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Sex Differences in Alcohol Consumption and Alcohol-Associated Liver Disease

Camille A. Kezer, MD; Douglas A. Simonetto, MD; and Vijay H. Shah, MD

Abstract

Alcohol-associated liver disease is becoming increasingly prevalent throughout the United States. Previously alcohol-associated liver disease was known to affect men more often than women; however, this gap between the sexes is narrowing. Studies show that women develop liver disease with lesser alcohol exposure and suffer worse disease as compared with men. This review article explores the increasing prevalence of alcohol-associated liver disease in women, reasons for changing patterns in alcohol consumption and liver disease development including obesity and bariatric surgery, proposed mechanisms of sex-specific differences in alcohol metabolism that may account for this discrepancy between men and women, and sex differences in treatment enrollment and response. Studies were identified by performing a literature search of PubMed and Google Scholar and through review of the references in retrieved articles. Search terms included alcohol-associated liver disease, alcoholic hepatitis, alcoholic cirrhosis, sex, gender, female, epidemiology, bariatric surgery, obesity, treatment. Due to the paucity of literature on some of the relevant subject matter and inclusion of landmark studies, no date range was selected. Studies were included if their methods were sufficiently robust and they made a comparison between the sexes that is clinically relevant. Understanding of the changing epidemiology and mechanisms of liver disease development unique to women are paramount in creating appropriate and effective interventions for women who represent a rapidly growing subset of patients with alcohol-associated liver disease.

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EPIDEMIOLOGY OF SEX AND ALCOHOL CONSUMPTION

Sex Differences in Alcohol Consumption and Alcohol-Associated Liver Disease

Alcohol use disorder is highly prevalent in the United States and causes significant morbidity and mortality. Alcohol-related liver disease is second to nonalcoholic fatty liver disease as the leading cause of cirrhosis in the United States.[1] Literature demonstrates a lifetime prevalence of severe alcohol use disorder in the United States in 18.3% of men and 9.7% of women.[2] This review article evaluates sex differences in alcohol-associated liver disease. Studies were identified by performing a literature search of PubMed and Google Scholar and through review of the references in retrieved articles. Search terms included alcohol-associated liver disease, alcoholic hepatitis, alcoholic cirrhosis, sex, gender, female, epidemiology, bariatric surgery, obesity, treatment. Due to the paucity of literature on some of the relevant subject matter and inclusion of landmark studies, no date range was selected. Studies were included if their methods were sufficiently robust and they made a comparison between the sexes that is clinically relevant. Multiple studies have demonstrated that men have significantly higher rates of alcohol consumption and high-volume drinking in comparison to women.[3] Men have been shown to consistently surpass women in drinking frequency, quantity, and rate of binge drinking; and this pattern has been demonstrated throughout the world and across different cultures. Women who previously consumed large amounts of alcohol are more likely to quit drinking than their male counterparts. The sizes of these sex differences vary across different

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cultures, demonstrating the multifactorial nature of alcohol consumption and drinking behavior.[4] A US study using the Centers for Disease Control and Prevention Underlying Cause of Death database found that the overall mortality from alcoholic liver disease in the United States has increased since 2006 in almost every age group and race, with the exception of non-Hispanic black men.[5]

Despite the overall increasing prevalence of alcohol consumption, multiple studies have shown that women develop alcohol-associated liver disease with lesser exposure and suffer worse disease than their male counterparts. A systematic review and meta-analysis of more than 2 million patients found that consumption of one to two drinks per day as compared with long-term alcohol abstinence was associated with an increased risk of liver cirrhosis in women, but not in men. Moreover, this study showed that the risk for the development of cirrhosis was consistently higher in women than in men for all levels of alcohol consumption.[6] A US population-based study comparing alcohol-associated liver disease in young (≤35 years old) versus older (>35 years old) patients found that younger patients admitted with alcohol-associated liver disease with acute-on-chronic liver failure were more likely to be women, Hispanic, and obese.[7] A retrospective observational study evaluating alcohol-associated liver disease epidemiology in three US databases found that the total number of hospitalizations in all patients with alcoholic cirrhosis increased by 19.8% from 2007 to 2014; this increase was more prominent in women who had an increased hospitalization rate by 33.5% as compared with an increase of only 14.7% in hospitalizations seen in men with alcoholic cirrhosis.[8]

