

The Use of Anticonvulsant Adjuncts to Treat Alcohol Withdrawal Syndrome in Older Adults



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ABSTRACT

Background

We evaluated the prescribing practices of anticonvulsant (AC) adjuncts to benzodiazepines in managing Alcohol Withdrawal Syndrome (AWS). We also examined the prescription of relapse prevention agents for Alcohol Use Disorder (AUD), and adverse events related to AWS treatment.

Methods

Records were reviewed retrospectively pertaining to medically ill adults aged 60 and above with AWS and admitted to a medicine or hospitalist unit of a Canadian centre between June 2013 and June 2018. Duration and dosing of benzodiazepine, dosing and type of AC and AUD agent, and adverse events were collected. A multivariable regression model was employed.

Results

83 encounters were included in the study and 28 were prescribed an AC. The amount and duration of benzodiazepine administered were not statistically different between the benzodiazepine only and the AC adjunct groups, once severe AWS complications were accounted for. Five new prescriptions of traditional AUD agents were provided on discharge. No AC-associated adverse events occurred.

Conclusions

AC adjuncts for AWS did not decrease the amount of benzodiazepine administered nor shorten the duration of treatment. Their routine use is not supported by our findings. Our study highlights a missed opportunity for AUD agents to be prescribed during hospitalization.

Key words: geriatric, alcohol, withdrawal, benzodiazepines, anticonvulsant, older adult

INTRODUCTION

Excessive alcohol consumption is an underlying factor for a myriad of health complications including cancer, cognitive impairment, and psychiatric comorbidity.⁽¹⁻³⁾ The National Health Survey in 2012 found 50% of men and 39% of women endorsed daily alcohol consumption.⁽⁴⁾ It is estimated that 1–3% of community-dwelling adults over the age of 60 meet the criteria for alcohol use disorder (AUD), while the estimate increases up to 30% in those hospitalized.^(3,5) Chronic alcohol exposure leads to down-regulation of inhibitory gamma-aminobutyric acid type A (GABA-A) receptors and up-regulation of excitatory glutamate in the N-methyl-D aspartate (NMDA) receptors.⁽⁶⁾ This contributes to alcohol withdrawal syndrome (AWS) developing within 6 to 24 hours after abrupt alcohol cessation.^(6,7) Symptoms include tremor, diaphoresis, anxiety, nausea, or insomnia, while severe complications include hallucinations, seizures, delirium tremens, and death.⁽⁸⁾ Adults over the age of 60 are at increased risk for these severe complications due to medical comorbidities, cognitive deficits, and concurrent pharmacotherapies.⁽⁵⁾ Patients with repeated episodes of AWS are at risk for increased neuronal sensitivity known as the kindling effect, which leads to more severe subsequent episodes with risk of complications.⁽⁹⁾

Benzodiazepines remain the gold standard pharmacotherapy for AWS as they reduce symptoms and are neuroprotective against seizures and delirium tremens.⁽⁷⁾ This class of medication is not without its potential adverse effects in the hospitalized elderly, such as oversedation, respiratory depression, delirium, and falls.^(10,11) In light of this, the use of adjunctive anticonvulsants (ACs) to manage AWS has been investigated. ACs enhance GABAergic transmission, provide anti-kindling effects, possibly provide seizure protection, and may be continued as treatment for AUD.^(8,10,11) While there is limited evidence to support AC monotherapy in the inpatient setting for moderate-to-severe AWS,^(12,13) adjunctive therapy with carbamazepine, gabapentin, or divalproex has shown benefits.^(10,11,13)

