Alcohol Withdrawal Syndrome:
Does Sex Matter?

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Abstract

Background

Alcohol Withdrawal Syndrome (AWS) occurs after an individual significantly reduces or completely stops consuming alcohol after a period of consumption. Existing literature describes key differences in drinking patterns, metabolism, effects of alcoholism, and effects of alcohol withdrawal on men and women. Given these differences, does sex matter in patients admitted with a diagnosis of alcohol withdrawal? Our objective was to examine and compare outcomes between men and women admitted to a publicly funded urban hospital with a diagnosis of alcohol withdrawal.

Methods

A retrospective single-center cohort comparison study was performed to examine all patients admitted to Maricopa Integrated Health System with a diagnosis of alcohol withdrawal from January 1, 2010 to December 31, 2014. Data regarding total hospital length of stay (LOS), Medical Intensive Care Unit (MICU) LOS, non-MICU LOS, comorbidities, non-MICU Benzodiazepine requirements, and mortality rates of male and female patients were obtained. Male MICU patients were compared with female MICU patients. A randomized selection of male non-MICU admissions equal to the number of female non-MICU admissions was performed. Male and female non-MICU admissions were compared. Patients with diagnoses of trauma, burns, or other surgical diagnoses were excluded from this study.

Results

A total of 1496 patient charts were identified.

There were 220 male and 19 female patients admitted to the MICU. MICU women were younger than MICU men, 41.2 (SD 9.5) vs. 46.2 (SD 9.8, P=0.03). Men had a longer total LOS, 9.36 days (SD 6.1) vs 7.31 days (SD 5.0, P=0.10). Men had longer MICU LOS, 5.23 days (SD 4.8) vs 4.05 days (SD 4.9, P=0.06). Men required intubation more often, 89 (40.5%) vs 7 (36.8%, P=0.75)). Men and women had similar ventilator requirements 2.5 days (SD 4.8) for men vs 2.3 days (SD 5.4, P=0.60) for women. Men developed pneumonia and sepsis more often; 90 men (40.9%) vs 4 women (21.1%, P=0.14) and 12 men (5.5%) vs no women (0%, P=0.60), respectively. Women developed seizures, hepatitis, and pancreatitis more frequently than men;

6 women (31.6%) vs 48 men (21.8%, P=0.32), 6 women (31.6%) vs 42 men (19.1%, P=0.23), and 4 women (21%) vs 13 men (5.9%, P=0.03), respectively. One man (0.45%, P=1.0) and no women perished in the MICU.

A total of 99 female and 99 randomly selected male patients admitted to non-MICU care were compared. Women were younger, 44.4 years (SD 11) vs 46.1 years (SD 10.1, P=0.30). Men had longer LOS, 4.21 days (SD 2.86) vs 3.96 days (SD 2.2, P=0.64). There were 14 women (14.1%) vs 15 men (15.1%, P=0.84) who developed seizures. Hepatitis and pancreatitis occurred more frequently in women; 21 women (21.2%) vs 16 men (16.2%, P=0.36) and 6 women (6.1%) vs 4 men (4.1%, P=0.51), respectively. One woman (1.1%, P=1.0) and no men were diagnosed with sepsis. Women required more overall Benzodiazepines than men did; 0.60 mg/kg (SD 0.71) vs 0.49 mg/kg (SD 0.69, P=0.57). No men or women died during non-MICU admission.

Conclusion:

Women had more hepatic complications, were at least equally likely to develop seizures, and recovered from withdrawal sooner than men with shorter LOS and shorter duration of Benzodiazepine administration.

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Introduction

Alcohol Withdrawal Syndrome: Background

Alcohol Withdrawal Syndrome (AWS) is a constellation of symptoms that may occur after an individual significantly reduces or completely stops consuming alcohol after a prolonged period of consistent consumption. This syndrome can occur in individuals who drink heavily for a period of several week to several years and initial signs of this syndrome may be present as early as two hours after the individual ceases to consume alcohol. Symptoms of alcohol withdrawal range from anxiety to potentially life threatening Delirium Tremens.

