Prevalence and Predictors of Non-Benzodiazepine Use in Patients with Alcohol Withdrawal Syndrome in United States Emergency Departments – a cross-sectional study

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Abstract

Purpose: Benzodiazepines are the mainstay treatment in Alcohol Withdrawal Syndrome (AWS), though they have the potential for abuse and cognitive side effects. Non-benzodiazepines are of growing interest for treatment of AWS; however, the prevalence of non-benzodiazepine use remains unknown. The purpose of this study is to evaluate the prevalence and predictors of non-benzodiazepine use for AWS in the Emergency Department (ED). *Methods:* A cross-sectional, retrospective study utilizing data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) spanning the years 2014-2020 investigated patients presenting to the ED with AWS. The primary outcome of this study is the prevalence of patients with AWS who received non-benzodiazepine treatment during their ED visit. The secondary outcome was the identification of predictor variables for non-benzodiazepine use. A multivariate logistic regression with a backward elimination approach was employed to identify predictor variables. *Results:* A total of 2,300 unweighted ED visits included over the study years. When weighted, this represented over 15.2 million ED visits. Across the study period, 3.1% (95% CI, 1.6-6.1%) of patients received non-benzodiazepines. Positive predictors of non-benzodiazepine use included the year 2020 compared to 2014 (OR 6.32, 95% CI, 1.39-28.73) and comorbid depression (OR 4.13, 95% CI, 1.38-12.36). Negative predictors of non-benzodiazepine use included ages 18-40 compared to ages 41-64 (OR 0.34, 95% CI, 0.13-0.91), nursing home residence compared to private residence (OR 0.02, 95% CI, 0.001-0.80), and the South compared to the Midwest region of the United States (OR 0.19, 95% CI, 0.07- 0.51). *Conclusion:* This study found that non-benzodiazepine use, despite being less common, is becoming more prevalent. Further research is needed to determine the optimal dosing and duration of non-benzodiazepines for AWS. Understanding the factors influencing the prescription patterns of non-benzodiazepines can contribute to informed decision-making and improve the management of AWS.

Keywords: alcohol, withdrawal, non-benzodiazepine, emergency, predictors

Introduction

Alcohol withdrawal syndrome (AWS) is a potentially life-threatening condition that can occur when an individual who has been drinking excessively stops or significantly reduces alcohol consumption[1]. The management of AWS in the emergency department (ED) is crucial, as it presents unique challenges and opportunities for effective treatment. Traditional treatment relies heavily on benzodiazepines, which, while effective, come with a risk of abuse and side effects, particularly in certain populations[2]. In recent years, there has been increasing interest in exploring non-benzodiazepine alternatives that may offer improved side effect profiles and reduce the potential for misuse, including carbamazepine, phenobarbital, valproic acid, and gabapentinoids [3]. Moreover, the 2020 American Society of Addiction Medicine (ASAM) guidelines suggest that non-benzodiazepine medications, while not first-line therapies, may be reasonable alternatives for managing mild to moderate AWS or as an adjunct to benzodiazepine therapy for patients with mild to moderate AWS who do not have risk factors for severe or complicated withdrawal[4].

Despite the established position of benzodiazepines in AWS treatment protocols, recent studies have indicated the potential benefits of non-benzodiazepine medications for reducing AWS symptoms[5-8]. A 2019 study by Levine, et al., examined the use of high-dose gabapentin for the treatment of severe AWS in a retrospective cohort analysis[5]. Gabapentin was administered at a dose of 600mg every 8 hours over the course of the hospital stay for the treatment for AWS. The primary outcome was the reduction in total benzodiazepine administered. The study found that patients receiving high-dose gabapentin had a significant reduction in benzodiazepine administered compared to the control group, with a mean difference of 21mg of lorazepam equivalents ($p = 0.023$)[5]. Additionally, the time to transfer to lower level of care was significantly reduced in the gabapentin group compared to the

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control group (3.6 vs 4.9 days; p = 0.011), highlighting the potential of gabapentin as an effective alternative for managing severe AWS[5].

A meta-analysis compared the efficacy and safety of non-benzodiazepines versus benzodiazepines for treating AWS[9]. Analysis of thirty randomized controlled trials revealed that non-benzodiazepines, particularly gabapentin and carbamazepine, were favored over benzodiazepines such as chlordiazepoxide, lorazepam, and oxazepam in reducing Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA) scores ($p < 0.001$ for gabapentin over chlordiazepoxide and lorazepam; $p = 0.029$ for carbamazepine over oxazepam and lorazepam). Additionally, non-benzodiazepines outperformed benzodiazepines on various AWS assessment scales and in alleviating autonomic, motor, awareness, and psychiatric symptoms. While benzodiazepines were associated with sedation and fatigue, non-benzodiazepines had a higher incidence of seizures ($p = 0.048$). The study concluded that non-benzodiazepines are either superior or equally effective when compared to benzodiazepines in managing AWS, though their adverse event profiles require further investigation[9].