For ACs, double-blind studies suggest carbamazepine may be as effective as lorazepam for symptom management; however, it has significant gastrointestinal and neurotoxic side effects.^(9,13,14) A randomized controlled trial (RCT) comparing carbamazepine and lorazepam in the outpatient setting found both to be effective, but carbamazepine also significantly reduced drinking in the post-treatment period.⁽¹⁵⁾ Gabapentin was found to be helpful in the outpatient setting for mild-to-moderate AWS,^(16,17) but it has not consistently demonstrated effectiveness in severe AWS or in inpatient settings.⁽¹⁷⁻¹⁹⁾ Relatively high doses of gabapentin (1200–3200 mg/day) may be required to see a positive effect in non-elderly patients, with low doses unlikely to provide sufficient anti-seizure protection.^(17,19) Lower doses of gabapentin were found to be helpful in mild AWS symptoms, but not for more severe symptomatology.⁽²⁰⁾ A recent meta-analysis found moderate evidence to support gabapentin's use in both AWS and the reduction of cravings in dependence; however, limitations include a small number of studies with modest sample sizes and variable dosing regimens.⁽²¹⁾ Gabapentin is generally well tolerated, considered safer due to few adverse events, has fewer drug–drug interactions than other ACs (e.g., carbamazepine), and can be used in those with hepatic impairment.⁽¹⁹⁾ Small double-blind, placebo-controlled RCTs using divalproex for AWS have shown mixed results, with one RCT showing benefit in decreasing AWS symptoms,⁽²²⁾ while the other found no difference over the placebo.⁽²³⁾ A systematic review found that there was insufficient evidence to support the use of valproic acid for prevention and treatment of AWS.⁽²⁴⁾

Inpatient management on acute medical units is often focused on the patient's acute withdrawal symptoms. It is unclear if attention is given to the initiation of longer-term treatment of the underlying alcohol use disorder (AUD) with evidence-based agents such as disulfiram, naltrexone, and acamprostate, with the relapse prevention goal of reduction or cessation of alcohol use.⁽⁵⁾ There is limited research to guide clinicians on the use, safety, and efficacy of these agents in hospitalized geriatric populations.

The objectives of this study were to evaluate the prescribing practices of adjunctive ACs in AWS and the use of agents for AUD in hospitalized adults aged 60 years old or over.

METHODS

This study was a retrospective chart review of medically ill patients identified with probable AUD and admitted for concurrent management of their AWS with the centre's two CIWA-Ar pre-printed order sets between June 2013 and June 2018: one for age ≤ 69 and the other for age ≥ 70 .^(25,26) They include the Clinical Institute Withdrawal Assessment-Alcohol revised (CIWA-Ar) scale, a validated 10-item scale that guides symptom-triggered benzodiazepine administration.⁽²⁷⁾ The age-based division is largely due to our hospital having dedicated Acute Care for the Elderly units, which are separate from the internal medicine inpatient units and for the goal of reducing diazepam prescription in older adults, where

lorazepam is the preferred agent. Neither of the order sets includes an option for AC prescription. This study's cohort is different to the ones previously studied.^(25,26) Ethics approval was obtained from the University of British Columbia Clinical Research Ethics Board. Operational approval to conduct the study was obtained from Vancouver Coastal Health Authority.

The *International Classification of Diseases* diagnostics codes for alcohol withdrawal, alcohol intoxication, alcohol dependence, alcohol abuse, or alcohol use disorder (F10.2, F10.3, and F10.4) were used to identify subjects. Subjects were included if they were initiated on one of the pre-printed alcohol withdrawal order sets, were aged 60 years old and above, and were admitted for greater than 24 hours to an internal medicine or hospitalist service. Those with multiple admissions were counted as separate encounters. Participants were excluded if they transferred to a unit that did not utilize these protocols, left against medical advice, had a documented allergy to benzodiazepines, ACs, or AUD agents, were treated with clonidine, or were prescribed ACs for another medical indication such as mood or seizure disorders. To avoid confusion of withdrawal symptoms, those in active withdrawal from other substances and those with regular benzodiazepine use prior to admission were excluded. Also excluded were patients with severe liver disease as evidenced by a Model for End-stage Liver Disease (MELD) score > 9 , aspartate transaminase (AST) or alanine transaminase (ALT) levels that were greater than five times from the upper limit of normal (units/L), or platelet counts $\leq 100 \times 10^9/L$.

Primary outcomes included total cumulative benzodiazepine dose and duration, and the dosing regimens of ACs. Secondary outcomes included identifying the initiation of AUD agents, the complications of AWS, and the complications due to AC or benzodiazepine use.