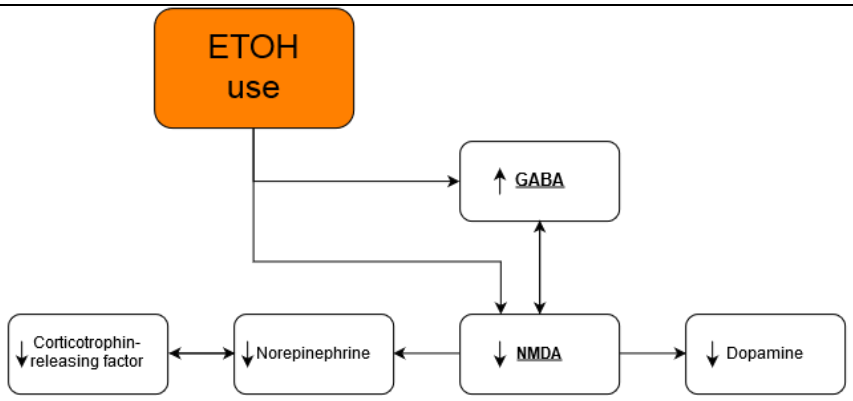
Alcohol Intoxication: Pathophysiology

The symptoms present in Alcohol Withdrawal are due to a state of hyper-excitability of the central nervous system. This state of hyper-excitability is made possible by the enhanced neuroinhibitory state that results after prolonged periods of consistent alcohol ingestion. During episodes of acute alcohol ingestion neurotransmitter function in the brain altered. The two main functions that are altered are the gamma-Aminobutyric acid (GABA) neuroinhibitory and the N-methyl-D-Aspartate (NMDA) neuroexcitatory systems (see Fig. 1).

Normally, the activation of the GABA receptor causes an influx of chloride ions through the postsynaptic membrane which, in turn, causes an inhibition of transmission due to hyperpolarization of the nerve ending. Because transmission is inhibited, GABA is said to have a neuroinhibitory effect. Alcohol consumption is known to increase GABA receptor function thereby increasing its neuroinhibitory effects.

Activation of the NMDA receptor is a step in the process of Norepinephrine and Dopamine release signaling. Increased Norepinephrine and Dopamine release cause systemic excitatory responses. Thus, NMDA is said to have a neuroexcitatory effect. Alcohol consumption is known to decrease the function of the NMDA receptor thereby decreasing its neuroexcitatory response.

Figure 1. Pathophysiology of Alcohol Use



Acute alcohol intoxication increases the actions of the GABA neuroinhibitory system while at the same time reducing the actions of the NMDA neuroexcitatory system. The figure demonstrates the
Adapted from Carlson RW, et al. 2012.

Alcohol Withdrawal Syndrome: Pathophysiology

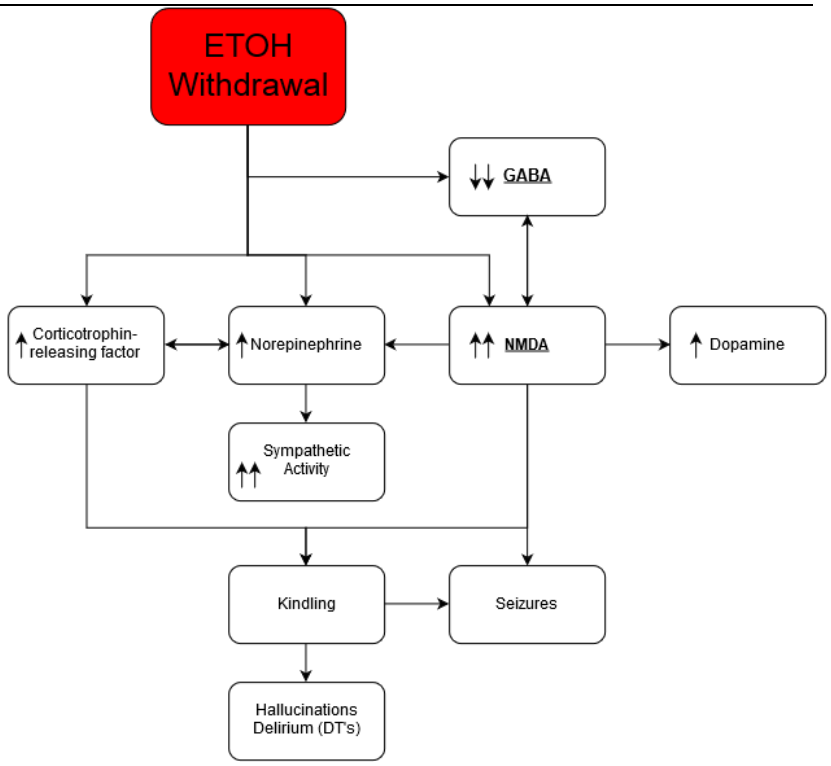
Prolonged alcohol consumption leads to compensatory changes in the GABA and NMDA receptors that result in symptoms of AWS (see Fig. 2).

