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ARTICLE

Alcohol withdrawal is associated with poorer outcome in acute ischemic stroke

Emmanuel O. Akano, MD,* Fadar Oliver Otite, MD, ScM,* and Seemant Chaturvedi, MD

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Correspondence
Dr. Akano
emmanuel.akano@nih.gov
or Dr. Otite
otitef@upstate.edu

Abstract

Objective

To determine the association between alcohol abuse (AA) and alcohol withdrawal (AW) with acute ischemic stroke (AIS) outcomes.

Methods

All adult AIS admissions in the United States from 2004 to 2014 were identified from the National Inpatient Sample (weighted n = 4,438,968). Multivariable-adjusted models were used to evaluate the association of AW with in-hospital medical complications, mortality, cost, and length of stay in patients with AIS.

Results

Of the AA admissions, 10.6% of patients, representing 0.4% of all AIS, developed AW. The prevalence of AA and AW in AIS increased by 45.2% and 40.0%, respectively, over time (p for trend <0.001). Patients with AA were predominantly men (80.2%), white (65.9%), and in the 40- to 59-year (44.6%) and 60- to 79-year (45.6%) age groups. After multivariable adjustment, AIS admissions with AW had >50% increased odds of urinary tract infection, pneumonia, sepsis, gastrointestinal bleeding, deep venous thrombosis, and acute renal failure compared to those without AW. Patients with AW were also 32% more likely to die during their AIS hospitalization compared to those without AW (odds ratio 1.32, 95% confidence interval 1.11–1.58). AW was associated with ≈15-day increase in length of stay and ≈$5,000 increase in hospitalization cost (p < 0.001).

Conclusion

AW is associated with increased cost, longer hospitalizations, and higher odds of medical complications and in-hospital mortality after AIS. Proactive surveillance and management of AW may be important in improving outcomes in these patients.

*These authors contributed equally to this work.

From the Molecular Neuropharmacology Unit (E.O.A.), National Institutes of Neurologic Disorders and Stroke, NIH, Bethesda, MD; Division of Neurocritical Care (F.O.O.), Department of Neurology, Massachusetts General Hospital/Harvard Medical School, Boston; and Department of Neurology (S.C.), University of Maryland School of Medicine, Baltimore.

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Glossary

AA = alcohol abuse; **AHRQ** = Agency for Healthcare Research and Quality; **AIS** = acute ischemic stroke; **AW** = alcohol withdrawal; **CCI** = Charlson Comorbidity Index; **CI** = confidence interval; **HCUP** = Health Care Utilization Project; **ICD-9-CM** = *International Classification of Diseases–Clinical Modification, 9th revision*; **LOS** = length of stay; **NIS** = National Inpatient Sample; **OR** = odds ratio.

Alcohol abuse (AA) is a growing public health problem in the United States. Six percent to 10% of US adults now have alcohol use disorder, and this proportion increased by almost 50% over the last decade.[1,2] Heavy alcohol use is associated with increased risk of acute ischemic stroke (AIS).[3] Because of the period of abstinence necessitated by acute illnesses and hospitalizations, patients with alcohol use disorder, including those with AIS, are predisposed to alcohol withdrawal (AW) syndrome. AW is a constellation of symptoms that encompass anxiety, tremors, insomnia, dysautonomia, and seizures. In its most severe form (delirium tremens), attentional deficits, confusion, hallucination, and other encephalopathic features occur.[4,5]

AW may increase morbidity and mortality in various groups of hospitalized patients,[6] but there is a dearth of data on the influence of AW on outcomes among patients with AIS. AIS is the foremost cause of disability and one of the leading causes of mortality in the United States.[7] Therefore, early identification of modifiable factors that may negatively influence outcome is necessary to reduce the health and economic burden of AIS.

The primary aim of this study is to evaluate the association between AA and AW with in-hospital medical complications, mortality, cost, and length of stay (LOS) in AIS.

Methods

The data for this study was obtained from the National Inpatient Sample (NIS), maintained as part of the Health Care Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ). The database contains an ≈20% stratified sample of all hospital discharges in the United States. It is the largest database of hospitalizations in the United States, with coverage of ≈97% of the US population. Details of the design of the NIS database are available at hcup-us.ahrq.gov/nisoverview.jsp.

Informed consent and protocol approvals

The NIS database is completely deidentified. We received Institutional Review Board exemption status for this study from the NIH Institutional Review Board.