While recent evidence shows benefit of non-benzodiazepine therapy, patients at risk for severe or complicated withdrawal, such as those with a history of delirium tremens, seizures, or those with very high alcohol consumption, may be less likely to receive non-benzodiazepines. ASAM guidelines recommend benzodiazepines and phenobarbital as monotherapy options for these populations due to their proven efficacy in preventing severe complications[4]. Therefore, while non-benzodiazepine medications offer promising alternatives for certain patient groups, their use in ED settings must be carefully considered against the backdrop of individual patient risk factors and the severity of AWS. Despite this, there remains a gap in the widespread adoption of these agents as standard of care in ED settings.

This study aims to explore the prevalence and predictors of non-benzodiazepine prescribing in the treatment of AWS in the ED from 2014 to 2020 to better understand their role in clinical practice. The primary objective is to establish a clearer picture of the real-world application of non-benzodiazepine medications in AWS. By examining prevalence rather than efficacy, this study seeks to elucidate the extent to which evidence and guidelines are reflected in actual prescribing habits, which is essential for addressing the gap between research, policy, and clinical practice. Secondarily, this study seeks to identify predictors for non-benzodiazepine usage and explore the implications of these findings in the context of evolving treatment protocols for AWS.

Methods

This cross-sectional, retrospective, observational study aimed to investigate the frequency of non-benzodiazepine utilization for acute AWS treatment in adults presenting to the ED from 2014 to 2020. The National Hospital Ambulatory Medical Care Survey (NHAMCS) dataset was utilized for this study. NHAMCS is a nationally representative survey conducted by the Centers for Disease Control and Prevention (CDC) that collects data on ED visits in the United States (US)[10]. The survey is administered annually, and data are collected by trained personnel who visit selected hospitals and de-identify information from patients' medical records. The NHAMCS data used in this study is publicly available. This study focused exclusively on patients presenting to the ED, excluding hospitalized patients and outpatient visits. Data collected included patient demographics, past medical history, institutional factors (rural or urban setting, region of the country), provider factors (ED physician, resident, physician consult), and medication class (benzodiazepines, phenobarbital, valproic acid, carbamazepine, and gabapentinoids). Patients were included if they were 18 years or older and if the reason for the visit was related to AWS. Patients were excluded if the reason for the visit was related to seizure disorders, restless leg syndrome, neuropathy, end-stage renal disease, post-herpetic neuralgia, and trigeminal neuralgia.

Variables of interest included demographics (age, sex, race/ethnicity, region, rural/urban status, patient residence, discharge disposition, insurance payor), past medical history (cirrhosis/end-stage liver disease, depression, anxiety/generalized anxiety disorder/post-traumatic stress disorder [PTSD], substance abuse, dementia), healthcare provider types, and medication use. The primary outcome was the prevalence of non-benzodiazepines prescribed in ED visits with an associated diagnosis of AWS. Non-benzodiazepine use was defined as the administration of gabapentin, pregabalin, phenobarbital, carbamazepine, or valproic acid. The secondary objective was to identify predictors of non-benzodiazepine use in this population.

The statistical analysis was conducted utilizing SPSS software (IBM, version 28). All data underwent collection and analysis by study personnel. The NHAMCS dataset includes both unweighted patient records and weighted patient visits. Unweighted ED visits refer to the raw data collected from patient encounters prior to weighting procedures being applied. Weighting is applied to account for the complex survey design and to provide estimates representative of national ED visits. Diagnoses were coded using the International Classification of Diseases, Ninth Revision (ICD-9), and Tenth Revision (ICD-10) codes, depending on visit year. Descriptive statistics were used to summarize patient characteristics, and the prevalence of non-benzodiazepine use was calculated with corresponding 95% confidence intervals. Logistic regression analysis was conducted to identify predictors of non-benzodiazepine use, employing a backward elimination approach to ascertain significant predictors. Variables were selected for inclusion in the regression model based on clinical relevance and were chosen *a priori*. The backward elimination threshold for

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inclusion in the final model was a p-value < 0.2. This study was deemed exempt from full review by the University Hospitals Institutional Review Board, as it involved the retrospective analysis of de-identified, publicly available data obtained from the NHAMCS.