Alcohol use increases GABA receptor function. Prolonged alcohol use exposes these receptors to constant activation. In order to compensate, there is an increase in the number of low-affinity GABA receptor sites. Despite the low-affinity of the GABA receptors, the presence of constant activation by consistent alcohol use allows for a constant GABA activity. However, when alcohol use is stopped there is no longer a constant activation of the now low-affinity GABA receptors sites and GABA neuroinhibitory activity is blunted. Thus GABA is unable to maintain its usual inhibitory effects.

Alcohol use decreases NMDA receptor function. Prolonged alcohol use provides constant inhibition of these receptors. In order to compensate, there is an upregulation of NMDA receptor function. Despite the upregulation of NMDA receptors, the presence of constant inhibition by consistent alcohol use allows for constant NMDA activity without signs of hyper-excitability. However, when alcohol use is stopped there is no longer a constant inhibition of the now upregulated NMDA receptors and NMDA neuroexcitatory activity is enhanced. Thus NMDA demonstrates elevated function and leads to increased production of Norepinephrine and Dopamine which result in symptoms consistent AWS.

In the United States, Benzodiazepines are the mainstay of therapy for AWS. Benzodiazepines are GABAergic compounds that that substitute for the GABA-modulating effects of alcohol. By increasing GABA activity, Benzodiazepines increase neuroinhibition and decrease the excitatory effects that cause the symptoms of AWS [McKeown].

Figure 2. Pathophysiology of Long-Term Alcohol Abuse



Chronic alcohol use downregulates GABA and upregulates NMDA. Sudden cessation of alcohol consumption results in symptoms caused by a physiologic state of hyper-excitability.
Adapted from Carlson RW, et al. 2012.

Alcohol Withdrawal Syndrome: Epidemiology

In general, approximately 10% of the U.S. population meet the criteria for an alcohol use disorder. Less than 50% of alcohol-dependent persons develop any significant withdrawal symptoms that require pharmacologic treatment upon cessation of alcohol intake [Burns, Goodson, Mckeown]. Of those individuals that do develop withdrawal symptoms, approximately 5% will develop delirium tremens (DTs) which is a potentially life-threatening severe form of withdrawal that includes symptoms of confusion, disorientation, hallucinations, fever, hypertension, profuse diaphoresis, and tachycardia [Burns]. Factors that increase risk and severity of AWS include higher levels of drinking, evidence of more severe alcohol related medical problems, and greater number of prior episodes of AWS [Schuckit]. In general, chronic alcoholism and withdrawal are more common among men than women [Mckeown].

Women in general have a decreased risk for alcohol dependence. Women have been found to start drinking at a later age, drink less per occasion, report fewer negative socioeconomic and legal consequences, are less likely to meet formal criteria for alcohol dependence, and are less likely to seek treatment than men [Deshmukh]. Despite this, Female alcoholics have several specific predispositions for higher risk of alcohol withdrawal. On average, women have a more elevated blood alcohol level than men after consuming a similar amount of alcohol secondary to the comparatively smaller body size and higher percentage of body fat and body water [Deshmukh, Schenker, US dept HHS, Wilsnack]. Women are also noted to produce greater amounts of acetaldehyde, a toxic byproduct of alcohol metabolism, due to greater amount alcohol dehydrogenase available to metabolize alcohol secondary to larger liver volumes per body weight [US dept HHS]. Higher levels of acetaldehyde have also been seen after alcohol ingestion in women taking oral contraceptives or during high estradiol phases of menstrual cycle. Although not yet confirmed in humans, rodent studies have shown that increased relative rates of alcohol elimination would result in more rapid formation of acetaldehyde and other toxic metabolites. With that in mind, men with decreased testosterone levels due to having undergone orchiectomy for prostate cancer have been shown to have increased rates of alcohol elimination whereas healthy men who were administered dihydrotestosterone each day for 14 days were noted to have lowered rates of alcohol

elimination [US dept HHS]. Ultimately, women are at higher risk of developing liver disease at any given level of alcohol intake when compared to men and they develop alcohol-related complications such as alcoholic hepatitis and alcoholic cirrhosis after drinking smaller daily amounts of alcohol than men do [US dept HHS].

