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Are Cisgender Women and Transgender and Nonbinary People Drinking More During the COVID-19 Pandemic? It Depends.

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PURPOSE: This narrative review of research conducted during the first 2 years of the COVID-19 pandemic examines whether alcohol use among cisgender women and transgender and nonbinary people increased during the pandemic. The overarching goal of the review is to inform intervention and prevention efforts to halt the narrowing of gender-related differences in alcohol use.
SEARCH METHODS: Eight databases (PubMed, APA PsycInfo, CINAHL, Embase, Scopus, Gender Studies Database, GenderWatch, and Web of Science) were searched for peer-reviewed literature, published between March 2020 and July 2022, that reported gender differences or findings specific to women, transgender or nonbinary people, and alcohol use during the pandemic. The search focused on studies conducted in the United States and excluded qualitative research.
SEARCH RESULTS: A total 4,132 records were identified, including 400 duplicates. Of the remaining 3,732 unique records for consideration in the review, 51 were ultimately included. Overall, most studies found increases in alcohol use as well as gender differences in alcohol use, with cisgender women experiencing the most serious consequences. The findings for transgender and nonbinary people were equivocal due to the dearth of research and because many studies aggregated across gender.
DISCUSSION AND CONCLUSIONS: Alcohol use by cisgender women seems to have increased during the pandemic; however, sizable limitations need to be considered, particularly the low number of studies on alcohol use during the pandemic that analyzed gender differences. This is of concern as gender differences in alcohol use had been narrowing before the pandemic; and this review suggests the gap has narrowed even further. Cisgender women and transgender and nonbinary people have experienced sizable stressors during the pandemic; thus, understanding the health and health behavior impacts of these stressors is critical to preventing the worsening of problematic alcohol use.

KEYWORDS: alcohol; cisgender women; transgender persons and nonbinary populations; sexual and gender minorities; college students; COVID-19; pandemic; culturally responsive treatment

Although historically cisgender women (i.e., women whose sex assigned at birth is consonant with their gender) in the United States have had lower levels of alcohol consumption than cisgender men, recent analyses of historical and cohort data suggest that overall gender differences are narrowing.[1] This narrowing is largely due to substantial increases in cisgender women's alcohol use, binge drinking (operationalized as four or more drinks in 1 day for cisgender women; five or more drinks in 1 day for cisgender men)[1,2] and alcohol use disorder (AUD; meets criteria for past 12-month dependence or abuse as established in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders [DSM-V]*).[3] Cisgender women also report more barriers to treatment[4,5] and lower treatment utilization than cisgender men.[6-9] Given that cisgender women may experience more severe alcohol-related problems (e.g., problems in relationships or at work[10]) and health impacts than do cisgender men, even at lower levels of alcohol use,[11] understanding whether the pandemic has led to an increase in alcohol use among cisgender women is critically important.

Rates and risks for problematic alcohol use vary by sexual identity,[12-14] race/ethnicity,[15] and other factors, including socioeconomic status and relationship status.[16] These differences may be partially explained by differences in stress levels, including economic stressors and psychological distress[17] and may have been further modified by the coronavirus disease 2019 (COVID-19) pandemic. Research on mental health during the pandemic suggests that cisgender women experienced elevated rates of stress, anxiety, and depression compared to pre-pandemic rates,[18-20] at least in the early stages of the pandemic. In contrast, some research has suggested no gender differences in pandemic-related emotional distress.[21,22]

Stress is one of the strongest predictors of substance use, including alcohol use,[23] and higher levels of stressors increase risks for problematic alcohol use, including AUD.[24,25] The COVID-19 pandemic often has been described as a "perfect storm" of multiple sources of stress and has been linked to worsened mental health and health behaviors overall.[21,22,26-29] There is evidence of increased problematic alcohol use during previous pandemics;[30] however, the COVID-19 pandemic is unique among recent pandemics in the breadth and duration of its impacts and thus may have more substantial effects on health and well-being, including alcohol use. Cisgender women, compared to cisgender men, may be particularly affected by the pandemic due to higher levels of stressors.[31,32] These stressors may be related to negotiating working from home[28] while balancing remote schooling for children,[21,28] higher likelihood of working in frontline and/or caregiver jobs,[28,33] increased risks for intimate partner violence,[34-38] delays in accessing needed health care,[39] isolation,[40-42] and potentially higher risks for unintended pregnancies.[31] In a prospective study of families, cisgender women, compared to cisgender men, reported higher levels of stressors across four out of five domains. Specifically, cisgender women experienced higher levels of stressors in work/finances (31% increase), home disruptions (64%), social isolation (13%), and health care barriers (94%).[42] The burden of pandemic-related stressors, combined with chronic and cumulative stressors disproportionately impacting cisgender women (e.g., sexism and/or violence across the life span[43]), may result in allostatic overload, which heightens health risks.[44] When faced with higher levels of stressors during the pandemic, cisgender women may be at higher risk than cisgender men for alcohol consumption because cisgender women are more likely than cisgender men to use alcohol to cope with negative emotions.[24,45] Using alcohol to cope may have potentially disproportionate impacts on those experiencing the highest levels of stressors (e.g., frontline workers, parents).[42]

Transgender and nonbinary (TNB, i.e., people whose gender differs from their sex assigned at birth) individuals experience significant health disparities, and their health is negatively affected by high levels of stigma, discrimination, and violence, as well as low levels of support.[46-51] The COVID-19 pandemic may have been particularly stressful for TNB people compared to cisgender people due to elevated socioeconomic impacts such as job loss,[52] food[52] and housing insecurity,[53,54] as well as reductions in social and community support.[55-57] TNB people also have experienced disruptions to medical care (including gender-affirming services), which heightens stress.[53,56] Coping is a key motivation for alcohol use among TNB populations,[51,58,59] which might suggest increased use of alcohol to cope during a stressful event such as a global pandemic. Yet, research findings on rates of alcohol use among TNB populations are more mixed compared to cisgender people.[60-64] Problematic alcohol use is associated with increased risks for secondary harms that disproportionately affect TNB individuals, such as suicidal ideation, intimate partner violence, sexual violence, and the exacerbation of mental and physical health problems,[62,65,66] highlighting the importance of a deeper understanding of alcohol use among TNB individuals. Additionally, TNB people experience barriers to treatment,[67] including a lack of culturally responsive care options[68-73] and discrimination by providers.[68] Of note, the umbrella term "TNB" encompasses a diverse range of identities and experiences, but existing research often does not disentangle this diversity, instead aggregating across groups who fall outside of cis-normative gendered expectations and who then are compared with cisgender peers.

Understanding alcohol use among cisgender women and TNB people during the pandemic is particularly important due to risks for severe health outcomes. Not only are COVID-19 patients with AUD more likely to be hospitalized and to have higher all-cause mortality,[74] but alcohol-related mortality spiked with the onset of the COVID-19 pandemic.[75,76] Problematic alcohol use also is a major risk factor for COVID-19 infections and mortality.[77] Although the connections between COVID-19 and alcohol use have widespread effects, specific alcohol-related health impacts of the pandemic have been particularly harmful for cisgender women, as indicated by a 125% increase in alcohol-

associated hepatitis[78] and a stark increase in the proportion of patients screening positive for substance use (including alcohol use) in emergency departments.[79] To our knowledge, similar research has not been done among TNB populations.

This review aims to understand the unique experiences of cisgender women and TNB people, as well as among understudied groups of cisgender women such as women of color, sexual minority women (SMW, e.g., lesbian, bisexual, queer women), and older women to describe subgroup impacts of the COVID-19 pandemic on alcohol use. A recent scoping review of substance use during the pandemic noted the importance of examining substance use (including alcohol) during the pandemic among cisgender women and TNB populations.[80] Thus, this review aims to evaluate the extant literature testing whether cisgender women drank at similar or higher levels than cisgender men during the pandemic. The review further explores alcohol use among TNB populations during the pandemic, with a focus on gender differences in rates of alcohol use (e.g., binge drinking, alcohol dependence, quantity/frequency of drinking) in research conducted during the pandemic (since March 2020) in the United States.

Methods

Search Methods Employed

This narrative review of alcohol use during the pandemic was conducted to document whether alcohol use had increased among women—a population already experiencing inclines in alcohol use before the pandemic—and among TNB people in order to inform needed prevention and interventions, as well as to inform policy. The review process included seven steps:[81-83] (1) refining the topic and identifying the research question; (2) developing a protocol; (3) identifying relevant studies; (4) screening and selecting studies; (5) extracting the data; (6) critically appraising and synthesizing the data; and (7) reporting the results.

One author, a Health Sciences Library Informationist conducted the literature searches on July 15, 2022, in eight databases: PubMed (pubmed.gov); APA PsycInfo (EBSCO); CINAHL [Cumulative Index to Nursing and Allied Health Literature] (EBSCO); Embase (embase.com); Scopus (scopus.com); Gender Studies Database (EBSCO); GenderWatch (ProQuest); and Web of Science (webofscience.com). Because the review addresses two separate questions, two search strategies were used. The first strategy comprised a combination of search strings related to alcohol use, COVID-19, and women. The second strategy combined search strings for alcohol use, COVID-19, SMW, and TNB populations. No filters were applied to the search results.

All records found via the database searches were exported to an EndNote library (version X9). Duplicates were identified and removed in EndNote, and the remaining library was imported into the Covidence review software to facilitate identifying relevant articles for the narrative review. Articles were eligible for inclusion in this review if they met the following criteria hierarchically: (1) were published in peer-reviewed journals between March 2020 and July 2022; (2) were written in English; (3) used human participants in the United States (to reduce variability in responses to the pandemic); (4) included measurement of alcohol use (broadly defined); (5) collected data during the COVID-19 pandemic; and (6) included analyses of gender differences in rates of alcohol use or focused solely on cisgender women or TNB people and alcohol use during the pandemic. Articles were excluded if they were review papers or qualitative studies, if they did not conduct any gender differences analyses (unless the study focused on women or TNB samples only), and if alcohol was not an outcome.