There may be factors related to how alcohol is consumed that make women more vulnerable to liver disease than men. The United Kingdom Million Women Study evaluated alcohol consumption with meals, daily use of alcohol, and liver cirrhosis in more than 400,000 women without history of cirrhosis or hepatitis. This study demonstrated that women who consumed alcohol with meals had a relative risk (RR) of 0.69 for cirrhosis development compared with those who typically did not consume their alcohol with meals, after adjustment for amount consumed. Furthermore, this study showed that daily alcohol consumption in addition to not consuming alcohol with meals was associated with more than a doubling of cirrhosis incidence.[9] Although this article did not compare alcohol consumption between women and men, it highlights the effect of meal timing as an important risk factor for alcoholic cirrhosis in women.

There also appears to be sex-specific differences in liver disease progression in patients who achieve sobriety. A study of patients with biopsy-proven alcoholic hepatitis in the absence of cirrhosis evaluated serial biopsy specimens over an average of 1.7 years. This study found that four of seven women who abstained from alcohol developed cirrhosis within 1 to 2 years compared with zero of six men.[10] This study demonstrates that women may have increased liver disease progression despite sobriety in comparison to men.

ARTICLE HIGHLIGHTS

- Women are increasingly affected by alcohol-associated liver disease and develop more severe disease at lower levels of exposure than their male counterparts.
- Increasing overall prevalence of obesity and increasing bariatric surgery in women may contribute to the increasing prevalence of women with alcohol-associated liver disease.
- There are multiple proposed mechanisms that help account for the development of more severe alcohol-associated liver disease in women including differences in first-pass metabolism, differences in hormones, and differences in Kupffer cell activation.
- Women are less likely to seek treatment for alcohol-associated liver disease and are under-represented in the current literature on behavioral interventions and pharmacotherapy for alcohol addiction; however, the available literature supports that women do benefit from interventions even if their motivations for treatment and barriers for care are different from their male counterparts.

Alcohol-associated liver disease poses a significant opportunity for intervention in the prevention and treatment of chronic liver disease. Women represent a growing subset of the alcohol-associated liver disease patient population; and sex differences in trends in alcohol consumption and disease development and progression are important aspects of understanding the worse trajectory women tend to have as compared with men.

Sex Differences in Risk Factors for Alcohol-Associated Liver Disease

Obesity. Obesity is a known risk factor for the development and progression of alcohol-associated liver injury.[11] A study of more than 1500 patients evaluated whether age, sex, daily consumption of alcohol during the previous 5 years, duration of alcohol use, and being overweight or obese were risk factors for alcohol-associated liver disease. Results showed that age, female sex, and duration of alcohol use were independently correlated with cirrhosis. This study also found that being female and overweight were independent risk factors for the development of acute alcoholic hepatitis. Additionally, this study found that being overweight for 10 years or more was an independent risk factor for cirrhosis, acute alcoholic hepatitis, and steatosis.[12]

A cohort study of more than 1 million patients in the United Kingdom evaluated the association between body mass index (BMI) and alcohol consumption and the incidence of liver cirrhosis of any etiology in middle-aged women. This study found that as BMI increased above 25 kg/m^2, the incidence of cirrhosis increased. Approximately 17% of liver cirrhosis was found to be attributable to excess body weight and 42% was attributable to alcohol.[13] This study demonstrates that obesity is an important risk factor in the development of liver disease.

Interestingly, medications used for minimizing cravings for substances of abuse (such as naltrexone and bupropion) have been associated with reduced BMI in weight loss studies.[14,15] Therefore, these medications may have an additional benefit aside from sobriety assistance in promoting weight loss and liver disease risk reduction in overweight and obese patients with alcohol-associated liver disease. There is a paucity of literature comparing sex-differences as related to BMI in alcoholic liver disease, and further studies must be performed to evaluate if and how BMI affects alcohol-associated liver disease in both sexes.