Women are also more vulnerable than men to alcohol-related brain damage. They show brain volume losses on computer tomography scans after shorter lengths of excessive drinking compared to alcoholic men and they perform worse on neuropsychological tests of immediate recall and psychomotor speed than do alcoholic men with similar drinking histories [US dept HHS]. However, animal studies suggest that circulating estradiol exerts protective neurological effects in female rats that may very well occur in human women [Goodson]. Other animal studies have also demonstrated shorter recovery times from alcohol withdrawal in female rats [Devaud]. One notable animal study showed that, in rats with AWS, males show impairments in coordination but females do not and that ovarian steroids and/or their neuroactive derivatives are protective against seizure induction [Koirala].

In summary, factors that increase risk and severity of AWS include higher levels of drinking, evidence of more severe alcohol related medical problems, and greater number of prior episodes of AWS. Women are less likely than men to develop alcohol dependence. At the same time, alcohol dependent women are more likely to develop alcohol-related hepatic complications. Finally, rodent studies show that female rats with AWS recover sooner and are less likely to develop seizures.

Materials and Methods

Before initiation of the study and data collection, approval to access records and IRB approval was obtained through Maricopa Integrated Health System. This study is a retrospective single-center cohort comparison study of patients admitted to Maricopa Integrated Health System with a discharge diagnosis of Alcohol Withdrawal Syndrome (AWS) between January 1, 2010 and December 31, 2014. Medical record numbers (MRN) for these patients were obtained and utilized to access and review each patient chart in the hospital's electronic medical records (EMR); EPIC and ChartMaxx. This investigation separated patients into two groups to assess sex related differences in patients with AWS as well differences in patients in severe AWS. This distinction was made by level of care required during admission. Patients admitted to the Medical Intensive Care Unit (MICU) were considered to be in severe AWS. Patients with diagnoses of trauma, burns, or other surgical diagnoses were excluded from this study. Care was taken to exclude these patients due to the fact that these treatment settings are riddled with non-AWS related factors that prolong hospital stay. Factors include, but are not limited to, medically induced comas, injuries requiring extensive monitoring, and settings where alcohol is given prophylactically to prevent AWS.

All patients meeting inclusion criteria that were admitted to the MICU were compared. This group was considered to be the severe AWS group and included 19 women and 220 men. There were 99 women that met inclusion criteria for the non-severe AWS group. There were 16 women in 2010, 31 in 2011, 19 in 2012, 15 in 2013, and 18 in 2014 that met criteria. In order to make a direct comparison, 99 non-severe AWS men were randomly selected and matched per year. There were 12 males admitted for every 1 woman. Thus every 12^{th} male patient that met inclusion criteria was selected in chronological order.

This study sought to address a few specific questions regarding sex and AWS. Do women have more alcohol related hepatic complaints? Data regarding presence of hepatitis was obtained in both the MICU and non-MICU setting. Existing literature describes increased susceptibility to hepatic disease among women with alcohol dependence. We predicted that women included in this study would have higher incidence of hepatic disease than men.

Do women have fewer seizures? Data regarding presence of seizure was obtained in both the MICU and non-MICU setting. Animal studies suggest that ovarian hormones exert a protective effect against seizure. We predicted that women would have lower incidence of seizure. Do women recover from AWS sooner? Data regarding total MICU LOS was obtained for patients in severe AWS. Animal studies show that recovery from AWS occurs sooner in females. We predicted women would have shorter MICU LOS. Furthermore, overall LOS was obtained for patients in the MICU and non-MICU setting. We predicted that overall LOS would be shorter for women than men. In the non-MICU setting we also obtained data regarding Benzodiazepine administration. We predicted that women would require shorter length of Benzodiazepine therapy than men

Statistical Analysis

Patient demographic and clinical characteristics were assessed using mean, standard deviations for continuous variables and frequencies, percentages for categorical variables. To determine sex related differences in patients with severe AWS, patient age, total hospital length of stay (LOS), MICU LOS, need for intubation, length of time on ventilator, comorbidities (seizure, hepatitis, pancreatitis, sepsis, and pneumonia), and mortality rates of female patients admitted to the MICU were compared with those of male patients admitted to the MICU using the Wilcoxon Rank Sum for continuous variables and Fisher's Exact for categorical variables.