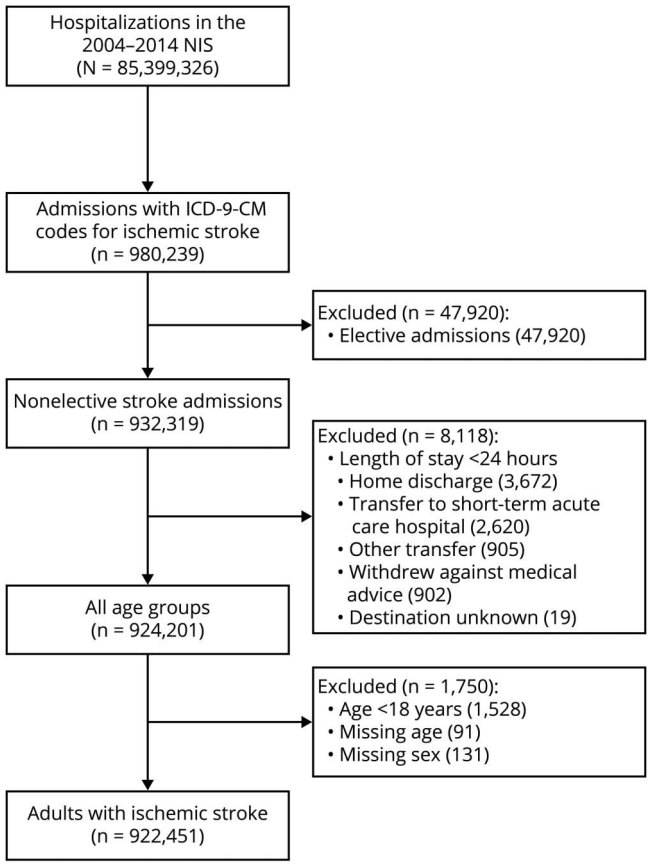
Study population

All adult inpatient admissions (age ≥18 years) with a primary diagnostic code of AIS were extracted from the 2004–2014 NIS with ICD-9-CM codes. AIS admissions were identified using codes in the range of 433.x1, 434.x1, and 436 in line with current AHA definitions.[8] These codes have a combined positive predictive value of >85% for AIS.[9] Details of inclusions and exclusions have been described previously[10] and are shown in figure 1. We excluded all admissions in which patients were transferred or discharged to home within 24 hours of admission to reduce the risk of double counting. We also excluded elective admissions to prevent the inclusion of nonacute strokes. Furthermore, admissions with diagnostic codes (433.x and 433.x0) for occlusion or stenosis of cerebral arteries without associated infarction or ischemia were excluded.

Definition of exposure and outcomes

The primary exposure of interest was AW, and this was defined by the presence of any secondary ICD-9-CM codes

Figure 1 Flowchart summarizing data extraction and inclusion and exclusion criteria for the study



ICD-9-CM = *International Classification of Diseases, 9th revision*: NIS = National Inpatient Sample.

corresponding to AW syndrome (291.81) or AW with delirium (291.0). Chronic AA was defined with AHRQ comorbidity software.[11] This software identifies preadmission comorbid conditions using ICD-9-CM codes and Diagnosis Related Group. The ICD-9-CM codes for AA encompass those in the range of 291.0 to 291.3, 291.5, 291.8, 291.81, 291.89, 291.9, 303.00 to 303.93, 305.00 to 305.03, and V11[12] and have a positive predictive value of 88% for AA.[13,14]

In-hospital mortality was defined with the HCUP variable DIED, which corresponds to death during that hospitalization, and LOS, defined with the HCUP variable LOS. The HCUP variable DISPUNIFORM, which represents disposition at the end of hospital stay, was used to identify patients who were discharged home at the end of their hospitalization.

We calculated hospitalization cost by multiplying the cost-to-charge ratios, available as a supplementary file in the NIS, and the hospital charge. We obtained inflation-adjusted cost of hospitalization in terms of 2016 US dollars by multiplying the cost of hospitalization with a correction factor obtained from the Bureau of Labor and Statistics website (bls.gov/data/inflation_calculator.htm).

Medical complications during AIS hospitalization studied include deep vein thrombosis, pulmonary embolism, acute renal failure, urinary tract infection, acute myocardial infarction, pneumonia, and sepsis. These complications were extracted with the HCUP's Clinical Classification Software as previously published[15] and were specifically chosen because they reflect in-hospital morbidity and may be mediators in the pathway from AW to mortality.

Covariate assessment

Other comorbid conditions associated with AIS hospitalization were identified with the AHRQ comorbidity software. We used these comorbid conditions to calculate the modified Charlson Comorbidity Index (CCI), a validated weighted severity score, and subsequently categorized patients into quartiles based on their CCI scores.