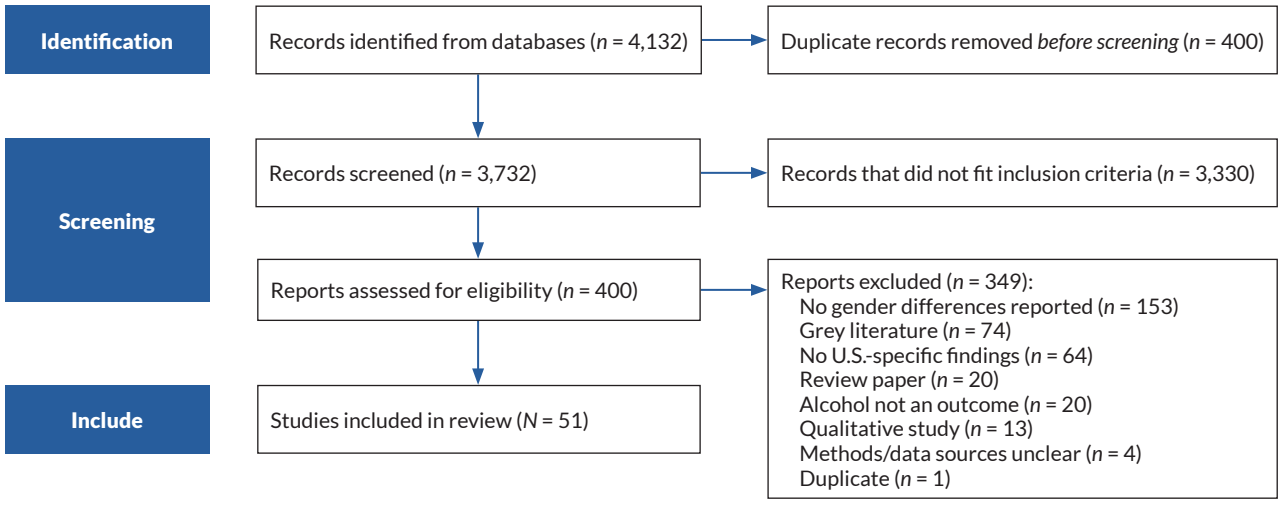

Figure 1. PRISMA flow diagram of search strategy used during the narrative review of women's alcohol use during the pandemic.
Note: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data Extraction

After conducting a title and abstract review of all articles, the authors reviewed the full text of the remaining papers to determine final inclusion. Differences were discussed amongst three authors until agreement was reached. The full texts of the 400 articles were assessed for relevance to the review's aims. When an article was excluded during the full review, authors documented the reason for its exclusion. (See Figure 1 for the search strategies for both questions combined.) Three authors critically reviewed and synthesized data from the 51 included articles.

Results

Results of the Literature Search

The literature search identified a total of 4,132 records. There were 400 duplicates, leaving 3,732 unique records for consideration in the review; of these, 51 articles ultimately were included.

Results of the Reviewed Studies

Appendices 1 and 2 (located after the references) list the 51 reviewed articles and include all data from the abstraction protocol. Consistent with the goals of a narrative review, potential methodological limitations of the research are highlighted to help the reader better evaluate the validity and generalizability of the findings. The results are broken into four sections: (1) prevalence; (2) specific populations and demographic differences (age, race/ethnicity) or life experiences (pregnancy, intimate relationships, frontline work); (3) linkages between alcohol and mental health, stress, or coping; and (4) TNB individuals and SMW.

Table 1 includes descriptive data of the studies reviewed. Of those, 24% included nationally representative samples, 36% included pre-pandemic data (as opposed to retrospective reporting or only having within-pandemic data), 51% had data collection that ended early in the pandemic (March–May 2020), and 16% had data collection that ended in 2021. Slightly more than one-quarter (26%) used the Alcohol Use Disorders Identification Test (AUDIT) or AUDIT-Consumption (AUDIT-C), with several studies using just one or two items from the AUDIT. In addition, 6% used another validated measure, and 29% examined quantity and frequency only. Of those studies that looked at gender differences (as opposed to having a sample of cisgender women only), 73% found gender differences in alcohol use.

Of the 51 studies that met inclusion criteria, 20 studies tested for trends over time in alcohol use, including the pandemic period. Table 2 summarizes the results of those 20 studies, including the number of studies that found increases, decreases, or no change in alcohol use. Overall, 12 of the 20 studies documented increases in alcohol use during the pandemic period. More studies documented increases among cisgender women than among cisgender men (8 and 6 out of 13, respectively), and the only study with sufficient data to test for trends among TNB individuals found increases in alcohol consumption.

The following sections present the results in more detail, organized by prevalence data; specific subpopulations; stress, coping, and mental health; and alcohol use among SMW and TNB people. Not all studies had mutually exclusive samples; thus, studies may be mentioned in more than one section.

Prevalence

Eighteen studies were primarily aimed at describing prevalence of alcohol use among adults during the pandemic and included analyses of gender differences. These studies were divided into two groups: cross-sectional studies (including repeated cross-sectional studies) of adults and longitudinal/prospective studies of adults.

Cross-sectional general population adult studies

Nine cross-sectional studies,[79,84-91] all conducted during the early pandemic, met inclusion criteria. All used convenience samples, with two samples recruited from social media. In three studies that asked participants to compare retrospectively their pre-pandemic AUD symptoms to current symptoms,[85-87] all found increased reports of AUD symptoms among cisgender women during the early pandemic compared with retrospective reports of pre-pandemic symptoms. In one study, cisgender men also reported increases;[85] in another, they did not;[86] and in the third study cisgender women reported increased drinking more often than did cisgender men.[87] A fourth study found no gender differences in self-defined "drinking behaviors" during the early pandemic.[88] Across these studies, the cross-sectional design—including retrospective reporting of pre-pandemic drinking behaviors and AUD symptoms as well as use of convenience samples based on volunteers from social media—limit the conclusions that can be drawn from these studies.

Three general population adult studies used repeated cross-sectional assessments (with different samples at each time point) before and during the pandemic to compare rates across time.[79,84,89] Using nationally representative samples, Kerr et al.[89] documented that daily drinking and alcohol volume were higher among cisgender women interviewed during the pandemic through 2021 compared to those interviewed pre-pandemic. AUD prevalence across the continuum from mild to severe was also higher during the pandemic. Sensitivity analyses indicated that results were robust to the timing of interviews and thus unlikely to be affected by pandemic-related social distancing policies. Electronic health record data of more than 100,000 patients visiting emergency departments showed higher alcohol admissions and evaluations for cisgender women during the pandemic compared with rates before the

Table 1. Descriptives of Studies Included in Review

	n	%
Data collection start		
Early pandemic (March–May 2020)	26	51.0%
Late 2020	7	13.7%
Pre-pandemic	18	35.3%
Data collection end		
Early pandemic	26	51.0%
Late 2020	17	33.3%
Early 2021	7	13.7%
Late 2021	1	2.0%
Study design		
Prospective	20	39.2%
More than one cross-sectional time point	7	13.7%
Cross-sectional	24	47.1%
Samples included		
Cisgender women only	4	7.8%
Cisgender women and men	33	64.7%
Cisgender women, men, and TNB people	4	7.8%
Cisgender women and TNB people	10	19.6%
Comparison groups		
Cisgender men	36	70.6%
TNB individuals	1	2.0%
Cisgender men and TNB individuals	9	17.6%
No comparison group	5	9.8%
Sample recruitment		
Nationally representative	12	23.5%
Convenience	8	15.7%
Convenience: Online/social media	20	39.2%
Clinic sample	5	9.8%
Undergraduates (various recruitment methods)	5	9.8%
Other	1	2.0%
Drinking measurement		
AUDIT or AUDIT-C	13	25.5%
Daily drinking questionnaire	3	5.9%
Quantity and frequency	15	29.4%
Quantity	3	5.9%
Frequency	7	13.7%
Perceptions	5	9.8%
Other validated scale	3	5.9%
Other	2	3.9%
How change was measured		
Pre- and post/during pandemic data	10	19.6%
Retrospective recall of pre-pandemic AUDIT	1	2.0%
Retrospective report of current drinking in past vs drinking now	4	7.8%
Self-perceived changes in alcohol use	14	27.5%
Self-report of current drinking at more than one time point	12	23.5%
Did not measure changes in drinking	10	19.6%

Note: AUDIT, Alcohol Use Disorders Identification Test; AUDIT-C, AUDIT-Consumption; TNB, transgender or nonbinary

Table 2. Summary of Results for Changes in Drinking After Onset of COVID-19 Pandemic

	Number of Possible Studies	Proportion With Finding*	
		n	%
Overall			
Alcohol use or problems increased	20	12	60.0%
Alcohol use or problems decreased	20	5	25.0%
Alcohol use or problems did not change	20	3	15.0%
Cisgender Women			
Alcohol use or problems increased	13	8	61.5%
Alcohol use or problems decreased	13	2	15.4%
Alcohol use or problems did not change	13	3	23.1%
Cisgender Men			
Alcohol use or problems increased	13	6	46.2%
Alcohol use or problems decreased	13	3	23.1%
Alcohol use or problems did not change	13	4	30.8%
Transgender and Nonbinary Individuals			
Alcohol use or problems increased	1	1	100%
Alcohol use or problems decreased	1	0	0%
Alcohol use or problems did not change	1	0	0%

*Percentages within each group may not total 100% due to rounding. *Note:* COVID-19, coronavirus 2019.

pandemic.[79] In contrast, expenditure data, as an indirect measure of alcohol consumption, indicated lower household alcohol expenses during the pandemic, compared with pre-pandemic levels, for both cisgender men and cisgender women. However, expenditures may not correlate precisely with volume sales—for example, if purchases moved from on-premise to off-premise.[84]

Repeated cross-sections of data provide sufficient rigor for assessing changes in time trends, and all three studies included pre-pandemic time points, a notable strength. Given that two of the three studies found that increases in relatively serious alcohol-related harm (e.g., AUD, alcohol-related emergency department admissions) are concentrated among cisgender women, these data indicate an emerging concern.

Longitudinal general population adult studies

Nine longitudinal studies of adults in the general population met inclusion criteria.[92-100] Three of these were based on a single data source, the Understanding America Study (UAS),[92,95,97] a nationally representative panel study conducted monthly, with published data through mid-2020. All three studies from UAS demonstrated increases in alcohol consumption during the pandemic using repeated-measures longitudinal analyses, including increases in drinking days and near-daily drinking among cisgender women. However, these increases generally were less than those seen in cisgender men and remained below drinking levels among cisgender men.[92,95,97] In a representative online sample of adults, among those who reported any alcohol use, cisgender men had higher levels of alcohol use (i.e., average number of drinks per day) than cisgender women at baseline (April–June 2019). However, alcohol use in cisgender men declined over time (last wave of data collection was in March 2021), whereas it stayed the same over time in cisgender women.[100] In an additional nationally representative study with data from 2019 through the early months of the pandemic, days consuming alcohol and heavy drinking days (defined as five or more drinks within "a couple of hours" for cisgender men and four or more drinks for cisgender women) increased among cisgender women.[99] Of note, however, no longitudinal studies of the general adult population included data beyond January 2021, and no studies published in 2022 met inclusion criteria for this review.

Given that surveys were completed by telephone both before and during the pandemic, it is unlikely that study methodology was substantially impacted by COVID-era research policies, although an impact on willingness to participate in research (either more or less willing) cannot be excluded and could be a limitation. However, taken together, the available research indicates that days consuming alcohol and heavy drinking days on average increased among cisgender women in the general population during the early and middle periods of the pandemic, but that for both variables, their consumption levels largely remained lower than, and did not change at the same rate as, those of cisgender men.