To determine sex related differences in patient with non-severe AWS patient age, total hospital LOS, comorbidities (seizure, hepatitis, pancreatitis, sepsis, and pneumonia), and mortality rates for female patients admitted to the hospital but not requiring MICU care were compared with those of male patients admitted but not requiring MICU care using the Wilcoxon Rank Sum for continuous variables and Fisher's Exact for categorical variables. For this group, data regarding Benzodiazepine administration was also collected. Benzodiazepines given at initial presentation while patients were receiving care in the Emergency Department (ED) as well as those administered while patients were admitted to non-MICU care were documented. Total amount of Benzodiazepines given in the ED were converted to mg/kg for both men and women. Total amount of Benzodiazepines administered during non-MICU admission were converted to mg/kg/day. Length of Benzodiazepine therapy, in days, was also recorded. The estimated mean difference in Benzodiazepines were assessed using linear regression after adjusting for other medications given during the patients' stay. All p-values were 2-sided and $p<0.05$ were considered statistically significant.

Results

A total of 1496 patient charts were identified. Of these, 437 charts were reviewed for this study. Overall, men treated for AWS were older than women by an average of 2.3 years. Men also had greater length of stay (LOS) in the Medical Intensive Care Unit (MICU) and overall. Women developed hepatitis and pancreatitis with greater frequency while men experienced seizure, pneumonia, and sepsis more often. See Table 1.

A total of 99 female and 99 randomly selected male patients meeting inclusion criteria were admitted to the hospital but did not require MICU care. Women were younger (44.4 years (SD 11) vs 46.1 years (SD 10.1). Men had longer LOS, 4.21 days (SD 2.86) for men and 3.96 days (SD 2.2) for women. There were 14 women (14.1%) that developed seizures compared to 15 men (15.1%). Hepatitis and pancreatitis occurred more frequently in women (21 women (21.2%) vs 16 men (16.2%) with hepatitis and 6 women (6.1%) vs 4 men (4.1%) with pancreatitis. One woman (1.1%) was diagnosed with sepsis. No men were diagnosed with sepsis. No men or women who died during non-MICU admission. See Table 2.

Furthermore, on average, women required more Benzodiazepines (in mg/kg) throughout their entire hospital stay than men did. They also required more of each individual Benzodiazepine than men did with the exception of Midazolam; women required 0.0002 mg/kg (SD 0.002) vs 0.0009 mg/k (SD 0.006) required by men. See Table 3.

In the Emergency Department, women required more overall Benzodiazepines than men did; 0.30 mg/kg (SD 0.68) vs 0.21 mg/kg (SD 0.30). Women also required more of each individual Benzodiazepine than men with the exception of Alprazolam and Midazolam; 0.0 mg/kg (SD 0.0) vs 0.0001 mg/kg (SD 0.001) and 0.0 mg/kg (SD 0.0) vs 0.0002 mg/kg (SD 0.002), respectively. See Table 4.

Table 1. Demographic and Clinical Characteristics

Characteristics	Overall N=437 (mean, SD)	Females N=118 (mean, SD)	Males N=319 (mean, SD)	P-Value[1]
Age, Years	45.6 (10.2)	43.9 (10.8)	46.2 (9.8)	0.05
Total Length of Stay, Days	6.9 (5.4)	4.5 (3.1)	7.7 (5.8)	<0.001
ICU Length of Stay, Days*	5.1 (4.7)	4.1 (4.8)	5.2 (4.8)	0.06
Intubation Length of Stay*	2.5 (4.9)	2.3 (5.4)	2.5 (4.8)	0.60
	N (%)	N (%)	N (%)	
Seizure	83 (18.9)	20 (16.9)	63 (19.8)	0.50
Hepatitis	85 (19.5)	27 (22.9)	58 (18.2)	0.27
Pancreatitis	27 (6.2)	10 (8.5)	17 (5.3)	0.22
Sepsis	13 (2.9)	1 (0.85)	12 (3.8)	0.20
Death	1 (0.23)	0 (0.0)	1 (0.31)	1.0
Setting				
Wards	198 (45.3)	99 (83.9)	99 (31.0)	<0.001
ICU	239 (54.6)	19 (16.1)	220 (68.9)	
Intubation*	96 (40.2)	7 (36.8)	89 (40.5)	0.75
Pneumonia	98 (22.4)	4 (3.4)	94 (29.5)	<0.001

[1]Wilcoxon Rank Sum Used to compare continuous variables. Chi-Squared/Fisher's Exact used to compare categorical variables.

*Includes those only admitted into the ICU.