Mechanical ventilation in all patients was identified with ICD-9-CM procedural codes 967, 967.1, and 967.2. Early mechanical ventilation, defined as mechanical ventilation that occurred in the first 48 hours, was used as one of the surrogate measures for AIS severity. Inpatient IV thrombolysis was captured with the ICD-9-CM procedural code 99.10. Patients who received thrombolytics and were subsequently transferred to another facility were identified with ICD-9-CM diagnostic code V45.88.[16] Patients who had mechanical thrombectomy were identified with ICD-9-CM procedure code 39.74, Medicare Diagnosis-Related Group code 543 for percutaneous mechanical thrombectomy, or ICD-9-CM code 99.10 followed by subsequent ICD-9-CM procedural code 00.41 to 00.43.[17] Patients undergoing any craniotomy or decompressive hemicraniectomy were identified with ICD-9-CM codes 01.23 or 01.24.

Statistical analysis

Baseline characteristics of admissions with and without AW were summarized with descriptive statistics. The NIS has weights that allow calculation of national estimates from the 20% of hospitalizations in the NIS.[18] We used the provided weights to estimate the overall unadjusted weighted national prevalence of AW in AIS and in subgroups categorized by age and sex. We evaluated for linear trends in AW and AA prevalence over time using logistic regression model with proportion of admissions with AA or AW as the dependent variable and year modeled continuously as the independent variable.[19] Significant trend in each dependent variable over time was determined with the Wald test.

To adjust for confounding and to study potential mediators, we used a series of nested logistic regression models to evaluate the association of AW with each aforementioned medical complication, mortality, and odds of good outcome. Models for each outcome were constructed first by including AA with baseline demographic and hospitalization factors, followed by models that also include AW, and then by models that contain AA, AW, and all baseline factors and medical complications. We used CCI as a measure of the baseline health status of the patients and the risk of developing in-hospital complication or mortality. We used early mechanical ventilation, hemiplegia, dysphagia, aphasia, tracheostomy, coma, and craniectomy as surrogate measures for AIS severity. We conducted formal mediation analysis of the association of AW with mortality to quantify how much of the association of AW with mortality could be explained or mediated by medical complications. This was done with the Stata package binary mediation, with AW as the independent variable, all medical complications as mediator variables, and baseline demographic and hospital factors as covariates. The confidence interval (CI) around point estimates was obtained via bootstrapping.

We evaluated the relationship between AW and hospitalization cost and LOS in AIS by fitting generalized linear models with a gamma variance distribution and adjusting for patient and hospital factors.

All analyses were performed with Stata 14 (StataCorp, College Station, TX). We accounted for the stratified cluster sampling of the NIS in all our models using the Stata survey (SVY) suite of commands, with use of the hospital as the primary sampling unit and use of applicable probability sampling weights for robust variance estimation in all multivariate models. NIS trend weights were used in all analyses to make data comparable before and after the NIS redesign in 2012 as recommended. Statistical level of significance was set a 2-tailed value of $p = 0.05$.

Missing variables

The frequency of missing values was <2.5% for most variables in the NIS with the exception of cost of hospitalization

and race with 5.5% and 15.5% missing values. Missing cost data were handled with reweighting technique,[20] while missing race data were handled with multiple imputation recommended by the HCUP.[21] For all patients ≥65 years of age, missing insurance status was imputed to Medicare. For all other variables, we imputed missing data to the dominant category.

Data availability

The NIS is a publicly accessible dataset that can be obtained easily after completion of the HCUP data-use agreement.

Results

Baseline characteristics

The 922,451 hospitalizations contained in the NIS represent 4,438,968 weighted AIS admissions in the United States from 2004 to 2014. Of all AIS admissions during this period, 3.9% had comorbid AA (table 1). AA admissions includes those without comorbid AW codes (3.4% of all AIS admissions) and those with coexisting codes for AA (10.6% of all AA hospitalizations and 0.4% of all AIS admissions (table 1). As expected, all admissions with AW had coexistent codes for AA (table 1).

The majority of AIS admissions with AA were in patients in the 40- to 59-year (AA with AW 44.9%, AA with no-AW and 42.1%) and 60- to 79-year (AA with no AW 45.2%, AA with AW 49.1%) age groups (table 1). About 80% of admissions with AA were in men, and approximately two-thirds of these were in white patients. Traditional vascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation, were significantly less prevalent in admissions with comorbid AA, but patients with AA were more likely to have chronic liver disease, baseline coagulopathy, and chronic lung disease. Almost half of all patients with AA also smoked tobacco (AA with no-AW 52.1%, AA with AW 43.9%), and >10% also abused drugs (table 1).

Trends in chronic AA and AW in AIS

The prevalence of AA in AIS increased from 3.0% in 2004 to 4.4% in 2014 (relative increase 45.2%, p for trend <0.001) but prevalence differed significantly by age (figure 2A). Consistent with this increase, the proportion of patients with AIS with AW also increased by 40% from 0.3% in 2004 to 0.5% in 2014 (p for trend <0.001). AW prevalence also differed significantly by age, with the highest prevalence seen in individuals in the 40- to 59-year and 60- to 79-year age groups (figure 2B).