Specific Populations and Demographic Differences

Several studies focused on unique subpopulations of cisgender women and alcohol use during the pandemic. The following sections discuss unique impacts on different age groups, different racial/ethnic populations, cisgender women in couple relationships, those who are pregnant or who are parents, and those who are frontline workers.

Adolescents, young adults, and older adults

Five cross-sectional studies met inclusion criteria; four[101-104] were among young adult college undergraduates, and one was a nationally representative survey of high school students.[105] No study had pre-pandemic data, and data collection spanned from early in the pandemic through early 2021. In the only nationally representative study of high school students meeting inclusion criteria,[105] cisgender women students had higher rates of current alcohol consumption (defined as at least one drink in the past 30 days) than cisgender men students but did not report that they thought they drank more due to the pandemic. A cross-sectional survey of undergraduate college students conducted in fall 2020, with retrospectively reported pre-pandemic drinking, indicated increased consumption during the pandemic among all groups.[103] Moreover, consumption and increases in consumption were greater among cisgender men compared with cisgender women and TNB individuals. Sexual minority groups generally reported higher levels of alcohol consumption and greater increases compared with pre-pandemic levels in both the high school and college samples; however, none of the studies examined interactions between sexual identity and gender. When coupled with the use of convenience samples, the cross-sectional designs and retrospective reporting limit inference from studies among college students.

Two studies included repeated cross-sectional samples of college students,[103,104] one of which included pre-pandemic data collection.[103] AUD prevalence was higher during the pandemic compared with pre-pandemic, with increases concentrated among cisgender women compared with cisgender men. For example, 49.7% of cisgender women met criteria for AUD during the pandemic, compared with 34.4% before the pandemic.

Seven studies[106-112] included longitudinal data among young adults (two of the seven from the same data source[109,110]). All had pre-pandemic data points, a major strength of the evidence base. However, the span of pandemic data collection was limited to the early pandemic through late 2020. Two had nationally representative data (most used convenience samples).[108,112] Most of these studies only reported data through spring 2020, which provides a limited assessment of pandemic-era changes in alcohol consumption, and findings regarding gender differences were mixed. Five of seven studies reported no gender differences in drinking as indicated by average past 3-month drinking quantity;[108] self-assessment of changes in drinking during the pandemic; and binge drinking (i.e., five or more drinks in a row).[110,111] A sixth study reported higher odds of drinking (any drinking on previous day) among cisgender men compared with cisgender women but noted no changes during the pandemic period.[112]

The remaining studies of college students and young adults generally found either faster declines in drinking among cisgender men,[106] or faster increases,[109] compared with cisgender women. A study comparing alcohol consumption during college spring semester across 3 years (2018, 2019, and 2020) found that whereas alcohol consumption (operationalized as number of drinking days and drinks per day) generally increased during spring semesters pre-pandemic, alcohol consumption either did not increase or declined in 2020 depending on the measure;[107] no gender differences were found. The most robust studies (e.g., Jaffe et al. 2021[107]) indicate that college drinking largely declined in the early pandemic period, which is expected as students moved off campus, but there is little evidence for gender differences in these declines.

In sum, research among college students and young adults is mixed. Some studies found higher levels of alcohol use among cisgender men and some among cisgender women; however, overall, there were no increases in alcohol use among cisgender young women during the pandemic. Only one study identified for this review focused on older adults.[113] In this study, which included a nationwide sample of older adults, cisgender women accounted for 59% of those who reported drinking more than usual during the pandemic.

Demographic differences by race/ethnicity

Only two studies focused on race/ethnicity and alcohol consumption during the pandemic.[114,115] Among a sample of American Indian cisgender women followed prospectively through October 2021, approximately a quarter reported self-perceived increased consumption and half reported binge drinking (i.e., four or more "standard" drinks per day) during the pandemic.[114] Among Black, indigenous, and other people of color (BIPOC) undergraduate students prospectively followed from before the pandemic through spring 2020, declines in drinking frequency were reported, but cisgender women, compared with cisgender men, were less likely to show declines.[115] Overall, the sparse research is mixed on alcohol use among BIPOC cisgender women during the pandemic, suggesting that more research is needed.

Couple relationships and pregnancy

Three studies that met criteria for inclusion examined potential differences in alcohol use among cisgender women and their partners in heterosexual couple relationships and among cisgender pregnant women; one study also investigated how early parenthood might impact cisgender women's alcohol use during the pandemic.[116-118] The study of cisgender women and

their men partners during the pandemic detected no gender differences in drinking levels; however, cisgender men reported more alcohol problems than did cisgender women. Cisgender women's general stress and financial stress had no impacts on their partners' drinking (drinks per week); however, cisgender men's stress was associated with an increase in their partners' drinking and a 22% increase in their own and their partners' high-intensity drinking (defined as 10 or more drinks per day for men and eight or more drinks per day for women).[118]

There are mixed findings among pregnant cisgender women in reports of changes in alcohol use during the pandemic. Among a convenience sample of pregnant cisgender women, 11% reported perceived increases in their own and 28% in their partners' alcohol use since the pandemic's beginning. In contrast to these findings, none of the pregnant cisgender women in a study of centers for high-risk pregnancies reported self-perceived increases in alcohol use since the start of the pandemic.[116] Notably, in the same study, 10% of postpartum cisgender women reported increased alcohol use.[116]

Together these findings suggest that in couple relationships during the pandemic, cisgender men's stress levels and drinking may be associated with increased alcohol use and high intensity drinking among cisgender women. Findings among pregnant and postpartum women are mixed but suggest pregnancy and postpartum periods may heighten risk for some cisgender women. However, research was lacking on pregnant and postpartum TNB people during the pandemic, and further work should examine the impact of pregnancy more inclusively.

Frontline workers

Due to high levels of stress and risks for exposure to COVID-19 for health care and other frontline workers during the pandemic, research on health and health behaviors is important for understanding the broad impacts on this population. Yet, only two studies on frontline workers met inclusion criteria.[85,119] Among health care workers in New Orleans, there were no significant gender differences in AUDIT-C scores. However, cisgender men's rates of high-risk drinking (defined as a score of 4 or greater) stayed the same over time (45% at both time points), whereas cisgender women's rates of high-risk drinking were higher during the pandemic compared to pre-pandemic (48% vs. 45%, respectively).[85] In another study among health care workers at 25 hospitals, adjusted analyses found that cisgender women were no more likely than cisgender men to have symptoms consistent with probable AUD despite significantly higher likelihood of probable post-traumatic stress disorder (PTSD).[119]

Coping, Stress, and Mental Health

The literature search yielded 10 studies that analyzed gender differences in alcohol use and also tested associations between stress or mental health and alcohol use during the pandemic.[94,100,119-126] However, only five of these studies examined whether the associations between alcohol and stress or mental health differed by gender,[94,100,120,121,124] three of which included pre-pandemic data.[100,120,124] Two studies demonstrated mixed findings about drinking to cope early in the pandemic among cisgender women.[100,120] One study found significant associations between COVID-related stressors and drinking to cope, with stronger associations for cisgender men than cisgender women.[120] In the other study, stronger coping motives for drinking were associated with higher drinking levels at baseline for cisgender women, and loneliness and coping were related to changes in drinking levels over time.[100]

Analyses using data from a quasi-experimental study of a nationally representative sample determined that cisgender women interviewed during the pandemic (compared to cisgender women interviewed pre-pandemic) were nearly 1.5 times more likely to report that drinking helped them forget their worries.[124] Among cisgender women, single women (compared to married women) were more likely, and Black women (compared to white women) were less likely to report drinking to forget their worries. Cisgender women with moderate to severe symptoms of depression (compared to no depressive symptoms; adjusted odds ratio: 2.45) and mild symptoms of anxiety (compared to no anxiety symptoms; adjusted odds ratio: 1.62) were significantly more likely to say that drinking helped them cope with their worries.[124] There were no differences among cisgender men and no differences in comparisons between cisgender women and cisgender men. Depression and anxiety were associated with heightened risks for alcohol use[121] and drinking to cope[124] among cisgender women during the pandemic.

TNB Individuals and SMW

TNB populations

Seven studies documented how the COVID-19 pandemic has impacted TNB people's drinking.[101,115,127-131] These studies included five cross-sectional and two prospective analyses, primarily began data collection in early pandemic, and all had trans-specific sample sizes of 200 or less. Within the literature that examined the drinking behaviors and trajectories of TNB people following the onset of COVID-19, the referent group to which TNB people were compared varied across studies. In some studies, the comparison was between TNB people and cisgender (or specifically cisgender and heterosexual) peers.[128,130,131] In other studies, TNB people were aggregated and compared against cisgender women.[115,127,129] One study included solely TNB people and evaluated their current behaviors against their retrospectively reported pre-pandemic behaviors.[101]

These comparisons provide differing information on TNB people's drinking during the COVID-19 pandemic. Comparisons

between TNB people and cisgender women, which were assessed at a variety of pandemic time points, typically found no significant differences between these groups in terms of alcohol use frequency (e.g., number of drinks consumed in a given day), alcohol use changes (e.g., self-reported drinking frequency before and during the pandemic), and likelihood of drinking to cope.[115,127,129] For the literature comparing TNB populations to cisgender or cisgender/heterosexual peers more generally, TNB people and cisgender/heterosexual peers had comparable rates of increased drinking during the pandemic (TNB: 10.5%; cisgender/heterosexual: 13%) and were equally likely to exhibit problem drinking (based on PROMIS scores).[131]

Compared to cisgender men and SMW peers, TNB respondents reported a lower likelihood of problem drinking (using AUDIT),[130] even though they reported higher psychological distress during the early pandemic.[128] However, based on self-report, TNB respondents were more likely to report substantial increases in drinking during the pandemic. Notably, these results are drawn solely from college students.[130]

Other research on college students that drew from a more general sample addressed these substantial changes in drinking due to the pandemic, finding that mean number of drinks in the past 30 days among "non-cisgender" people, using the phrasing of that study, rose from 9.2 pre-pandemic (February 2020) to 16.8 during the pandemic (October 2020). However, these levels were lower than among either cisgender men or women peers.[101] Extant research on TNB people's drinking during the pandemic yielded conflicting results, with the most common result being null findings of differences between TNB people and cisgender peers across a number of drinking outcomes (though this varied based on the specific comparison being drawn). This small pool of research also lacked examinations of other TNB-specific factors that may influence drinking during the pandemic, such as transphobic experiences or sustained access to trans-related and trans-affirming health care as a preventive measure against psychological distress.