Bariatric Surgery. Bariatric surgery is a treatment option for obesity and its associated medical comorbidities in patients with BMI greater than or equal to 40 kg/m^2 or those with BMI greater than or equal to 35 kg/m^2 with two or more obesity-related medical comorbidities. Approximately 80% of patients who undergo this surgery are female.[16] A survey of more than 300 readers of the *Bariatric Times*, 98% of whom had received gastric bypass and 94% of whom were female, found that 28% of participants endorsed problems with alcohol control after surgery in comparison to only 5% who endorsed problems with alcohol control before surgery.[17] A retrospective study compared patients with alcohol use disorder seeking treatment after undergoing Roux-en-Y gastric bypass surgery with obese controls also seeking treatment for alcohol use. This study found that the gastric bypass group had significantly more women and that they met criteria for alcohol use disorder at a younger age. Additionally, within the gastric bypass surgery group, patients drank significantly more alcoholic beverages per day after their surgery as compared with before their surgery.[18]

There are also likely neurohormonal consequences of gastric resection that contribute to alcohol use. Studies from rodent models show that the gastrointestinal feeding peptide, ghrelin, acts on receptors in the central nervous system to stimulate alcohol intake. Literature shows that alterations in ghrelin signaling as a consequence of surgical resection may contribute to changes in alcohol intake after gastric bypass surgery. Therefore, there may also be a neurobehavioral component of the reward pathway that is altered by gastric bypass surgery.[19] Interestingly,

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both in the media and even among the medical community, there is controversy over the topic of "addiction transfer" wherein a patient replaces an addiction to one substance for another, in this case being food for alcohol. This is a controversial topic for multiple reasons including lack of acceptance of food as a true addiction and the timeline of the development of alcohol use disorder after bariatric surgery is often delayed, occurring many months or years after surgery.[20] Therefore, despite there likely being neurobehavioral consequences of gastric bypass surgery, there is not widespread scientific acceptance of addiction transfer as an explanation for increased alcohol addiction after bariatric surgery.

Not only is alcohol consumption affected by gastric bypass surgery, but alcohol metabolism appears to be altered as well. A study of 36 subjects, half of whom had undergone gastric bypass surgery and the other half of whom served as controls, explored differences in alcohol metabolism as a consequence of gastric bypass surgery. The gastric bypass group had a significantly higher peak alcohol breath level and required greater time to return to zero on breath alcohol testing in comparison to normal weighted controls.[21] Bariatric surgery is far more common in women than in men, and this may be an additional risk factor contributing to sex differences in the development and progression of alcohol-associated liver disease.

Sex Trends in Alcohol Consumption

Although multiple studies have demonstrated that men are more likely to consume alcohol and are more likely to binge drink as compared with women, recent studies have shown that this gender gap is narrowing.[3,22] A study of more than 70,000 US citizens compared the prevalence of alcohol use trends among different demographics and socioeconomic statuses between 2001−2002 and 2012−2013. This study showed an average of 11% increase in alcohol use, particularly among women who had a 16% increase in consumption. This study also showed an overall increase in high-risk drinking, approximately a 30% increase overall, but again more notable among women who had a 58% change as compared with only a 16% change in men. Lastly, this study showed a 50% increase in the prevalence of alcohol use disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) with women showing an 84% change as compared with a 35% change seen in men.[23] This article hypothesized that, as the number of women in the workforce continues to increase and women attain increasing educational and occupational opportunities, these may contribute to normalization of alcohol consumption and increased high-risk drinking.[23,24] Similar results were demonstrated by another study of more than 70,000 patients worldwide which found that while men have more substance use disorders than women, there is a significant narrowing of the difference between men and women. This study showed that high gender role "traditionality" is associated with a decrease in the ratio of female to male substance use disorders.[25]