Association of AW with medical complications, mortality, hospitalization cost, and LOS

In multivariable models adjusted for all demographic, clinical, and hospital factors, but excluding AW (table 2, model 1), patients with AA had greater odds of urinary tract infection, pneumonia, sepsis, gastrointestinal bleeding, acute myocardial infarction, and acute renal failure, but not venous thromboembolism. After inclusion of AW in the multivariable models (table 3, model 2), the association between AA and each of these complications was attenuated except for pulmonary embolism. This means that association of AA with each of these complications could possibly be explained in part by AW. As seen in the final models for each complication (model 2, table 2), after adjustment for all baseline covariates, including AA, patients with AW had 2 times the odds of pneumonia compared to those without AW (odds ratio [OR] 2.03, 95% CI 1.74–2.35) (table 3, model 2). The odds of other in-hospital medical complications, including urinary tract infection, sepsis, deep venous thrombosis, and acute renal failure, were >50% greater in patients with AW compared to those without AW, but the odds of pulmonary embolism did not differ between both groups of patients (table 2, model 2).

Similarly, without the inclusion of AW in multivariable models, the odds of in-hospital mortality were marginally higher in patients with AA compared to those without (OR 1.07, 95% CI 1.00–1.14, p 0.045) (table 3, model 1). After inclusion of AW in these models, the association of AA with mortality was attenuated (table 3, model 2). Patients with AW had 32% greater odds of in-hospital mortality compared to those without AW (OR 1.32, 95% CI 1.10–1.56, p = 0.002) after multivariable adjustment (table 3, model 2). After further adjustment for medical complications (table 3, model 3), the association of AW with mortality was also significantly attenuated. These results indicate that the association of AW with mortality may be mediated partly through increased odds of in-hospital medical complications. Formal mediation analysis using multivariable adjusted binary mediation showed that 46.9% (95% CI 44.6%–51.9%) of the effect of AW on mortality was explained indirectly through increased medical complications (data not shown).

Compared to those without AW, the cost of hospitalization was approximately $5,000 greater in patients with AW. Mean LOS was also ≈15 days longer in patients with AW compared to those without AW (table 3, model 2). Patients with AW were also less likely to have good outcome as measured by routine home discharge (OR 0.54, 95% CI 0.49–0.59). Multivariable-adjusted odds of IV thrombolysis and mechanical thrombectomy did not differ between patients with AA and those without (data not shown).

Discussion

In this study, we show that 4% of all AIS admissions in the United States were for individuals with comorbid chronic AA and that this proportion increased by >40% over the period from 2004 to 2014. Greater than 80% of these admissions with AA in the United States were for men, and >80% of these patients were between 40 and 79 years of age at the time of their admission. Approximately 10% of these chronic alcohol

Table 1 Baseline characteristics of ischemic stroke admissions in the US hospitals from 2004 to 2014 according to their alcohol withdrawal status

Variable	Description	No alcohol abuse	Alcohol abuse and no withdrawal	Alcohol abuse and withdrawal	*p* Value
Weighted No., %		4,266,567 (96.1)	153,903 (3.5)	18,228 (0.4)	
Age, y	Mean (SE)	71.6 (0.06)	60.8 (0.09)	62.0 (0.21)	<0.0001
Age, proportion, %					<0.0001
	18–40 y	2.1	3.2	1.9	
	41–60 y	18.8	44.9	42.1	
	61–80 y	43.9	45.2	49.1	
	>80 y	35.2	6.7	6.9	
Sex, proportion, %	Male	45.7	79.8	83.5	<0.0001
Race, proportion, %					<0.0001
	White	71.6	64.8	72.3	
	Blacks	16.3	23.4	17.8	
	Hispanic	6.8	7.8	6.3	
	Others	5.2	4.0	3.6	
Median income quartile, %					<0.0001
	$1–$39,999	29.2	35.9	33.4	
	$40,000–$50,999	26.5	26.2	25.7	
	$51,000–$65,999	23.6	21.8	22.7	
	≥$66,000	20.6	16.1	18.2	
Hospital region, %					<0.0001
	Northeast	18.4	16.7	18.7	
	Midwest	22.6	22.3	20.9	
	South	40.6	42.4	41.8	
	West	18.4	18.5	18.7	
Location/teaching status					<0.0001
	Rural	12.4	9.8	10.2	
	Urban nonteaching	41.7	38.5	37.4	
	Urban teaching	45.9	51.7	52.5	
Vascular risk factors	Dyslipidemia	47.1	42.1	31.6	<0.0001
	Diabetes mellitus	34.4	21.6	17.1	<0.0001
	Hypertension	79.2	76.8	73.4	<0.0001
	Chronic renal failure	11.9	6.7	6.59	<0.0001
Cardiovascular diseases	Heart failure	14.3	9.4	11.0	<0.0001
	Atrial fibrillation	22.9	13.5	17.7	<0.0001
	Coronary artery disease	26.9	18.0	15.9	<0.0001
	Peripheral vascular disease	8.8	9.1	8.2	<0.0536