Table 2. Demographic and Clinical Characteristics of Ward only patients

Characteristics	Overall N=198	Females N=99	Males N=99	P-Value[1]
	(mean, SD)	(mean, SD)	(mean, SD)	
Age, Years	45.3 (10.6)	44.4 (11.1)	46.1 (10.1)	0.30
Total Length of Stay, Days	4.09 (2.5)	3.96 (2.2)	4.21 (2.86	0.64
	N (%)	N (%)	N (%)	
Seizure	29 (14.7)	14 (14.1)	15 (15.1)	0.84
Hepatitis	37 (18.7)	21 (21.2)	16 (16.2)	0.36
Pancreatitis	10 (5.1)	6 (6.1)	4 (4.1)	0.51
Sepsis	1 (0.51)	1 (1.1)	0 (0.0)	1.0
Death	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Pneumonia	4 (2.02)	0 (0.0)	4 (4.1)	0.12

[1]Wilcoxon Rank Sum Used to compare continuous variables. Chi-Squared/Fisher's Exact used to compare categorical variables.

Table 3. Total Benzodiazepine Administration

	Overall N=198	Female N=99	Male N=99	Coefficient (95% CI)	P-value
All Drugs, mg/kg (mean, SD)	0.81 (0.94)	0.90 (1.09)	0.71 (0.75)	-0.05 (-0.13, 0.04)	0.27
Lorazepam, mg/kg (mean, SD)	0.37 (0.45)	0.36 (0.39)	0.37 (0.51)	0.01 (-0.12, 0.14)	0.83
Diazepam, mg/kg (mean, SD)	0.31 (0.59)	0.39 (0.75)	0.22 (0.34)	-0.17 (-0.33, -0.007)	0.04
Alprazolam, mg/kg (mean, SD)	0.0004 (0.003)	0.0004 (0.003)	0.0004 (0.003)	2.67e-5 (-0.001, 0.001)	0.95
Midazolam, mg/kg (mean, SD)	0.0006 (0.004)	0.0002 (0.002)	0.0009 (0.006)	8.3e-4 (-0.0003, 0.003)	0.17

[1]P-values calculated using Multiple Linear Regression adjusting for all other drugs given.

Table 4. Benzodiazepines Administered in the Emergency Department

	Overall N=198	Female N=99	Male N=99	Coefficient (95% CI)	P-values
All Drugs, mg/kg (mean, SD)	0.26 (0.52)	0.30 (0.68)	0.21 (0.30)	-0.12 (-0.26, 0.02)	0.10
Lorazepam, mg/kg (mean, SD)	0.03 (0.06)	0.04 (0.07)	0.02 (0.03)	-0.01 (-0.03, 0.003)	0.11
Diazepam, mg/kg (mean, SD)	0.22 (0.49)	0.26 (0.63)	0.18 (0.31)	-0.003 (-0.12, 0.12)	0.96
Alprazolam, mg/kg (mean, SD)	5.3e-5 (0.0007)	0 (0.0)	0.0001 (0.001)	0.0001 (-0.0001, 0.0003)	0.30
Midazolam, mg/kg (mean, SD)	0.0002 (0.002)	0 (0.0)	0.0005 (0.003)	0.0005 (-0.0002, 0.001)	0.17

[1]P-values calculated using Multiple Linear Regression adjusting for all other drugs given.

Of the patients admitted to non-MICU care, women required more overall Benzodiazepines than men did; 0.60 mg/kg (SD 0.71) vs 0.49 mg/kg (SD 0.69). Women required more Diazepam, Alprazolam, Clonazepam, Temazepam, and Midazolam; 0.12 mg/kg (SD 0.33) vs 0.04 mg/kg (SD 0.14), 0.0004 mg/kg (SD 0.003) vs 0.0003 mg/kg (SD 0.003), 0.0005 mg/kg (SD 0.005) vs 0 mg/kg (SD 0.0), and 0.004 mg/kg (SD 0.03) vs 0 mg/kg (SD 0.0), respectively. However, men required slightly more Lorazepam and Midazolam than women did during admission; 0.35 mg/kg (SD 0.49) vs 0.32 mg/kg (SD 0.37) and 0.0002 mg/kg (SD 0.002) vs 0.0004 mg/kg (SD 0.004), respectively. See Table 5.