Reasons for Changing Trends in Women's Alcohol Consumption

The scientific literature demonstrates narrowing of the gap in alcohol consumption between men and women, but why are these changes in trends occurring? A multinational study entitled "Gender Differences in Public and Private Drinking Contexts: a multi-level GENACIS analysis" evaluated sex differences in public and private drinking that help answer this question. The study showed that country-level gender equality, equality in economic participation, educational attainment, and reproductive autonomy were variables predictive of drinking behavior in public venues. These results support the theory that countries with higher gender-equality have a smaller discrepancy in alcohol consumption in public venues between the sexes. This study also demonstrated that gender equality in education and reproductive autonomy may be relatively less contributory and political participation noncontributory to sex differences in alcohol use in public venues. This study

showed that the mean frequencies of men's and women's drinking in both public and private settings across various countries are highly correlated, indicating that there are non—sex related factors that contribute to drinking behavior. Interestingly, this study did not demonstrate any variables that explained the difference between men's and women's drinking in the private setting after controlling for country-level economic status. While the relationship was not significant, the direction of association was the opposite in the private setting from the public setting, wherein greater gender equality predicted a larger sex difference in men's and women's drinking in the private setting. This study demonstrates that alcohol consumption in the public and private settings are two different entities and both require evaluation, and therefore potential interventions will be different depending on the targeted setting.[26]

Sex Differences in Severity of Alcohol-Associated Liver Disease

Despite the continued higher prevalence of alcohol consumption in men than in women, women are more commonly affected by alcohol-induced liver injury.[27] The liver is the primary organ of alcohol metabolism and as such is the main site of injury in patients with excessive alcohol consumption. Alcohol-associated liver diseases include alcoholic hepatitis, alcoholic steatosis, alcoholic steatohepatitis, alcoholic fibrosis, alcoholic cirrhosis, and alcoholic hepatocellular carcinoma.[28]

In a 12-year prospective study of alcohol use of more than 12,000 patients in Denmark, in people who consumed 28 to 41 alcoholic drinks per week, women had an RR of 17.0 for alcohol-induced cirrhosis compared to an RR of 7.0 in men. This study also demonstrated that for any given level of alcohol intake, women had a higher relative risk of developing alcohol-induced liver disease and alcohol-induced cirrhosis compared with men.[29] A retrospective study of 701 patients with alcohol-induced liver disease found that in women, there was a significantly more rapid progression to cirrhosis (20 years on average) as compared with the rate of progression to cirrhosis in men (35 years on average).[30] In a study of 56 patients with alcohol relapse after recovery from severe alcoholic hepatitis, 17% of patients had recurrent severe alcoholic hepatitis, and there was a slight trend towards recurrence being more common in females, although this was not statistically significant.[31]

Although multiple studies have demonstrated sex differences in the development and progression of alcoholic liver disease, it remains unclear if there is a survival difference between men and women with alcoholic liver disease. In a large US trial of 490,000 men and women who reported their alcohol and tobacco use, mortality from alcohol-associated disease as a whole was not significantly different between men and women for those consuming two to three drinks per day. Mortality did increase in men who consumed four or more drinks per day.[27,32] Gender also has not been shown to be predictive of survival in acute liver failure.[33]

PROPOSED MECHANISMS OF SEX DIFFERENCES IN ALCOHOL-ASSOCIATED LIVER DISEASE

Alcohol Metabolism Overview

Serum alcohol levels are determined by the rate of alcohol absorption from the gastrointestinal (GI) tract, the volume of distribution in the body, and the rate of elimination.[34] Alcohol is absorbed throughout the GI tract, the majority of which occurs in the small intestine. Next it travels to the liver and then is distributed throughout the body water.[35,36] First-pass metabolism of alcohol occurs in the GI tract and first passage through the liver after which time the liver serves as the primary metabolizer.[36] Alcohol is eliminated from the body primarily through oxidation via the enzyme alcohol dehydrogenase (ADH); these enzymes are located throughout the GI tract and the liver as well as in other tissues including adipose, breast, brain, and whole blood.[34,36,37] Alcohol-related liver injury is caused by ethanol metabolism by ADH and cytochrome P450 2E1 pathways that produce the hepatotoxin acetaldehyde.[38]

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TABLE. Mechanisms of Sex Differences in Alcohol-Associated Liver Disease[a]