Continued

Table 1 Baseline characteristics of ischemic stroke admissions in the US hospitals from 2004 to 2014 according to their alcohol withdrawal status *(continued)*

Variable	Description	No alcohol abuse	Alcohol abuse and no withdrawal	Alcohol abuse and withdrawal	*p* Value
Lifestyle risk factors	Smoking	13.6	52.1	43.9	<0.0001
	Drug abuse[a]	1.6	14.6	10.9	<0.0001
Other medical diseases	Liver disease	0.9	5.8	5.9	<0.0001
	Coagulopathy	2.7	4.4	6.7	<0.0001
	Depression	9.2	10.1	10.0	<0.0001
	Obesity	7.8	6.4	4.3	<0.0001
	Chronic lung disease	14.6	19.5	22.4	<0.0001
In-hospital course					
	Thrombolysis	5.6	6.0	8.2	<0.0001
	Any mechanical ventilation	4.0	5.2	15.3	<0.0001
	Early mechanical ventilation	2.8	3.6	8.6	<0.0001
	Length of stay	5.2	5.8	10.4	<0.0001
	Died in hospital	5.1	3.7	6.7	<0.0001

[a] Includes but not limited to cannabis use; hallucinogen abuse; sedative, hypnotic, or anxiolytic abuse; opioid dependence or abuse; cocaine abuse; amphetamine abuse; antidepressant abuse; and unspecified drug abuse.

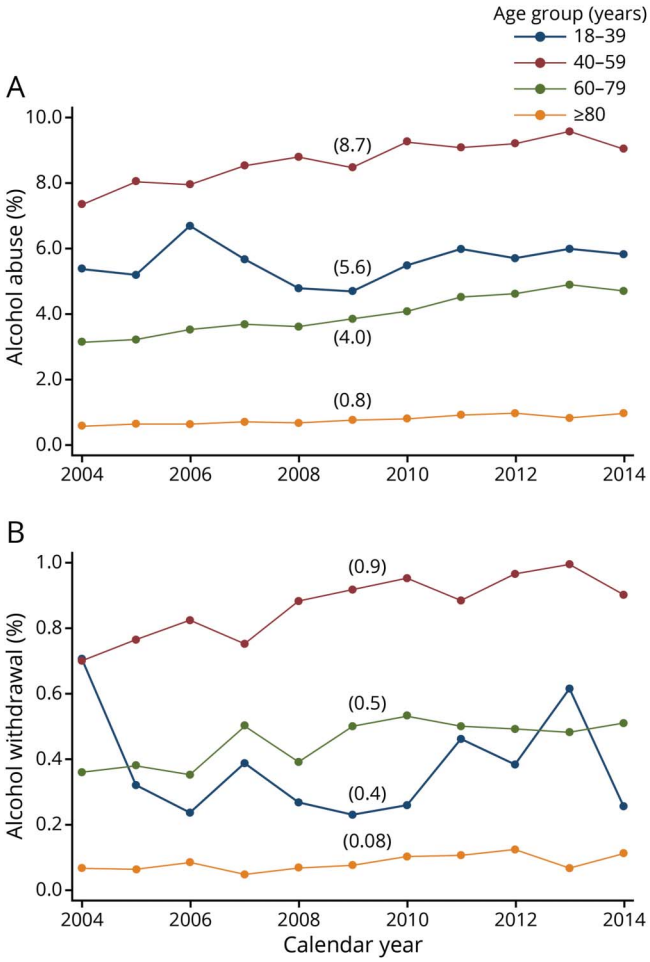
abusers also have coexistent codes for AW during their AIS admission. Patients with AA who developed withdrawal syndrome were significantly more likely to have infectious (pneumonia, urinary tract infection, and sepsis) and noninfectious (gastrointestinal bleeding, deep venous thrombosis, acute renal failure, and acute myocardial infarction) complications during hospitalization for AIS. They were also more likely to die during admission and less likely to be discharged home despite having similar odds of receiving IV thrombolysis or mechanical thrombectomy compared to those without AA. These findings suggest that proactive measures to identify and treat patients with AIS at risk of AW may provide additional avenues to improve the clinical outcomes in these patients.