220 male and 19 female patients meeting inclusion criteria were admitted to the MICU. MICU women were an average of 5 years younger than MICU men, 41.2 (SD 9.5) vs. 46.2 (SD 9.8). Men had a longer total LOS, 9.36 days (SD 6.1) vs 7.31 days (SD 5.0). Men also had a longer MICU LOS, 5.23 days (SD 4.8) vs 4.05 days (SD 4.9). Men required intubation more often, 89 men (40.5%) vs 7 women (36.8%), but both men and women had similar ventilator requirements 2.5 days (SD 4.8) of ventilation for men vs 2.3 days (SD 5.4) for women. Men developed pneumonia and sepsis more often; 90 men (40.9%) men vs 4 women (21.1%) with pneumonia and 12 men (5.5%) vs no women (0%) with sepsis. Women developed seizures, hepatitis, and pancreatitis more frequently than men; 6 women (31.6%) vs 48 men (21.8%) with seizures, 6 women (31.6%) vs 42 men (19.1%) with hepatitis, and 4 women (21%) vs 13 men (5.9%) with pancreatitis. 1 man (0.45%) perished in the MICU. There were no deaths among the women admitted to the MICU. See Table 6.

Table 5. Benzodiazepines Administered in non-MICU Floor

	Overall N=198	Female N=99	Male N=99	Coefficient (95% CI)	P-values
All Drugs, mg/kg (mean, SD)	0.55 (0.71)	0.60 (0.71)	0.49 (0.69)	-0.05 (-0.23, 0.12)	0.57
Lorazepam, mg/kg (mean, SD)	0.34 (0.44)	0.32 (0.37)	0.35 (0.49)	0.04 (-0.08, 0.15)	0.55
Diazepam, mg/kg (mean, SD)	0.08 (0.26)	0.12 (0.33)	0.04 (0.14)	-0.08 (-0.14, -0.02)	0.009
Alprazolam, mg/kg (mean, SD)	0.0004 (0.003)	0.0004 (0.003)	0.0003 (0.003)	-9.5e-5 (-0.00009, 0.0008)	0.82
Clonazepam, mg/kg (mean, SD)	0.0002 (0.003)	0.0005 (0.005)	0 (0.0)	0.0002 (-0.0007, 0.001)	0.64
Temazepam, mg/kg (mean, SD)	0.002 (0.02)	0.004 (0.03)	0 (0.0)	-0.004 (-0.01, 0.002)	0.16
Midazolam, mg/kg (mean, SD)	0.0003 (0.003)	0.0002 (0.002)	0.0004 (0.004)	0.0007 (-0.002, 0.002)	0.15

[1]P-values calculated using Multiple Linear Regression adjusting for all other drugs given.

Table 6. Demographic and Clinical Characteristics for ICU only patients

Characteristics	Overall N=239	Females N=19	Males N=220	P-Value[1]
	(mean, SD)	(mean, SD)	(mean, SD)	
Age, Years	45.8 (9.8)	41.2 (9.5)	46.2 (9.8)	0.03
Total Length of Stay, Days	9.20 (6.1)	7.31 (5.0)	9.36 (6.1)	0.10
ICU Length of Stay, Days*	5.14 (4.8)	4.05 (4.9)	5.23 (4.8)	0.06
Intubation Length of Stay*	2.50 (4.9)	2.26 (5.4)	2.52 (4.8)	0.60
	N (%)	N (%)	N (%)	
Seizure (yes, %)	54 (22.6)	6 (31.6)	48 (21.8)	0.32
Hepatitis (yes, %)	48 (20.1)	6 (31.6)	42 (19.1)	0.23
Pancreatitis (yes, %)	17 (7.1)	4 (21.0)	13 (5.9)	0.03
Sepsis (yes, %)	12 (5.0)	0 (0.0)	12 (5.5)	0.60
Death (yes, %)	1 (0.42)	0 (0.0)	1 (0.45)	1.0
Intubation (yes, %)*	96 (40.2)	7 (36.8)	89 (40.5)	0.75
Pneumonia (yes, %)	94 (39.3)	4 (21.1)	90 (40.9)	0.14

[1]Wilcoxon Rank Sum Used to compare continuous variables. Chi-Squared/Fisher's Exact used to compare categorical variables.

Discussion

Major highlights of this study demonstrate important differences between men and women with regards to AWS. To our knowledge, this is first study to directly compare demographic and AWS related outcomes between men and women. The demographic data analysis demonstrates trends which are in-line with current literature. More specifically, data analysis suggests that women are less likely to develop alcohol dependence, more likely to develop alcohol-related hepatic complications, equally if not more likely to develop seizures, and recover from AWS sooner than men. The results of this study merit further exploration to better further the medical communities understanding of sex related differences that contribute to the manifestation of AWS.