Two investigators (SM, JK) conducted the chart review. If there were disagreements between the collected data, one of the other investigators (KD, PC) resolved any disputes. An audit of 10% of the charts was conducted by the other investigators (KD, PC). Baseline demographics, medical history, and substance use history were collected. To allow for equivalent comparison of alcoholic beverages, the quantities were converted to standard drinking units based on the Canada's Low Risk Alcohol Drinking Guidelines.⁽²⁸⁾ To allow for equivalent comparison, all benzodiazepine doses were converted to lorazepam equivalents.⁽²⁹⁾ The cumulative dose of benzodiazepine was calculated by summing the first to last administered dose of benzodiazepine based on the nursing medication administration record. This included both fixed schedule and symptom triggered benzodiazepine doses. The duration of AWS treatment was calculated as the time the order set was ordered to the last dose of benzodiazepine administered or when the order set was discontinued in the physician's orders. The type of AC and AUD agent prescribed and their dosing regimens were collected. Severe alcohol withdrawal complications (specifically delirium tremens, seizures, hallucinations or death) and serious adverse events resulting from treatment with AC or benzodiazepine therapy were documented.

Statistical Methodology

Data collected were entered into a spreadsheet and analyzed using the JMP 14 software package (JMP Statistical Discovery LLC, Cary, NC). Statistical analysis was completed by two investigators (KR and SM). Baseline characteristics were described using standard descriptive statistics: proportions, mean, median, interquartile range (IQR), and standard deviation. Nine individuals had repeat encounters and made up 25 of the total 83 encounters, so that there were 67 different subjects. A time parameter and blocking by subject identification number were employed to account for the repeat encounters. The baseline characteristics of each group were compared using *t*-tests, chi square tests, and multi-factor regression analyses to assess for group differences. Multi-factor regression analysis was used to compare the total cumulative benzodiazepine doses and treatment duration between each group. Given the spread of ages in the study, age as a factor was included in the regression model. To account for the effect of past and current alcohol withdrawal complications, a dichotomous nominal variable was created and incorporated into the previously described regression model (incorporating treatment variable and number of treatments received). Due to small sample size, the quality assessment and the initiation of AUD agents were analyzed using simple statistics of proportions. A chi-square test was completed to assess significant differences in adverse events between treatment groups. All comparisons were considered statistically significant if $p < .05$.

RESULTS

Our cohort included 216 encounters, but 133 encounters were excluded for the following reasons: significant liver disease ($n = 32$), platelet count $\leq 100 \times 10^9$ ($n = 28$), taking an AC or benzodiazepine prior to admission ($n = 27$), transfer to a unit that did not utilize the protocols ($n = 19$), not started on one of the pre-printed alcohol withdrawal protocols ($n = 11$),

left against medical advice during active AWS treatment ($n = 5$), concurrent clonidine therapy ($n = 4$), concurrent alcohol consumption ($n = 3$), allergy to anticonvulsants ($n = 1$), and concurrent withdrawal from other substance ($n = 1$). Eighty-three encounters met the inclusion criteria.

Baseline characteristics between the benzodiazepines only group ($n = 55$) and the AC adjunctive group ($n = 28$) were not statistically different, except for the number of medical comorbidities (Table 1), which was not thought to be clinically relevant. Also despite this difference, the number of medical comorbidities when accounted for in the multivariate regression did not change the study conclusions.

ACs were prescribed outside of the pre-printed order set and our study found gabapentin was the most frequently prescribed anticonvulsant ($n = 17$, 20.5%), followed by divalproex ($n = 9$, 10.8%), and then the combination of divalproex and gabapentin ($n = 2$, 2.4%). No other ACs were prescribed. Median (IQR1, IQR3) gabapentin total daily dose was 900 (375, 900) mg. Median (IQR1, IQR3) divalproex total daily dose was 1000 (500, 1000) mg. Of those on ACs, 54% ($n = 15$) were continued post-discharge, and it is unclear if this was for relapse prevention or whether it was unintentionally continued (Table 2). The AC group had a higher proportion of histories of AWS requiring hospitalization, histories of severe AWS complications, severe AWS complications on the current admission, and more frequent consultations with addictions medicine and/or psychiatry services. There were no documented adverse events or serious complications secondary to AC use. There were four documented adverse events secondary to benzodiazepine only treatment: namely delirium ($n = 2$, 2.4%) and oversedation ($n = 2$, 2.4%). There was no statistical difference found and, therefore, we cannot conclude that ACs are protective against delirium.