	Sex differences	Outcome
Mechanism		
Alcohol metabolism	Women typically have decreased body weight Women have decreased body water	Decreased volume of distribution of alcohol in women
First-pass metabolism	Women have decreased gastric ADH Women have slower gastric emptying of alcohol	Increased bioavailability of alcohol in women
Estrogen	Chronic alcohol consumption increases estrogen in male and female rodent models	Increased estrogen coincides with more significant liver injury in rodent models
Growth hormone	Female rodent models show continuous secretion of GH which leads to increased hepatic ADH activity	Increased accumulation of toxic acetaldehyde
Endotoxin and Kupffer cell activation	Estrogen sensitizes Kupffer cells to LPS in rodent models	Increased accumulation of pro-inflammatory cytokines

[a]ADH, alcohol dehydrogenase; GH, growth hormone; LPS, lipopolysaccharide.

There are known sex differences in the pharmacokinetics of alcohol. For equal alcohol intake, women develop higher blood alcohol levels when compared with men.[39] The reason for this is multifactorial. Females are generally smaller than males; therefore, the same alcohol consumption results in higher serum alcohol levels in females as compared with males.[38] Additionally, females have smaller body water content per kilogram of body weight when compared with males leading to a smaller volume of distribution.[38] The next sections of this review article will focus on sex-specific differences in alcohol metabolism and how this contributes to sex differences in alcohol-associated liver disease (summarized in the Table).

Differences in First-Pass Metabolism of Alcohol

Multiple studies have shown a difference between gastric ADH activities in women versus men. The metabolism of alcohol by gastric ADH decreases its systemic bioavailability. Therefore, the stomach protects against systemic absorption of alcohol via ADH activity.[38] A study of 17 nonalcoholic women, 14 nonalcoholic men, six alcoholic women, and six alcoholic men investigated sex differences in alcohol first-pass metabolism.[40] In this study, subjects were administered weight-based doses of ethanol either orally or intravenously. Both the alcoholic and nonalcoholic women had significantly higher blood alcohol concentrations compared with their male counterparts when the alcohol was ingested; there was no significant difference between the sexes when the alcohol was administered intravenously. As such, this study demonstrates that sex differences in alcohol-related liver disease cannot be solely accounted for by differences in volume of distribution. Furthermore, this study showed that nonalcoholic men had 70% to 80% higher gastric ADH activity compared with nonalcoholic women. Chronic alcohol abuse reduced gastric ADH by 37% to 46% in men as compared with only an 11% to 20% reduction in women. This study demonstrated that women have increased bioavailability of alcohol due to decreased first-pass metabolism, leading to increased susceptibility to liver disease.[40]

A study of 65 healthy patients examined differences in alcohol metabolism between men and women.[39] Subjects drank 0.3 g of ethanol/kg of body weight as 5%, 10%, or 40% solutions. With both the 10% and 40% concentrations, women had less first-pass metabolism than men and this was associated with significantly lower activity of gastric ADH in women as compared with men. Additionally, gastric emptying of alcohol was 42% slower in women and hepatic oxidation was 10% higher in women. This study concluded that decreased gastric metabolism in females due to significantly less active gastric ADH is

the primary reason for sex differences in serum alcohol levels.[39] Sex differences in gastric ADH activity are amplified in patients who have undergone gastric bypass surgery, wherein gastric alcohol dehydrogenase is circumvented, contributing to an increased risk of alcohol-associated liver disease related to first-pass metabolism.[21]

Hormones

Estrogen. Although the initial absorption and metabolism of alcohol differs between the sexes, there are additional mechanisms at the level of the liver that further contribute to sex differences in alcoholic liver injury. Multiple studies show that chronic alcohol intake alters hormone expression in both sexes. Not only is the liver the site of steroid hormone metabolism, but also it is responsive to sex hormones, and as such there is ongoing research being done to further characterize the role of hormones in alcoholic liver disease.[41] Estrogen modulates liver activity via estrogen receptors on hepatic cells. An experimental model in rats demonstrated alcohol increases estrogen receptor expression in male rat livers and that this is associated with hepatocyte proliferation. This was in contrast to female rat livers wherein alcohol intake did not increase estrogen receptor expression and, as such, hepatocellular apoptosis predominated over hepatocellular proliferation.[42] Additional rodent studies show that with chronic alcohol exposure, androgen-responsive functions in the male rat liver decrease and, subsequently, testosterone levels decrease and estrogen levels increase due to changes in liver estrogen metabolism. In these studies, the most significant liver injury occurred under the influence of high estrogen and low testosterone.[41,43] Studies of postmenopausal women show that those with chronic alcohol consumption have approximately two-fold higher estrogen levels.[41,44,45] Additional studies are needed to further evaluate the clinical implications of alcohol on hormone metabolism in humans, including research among different patient populations including pre- and postmenopausal women and those receiving hormone replacement therapy.