The exact reasons behind the association of AA and AW with increased mortality or poor outcome in AIS are unknown, but multiple potential mechanisms are possible. In preclinical models of stroke, animals with comorbid alcoholism had larger infarction and attenuated benefits from thrombolytic therapy compared to controls.[22–25] Chronic alcohol intoxication aggravates motor cortex disruption and motor dysfunction caused by ischemia in rodent models of alcoholism and stroke.[26,27] Mechanisms implicated in these findings include glutamate excitotoxicity,[22] increased susceptibility to neuronal injury,[26,28] impaired calcium signaling, and oxidative stress.[26,29]

It has been well established that chronic AA is associated with increased medical complications or mortality in multiple surgical, trauma, and medical patient populations, including patients with myocardial infarction.[30–32] AA is a known risk factor for severe or lethal bacterial pneumonia, empyema, and parapneumonic effusion.[33,34] AA also predisposes to and worsens the outcome of sepsis, one of the leading causes of in-hospital deaths.[33] Severe sepsis in patients with AA has been shown to result in a 2-fold higher risk of mechanical ventilation and up to 4-fold higher risk of acute respiratory distress syndrome.[34] Other medical complications seen in this study such as gastrointestinal bleeding have previously been shown to occur at increased frequency in patients with AA as a result of a variety of factors, including liver disease and disproportionate coagulopathy.[33]

AW may result in poor outcome in AIS in ways that go beyond being a marker for the most severe forms of alcoholism. Autonomic dysfunction is common after stroke, and this has been shown to increase the risk of poststroke tachyarrhythmias, myocardial infarction, and other poor outcomes.[35] Hyperpyrexia, tachycardia, and hypertension from autonomic hyperactivity in AW increase cardiometabolic demands and create additional problems for patients with AIS not only by increasing the risk of these cardiac complications but also by increasing the risk of secondary brain injury and edema through sympathetically driven inflammation and increased

Figure 2 Trends in the prevalence of (A) AA and (B) AW in AIS hospitalizations in the United States from 2004 to 2014 according to age groups



Prevalence of alcohol withdrawal (AW) and alcohol abuse (AA) is expressed as percentage of total acute ischemic stroke (AIS) admissions for each year. Numbers in parentheses represent overall proportion in each age group across the entire study period.

blood-brain barrier permeability.[35] Delirium, one of the serious manifestations of AW, is an independent predictor of increased mortality or prolonged hospitalization.[36,37] Accurate diagnosis of delirium as secondary to AW in patients with AIS may be challenging because patients with AIS often have other reasons to be encephalopathic, and this may lead to delayed treatment. Delayed therapy of delirium may worsen AIS outcome by increasing the risk of nosocomial infections, prolonging mechanical ventilation, and increasing the risk of death.[37] Encephalopathy from AW and sedating medications used to treat AW may also lead to increased aspiration risk in patients stroke, who already have a baseline predisposition to aspiration and pneumonia.

In this study, use of mechanical ventilation at any time during hospitalization was >3-fold higher in AW admissions (15.3%) compared to those without AA (4.0%). Prior studies have shown that AA increases the need for mechanical ventilation by up to 49%.[34] Patients with AA, including those with AW who undergo mechanical ventilation, are at increased risk of developing ventilator-associated pneumonia,[34] a complication associated with up to 2-fold higher odds of death.[34,38] Patients who develop AW are predisposed to longer mechanical ventilation duration, longer intensive care unit stay, urinary tract infection, sepsis, and mortality. These adverse effects may not be due to AW alone but also to immune downregulation that occurs from the pharmacologic effects of benzodiazepines, propofol, and other medications used to treat AW.[39]

Prolonged hospital stay in patients with AIS who may be immobile and platelet hyperaggregability[40] that occurs as AW ensues increase the risk of deep vein thrombosis, as noted in this study. This study suggests that AW is associated with increased odds of medical complications, and this increased odds of in-hospital medical complications mediates part of the association of AW with poor stroke outcome. Nonetheless, additional factors are responsible because the association of AW with mortality and other poor outcomes remained significant after adjustment for these medical complications.

The increased prevalence of AA in AIS admissions over time noted in our study is likely a reflection of the national increase in alcohol use disorders.[2,41] This indicates that AA may also be constituting a growing problem for stroke prevention and that efforts targeted at mitigating AA may also reduce stroke incidence. Increasing awareness of AA, changes in physician history-taking practices, and changes in coding practices may also have contributed significantly to increased documented AA prevalence over time.

Previous studies suggest that binge drinking and alcohol intoxication are independent risk factors for stroke, especially in the young.[42–44] The lower prevalence of hypertension, diabetes mellitus, atrial fibrillation, and dyslipidemia in patients with AA may be partly explained by the younger age of these patients because the prevalence of these risk factors increases with age.