A significant difference in the mean cumulative dose between those treated with benzodiazepines only and those who also received ACs was found (Table 2). However, when

TABLE 1.
Baseline characteristics

Factor	Combined ($N = 83$)	Benzodiazepine Only ($N = 55$)	Anticonvulsant Adjunct ($N = 28$)	Test Statistic ^a	<i>p</i> value ^d
Age (mean \pm SD)	68.1 \pm 6.6	68.8 \pm 7.2	66.7 \pm 5.1	0.25 ^b	0.63
Male N (%)	58 (69.9%)	39 (70.9)	19 (67.9)	0.08 ^{cb}	0.77
Comorbidities, median (IQR1, IQR3)	6 (4, 8)	6 (4, 9)	5 (4, 7)	5.22 ^{ba}	0.027 ^c
Standard drinks per day, median (IQR1, IQR3)	8.7 (5, 14)	8.7 (4.5, 11.2)	8.7 (5.7, 17.3)	0.13 ^{ba}	0.72
Prior AWS hospitalizations N (%)	43 (51.8%)	22 (40%)	21 (75%)	6.06 ^c	0.014 ^c
Prior and current severe AWS complications N (%)	36 (43.3%)	17 (30.9%)	19 (67.9%)	6.69 ^c	0.0097 ^c

AWS = alcohol withdrawal syndrome

^aStatistics carried out to test for differences between the two treatment groups. For tests on continuous variables, subjects measured at multiple time point were accounted for through inclusion of a time parameter in the regression model and through blocking by subject identification code^(b). Difference in the proportions of nominal variables was tested using a Chi-squared test^(c).

^d $p < 0.05$.

^eStatistical significance.

TABLE 2.
Alcohol withdrawal syndrome treatment outcomes

Factor	Benzodiazepine Only (N = 55)	Anticonvulsant (N = 28)	Test Statistic ^a	p value
Cumulative benzodiazepine dose (mg) when accounting for severe AWS complications ^d (mean ± SEM)	9.21 ± 4.25	14.52 ± 4.63	2.51 ^{b,dc}	0.12
Total duration of treatment (hours) when accounting for severe AWS complications ^d mean ± SEM	90.76 ± 21.87	82.59 ± 23.91	0.21 ^{bdc}	0.65
Cumulative benzodiazepine dose (mg) mean ± SEM	6.98 ± 4.45	15.58 ± 4.88	6.47 ^b	0.013 ^e
Total Duration of treatment (hrs) mean ± SEM	88.06 ± 21.99	89.79 ± 24.05	0.010 ^b	0.92
Anticonvulsant continued post-discharge, N(%)	N/A	15 (53.6%)	N/A	N/A
Gabapentin		12 (42.9%)		
Divalproex		3 (10.7%)		

Factor	AWS Complication	No AWS Complication	Test Statistic	p-value
Cumulative benzodiazepine dose (mg) mean ± SEM	17.16 ± 4.44	6.57 ± 4.38	10.95 ^b	0.0015 ^e
Total duration of treatment (hrs) mean ± SEM	101.66 ± 22.73	71.68 ± 22.75	3.13 ^b	0.081

AWS = alcohol withdrawal syndrome; SEM = standard error of the mean.

^a Statistics carried out to test for differences between the two treatment groups. For tests on continuous variables, subjects measured at multiple time point were accounted for through inclusion of a time parameter in the regression model and through blocking by subject identification^(b). Difference in the proportions of nominal variables was tested using a Chi-squared test^(c).

^d Severe AWS complications (past or present) accounted for in multi-variate regression.

^e Statistical significance.

severe complications are accounted for in the multivariable regression, the statistical significance in the mean cumulative benzodiazepine dose between those on benzodiazepines only versus those on AC adjuncts is lost (Figure 1 and Table 2). The durations of benzodiazepine treatment between the two groups were not statistically different and continued to be so when severe complications are accounted for (Figure 1 and Table 2).

The amount of benzodiazepines administered reduced with increasing age (Figure 2). When age is included in the

multifactor regression, the AC group had significantly higher mean cumulative benzodiazepine doses compared to the benzodiazepine only group. Age had no impact on the duration of treatment between treatment groups.

Lastly, we found the mean cumulative benzodiazepine dose was significantly higher in those who had past or present severe AWS complications compared to those who did not (Table 2). No difference was observed in the duration of treatment between those with and without severe complications.