Results

This study included 2,300 unweighted ED visits from the 2014 to 2020 NHAMCS database which represented over 15.2 million weighted ED visits[10]. The study population was composed primarily of male patients (66.2%) of the non-Hispanic white race/ethnicity (65.8%) between the ages of 41 to 64 years of age (45.6%). The study population had several comorbid conditions with substance abuse disorder (38.8%) and depression (24.8%) being the most common chronic conditions identified. The full list of baseline characteristics is described in Table 1.

Across the study years, 3.1% of patients received non-benzodiazepines for the treatment of AWS (95% CI, 1.6-6.1%), representing more than 67,000 ED visits per year on average. Gabapentinoids were the most prevalent, accounting for over 77% of non-benzodiazepine orders, followed by valproic acid derivatives (12.9%), phenobarbital (9.7%), and carbamazepine (3.2%). Non-benzodiazepine prescribing varied year to year with the highest rate of prescribing occurring in 2020 (9.3% of ED visits for AWS).

The following variables were associated with increased prescribing of non-benzodiazepines for AWS: the year 2020 compared to 2014 (OR 6.32, 95% CI, 1.39-28.73), the year 2018 compared to 2014 (OR 4.50, 95% CI, 1.06-19.06), and diagnosis of depression (OR 4.13, 95% CI, 1.38-12.36). The following were associated with decreased prescribing of non-benzodiazepines for AWS during their ED visit: ages 18-40 compared to ages 41-64 (OR 0.34, 95% CI, 0.13-0.91), nursing home residence compared to private residence (OR 0.02, 95% CI, 0.001-0.80), and the South compared to the Midwest region of the US (OR 0.19, 95% CI, 0.07- 0.51) (see Table 2 and Figure 1).

Discussion

The results of this study reveal several significant findings. First, non-benzodiazepines remain a small fraction of the treatments utilized for AWS in the ED, though utilization rates are increasing. Patients were significantly more likely to be prescribed a non-benzodiazepine in the years 2018 and 2020 versus 2014, which may reflect the evolution of clinical guidelines and emerging evidence favoring non-benzodiazepine options over time. Earlier guidelines primarily supported benzodiazepines for AWS, but recent updates have acknowledged the potential benefits of non-benzodiazepine medications, contributing to the increased prescribing observed in recent years[11]. While benzodiazepines are still considered first-line in severe AWS, non-benzodiazepines such as phenobarbital, gabapentinoids, carbamazepine, and valproic acid—as an adjunct to benzodiazepines—are considered reasonable alternatives for those with moderate (CIWA score 10 – 18) and mild (CIWA score < 10) AWS according to the 2020 ASAM guidelines[4]. Secondly, patients with a history of depression were significantly more likely to be prescribed non-benzodiazepines compared to benzodiazepines. This suggests medical teams selected AWS treatment based on the patient's past medical history, as benzodiazepines may worsen symptoms of depression[9, 12].

There was also a decrease in the use of non-benzodiazepines in patients in the 18 – 40-year-old cohort compared to those in the 41 – 64 year-old cohort. This may be expected due to the risks associated with benzodiazepines in older patients, such as mental status changes and increased risk for falls[3, 13]. Lastly, patients in the South region of the US were significantly less likely to receive non-benzodiazepines than those in the Midwest. This may be a result of geographic variations in clinical practice, or it may be related to differences in the prevalence of comorbid chronic diseases which influenced the decision to use non-benzodiazepines in the South compared to the Midwest[14].

The strengths of the current study are the use of real-world data from a nationally representative dataset collected from EDs across the US. The patient population is large and diverse, improving the external validity of the results. To accurately capture the prescribing trends of non-benzodiazepines for AWS, the study excluded patients with conditions for which these agents are routinely utilized, including neuralgias, seizure disorders, and restless leg syndrome, thus ensuring the non-benzodiazepine is likely being utilized for AWS.

Limitations of the study include the retrospective nature of the analysis, reliance on the accuracy of the data collected in the NHAMCS, and potential confounding factors that were not captured in the dataset. Additionally, the study did not evaluate the effectiveness or safety of non-benzodiazepines in treating AWS, but rather focused on the prevalence and predictors of use in the ED setting. Lastly, the NHAMCS data does not contain the doses or duration of the medications used. Therefore, it is not possible to draw conclusions about whether patients were receiving effective doses or when drug therapy was stopped.