This study has some limitations. In this observational study using retrospective data from a national database, no inference can be made regarding a causal relationship between AA and AW with outcome after AIS. Compared to the general US population, the ≈4% prevalence of AA in AIS admissions noted in our study is significantly lower than the 6% to 10% prevalence of AA in the adult US population. These estimates are, however, consistent with the 40% to 42% detection rate of alcoholism in general hospital admissions in the United States,[45] likely due to underreporting or reduced ascertainment of AA in hospitalized patients. Not all clinicians ask their patients about their degree of alcohol consumption.[46] Ascertainment of the degree of alcohol consumption in some AIS hospitalizations may be difficult because some patients

Table 2 Association of alcohol withdrawal and alcohol abuse with odds of in-hospital medical complications in all adult acute ischemic stroke hospitalizations in the United States from 2004 to 2014

Models	Independent variables	Odds ratio[a]	95% Confidence interval	*p* Value
Urinary tract infection				
Model 1	Alcohol abuse	1.15	1.10–1.20	<0.001
Model 2	Alcohol abuse	1.09	1.04–1.14	<0.001
	Alcohol withdrawal	1.56	1.39–1.75	<0.001
Pneumonia				
Model 1	Alcohol abuse	1.22	1.14–1.30	<0.001
Model 2	Alcohol abuse	1.07	1.00–1.15	0.044
	Alcohol withdrawal	2.04	1.77–2.35	<0.001
Sepsis				
Model 1	Alcohol abuse	1.12	1.03–1.22	0.007
Model 2	Alcohol abuse	1.01	0.92–1.11	0.848
	Alcohol withdrawal	1.79	1.48–2.17	<0.001
Deep venous thrombosis				
Model 1	Alcohol abuse	0.97	0.87–1.08	0.623
Model 2	Alcohol abuse	0.90	0.79–1.01	0.076
	Alcohol withdrawal	1.58	1.22–2.04	<0.001
Pulmonary embolism				
Model 1	Alcohol abuse	1.04	088–1.23	0.634
Model 2	Alcohol abuse	1.06	0.89–1.27	0.509
	Alcohol withdrawal	0.87	0.54–1.39	0.554
Gastrointestinal hemorrhage				
Model 1	Alcohol abuse	1.54	1.41–1.70	<0.001
Model 2	Alcohol abuse	1.49	1.29–1.59	<0.001
	Alcohol withdrawal	1.57	1.26–1.96	<0.001
Acute myocardial infarction				
Model 1	Alcohol abuse	1.25	1.15–1.35	<0.001
Model 2	Alcohol abuse	1.18	1.08–1.28	<0.001
	Alcohol withdrawal	1.43	1.17–1.75	<0.001
Acute renal failure				
Model 1	Alcohol abuse	1.09	1.04–1.14	<0.001
Model 2	Alcohol abuse	1.03	0.98–1.08	0.295
	Alcohol withdrawal	1.57	1.40–1.76	<0.001

All models included all adult acute ischemic stroke hospitalizations and were built by sequentially adding multiple variables to baseline models. Model 1: adjusted for all variables listed above without alcohol withdrawal. Model 2: model 1 + alcohol withdrawal.

[a] Odds ratio estimates were obtained from multivariable-adjusted logistic regression models with each outcome variable as a dependent variable. Each model was adjusted for age, sex, race, income, insurance, modified Charlson Comorbidity Index, atrial fibrillation, coronary artery disease, dyslipidemia, dysphagia, coma, cranial nerve palsy, baseline coagulopathy, drug abuse, smoking, mechanical thrombectomy, decompressive craniectomy, IV thrombolysis, tracheostomy, gastrostomy, mechanical ventilation, hospital size, hospital location/teaching status, hospital region, hospital stroke volume, and year of admission.

Table 3 Association of alcohol withdrawal and alcohol abuse and odds of in-hospital mortality in all acute ischemic stroke hospitalizations in the United States from 2004 to 2014

Mortality	Variables	Estimate		
		Odds ratio	95% CI	*p* Value
Model 1	Alcohol abuse	1.07	1.00–1.14	0.040
Model 2	Alcohol abuse	1.02	0.96–1.10	0.471
	Alcohol withdrawal	1.32	1.11–1.54	0.001
Model 3	Alcohol abuse	1.01	0.94–1.09	0.751
	Alcohol withdrawal	1.25	1.05–1.50	<0.001

Home disposition[a]	Variables	Estimate		
		Odds ratio	95% CI	*p* Value
Model 1	Alcohol abuse	0.73	0.70–0.74	<0.001
Model 2	Alcohol abuse	0.77	0.74–0.79	<0.001
	Alcohol withdrawal	0.53	0.49–0.58	<0.001
Model 3	Alcohol abuse	0.82	0.80–0.84	<0.001
	Alcohol withdrawal	0.57	0.52–0.62	<0.001

Length-of-stay	Variables	Estimate		
		Unit, Days	95% CI	*p* Value
Model 2	Alcohol abuse	1.47	1.39–1.55	<0.001
	Alcohol withdrawal	21.2	16.2–27.9	<0.001
Model 3	Alcohol abuse	1.43	1.36–1.51	<0.001
	Alcohol withdrawal	14.84	11.51–19.14	<0.001