Growth Hormone. Estrogen stimulates growth hormone secretion.[46] Rodent models of growth hormone secretion show sex differences, wherein female rats continuously secrete growth hormone in contrast to pulsatile secretion in male rats.[38,47] Growth hormone increases hepatic ADH activity.[38] Rodent studies show that hepatic ADH activity is higher in females compared with males.[38,48] It is hypothesized that this increased hepatic ADH activity in females leads to increased accumulation of toxic acetaldehyde and that this contributes to the increased susceptibility of females to alcohol-related liver disease.[38]

Endotoxin and Kupffer Cell Activation

Excessive alcohol consumption disrupts the GI barrier and promotes bacterial translocation from the GI lumen into the portal vein.[38] Endotoxin is a lipopolysaccharide, a part of the outer wall of gram-negative bacteria. Kupffer cells are macrophages localized to the liver, and one of the many functions of these cells is to remove endotoxin, which results in Kupffer cell activation and cytokine secretion.[49,50] Kupffer cells produce proinflammatory cytokines and reactive oxygen species.[38]

A rodent model in which rats were administered estrogen found that peak serum tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine, in the liver was twice as high in rodents who received estrogen when compared with controls. This study concluded that estrogen sensitizes Kupffer cells to lipopolysaccharide (LPS), resulting in increased toxic mediator production.[50] There is a paucity of literature on the relationship between estrogen and Kupffer cell activity in humans, and further research must be done to evaluate if these findings in rodent models are clinically relevant.

SEX DIFFERENCES IN THE TREATMENT OF ALCOHOL-ASSOCIATED LIVER DISEASE

Although there are significant differences between the sexes in alcohol metabolism and

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the development and severity of alcohol-associated liver disease as outlined above, abstinence from alcohol is the cornerstone of therapy in both men and women. This highlights the importance of identifying patients with or at risk of alcohol abuse and providing them with effective treatment options.

Seeking Treatment

Only 15% of people who have had alcohol use disorder at some point in their lives seek treatment, and only 28% of people who have had both alcohol use disorder and dependence report having sought treatment.[51] Whereas the majority of patients with alcohol use disorder do not undergo treatment, multiple studies show that there is a relatively low proportion of female participants in substance abuse treatment programs.[52,53] This gender disparity in fewer women seeking treatment for substance abuse disorder has been attributed to unique barriers that women face when seeking care.[53] A study of more than 700 people in the United States found that women identified treatment affordability and availability as the two major barriers to care. This study also showed that female drinkers at-risk for the development of alcohol use disorder were more likely than men to have a lifetime history of sexual and physical abuse.[54]

This trauma that women are more likely to have experienced may make women less likely to enroll in these male-predominant addiction treatment programs. Additionally, trauma and subsequent associated psychiatric conditions may represent a potential need for concurrent therapy and rehabilitation that would be of aid in maintaining long-term sobriety. More research is needed to further delineate motivators and barriers to treatment unique to women so that targeted interventions can be successful in helping these patients remain abstinent.