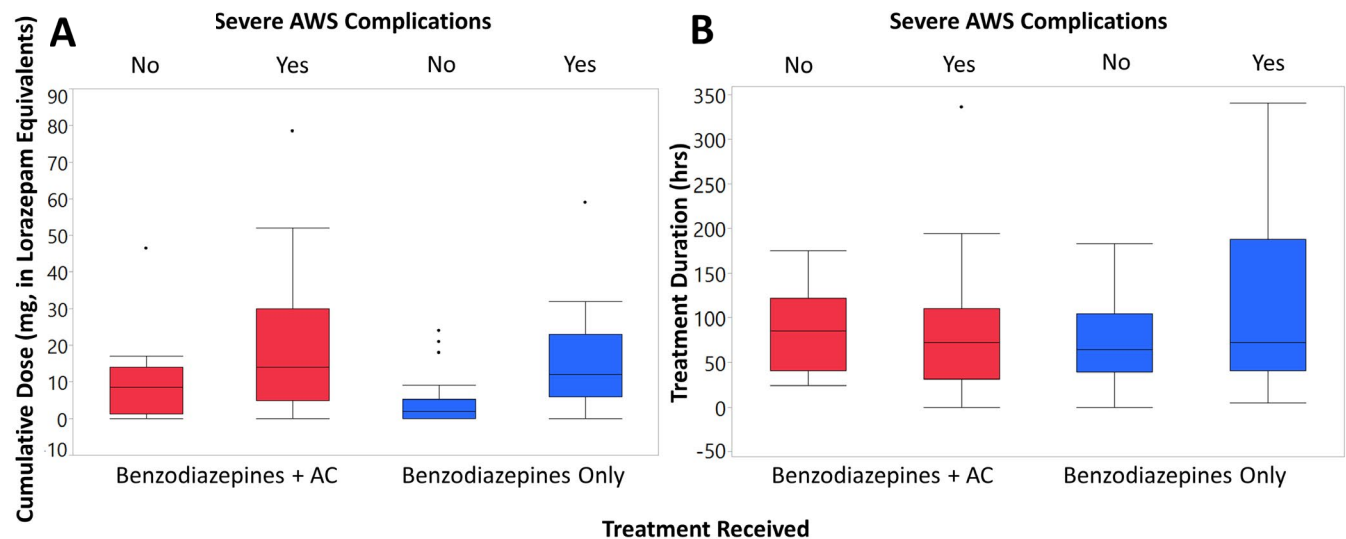


FIGURE 1. Effect of anticonvulsant use on the cumulative benzodiazepine dose (mg, in lorazepam equivalents) and total duration of treatment (hrs) while accounting for severe AWS complications

AC = anticonvulsant, AWS = alcohol withdrawal syndrome.

Upon discharge, two patients were newly prescribed acamprosate and three were newly prescribed disulfiram. For the disulfiram prescriptions, two were from the same individual on two separate admissions in which disulfiram was discontinued between hospitalizations. There were no new prescriptions of naltrexone.

DISCUSSION

To our knowledge, the prescribing practices of adjunctive ACs to medically ill, hospitalized older adults aged 60 and above for AWS management was previously unknown. Based on this study, 34% received adjunctive AC to the benzodiazepine-based CIWA-Ar order set. Interestingly, the cumulative dose of benzodiazepines administered was significantly higher in the AC group versus benzodiazepine alone when accounting for repeat encounters and age. However, when severe AWS complications (specifically: alcohol hallucinosis, seizures or delirium tremens) that occurred either in the past or present were included as a regression factor, the significance was lost. This suggests that the use of AC adjuncts do not decrease the amount of benzodiazepine administered as is therapeutically hoped for. Furthermore, the duration of AWS treatment using

benzodiazepines was not shortened by AC treatment. The cumulative dose of benzodiazepines was significantly higher in individuals with a history of or with current AWS complications, regardless whether they had AC adjuncts or not. This suggests that, even in cases of severe complications where AC adjuncts may be more appealing to use, ACs were not helpful in decreasing the amount of benzodiazepine administered.