Sexual minority women

Four studies included findings specific to cisgender SMW.[127,128,132,133] More SMW than any other group reported self-perceived increases in alcohol use since the start of the pandemic (39% vs. 33% of sexual minority men and 24.5% of cisgender heterosexual women).[133] Two of the studies used the same sample but reported on different time points in recruitment (earlier in recruitment[132] and after all participants had been recruited[127]). Among participants who were recruited earlier in the study/pandemic, most reported increased anxiety and depression since before the pandemic (more than 90%), but fewer reported increases in drinking (40% to 55% reported increases in drinking quantity, frequency, or both).[132] Increases in anxiety and depression were associated with more alcohol consequences and motivation to drink to cope. In the analysis of the entire sample, participants indicated drinking on 26% of days as compared to using cannabis on 32% of days. On drinking days, participants consumed an average of almost three drinks per day and endorsed coping motives on 57% of drinking days.[127] Overall, findings indicate higher incidence of increased alcohol use during the pandemic among sexual minority women compared to cisgender heterosexual women and sexual minority men; these increases were associated with higher risks for poor mental health. Notably, none of the studies reviewed included pre-pandemic data, and only one study was prospective.[127] Two studies including sexual identity difference analyses (e.g., bisexual compared to lesbian cisgender women) within sexual minority women found few to no differences.[127,128] Three studies included only young adults;[127,128,132] only one study included participants from a wider age range (anyone older than age 18 was eligible).[133]

Discussion

This review of the extant literature suggests that alcohol consumption, and especially reports of alcohol-related problems such as AUD symptoms, increased among adults in the United States during the pandemic. Although not all studies were entirely concordant, many increases in the most serious consequences of alcohol consumption seemed to be concentrated in cisgender women. That said, most studies, especially those representative of the U.S. population, indicate that alcohol consumption and alcohol-related harms remain higher among cisgender men. With respect to different subpopulations, data among young adults suggest that alcohol consumption in this age group declined in the early pandemic, with little evidence for gender differences in the decline. Too few studies have focused on cisgender BIPOC women, frontline workers, and older cisgender women to draw broader conclusions, suggesting a need for more research among these populations that have experienced stark disparities in the impacts of the pandemic.[33,42,134-138]

In the limited research that examined alcohol use among TNB populations, evidence suggests minimal differences in drinking frequency and other drinking outcomes (e.g., rates of increased drinking) between TNB and cisgender populations, at least when the comparison was between TNB people and either cisgender women or cisgender/heterosexual individuals.[115,127,129,131] When compared with sexual minority college students, TNB college students had a lower likelihood of problem drinking (as determined using AUDIT) and a higher likelihood of self-reporting substantial changes in drinking during the pandemic.[130] TNB college students exhibited increases in mean number of

drinks in the past 30 days over the pandemic, but baseline levels were lower than in cisgender men and women peers.[101] However, this body of research would benefit from clearer, more nuanced analyses that disentangle the rich diversity of TNB identities and stratify cisgender people by gender and sexual identity. Further research also is warranted on the specific experiences of TNB college students, as this population exhibited unique patterns. Additionally, research on pandemic drinking trajectories among TNB populations would benefit from a stronger emphasis on trans-specific experiences and stressors that may influence alcohol use; this research should be encouraged as an avenue of further inquiry.

Research among LGBTQ people during the pandemic broadly seems to suggest few to no differences compared with cisgender heterosexual populations.[104,139] Notably, however, alcohol use seems to have increased since before the pandemic among sexual minority women,[133] and these increases are associated with worsened mental health.[127,128] This is an alarming finding given large pre-pandemic disparities in both alcohol use and mental health between sexual minority women and heterosexual women.[14,140-145] More research is needed to understand the stressors and mechanisms underlying the higher rates of alcohol use among sexual minority women during the pandemic.

Efforts to combat elevated drinking must account for the complex reasons why people drink. Cisgender women were more likely to drink to help forget worries after (compared to before) the onset of the pandemic,[124] and economic stressors—such as pay decreases, difficulty paying bills, or losing one's job during the pandemic—have all been linked to increased drinking among cisgender women.[146] Using alcohol as a coping mechanism impacted both TNB populations and cisgender women, as drinking to cope during the pandemic occurred at similar levels for both groups[127] and was higher for TNB people and cisgender women than for cisgender heterosexual men.[147] Cisgender women also experienced greater levels of unpaid labor (e.g., taking care of family members) during the pandemic, which may have increased stress levels.[31,148] This may also be true for TNB people, who have faced distressing economic concerns and impacts[52,53,149] as well as reduced access to health care, housing, and social/community support.[53-55,150] Pandemic-related stressors may be particularly impactful for cisgender women's drinking,[151] but the potential impacts on TNB people's drinking is less clear. Further research is needed to fully articulate any stressors and coping practices unique to TNB populations during the pandemic, such as potential shifts in proximal stress (e.g., anticipated stigma, concealment, or internalized transphobia), which has been linked to problematic alcohol use and drinking to cope.[58]

Whether the associations between mental health concerns and alcohol use were heightened during the pandemic is under-researched; however, rates of depression and anxiety have increased,[22,26,27,152] which may put more people, particularly cisgender women, including SMW and TNB people, at higher risk of problematic alcohol use.

Limitations of the Review

One key limitation of this review is the focus on alcohol; different forms of substance use can co-occur, potentially amplifying associated health risks.[80] Research is limited on co-occurring substance use among cisgender women and TNB populations during the COVID-19 pandemic. Future research should address co-occurring substance use among cisgender women, sexual minority populations, and TNB populations to thoroughly examine its impact.

This review focuses solely on peer-reviewed publications, which may have led to a limitation of the research reviewed as only 16% of studies included time points in 2021 and none extended into 2022. Perhaps little research was conducted in 2021 that looked at the continued impacts of the pandemic on alcohol use; alternatively, findings may not yet be available in the peer-reviewed literature. Timing is important as different stages of the pandemic may have influenced population alcohol use heterogeneously; moreover, different geographic locations had discrete experiences of the pandemic. For example, the first case of COVID-19 in the United States was documented in January 2020 in Washington State, and cases were largely concentrated on the west coast until March 2020. Stay-at-home orders began in early to mid-March in some areas (e.g., Puerto Rico, California, New Jersey) whereas some states did not issue them until April (e.g., Iowa, South Carolina, Missouri).[153] Many cities and states temporarily suspended bar and restaurant operations in the initial stages of the pandemic, which may have made alcohol less accessible; however, countervailing alcohol policies in many states that eased restrictions on take-out and home delivery of alcohol may have counteracted restrictions on on-premise consumption.[154,155] Similarly, stressors associated with the initial stages of the pandemic could have contributed to higher rates of alcohol use compared with later stages of the pandemic. However, the extent to which stress eased as the pandemic continued remains understudied. Moreover, evidence suggests that boredom during the pandemic also may have been associated with increased alcohol use.[156,157]

Articles rarely mentioned when data collection occurred, much less with enough specificity to ensure it occurred during the pandemic, which made it difficult to screen out articles that collected data prior to 2020. To facilitate screening and identification of articles only looking at alcohol use during the pandemic, the authors made the decision to include "COVID" as part of the search strategy to capture relevant literature in the time available for the review and minimize the potential for not finding relevant studies. It would be beneficial to update this review in the future once more research has been published;

however, this review gives a preliminary look at the available evidence.

This review excluded studies conducted outside of the United States, given the great variance in how different countries responded to the pandemic. Indeed, a recent systematic review suggests sizable variance in alcohol use during the pandemic depending on the country.[158] This U.S.-centric review limited understanding of alcohol use by cisgender women and TNB people during the pandemic on a broader scale. Anecdotally, it was noted that many papers that examined gender differences or focused on cisgender women's alcohol use were conducted outside of the United States. Future reviews should broaden the search to be inclusive of these important studies. Finally, the review excluded qualitative research, as the focus was on rates of alcohol use rather than on more nuanced findings related to reasons for alcohol use or experiences during the pandemic.

Limitations of the Literature

Among the reviewed literature, the most robust designs were longitudinal, multi-cohort approaches and included pre-pandemic data (e.g., Jaffe et al.[107]). Pre-pandemic longitudinal data allow for assessment of pandemic-related deviations from existing patterns. For example, college students typically increase alcohol consumption during the spring semester; therefore, increases in alcohol use in spring 2020 during the pandemic period are not atypical and, in fact, might have been lower than expected.[107] Another limitation is that most studies did not test for gender-by-time interactions; as a result, there are limited data on whether or not gender differences existed in changes over time. Examination of gender differences was further complicated by a frequent lack of clarity as to whether studies were reporting on sex or gender, or simply reporting on "women" without specifying how many of these women were cisgender or TNB. Generally, if studies did not mention TNB people in their study population, it is likely that TNB status was either not measured or considered, or that TNB people were actively excluded. Thus, in this review, studies that did not discuss gender outside of cisgender women and men, or that only used the terms "women" and "men," were presumed to be not inclusive of TNB people.

Another limitation related to research design is measurement of alcohol use, changes in alcohol use, and other alcohol-related outcomes. Although many studies used validated measures of alcohol problems or commonly used measures of quantity and frequency, others relied on more subjective assessments. For example, 28% of the reviewed studies measured change in alcohol use by asking participants for their perceptions of change since the pandemic's start, and 8% of studies asked participants to retrospectively report drinking levels pre-pandemic and current drinking. Retrospective subjective comparisons of alcohol use before and during the pandemic with unvalidated measures were perhaps necessary given the lack of pre-pandemic data collection in many studies but may have resulted in substantial measurement error. Further, definitions of alcohol use (e.g., problems, binge drinking) varied, making comparisons across studies challenging. Finally, given the heterogeneity of measures employed and domains of alcohol use examined, the current literature is limited in its ability to allow for any kinds of conclusions about differential rates of drinking versus alcohol problems.

Very few studies focused on BIPOC populations, which is particularly troubling given the sizable racial/ethnic disparities in COVID-19 infections and deaths[159] and the compounding impacts of sociopolitical events, racism (including anti-Asian hate/attacks), xenophobia, and economic concerns on well-being.[160,161] The review also found few studies that included comparisons between cisgender and TNB populations, and those that did lacked sample sizes to conduct subgroup comparisons among TNB people (e.g., transgender men versus transgender women), despite discrete risks.[64] TNB populations are underrepresented in gender differences research; thus, more research on alcohol use among TNB people during the pandemic is needed to better understand rates of alcohol use and unique risk factors. Similarly, despite identified high risks among SMW, studies examining LGBTQ subgroups often had extremely small sample sizes for these groups, limiting the capacity for studies to identify significant differences. Few studies reported the intersections between gender and sexual identity (e.g., comparing bisexual men and bisexual women), thus limiting our understanding of gender differences.

No studies looked at gender differences in parenting and how that might be associated with potentially higher risk for alcohol use. Little research examined alcohol use among couples, despite ample research demonstrating partners' impacts on each other's drinking[162,163] and clear linkages between intimate partner violence and alcohol,[164,165] as well as the increased risks for intimate partner violence during the pandemic.[35,36,166]

One of the clearest limitations of the literature was the overall lack of research examining gender differences, which may be additionally related to the challenges of doing research during the height of the pandemic. The shift to working from home and the demands of social distancing made in-person research challenging, if not impossible, which had downstream implications for new research recruitment and data collection. Moreover, the pandemic had unequal impacts on the productivity of women and researchers from marginalized groups,[167-171] which may have had disproportionate impacts on rates of research focused on cisgender women, BIPOC women, and TNB populations during the pandemic.