Hospitalization cost	Variables	Estimate		
		Unit, $	95% CI	*p* Value
Model 2	Alcohol abuse	626.87	508.06–745.67	<0.001
	Alcohol withdrawal	5,608.94	5,006.78–6,211.11	<0.001
Model 3	Alcohol abuse	612.05	513.48–710.63	<0.001
	Alcohol withdrawal	4,673.05	4,213.36–5,132.75	<0.001

All models adjusted for age, sex, race, income, insurance, modified Charlson Comorbidity Index, atrial fibrillation, coronary artery disease, dyslipidemia, dysphagia, coma, cranial nerve palsy, baseline coagulopathy, drug abuse, smoking, mechanical thrombectomy, decompressive craniectomy, IV thrombolysis, tracheostomy, gastrostomy, mechanical ventilation, hospital size, hospital location/teaching status, hospital region, hospital stroke volume, and year of admission. All models included all adult acute ischemic stroke hospitalizations and were built by sequentially adding multiple variables to baseline models. Model 1: adjusted for all variables listed above without alcohol withdrawal. Model 2: model 1 + alcohol withdrawal. Model 3: model 2 + further adjustment for medical complications (pneumonia, urinary tract infection, pulmonary embolism, deep venous thromboembolism, acute renal failure, acute myocardial infarction).
[a] In surviving patients only.

with stroke are dysarthric or aphasic or have other cognitive changes that preclude discussion about their alcohol intake. A significant proportion of heavy drinkers underestimate their heavy alcohol use.[47] Misclassifying patients with AA in the non-AA group may have biased our effect estimates toward the null, indicating that the true impact of AW and AA on AIS outcome may be greater than currently reported in this study. Although we used well-validated codes for AIS, AA, thrombolytic therapy, and complications studied, the potential for coding inaccuracies remains. ICD-9-CM codes may underestimate tissue plasminogen activator use. That 100% of patients with AW in this study also had coexistent codes for AA is reassuring, but AA defined with ICD-9-CM codes may not capture the entire spectrum of alcohol use disorder in patients with AIS. Whereas ICD-9-CM codes are highly specific and have ≈88% positive predictive value for AA, the relatively modest sensitivity due to low the detection rate of AA as discussed above may mean that this study significantly underestimates the prevalence of alcohol use disorder in the AIS population. A considerable proportion of patients may

also continue to have signs of withdrawal after discharge from the hospital. There is great variability in how clinicians actually diagnose AW. This likely would have resulted in misclassification of some patients with AW as without, rendering our effect estimates conservative at best. There is also great variation in how physicians diagnose pneumonia, sepsis, and other complications. Such heterogeneity could have resulted in random misclassification that may have biased our effect estimates toward the null. We were unable to provide information on the quantity and duration of alcohol use.

The NIS lacks clinical severity scores of AIS, including the NIH Stroke Scale, and stroke outcome measures such as the modified Rankin Scale or the Glasgow Outcome Scale. However, we used alternative measures of AIS severity such as hemiplegia, dysphagia, mechanical ventilation, and coma. We also adjusted for comorbid disease status in all multivariable analyses. The finding of excess cost and LOS associated with AW should be interpreted with caution because we could not show a temporal correlation between AW and these complications. An alternative explanation is reverse causation. Although we adjusted for an extensive list of covariates, we cannot exclude residual confounding. For example, because the NIH Stroke Scale was unavailable in the NIS, it could not be included in the models and thus may represent a potential source of residual confounding.

In a large national database, we found that AW is associated with increased odds of in-hospital mortality, longer hospitalizations, and reduced odds of good outcome in patients with AIS. Therefore, measures targeted at early identification and proactive management of AW in at-risk patients may potentially improve ischemic stroke outcome. Further studies into the mechanisms of the adverse influence of AA and AW on outcomes in AIS and the best approaches to mitigate them are warranted.

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Appendix Authors

Name	Location	Role	Contribution
Emmanuel O. Akano, MD	NIH, Bethesda, MD	Author	Designed and conceptualized study; acquired, analyzed, and interpreted the data; drafted manuscript; revised manuscript for intellectual content; statistical analysis
Fadar Oliver Otite, MD, ScM	Massachusetts General Hospital/ Harvard Medical School, Boston	Author	Designed and conceptualized study; acquired, analyzed, and interpreted the data; drafted manuscript; revised manuscript for intellectual content; statistical analysis
Seemant Chaturvedi, MD	University of Maryland School of Medicine, Baltimore	Author	Acquired, analyzed, and interpreted the data; revised manuscript for intellectual content; supervised the study.

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