Higher cumulative benzodiazepine doses were found in two inpatient studies using gabapentin adjuncts in younger adults in psychiatric facilities.^(18,19) As well, two inpatient retrospective cohort studies similar to ours found the gabapentin-treated group had higher baseline CIWA-Ar scores,^(18,20) suggesting that severity of AWS may explain the higher benzodiazepine doses. This seems to follow the kindling hypothesis.⁽⁹⁾ In our study, however, while the AC group had a higher proportion of severe complications and addiction or psychiatry consultative service involvement, the amount of benzodiazepine administered was equivalent between both groups if severe complications were included as a factor in the regression model.

Given that older adults tend to be more sensitive to the effects of benzodiazepines, we found that the total dose of benzodiazepines used decreased with increasing age. Still, there

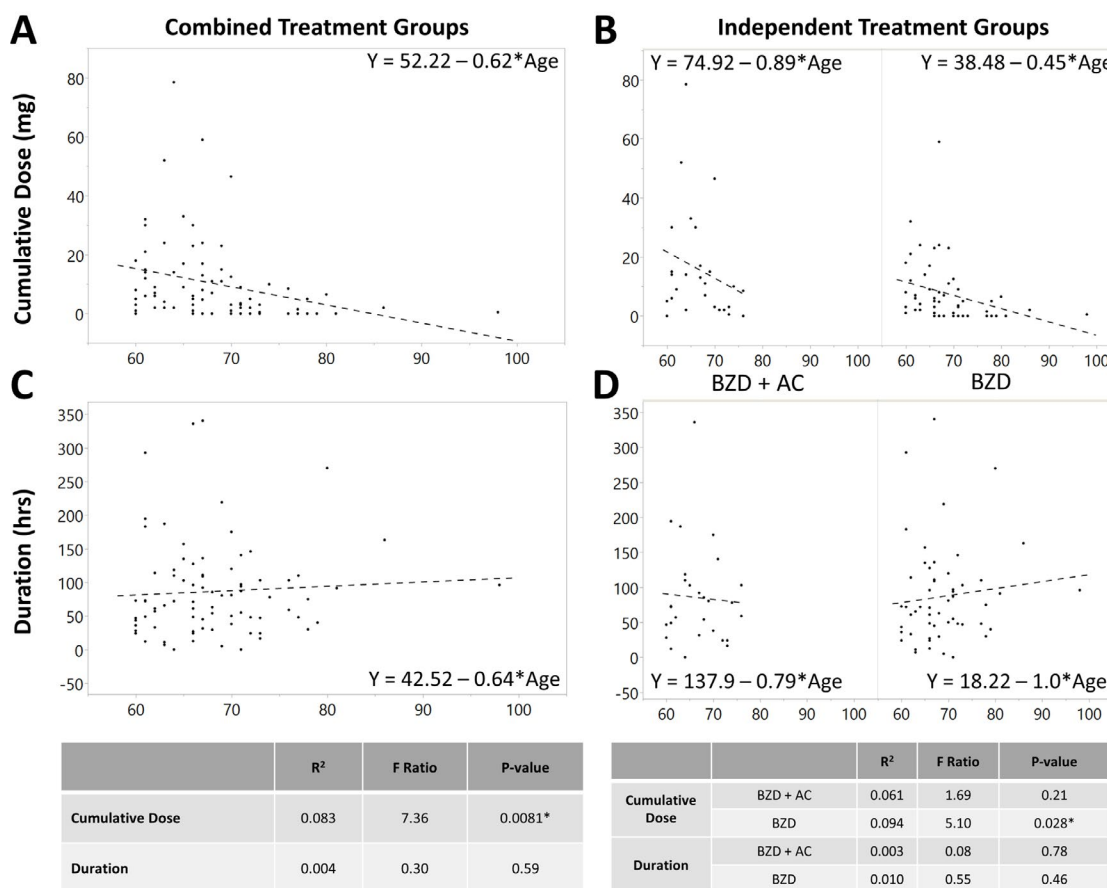


FIGURE 2. Decreased cumulative benzodiazepine dose observed in both treatment groups as age increases, while the duration of treatment remains the same
 BZD = benzodiazepine, AC = anticonvulsant

were four adverse events that did occur and were likely related to benzodiazepine use. No adverse events were reported due to ACs, suggesting they are generally well tolerated.