Implications

The findings of this review point to a continued need for alcohol-reduction interventions. A discussion of the complexities of cisgender women's and TNB people's treatment utilization is beyond the scope of this review. However, there are unique pandemic-related considerations that may be worth attention. Although the extent to which pandemic-related increases in alcohol consumption will persist over the long term remains unknown, available research from disasters indicates that AUDs exacerbated by disaster exposures can persist over time for some individuals;[172] thus, considering alcohol treatment and service capacity and pre-pandemic disparities is warranted. Interventions to reduce alcohol consumption and treat symptoms of AUDs have well-documented efficacy. However, before the pandemic, cisgender women[5] and TNB individuals[62,67,173] already had diminished rates of service utilization that may have been exacerbated in the pandemic setting. Digitally delivered services may increase access across populations,[174,175] yet cisgender women, including SMW, and TNB people have more complex comorbidities that may require higher levels of care.[5,67,176,177] For BIPOC women, SMW, and TNB people, treatment also needs to address minority stressors such as discrimination and stigma[51,173,178-183] and needs to be intersectional to address the overlapping and compounding impacts of multiple sources of oppression and marginalization.[184-187] Thus, an urgent research priority stemming from these findings is to evaluate accessibility and acceptance of service modalities.

There have been calls not to treat mental health concerns or problematic health behaviors as individual-level issues, particularly during a ubiquitous stressful and public health crisis such as a global pandemic.[188,189] Instead, interventions should take a public health approach by modifying social and contextual factors to build resiliency.[160,190,191] People have multiple motives for drinking, such as cravings[192] or enhancing social situations.[112] Yet, the unique impacts of pandemic-related stressors warrant enhancing access to resources, both emotional and economic, that may, in turn, help decrease stress- and coping-related motivations to drink. Efforts aimed at reducing distress and lowering risks for problematic alcohol use thus need to focus on ensuring consistent population-level access to resources such as social support, childcare and elder care, sick leave, affordable and accessible health care (including mental health care), affordable and permanent housing, education, living wages, and access to accurate health information. Whether these alone would be sufficient during a pandemic to reduce barriers to accessing help and uniquely support cisgender women and TNB people is unknown.

Further, alcohol policies to reduce access are effective in reducing harm.[193] Alcohol policies generally became more permissive during the pandemic (e.g., "to-go" drinks, home delivery). Some of those pandemic-related changes are becoming permanent in some states.[194] Revisiting alcohol regulation, including increasing price, as a public health approach could have considerable public health benefits.

Summary of Conclusions

The gender gap in alcohol use is narrowing between cisgender men and women—and seems to have gotten even narrower during the pandemic. Additionally, cisgender women and TNB people are less likely to seek treatment, and there may be unique health risks related to COVID-19 and alcohol use at least for cisgender women. Thus, research, prevention, and intervention efforts are needed to address this public health issue. Halting this worrisome trend in alcohol use by cisgender women—across sexual identities—requires a public health approach that considers the unique needs and concerns of cisgender women. More research also is needed to understand alcohol use by TNB individuals during the pandemic and how to best build resilience and support for this underserved population. Ultimately, this paper is about both sex and gender, capturing the drinking-related experiences of cisgender women (for whom these align) and TNB populations (for whom they do not), as well as various subpopulations that may face unique risks (such as pregnant people). Thus, findings suggest that research on alcohol use and other mental health concerns needs to take both sex and gender (including gender-diverse individuals beyond just comparisons between cisgender men and women) into account to understand not only differences in rates and changes over time but also differences in predictors and outcomes.

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Appendix 1. Description of Studies Included in This Review (*N* = 51): Sample Sizes, Recruitment Methods, Study Design, and Timing of Start and Stop of Data Collection*

#	First Author	Year	*N*	Sample Sizes of Subgroups	Sample	Recruitment	Study Design	Data Collection†	
								Start	End
Prevalence: Single and Repeated Cross-Sectional Studies of General Population Adults									
1	Chandran[79]	2021	107,930	57% cisgender women	EHR data; no age restrictions	Electronic health records	More than one cross-sectional time point	Pre-pandemic	Early pandemic
2	Acharya[84]	2022	18,808	54% cisgender women	Adults	Consumer data	More than one cross-sectional time point	Pre-pandemic	Late 2020
3	Beiter[85]	2022	102	48% cisgender women	Adult health care workers	Convenience	Cross-sectional	Early pandemic	Early pandemic
4	Boschuetz[86]	2020	417	84% cisgender women	Adults	Convenience: Online/social media	Cross-sectional	Early pandemic	Early pandemic
5	Capasso[87]	2021	5,850	53% cisgender women	Adult social media users in U.S.	Convenience: Online/social media	Cross-sectional	Early pandemic	Early pandemic
6	Grossman[88]	2020	832	84% cisgender women	Adults	Convenience: Online/social media	Cross-sectional	Early pandemic	Early pandemic
7	Kerr[89]	2022	1,819	52% cisgender women	Adults	Nationally representative	More than one cross-sectional time point	Pre-pandemic	Early 2021
8	Knell[90]	2020	1,809	67% cisgender women	Adults living in U.S.	Convenience: Online/social media	Cross-sectional	Early pandemic	Early pandemic
9	Walia[91]	2021	3,865	50% cisgender women	Health Information National Trends Survey	Nationally representative	Cross-sectional	Early pandemic	Late 2020
Prevalence: Longitudinal/Prospective Studies of General Population Adults									
1	Chartier[92]	2021	5,874	51% cisgender women	Adults	Nationally representative	Prospective	Early pandemic	Early pandemic
2	French[93]	2022	2,040	58% of sample at both time points were cisgender women	Adults living in U.S.	Convenience: Online/social media	Prospective	Early pandemic	Early pandemic
3	Lannoy[94]	2022	86	47% cisgender women	People who are HIV+, people with AUD, people with both, and controls with neither	Clinical sample recruited from longitudinal study	Prospective	Early pandemic	Early 2021
4	Leventhal[95]	2022	8,130	52% cisgender women	Adults	Nationally representative	Prospective	Early pandemic	Early 2021
5	Meanley[96]	2022	2,121	58% cisgender women	Participants from two prospective observational cohort studies	Pulled from MACS and WIHS cohorts	Prospective	Pre-pandemic	Late 2020

Appendix 1. Description of Studies Included in This Review (*N* = 51): Sample Sizes, Recruitment Methods, Study Design, and Timing of Start and Stop of Data Collection* (Continued)

#	First Author	Year	*N*	Sample Sizes of Subgroups	Sample	Recruitment	Study Design	Data Collection†	
								Start	End
6	Nordeck[97]	2021	4,298	49% cisgender women	Adults	Nationally representative	Prospective	Early pandemic	Late 2020
7	Osaghae[98]	2021	267	72% cisgender women	Outpatient primary care clinic patients who had received a COVID-19 test	Clinic sample	Prospective	Early pandemic	Early pandemic
8	Pollard[99]	2020	1,540	57% cisgender women	Adults	Nationally representative	Prospective	Pre-pandemic	Early pandemic
9	Tucker[100]	2022	1,118	52% cisgender women	Participants from RAND ALP study had to report past-year alcohol use.	Nationally representative	Prospective	Pre-pandemic	Early 2021
Specific Populations and Demographic Differences: Adolescents, Young Adults, and Older Adults									
1	Coakley[101]	2021	777	62% women; 4% non-cisgender; 31% non-heterosexual	College students	Convenience sample of undergraduates	Cross-sectional	Late 2020	Late 2020
2	Hill[102]	2022	501	71% cisgender women; 0.6% nonbinary or transgender	College students living in U.S.	Undergraduate research pool	Cross-sectional	Late 2020	Early 2021
3	Kim[103]	2022	Pre-pandemic: 3,643; Pandemic: 4,970	Pre-pandemic survey: 70% cisgender women, 4% TNB Pandemic survey: 68% cisgender women, 2% TNB	College students	All first- and second-year undergraduates	More than one cross-sectional time point	Pre-pandemic	Early pandemic
4	Schwartz[104]	2022	526	74% cisgender women	College students	Convenience: Online/social media	More than one cross-sectional time point	Early pandemic	Late 2020
5	Brener[105]	2022	7,705	Not reported	Grades 9–12	Nationally representative	Cross-sectional	Early pandemic	Late 2021
6	Graupensperger[106]	2021	572	61% cisgender women	Young adults reporting at least one alcoholic beverage in past year	Convenience	Prospective	Pre-pandemic	Early pandemic
7	Jaffe[107]	2021	1,365	Not reported	College students	Undergraduate research pool	Prospective	Pre-pandemic	Early pandemic
8	Miech[108]	2021	582	51% adolescent girls	12th graders from Monitoring the Future survey	Nationally representative	Prospective	Pre-pandemic	Late 2020
9	Romm[109]	2022	1,084	51% cisgender women; 3% "other"	Young adults	Convenience: Online/social media	Prospective	Pre-pandemic	Late 2020
10	Romm[110]	2021	1,082	51% cisgender women; 3% "other"	Young adults	Convenience: Online/social media	Prospective	Pre-pandemic	Late 2020

Appendix 1. Description of Studies Included in This Review (*N* = 51): Sample Sizes, Recruitment Methods, Study Design, and Timing of Start and Stop of Data Collection* (Continued)

#	First Author	Year	*N*	Sample Sizes of Subgroups	Sample	Recruitment	Study Design	Data Collection†	
								Start	End
11	Ryerson[111]	2021	302	2019 survey: 64% cisgender women 2020 survey: 68% cisgender women	College students	Undergraduates in health classes	Prospective	Pre-pandemic	Early pandemic
12	Stevenson[112]	2021	633	43% cisgender women	Young adults	Nationally representative	Prospective/ daily diary	Pre-pandemic	Early pandemic
13	Eastman[113]	2021	6,938	54% cisgender women	U.S. adults age 55 and older	Nationally representative	Cross-sectional	Early pandemic	Early pandemic
Specific Populations and Demographic Differences: Race/Ethnicity									
1	Hanson[114]	2021	62	100% cisgender women	American Indian women	Sample from RCT	Prospective	Pre-pandemic	Early pandemic
2	Hicks[115]	2022	323	77% cisgender women; 4% TNB participants	Racial/ethnic minority undergraduate students	Convenience: Online/social media	Prospective	Pre-pandemic	Early pandemic
Specific Populations and Demographic Differences: Frontline Workers									
1	Beiter[85]	2022	102	48% cisgender women	Adult health care workers	Convenience	Cross-sectional	Early pandemic	Early pandemic
2	Hennein[119]	2021	1,092	72% cisgender women	Health care workers at teaching hospitals	Convenience	Cross-sectional	Early pandemic	Early pandemic
Specific Populations and Demographic Differences: Couple Relationships, Pregnancy, and Parenting									
1	Ahlers-Schmit[116]	2020	114	100% cisgender women	Convenience sample of pregnant women or mothers of infants	Convenience	Cross-sectional	Early pandemic	Early pandemic
2	McMillan[117]	2021	49	100% cisgender women	Women age 18 and older who were at least 12 weeks pregnant	Convenience: Online/social media	Cross-sectional	Late 2020	Late 2020
3	Rodriguez[118]	2021	118 couples	50% cisgender women	U.S. adults who consumed at least 12 alcoholic beverages in past year and live with partner	Convenience: Online/social media	Cross-sectional	Late 2020	Late 2020
Coping, Stress, and Mental Health									
1	Lannoy[94]	2022	86	47% cisgender women	People who are HIV+, people with AUD, people with both, and controls with neither	Clinical sample recruited from longitudinal study	Prospective	Early pandemic	Early 2021
2	Tucker[100]	2022	1,118	52% cisgender women	Participants from RAND ALP study who had to report past-year alcohol use	Nationally representative	Prospective	Pre-pandemic	Early 2021
3	Hennein[119]	2021	1,092	72% cisgender women	Health care workers at teaching hospitals	Convenience	Cross-sectional	Early pandemic	Early pandemic

