study suggests that the use of gabapentin was associated with a lower risk of delirium which should prompt further investigation into its use.

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