At the outset of data collection it became abundantly clear that a significantly larger population of men presented to Maricopa Integrated Health System with a diagnosis of AWS. Over the five years of charts that were reviewed there were approximately 11 men for every 1 woman admitted to the MICU. There was a similarly disproportionate number of male patients admitted for non-MICU care. Existing literature highlights various social factors that contribute to a decreased risk of developing alcohol dependence among women. Women have been found to start drinking at a later age, drink less per occasion, report fewer negative socioeconomic and legal consequences, are less likely to meet formal criteria for alcohol dependence, and are less likely to seek treatment than men [Deshmukh]. However, we can only assume that these factors play a role in our patient population. Data regarding age of onset of drinking, number of drinks per occasion, etc. was not available in the EMR and could not be ascertained via chart review.

The results of this study may also support the notion that alcohol dependent women are more likely to develop alcohol related hepatic complications. As predicted, women in this study were more likely to develop hepatitis than men in both MICU and non-MICU settings. Existing literature outlines key physiologic mechanisms and sex differences that contribute to this outcome, including elevated blood alcohol level for a similar amount of alcohol consumed, and greater production of toxic byproducts from alcohol metabolism due to variations in relative liver size, availability of alcohol dehydrogenase, and potentially the lack of male sex hormone.

One major limitation of these findings, however, is the small sample size of women compared to men in the ICU. With regards to non-MICU patients, comparison of equally sized cohorts shows a greater number of females developed hepatitis.

This study also looked for variations in the development of seizures. Animal studies suggest that ovarian hormones may be neuroprotective against the effects of alcohol withdrawal. To our knowledge there are no other existing studies that directly compare the development of seizures between men and women with AWS. We predicted that women would develop seizures at a significantly lower rate than men. However, we found that women admitted to the MICU were more likely than men to develop seizures, while men and women had essentially the same occurrence of seizures in the non-MICU setting. Benzodiazepine administration is the mainstay of treatment for patients with AWS, and these agents also possess anticonvulsive properties. Non-MICU women received more Benzodiazepines throughout admission than men and still developed seizures at a similar rate. This more strongly suggests that ovarian hormones may not exert the same neuroprotective effect in humans that are found in animal models.

Ultimately, our study sought to fill a gap in the existing literature. To our knowledge, there are no studies that directly compare men and women with AWS. Our prediction, given existing animal studies, is that women would recover sooner from AWS. Our study shows that women in severe withdrawal admitted to the MICU have shorter MICU and overall LOS. Women admitted to non-MICU care required greater amounts of Benzodiazepines upon presentation to the Emergency Department and throughout admission, this suggests that the women included in this study presented with more advanced symptoms of AWS. Despite this, women admitted to non-MICU care have shorter LOS and require shorter duration of Benzodiazepine administration compared to men.

This study is the first to directly compare outcomes and demographic differences among men and women who are admitted with AWS. Demographic data shows that women are less likely to develop alcohol dependence, more likely to develop alcohol-related hepatic complications, and recover from AWS sooner than men. Our data refutes animal studies that

suggest ovarian hormones exert a neuroprotective effect against seizures. Future studies would benefit from larger sample size consisting of multiple sites.

Future Directions

There are many future directions that this research can take. Directly comparing men and women in alcohol withdrawal is a novel idea despite the plethora of existing literature that harps on major existing and potential physiological differences. Further retrospective demographic studies across different sites can further characterize sex related differences. Prospective studies may potentially utilize surveys in order to better identify and quantify social factors that may contribute to the decreased risk of alcohol dependence suggested in this study. Furthermore, prospective studies may produce better, sex specific, treatment regimens.

Future studies may also seek to find correlation between AWS severity and exogenous hormone use among patients on regimens of supplemental testosterone, estrogen, or hormonal contraception. Such research may introduce data to support new treatment options.

Conclusions

Alcohol withdrawal in a constellation of symptoms that occurs when there is a significant decrease or abrupt cessation of alcohol intake occurs after a period on consistent consumption. Existing literature suggests that women are less likely to develop alcohol dependence, more likely to develop alcohol-related hepatic complications, less likely to develop seizures, and recover from AWS sooner than men.

This study supports existing literature and shows that women admitted to Maricopa Integrated Health Service with a diagnosis of Alcohol Withdrawal Syndrome have more hepatic complications, and recover from withdrawal sooner than men. Simultaneously, women were at least equally as likely to develop seizures; contrary to animal studies that suggest ovarian hormones provide some mechanism for neuroprotective against seizures.

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