Conclusion

Overall, this research highlights the growing interest in alternative medications for the treatment of AWS that have fewer side effects and lower abuse potential compared to traditional benzodiazepines. Non-benzodiazepine medications have emerged as potential candidates for the treatment of AWS with medications such as gabapentin, carbamazepine, phenobarbital, and valproic acid have showing promise in clinical trials, effectively reducing the severity of AWS symptoms and improving treatment outcomes. This broader approach offers more options for tailoring treatment to

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individual patient needs and potentially mitigating the risks associated with benzodiazepine use. Further research is needed to determine the optimal dosing and duration of non-benzodiazepines for AWS, as well as to assess its effectiveness and safety compared to benzodiazepines. Understanding the factors influencing the prescription patterns of non-benzodiazepines can contribute to informed decision-making and improve the management of AWS in the ED setting.

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Table 1: Population Demographics

Characteristic	Unweighted n (%)	Weighted n per year (%)
Patient Characteristics		
Sex		
Female	747 (32.5)	5,148,000 (33.8)
Age (years)		
18-40	856 (37.2)	5,671,000 (37.2)
41-64	1,062 (46.2)	6,942,000 (45.6)
≥65	382 (16.6)	2,617,000 (17.2)
Primary Payor Type		
Medicare	470 (20.4)	3,443,000 (22.6)
Medicaid	811 (35.3)	4,942,000 (32.4)
Private	414 (18.0)	2,761,000 (18.1)
Other or Unknown	605 (26.3)	4,084,000 (26.8)
Race and Ethnicity		
White, Non-Hispanic	1,442 (62.7)	10,020,000 (65.8)
Black, Non-Hispanic	469 (20.4)	2,800,000 (18.4)
Hispanic	284 (12.3)	1,868,000 (12.3)
Other or Multiracial	105 (4.6)	546,000 (3.6)
Comorbidities		
Anxiety	111 (4.8)	747,000 (4.9)
Dementia	214 (9.3)	1,458,000 (9.6)
CKD	46 (2.0)	427,000 (2.8)
Depression	569 (24.7)	3,776,000 (24.8)
Substance Abuse Disorder	907 (39.4)	5,916,000 (38.8)
Total Number of Chronic Conditions		
0	115 (5.0)	742,000 (4.9)
1-2	1,386 (60.3)	9,087,000 (59.7)
3-4	618 (26.9)	4,297,000 (28.2)
≥5	181 (7.9)	1,103,000 (7.2)
Left Against Medical Advice	54 (0.2)	302,000 (2.0)
Admitted to the Hospital	340 (14.8)	2,509,000 (16.5)
Visit Year		
2014	339 (14.7)	1,946,000 (12.8)
2015	318 (13.8)	1,865,000 (12.2)
2016	339 (14.7)	2,302,000 (15.1)
2017	297 (12.9)	2,089,000 (13.7)
2018	339 (14.7)	1,963,000 (12.9)
2019	373 (16.2)	2,484,000 (16.3)
2020	295 (12.8)	2,581,000 (16.9)
Provider Characteristics		
Provider Type		
Attending Physician or Consultant	2084 (90.6)	13,939,000 (91.5)
Resident Physician	51 (2.2)	235,000 (1.5)
Midlevel Provider or Other	165 (7.2)	1,056,000 (6.9)
Region		
Northeast	587 (25.5)	3,532,000 (23.2)
Midwest	591 (25.7)	4,581,000 (30.1)
South	491 (21.3)	3,428,000 (22.5)
West	631 (27.4)	3,688,000 (24.2)
Rural Setting	211 (9.2)	1,758,000 (11.5)

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Table 2: Predictors of non-benzodiazepine utilization for AWS in the ED

Characteristic	Odds Ratio	95% Confidence Interval
Patient Characteristics		
Age (years)		
18-40	0.34	0.13-0.91
41-64	Referent	
≥65	0.45	0.01-1.78
Visit Year		
2014	Referent	
2015	2.12	0.49-9.18
2016	0.79	0.17-3.69
2017	1.37	0.29-6.61
2018	4.50	1.06-19.06
2019	1.78	0.38-8.22
2020	6.32	1.39-28.73
Depression		
No	Referent	
Yes	4.13	1.38-12.36
Patient Residence		
Private Home	Referent	
Nursing Home	0.24	0.001-0.80
Homeless or Shelter	1.09	0.47-2.49
Other	1.74	0.49-6.10
Provider Characteristics		
Region		
Midwest	Referent	
Northeast	0.88	0.32-2.40
South	0.19	0.07-0.51
West	0.58	0.19-1.75
Rural Setting		
No	Referent	
Yes	2.42	0.83-7.04

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Figure 1: Odds Ratios for Predictors of Non-benzodiazepine Use in Alcohol Withdrawal Syndrome (AWS) in the Emergency Department (ED)