Appendix 1. Description of Studies Included in This Review (*N* = 51): Sample Sizes, Recruitment Methods, Study Design, and Timing of Start and Stop of Data Collection* (Continued)

#	First Author	Year	*N*	Sample Sizes of Subgroups	Sample	Recruitment	Study Design	Data Collection†	
								Start	End
4	Cummings[120]	2021	2019: 247;2020: 868	February 2019: 45% cisgender women; 0% transgender; 2% gender fluid March 2020: 52% cisgender women; 0.3% transgender; 0.6% gender fluid	Adults living in U.S.	Convenience: Online/social media	More than one cross-sectional time point	Pre-pandemic	Early pandemic
5	Devoto[121]	2022	499	100% cisgender women	Adult women living in U.S. who agree to share Facebook data	Panel	Cross-sectional	Late 2020	Late 2020
6	Graupensperger[122]	2021	1,181	60% cisgender women	College students	Convenience	Cross-sectional	Early pandemic	Early pandemic
7	Helminen[123]	2021	68	100% cisgender women	Community sample of trauma-exposed adult women	Convenience	Cross-sectional	Early pandemic	Late 2020
8	Martinez[124]	2022	Pre-pandemic: 1,291; Early pandemic: 812	61% cisgender women at baseline	Two cross-sectional NAS samples	Nationally representative	More than one cross-sectional time point	Pre-pandemic	Early pandemic
9	Nesoff[125]	2021	2,175	85% cisgender women; 4% TNB people	Adults living in U.S.	Convenience: Online/social media	Cross-sectional	Early pandemic	Early pandemic
10	Vogel[126]	2021	180	65% cisgender women	Recruited through Qualtrics	Convenience: Online/social media	Cross-sectional	Early pandemic	Late 2020
					Transgender and Nonbinary Populations				
1	Coakley[101]	2021	777	62% women; 4% non-cisgender; 31% non-heterosexual	College students	Convenience sample of undergraduates	Cross-sectional	Late 2020	Late 2020
2	Hicks[115]	2022	323	77% cisgender women; 4% TNB participants	Racial/ethnic minority undergraduate students.	Convenience: Online/social media	Prospective	Pre-pandemic	Early pandemic
3	Dyar[127]	2022	429	73% cisgender women; 15% nonbinary; 5% genderqueer; 4% nonconforming; 3% "another identity"	Same criteria as Dyar 2021 study	Convenience: Online/social media	Prospective	Late 2020	Early 2021
4	Salerno[128]	2021	509	78% AFAB: 69% cisgender, 9% transgender, 1% nonbinary, 0.9% queer gender	Sexual and gender minority full-time college students	Convenience: Online/social media	Cross-sectional	Early pandemic	Late 2020

Appendix 1. Description of Studies Included in This Review (*N* = 51): Sample Sizes, Recruitment Methods, Study Design, and Timing of Start and Stop of Data Collection* (Continued)

#	First Author	Year	*N*	Sample Sizes of Subgroups	Sample	Recruitment	Study Design	Data Collection†	
								Start	End
5	Sumetsky[129]	2022	247	59% cisgender women, 15% TNB	Adults in Allegheny County, PA	Convenience: Online/social media	Cross-sectional	Early pandemic	Late 2020
6	Zhang[130]	2022	366	47% cisgender women, 4% trans women, 8% trans men, 15% nonbinary, 2% genderqueer, 3% another gender	LGBTQ+ college students	Convenience: Online/social media	Cross-sectional	Early pandemic	Early pandemic
7	Akré[131]	2021	3,245	84.9% cisgender straight; 3.7% cisgender gay or lesbian; 7.0% cisgender bisexual; 3.8% cisgender men who have sex with men and women who have sex with women but do not identify as LGBT; 0.6% transgender	Adults in Atlanta, GA; Chicago, IL; New Orleans, LA; New York, NY; and Los Angeles, CA	Panel	Cross-sectional	Early Pandemic	Late 2020
				Sexual Minority Women					
1	Dyar[127]	2022	429	73% cisgender women; 15% nonbinary; 5% genderqueer; 4% nonconforming; 3% "another identity"	Same criteria as Dyar 2021 study	Convenience: Online/social media	Prospective	Late 2020	Early 2021
2	Salerno[128]	2021	509	78% AFAB and 69% of sample was cisgender; 9% transgender; 1% nonbinary; 0.9% queer gender	Sexual and gender minority full-time college students	Convenience: Online/social media	Cross-sectional	Early pandemic	Late 2020
3	Dyar[132]	2021	212	74% cisgender women; 18% genderqueer or nonbinary; 9% another gender	Age 18–25; live in U.S.; lesbian, bisexual, pansexual, or queer; AFAB; reported four or more drinks at least twice and/or using cannabis in past month	Convenience: Online/social media	Prospective/EMA/daily diary study	Late 2020	Early 2021
4	Peterson[133]	2021	170	64% cisgender women	U.S. Adults	Convenience: Online/social media	Cross-sectional	Early pandemic	Early pandemic

*Articles are listed in the order in which they appear in the manuscript. Some studies are listed in more than one section of the table.
†Time periods for start and stop of research studies: Pre-pandemic (Before March 2020); Early pandemic (March–May 2020); Late 2020 (June–December 2020); Early 2021 (January–May 2021); Late 2021 (June–December 2021).
Note: AFAB, assigned female at birth; AUD, alcohol use disorder; COVID-19, coronavirus disease 2019; EHR, electronic health record; EMA, ecological momentary assessment; HIV+, human immunodeficiency virus–positive; LGBT, lesbian, gay, bisexual, transgender; LGBTQ+, lesbian, gay, bisexual, transgender, and queer or questioning; MACS, Multicenter AIDS Cohort Study; NAS, National Alcohol Survey; RAND ALP, RAND American Life Panel; RCT, randomized controlled trial; TNB, transgender and nonbinary; WIHS, Women's Interagency HIV Study.

Appendix 2. Description of Studies Included in This Review (*N* = 51): Measurement of Alcohol Use and Changes in Alcohol Use and Brief Findings*

#	First Author	How was alcohol use measured?	How were changes in alcohol use measured?	Gender Differences	
				Gender differences?	Findings
Prevalence: Single and Repeated Cross-Sectional Studies of General Population Adults					
1	Chandran[79]	SBIRT and intoxication admissions; AUDIT	Pre- and post/during pandemic data	Yes	Weekly SBIRT screens similar across gender in the pre-pandemic wave, then increased more for cisgender women than cisgender men.
2	Acharya[84]	Bi-weekly alcohol expenditures	Pre- and post/during pandemic data	No	Both cisgender men and women had decreased in spending on alcohol during pandemic, gender differences in spending during pandemic were not significant.
3	Beiter[85]	AUDIT	Retrospective recall of pre-pandemic AUDIT	Yes	Cisgender men higher AUDIT than cisgender women; all reported increases in AUDIT compared with pre-pandemic; no gender by time interaction assessed.
4	Boschuetz[86]	AUDIT-C, quantity and frequency, binge drinking	Retrospective report of current drinking in past vs. drinking now	Yes	Cisgender women reported more AUDIT-C symptoms after start of pandemic, cisgender men did not; no changes in alcohol frequency.
5	Capasso[87]	Self-perceptions of change in alcohol use	Self-perceived changes in alcohol use	Yes	Among those who reported increased drinking, 61% were cisgender women compared to 39% who were cisgender men (statistically significant). Younger participants more likely to report increased drinking, but no interactions examined between age and gender.
6	Grossman[88]	Days consumed, drinks consumed, binge drinking	N/A	No	No gender differences in number of days consumed alcohol, total drinks, or binge drinking.
7	Kerr[89]	Graduated frequency series. *DSM-V* AUD criteria	Pre- and post/during pandemic data	Yes	Daily drinking increased for both cisgender men and women, as did AUD mild and moderate/severe; moderate/severe AUD increased more for cisgender women than for men; volume, especially wine and spirit volume, increased more for cisgender women than men.
8	Knell[90]	Ever use and current quantity and frequency from BRFSS	Self-perceived changes in alcohol use	No	No gender differences in self-perceptions of changes in alcohol use since start of pandemic.
9	Walia[91]	Quantity	N/A	Yes	Significant gender differences, but no pairwise differences reported. Cisgender men had double the rates of reporting 13 or more drinks in a week than did cisgender women; other drinking levels did not differ.
Prevalence: Longitudinal/Prospective Studies of General Population Adults					
1	Chartier[92]	Alcohol use frequency	Self-report of current drinking at more than one time point	Yes	June 2020: cisgender women drank less than cisgender men; in change models, increased drinking during the month was no different between cisgender men and women, but cisgender women less likely to decrease drinking.
2	French[93]	"In the past three months, has alcohol consumption increased, stayed the same, or decreased?"	Self-perceived changes in alcohol use	Yes	Cisgender women significantly less likely than cisgender men to say that alcohol consumption had increased.
3	Lannoy[94]	AUDIT	Pre- and post/during pandemic data	No	No sex differences, stable AUDIT scores between assessments
4	Leventhal[95]	Frequency and intensity of drinking	Self-report of current drinking at more than one time point	Yes	Cisgender women comprised higher percentage of minimal and moderate/late decreasing trajectory group; lower percentage in moderate/early increasing, and near daily/early increasing
5	Meanley[96]	Reported frequency with which they consumed at least five (cisgender women) or six (cisgender men) alcoholic beverages in one sitting.	Pre- and post/during pandemic data	Yes	Cisgender men significantly more likely to be in the 'any binge drinking' trajectory group. Significant gender by time interaction; both cisgender men and women exhibited significant binge drinking decreases at time three compared to time one; decrease larger in cisgender men.