Our study found gabapentin was most commonly prescribed, followed by divalproex, and there were varying dosing regimens used. It is known that lower doses of gabapentin may not be effective in AWS, which may explain at least in part why our study's findings do not support the use of adjunctive ACs.^(13,17) The median gabapentin dose of 900 mg/d in our study is lower than the average dosages from previous studies, though it is unclear what the optimal dosage is for treating AWS in older adults with either gabapentin or divalproex.^(21,30)

Pharmacological treatment using naltrexone or acamprosate can lead to a statistically significant reduction in alcohol-related hospitalization and, therefore, costs.^(31,32) Unfortunately, our study found very few people were initiated on proven AUD agents. There can be several reasons for this finding. During AWS treatment in hospital, the focus is on management of the withdrawal, with less attention given to treating the underlying AUD. Application to provincially funded government medication plans is required to obtain coverage for newer AUD agents in our health authority. Physicians may be uncomfortable in prescribing an AUD agent when a patient is likely to be discharged without necessarily receiving community follow-up. Moreover, we are unclear why divalproex was continued in three patients post-discharge, as we could only find one small observational study supporting protracted treatment with valproate in AUD.⁽³³⁾ Conversely, in large placebo-controlled RCTs, the evidence for protracted treatment with gabapentin for relapse prevention is somewhat stronger, albeit conflicting.^(30,34,35) It can be helpful for relapse-triggering insomnia, anxiety or dysphoria,⁽³⁶⁾ but it can also lead to dizziness, ataxia, somnolence, and misuse.⁽³⁷⁾ Even if we included the 12 patients continuing gabapentin post-discharge as being prescribed for relapse prevention, only 21% of our cohort of 81 were newly prescribed an agent for relapse prevention. It leads us to question whether there is a gap in our delivery of AUD management.

Limitations in our study include the retrospective nature and the small sample size, which limited our ability to detect the safety of ACs and AUD agents in this population, to compare the potential differential effects of gabapentin versus divalproex, and to better determine the effectiveness of adjunctive AC use for AWS. An additional limitation identified during the data collection was that clinicians lack a standard format for documenting patients' alcohol intake. The lack of standardization leads to gaps in the information documented such as the amount, frequency, type of beverage, and duration of alcohol consumption. For example, many writers would document, "x bottles of hard liquor", but fail to mention the size of the bottles and frequency. The last drink, an important factor for AWS management, was also often missing in the documentation. Although our study did not evaluate the merits for initiating the CIWA-Ar protocol, previous studies have found some hospitalized patients are started on the CIWA-Ar protocol inappropriately.^(38,39) A

recent study found that in 57% of AWS encounters where the CIWA-Ar protocol was initiated, patients had either zero or one documented risk factor, and 20% had no documentation of recent alcohol use; some from the 20% developed adverse events due to benzodiazepines.⁽³⁹⁾ The authors suggested that the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) could be used to determine if the CIWA-Ar protocol should be implemented.⁽⁴⁰⁾ The PAWSS tool screens for patients who may have a higher risk for developing moderate to severe AWS, and has been validated in a medically ill, hospitalized population of younger and older adults.⁽⁴⁰⁾ This tool could have particular relevance for our population since there is a higher risk for iatrogenic complications in older adults when benzodiazepines are prescribed.

CONCLUSION

Medically ill, hospitalized older adults aged 60 or over were prescribed adjunctive anticonvulsants, which were often continued on discharge. While the belief may be that AC adjuncts may lessen the amount of benzodiazepine administered and their side effects and adverse events, our findings do not support the routine use of AC adjuncts for AWS. In fact, neither the duration nor the amount of benzodiazepine treatment was decreased, and in those with severe AWS complications where AC adjuncts may be more appealing to use, we found no benefit. The opportunity to initiate cost-effective AUD agents in our population is being missed. Future RCTs with a prospective design for older adults who have multiple medical comorbidities could provide more definitive evidence on whether adjunctive ACs could be beneficial or harmful in this population.

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Not Applicable

CONFLICT OF INTEREST DISCLOSURES

We have read and understood the Canadian Geriatrics Journal's policy on conflicts of interest disclosure and declare the following interests: Peter Chan is on the advisory board for Janssen-Ortho. The other authors have no conflicts of interest to declare.

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