Response to Behavioral Treatment

Alcoholics Anonymous (AA) is a widespread, well-known, and easily accessible addiction treatment program in the United States. Approximately one-third of AA members are women.[55,56] A study of more than 1700 adults, 24% of whom were female, evaluated if there were differences between the benefits of AA in men and women. This study found that the contribution of AA to days abstinent was similar between men and women. Although the beneficial effects of AA attendance on overall sobriety were consistent between men and women, this study did find differences in the ways in which AA benefits men versus women. Specifically, this study showed that social self-efficacy and the pro-abstinence social network accounted for approximately 91% of AA's effect for men as compared with only 57% of AA's effect for women. The investigators concluded that these differences may be related to gender-based social roles wherein the social community is of more significant benefit to men who may more frequently encounter high-risk drinking situations. This study also found a difference between men and women in negative affect, which is one's confidence in successfully abstaining from alcohol when experiencing negative emotions. For women, negative affect was associated with both abstinence and drinking intensity, highlighting that women's alcohol use may be more influenced by their ability to cope with negative emotions.[56]

Previously, there have been studies supporting the notion that women may have unique barriers to attending substance abuse treatment such as obtaining child care or lack of insurance coverage; however, much of this literature comes from studies that are of small sample size, limited to pregnant patients, and performed on patients with various substance use disorders. A study using data from the National Epidemiologic Survey on Alcohol and Related Conditions evaluated reasons why people do not seek treatment for substance abuse issues by gender and race. This study found that women endorsed attitudinal barriers to seeking care more frequently than men, but that there was no significant difference in reports of structural barriers (such as access to child care and cost). This article highlights that there may remain a stigma behind women consuming alcohol that has downstream repercussions including lack of insight

into recognizing oneself as having alcohol use disorder and therefore less incentive to seek care.[57]

There is a paucity of literature on the effectiveness of alcohol use disorder treatment programs in women, and women are underrepresented in most study cohorts; nevertheless, current studies do indicate that women benefit from AA and similar programs and as such should be referred by their physicians for addiction treatment. Women may benefit from women-only addiction treatment programs wherein their specific motivations for sobriety, such as negative affect and others yet to be identified, could be addressed.

Response to Pharmacotherapy

Few studies are available evaluating the response of women to pharmacotherapy in alcohol addiction treatment and men are frequently disproportionately represented in alcohol-related clinical trials.[58] Medications used for alcohol cessation include naltrexone, acamprosate, baclofen, and disulfiram. An open-label trial of 100 patients treated with increasing doses of baclofen for alcohol craving reduction found that the necessary maximal daily dose of baclofen in women was significantly lower than that in men to achieve craving control. The investigators believed that this was expected as the amount of daily alcohol consumption was also significantly less in women as compared with men.[59] Of the randomized control trials published on baclofen for alcohol use disorder, none provide analysis based on gender; therefore, further research is needed to study the efficacy and tolerability of baclofen in women.[60] A study evaluating differences between the sexes in alcohol addiction treatment in 380 women and 850 men compared the efficacy of placebo, naltrexone, and acamprosate, or their combination with or without a behavioral intervention. This study found that the percent of days abstinent and time to first heavy drinking day showed the same pattern in both sexes; both naltrexone therapy with medical management and behavioral intervention with medical management had better treatment responses in men and women than those taking placebo or any other individual or combination treatment. This study demonstrates that women are likely to benefit from naltrexone and/or behavioral therapy in the context of medical management with similar benefit to their male counterparts.[58]

CONCLUSION

There is a significant body of research showing increased susceptibility to alcohol-associated liver disease in women as compared with men. As the gap between increased alcohol consumption in men as compared with women continues to narrow, there will be increasing public health consequences related to alcohol-associated liver disease in women. The causes of this sex discrepancy in disease progression and severity are multifactorial, with many of the proposed mechanisms to date outlined above. More studies are needed to further delineate the mechanistic differences in alcohol metabolism between the sexes and potential contributing variables such as BMI and history of bariatric surgery, as these may be opportunities for therapeutic prevention and treatment. In order for any intervention to be meaningful, these patients must be able to maintain sobriety from alcohol in the future, and effective and accessible treatment options are integral to this process. Addiction treatment programs are more frequently attended by male patients, and more research needs to be done on the efficacy of these addiction treatment programs in women; however, the available literature favors that women do benefit from therapeutic intervention even though motivation for participation and barriers to care may differ. These differences must be further studied so that we can adequately care for this rapidly growing subset of patients with alcohol-associated liver disease.

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