Appendix 2. Description of Studies Included in This Review (*N* = 51): Measurement of Alcohol Use and Changes in Alcohol Use and Brief Findings* (Continued)

#	First Author	How was alcohol use measured?	How were changes in alcohol use measured?	Gender Differences	
				Gender differences?	Findings
6	Nordeck[97]	Number of drinking days per week	Self-report of current drinking at more than one time point	Yes	Cisgender women had lower number of drinking days overall; both cisgender women and men increased drinking days; cisgender men increased more.
7	Osaghae[98]	AUDIT-C	Self-report of current drinking at more than one time point	Yes	36.1% of cisgender women and 32.9% of cisgender men reported hazardous drinking at baseline. Did not test gender by time interaction.
8	Pollard[99]	Days drank, number of drinks, heavy drinking days	Self-report of current drinking at more than one time point	Yes	Days consumed increased more for cisgender women; number of drinks increased more for cisgender men; heavy drinking days increased more for cisgender women; SIP scale not different
9	Tucker[100]	Quantity and frequency; Alcohol problems assessed with the Short Inventory of Problems[195]	Pre- and post/during pandemic data	Yes	Analyses were stratified by gender. Cisgender men's alcohol use started out higher than cisgender women but declined whereas cisgender women's stayed static. By time 3, drinking levels were about the same. Both cisgender men and cisgender women had increased alcohol problems over time. Coping and social reasons for drinking and loneliness had distinct associations with alcohol use, alcohol problems, and change over time and these varied by gender.
Specific Populations and Demographic Differences: Adolescents, Young Adults, Older Adults					
1	Coakley[101]	Quantity and frequency	Self-report of current drinking at more than one time point	Yes	Pre-pandemic (retrospectively reported), cisgender men drank more than cisgender women who drank more than TNB participants; during pandemic, consumption increased across groups, but remained cisgender men > cisgender women > TNB; cisgender men and TNB participants had greatest percent change during pandemic.
2	Hill[102]	AUDIT	N/A	Yes	Cisgender men had higher AUD symptoms than cisgender women. No pre-pandemic data and no time by gender interaction tested.
3	Kim[103]	AUDIT	N/A	Yes	Increases in AUD more concentrated among cisgender women
4	Schwartz[104]	"During the last two months, how often have you engaged in alcohol use?"	Retrospective report of current drinking in past vs drinking now	No	Gender differences tested but not significant. Alcohol use worsened between spring and fall 2020.
5	Brener[105]	Quantity and frequency, current binge drinking	Self-perceived changes in alcohol use	Yes	Cisgender women higher than cisgender men for current and binge drinking; no differences in perceived changes since pandemic. Sexual minority students reported higher current alcohol use, binge drinking, and drinking during the pandemic than did heterosexual students.
6	Graupensperger[106]	Quantity/frequency; Drinks per occasion	Self-report of current drinking at more than one time point	Yes	At baseline, cisgender women lower drinking than cisgender men; drinking declined at follow-up; declines were greater for cisgender men than cisgender women (significant interaction).
7	Jaffe[107]	Quantity and frequency	Self-report of current drinking at more than one time point	Yes	Cisgender men greater drinking days, greater drinks per day (both across years and within 2020); college students did not increase drinking in spring 2020 as was typical in previous years; no gender by time interaction reported.
8	Miech[108]	"Think back over the last 2 weeks. How many times have you had five or more drinks in a row?"	Pre- and post/during pandemic data	No	Study found that past 2-week binge declined from spring to summer 2020 overall; no overall gender differences; did not test time by gender interaction.
9	Romm[109]	Past 30-day quantity and frequency	Self-report of current drinking at more than one time point	Yes	Baseline drinking was lower for cisgender men than cisgender women; increases in alcohol use during pandemic greater for cisgender men than cisgender women

Appendix 2. Description of Studies Included in This Review (*N* = 51): Measurement of Alcohol Use and Changes in Alcohol Use and Brief Findings* (Continued)

#	First Author	How was alcohol use measured?	How were changes in alcohol use measured?	Gender Differences	
				Gender differences?	Findings
10	Romm[110]	"Compared to before COVID-19, are you doing more or less of the following: drinking alcohol?"	Self-perceived changes in alcohol use	No	41.3% of participants reported increased alcohol use; no gender difference in self-reported increased alcohol use
11	Ryerson[111]	Typical total weekly volume of alcohol consumption	Self-report of current drinking at more than one time point	No	No gender differences in alcohol consumption; 2020 cohort decreased alcohol consumption compared with 2019 cohort, especially those > 21; gender interaction with time was statistically significant, but direction not reported.
12	Stevenson[112]	Any drinking; drinking intensity on drinking days	Self-report of current drinking at more than one time point	Yes	Cisgender men more likely to report any drinking; no change in drinking during COVID; no gender interaction reported.
13	Eastman[113]	"Over the past week, have any of your usual daily activities or behaviors changed?"	Self-perceived changes in alcohol use	Yes	Of those who said they were drinking more than usual, 58.9% were cisgender women.
Specific Populations and Demographic Differences: Demographic Differences by Race/Ethnicity					
1	Hanson[114]	Quantity/frequency	Retrospective report of current drinking in past vs. drinking now	N/A	24.2% of cisgender women reported drinking more now and 50% reported binge drinking since pandemic started; 54.8% had 8+ drinks per week.
2	Hicks[115]	Alcohol use frequency from AUDIT	Pre- and post/during pandemic data	Yes	No differences by sexual identity; cisgender men more likely to decrease alcohol use during pandemic compared to cisgender women. No significant gender differences between cisgender and TNB participants.
Specific Populations and Demographic Differences: Frontline Workers					
1	Beiter[85]	AUDIT	Retrospective recall of pre-pandemic AUDIT	Yes	Cisgender men higher AUDIT than cisgender women; all reported increases in AUDIT compared with pre-pandemic; no gender by time interaction assessed.
2	Hennein[119]	AUDIT-C	N/A	No	Cisgender women were no more likely than men to report AUD symptoms despite higher rates of PTSD.
Specific Populations and Demographic Differences: Couple Relationships, Pregnancy, and Parenting					
1	Ahlers-Schmit[116]	Unclear measurement	Self-perceived changes in alcohol use	N/A	Increases in alcohol use significantly higher postpartum than during pregnancy.
2	McMillan[117]	Epidemic Pandemic Impact Inventory (EPII)[196]	Self-perceived changes in alcohol use	N/A	Almost one-third (28%) reported that they or their partner's alcohol consumption had increased since the start of the pandemic.
3	Rodriguez[118]	Daily Drinking Questionnaire;[197] Shortened Inventory of Problems-Alcohol and Drugs scale;[198] Drinking to cope using two visual analog scales	N/A	Yes	Cisgender men reported significantly more alcohol-related problems than did cisgender women, but drinking levels did not differ by gender. Cisgender women's drinking was significantly associated with their partner's drinking and stress; cisgender men's drinking was unrelated to their partner's drinking or stress. Cisgender women's levels of stress were unrelated to their drinking.

Appendix 2. Description of Studies Included in This Review (*N* = 51): Measurement of Alcohol Use and Changes in Alcohol Use and Brief Findings* (Continued)

#	First Author	How was alcohol use measured?	How were changes in alcohol use measured?	Gender Differences	
				Gender differences?	Findings
			Coping, Stress, and Mental Health		
1	Lannoy[94]	AUDIT	Pre- and post/during pandemic data	No	No sex differences, stable AUDIT scores between assessments
2	Tucker[100]	Quantity and frequency; Alcohol problems assessed with the Short Inventory of Problems[195]	Pre- and post/during pandemic data	Yes	Analyses were stratified by gender. Cisgender men's alcohol use started out higher than cisgender women but declined whereas cisgender women's stayed static. By time 3, drinking levels were about the same. Both cisgender men and cisgender women had increased alcohol problems over time. Coping and social reasons for drinking and loneliness had distinct associations with alcohol use, alcohol problems, and change over time and these varied by gender.
3	Hennein[119]	AUDIT-C	N/A	No	Cisgender women were no more likely than cisgender men to report AUD symptoms, despite higher rates of PTSD.
4	Cummings[120]	Quantity, frequency, and two items adapted from Drinking Motives Questionnaire[199]	Pre- and post/during pandemic data	Yes	No differences in drinking to cope comparing pre- and during pandemic samples (did not look at gender differences). Significant associations between COVID-19 stress and drinking to cope for cisgender men and women but associations were stronger for men.
5	Devoto[121]	AUDIT-C; Alcohol, Smoking, and Substance Involvement Screening Test[200]	N/A	N/A	Among cisgender women, high-risk alcohol associated with significantly higher levels of depression and anxiety than lower risk use. Cisgender women with moderate drinking risks reported higher levels of social support than cisgender women with high-risk drinking. Almost 17% said that they increased their drug or alcohol use to cope with relationship problems.
6	Graupensperger[122]	Daily Drinking Questionnaire,[197] binge drinking item from Monitoring the Future questionnaire[201]	N/A	No	No gender differences in rates of binge drinking or number of drinks per week.
7	Helminen[123]	AUDIT-C	N/A	N/A	Nearly half (47.1%) of the sample reported alcohol use consistent with probable AUD.
8	Martinez[124]	Two drinking to cope questions adapted from the Drinking Motives Questionnaire[199]	Pre- and post/during pandemic data	Yes	Among cisgender women, 13.8% reported drinking to cope prior to the pandemic and 15.6% reported drinking to cope during the pandemic, compared to 10.7% before and 17% during the pandemic for cisgender men. These rates were not statistically different. Among cisgender women, those with moderate to severe symptoms of depression or mild symptoms of anxiety were significantly more likely to report drinking to cope. No significant associations were identified for cisgender men.
9	Nesoff[125]	Adapted quantity and frequency items from NSDUH	Self-perceived changes in alcohol use	Yes	Odds of high-risk drinking were significantly elevated for cisgender women when controlling for stress, depressive symptoms, and household job loss. Cisgender men had lower odds of high-risk drinking than cisgender women.
10	Vogel[126]	Short Inventory of Problems—Alcohol and Drugs (SIP-AD)[198]	N/A	No	Sex, race/ethnicity, marital status, and other pandemic-related variables were not associated with SIP-AD scores.
			Transgender and Nonbinary Populations		
1	Coakley[101]	Quantity and frequency	Self-report of current drinking at more than one time point	Yes	Pre-pandemic (retrospectively reported), cisgender men drank more than cisgender women who drank more than TNB people. During pandemic, consumption increased across groups, but cisgender men still drank more than cisgender women, who drank more than TNB people. Cisgender men and TNB people had greatest percentage change during pandemic.

Appendix 2. Description of Studies Included in This Review (*N* = 51): Measurement of Alcohol Use and Changes in Alcohol Use and Brief Findings* (Continued)

#	First Author	How was alcohol use measured?	How were changes in alcohol use measured?	Gender Differences	
				Gender differences?	Findings
2	Hicks[115]	Alcohol use frequency from AUDIT	Pre- and post/during pandemic data	Yes	No differences by sexual identity; cisgender men were more likely than cisgender women to decrease alcohol use during pandemic. No significant gender differences between cisgender and TNB participants.
3	Dyar[127]	Daily drinking questionnaire,[197] quantity	Self-report of current drinking at more than one time point	No	No significant differences between cisgender women and TNB participants for alcohol use or drinking to cope.
4	Salerno[128]	Indicated if alcohol use had changed since the start of pandemic.	Self-perceived changes in alcohol use	Yes	The effect of increased alcohol use on psychological distress since the start of COVID-19 was nonsignificant for AMAB but was significant for AFAB people.
5	Sumetsky[129]	Quantity and frequency of drinking and number of days of intoxication	Retrospective report of past drinking vs. current drinking	Yes	Compared to cisgender women, cisgender men had more drinks on drinking days during pandemic, and more days intoxicated pre-pandemic. There were no significant differences for TNB people.
6	Zhang[130]	AUDIT	Self-perceived changes in alcohol use	Yes	Transgender and GNC people had lower problem drinking, and were less likely to have perceived increase in their drinking during COVID-19 than cisgender participants.
7	Akré[131]	PROMIS Alcohol Use Negative Consequences 7-item short-form scale	Self-report of changes in alcohol consumption due to the pandemic	Yes	No substantial difference in rates of increased alcohol use between transgender and cisgender, straight respondents, but some elevated use among cisgender, sexual minority respondents.
Sexual Minority Women					
1	Dyar[127]	Daily drinking questionnaire,[197] quantity	Self-report of current drinking at more than one time point	No	No significant differences between cisgender women and TNB participants for alcohol use or drinking to cope.
2	Salerno[128]	Indicated if alcohol use had changed since the start of pandemic.	Self-perceived changes in alcohol use	Yes	The effect of increased alcohol use on psychological distress since the start of COVID-19 was non-significant for AMAB but significant for AFAB people.
3	Dyar[132]	AUDIT, Drinking motives, Brief Young Adult Alcohol Consequences Questionnaire[202]	Self-perceived changes in alcohol use	N/A	Nearly all participants reported more anxiety and depression in the past month compared to before the pandemic; approximately half also reported increases in alcohol and cannabis use.
4	Peterson[133]	AUDIT	Self-perceived changes in alcohol use	Yes	SMW more likely to report alcohol use increased since beginning of pandemic than SMM and cisgender heterosexual women

*Within each section, studies are listed in the order in which they are cited. Some studies are listed in more than one section.
Note: AFAB, assigned female at birth; AMAB, assigned male at birth; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; BRFSS, Behavioral Risk Factor Surveillance System; COVID-19, coronavirus disease 2019; *DSM-V, Diagnostic and Statistical Manual of Mental Disorders*, fifth edition; GNC, gender nonconforming; N/A, not applicable (in the Gender Differences column, N/A indicates that the sample includes cisgender women only); NSDUH, National Survey on Drug Use and Health; PROMIS, Patient-Reported Outcomes Measurement Information System; PTSD, post-traumatic stress disorder; SBIRT, screening, brief intervention, and referral to treatment; SIP-AD, Short Inventory of Problems–Alcohol and Drugs; SMM, sexual minority men; SMW, sexual minority women; TNB, transgender and nonbinary.

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Sex and Gender Effects in Recovery From Alcohol Use Disorder

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The current article provides a brief summary of biopsychosocial gender differences in alcohol use disorder (AUD), then reviews existing literature on gender differences in treatment access, retention, outcomes, and longer-term recovery. Among psychotherapies for AUD, there is support for the efficacy of providing female-specific treatment, and for female-only treatment settings but only when female-specific treatment is included. However, despite mandates from the National Institutes of Health to do so, there is little work thus far that directly compares genders on outcomes of specific psychotherapies or pharmacotherapies for AUD. Although existing research has mixed findings on sex and gender differences in overall outcomes, there are more consistent findings suggesting different mechanisms of behavior change among men and women in AUD treatment and long-term recovery. Thus, more work is needed that attends to gender and sex differences, including planning studies that are structured to examine not only gender-differentiated outcomes in treatment response, but equally important, differences in treatment access and attendance as well as differences in mechanisms of change in drinking behavior.

KEY WORDS: sex; gender; treatment; recovery; alcohol; substance use disorder; mechanisms

INTRODUCTION

Between 1994 and 2017, the National Institutes of Health (NIH) issued mandates that biomedical researchers include female participants in clinical research,[1] analyze sex/gender differences in NIH Phase III clinical trials,[2] and submit the results from these analyses to Clinicaltrials.gov.[3] Additionally, between 1992 and 2010, the NIH Office of Research on Women's Health strategic plan identified sex difference research as a focus in basic science, as well as incorporation of sex difference findings in treatment for girls

and women.[4,5] These U.S. national policies and strategic plans have had a profound impact on treatment development for alcohol use disorder (AUD) by accelerating attention to sex and gender differences in research, resulting in increased awareness of gender-specific treatment needs. Currently, evidence-based, female-specific AUD treatments are emerging;[6] however, there is still insufficient research (or reporting of research results) on gender differences in all areas of research on AUD treatment and its implementation.

Most recent epidemiological results indicate a higher prevalence among men than women of AUD—defined by criteria of the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) —with past-year rates of 10% among women and 18% among men, and respective lifetime rates of 23% and 36%.[7] However, from 2000 to 2013, prevalence rates of 12-month DSM-IV AUD increased by 84% among women compared with 35% among men.[8] Thus, attention to gender differences in clinical research for AUD is needed, given the steep trajectory of gender convergence over the last 20 years. The current article provides a brief overview of gender differences in biological, psychological, and social aspects of AUD, followed by a review of the existing literature on gender differences in AUD treatment, factors that affect long-term recovery from AUD, and mechanisms of behavior change.

Regarding the terminology used in this article—"sex," "gender," and "recovery"— the NIH definition of sex refers to biological differences between females and males in chromosomes, sex organs, and endogenous hormones, whereas gender refers to more socially based roles and behaviors that may vary by historical and cultural contexts.[9] For this article, American Psychological Association guidelines are used: gender refers to women and men as social groups, and sex refers to the predominantly biological distinction between males and females.[10]

Regarding recovery from AUD, there is currently no consensus in definition of this term. Historically, recovery has been associated with Alcoholics Anonymous as "ongoing cognitive, emotional, behavioral, and spiritual reconstruction of the sobered alcoholic"[11,12] and more recently, "a voluntarily maintained lifestyle characterized by sobriety, personal health, and citizenship."[13] In contemporary treatment research, AUD recovery is generally operationalized by primary outcomes related to reduction in drinking, increased abstinence rates, and/or reduction of AUD symptoms. Improvements in secondary outcomes such as other drug use, daily functioning, psychiatric symptoms, physical health, and employment status also are often assessed in AUD clinical trials and are increasingly viewed as outcomes inherent to recovery. Some recent research has focused on the relative importance of abstinence versus reduction of drinking and related symptoms (primary and secondary) in the definition of, and clinical implications for, recovery.[14] In the current article, the term "treatment outcome" is generally used in lieu of recovery, with the understanding that treatment outcome refers to both primary (drinking) and secondary outcome variables.

Lastly, the research reviewed in this paper uses diagnoses from DSM-IV and DSM-5. Whereas DSM-IV described two distinct disorders— alcohol abuse and alcohol dependence—DSM-5 combines these into a single alcohol use disorder (AUD) with mild, moderate, and severe subclassifications reflecting the number of symptoms met. The main criteria change from DSM-IV is that DSM-5 eliminates alcohol-related legal problems and adds alcohol craving as a criterion for AUD. Lastly, although the search did not exclude international research, the majority of findings reviewed are from studies conducted and/ or funded in the United States.

BIOPSYCHOSOCIAL SEX AND GENDER DIFFERENCES IN ALCOHOL USE AND AUD

Biological Sex Differences

Physical effects of alcohol

Alcohol is consistently shown to have more negative effects on women's health than men's, even at weight-adjusted lower levels of alcohol exposure, partly due to gender differences in pharmacokinetics of alcohol.[15] Because women typically have less total body water and greater total body fat, alcohol is more concentrated in women's bodies than in the bodies of men, creating greater blood alcohol content at similar doses and weights.[16] Women with AUD also are more likely to develop alcohol-related heart disease, cancer, and liver disease,[17] and more overall brain atrophy secondary to chronic drinking.[18]

Physiological stress response

Stress plays an important role in the development and maintenance of AUD among both men and women.[19] Yet, alcohol-induced alterations in emotional and biophysiological markers of adaptive stress response are more common in women than men.[20] The nature and extent of some alterations are also gender-specific (e.g., blunted physiological responses to stress cues, alcohol cues, and alcohol exposure; sensitized emotional response to stress; alterations in hormonal fluctuations).[21] Furthermore, inflammatory responses to alcohol exposure, stressors, and trauma are highly sex-specific and have widespread physiological effects.[16] Such altered responses to stress differentially increase risk for and/or maintain AUD, co-occurring emotional disorders, and/or secondary effects of alcohol use (such as neural degeneration) among men and women.

Hormones

Sex hormones affect all body systems directly and indirectly, and for women there appears to be a reciprocal effect of alcohol on sex hormones.[16] Chronic alcohol use has been shown to affect testosterone levels in men,[17] whereas female sex hormones (estradiol, progesterone, and their metabolites) reciprocally interact with alcohol use.[16,22] Specifically, alcohol induces alterations in estrogen receptor physiology and function,[16] which may contribute to osteoporosis, sexual dysfunction, and infertility in women.[17] Further, sex hormones may influence patterns of women's alcohol intake.[23] Research is beginning to elucidate the mechanisms of these interactions. For instance, estrogen levels may enhance the rewarding properties of substances and increase impulsive behavior, whereas progesterone may attenuate substance-rewarding effects.[22,23] Furthermore, decreases in progesterone may increase vulnerability to stress and potentiate stress-induced drinking.[21]

Psychosocial Gender Differences

Co-occurring psychiatric conditions

Women with AUD report higher levels of co-occurring psychiatric conditions than do men with AUD. Co-occurrences of mental health conditions with AUD were examined using data from two waves (2001–2002 and 2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).[24] Women were found to have higher rates of all mood and anxiety disorders as well as paranoid, histrionic, borderline, and avoidant personality disorders compared to men, who had higher rates of narcissistic and antisocial personality disorders. After adjusting for sociodemographic factors, among persons reporting alcohol abuse (not dependence), only major depressive disorder was identified to be more likely among women than men. Recent research by Karpyak et al. found that women with AUD, compared to men with AUD, had higher rates of lifetime major depression, substance-induced depression, anxiety disorder, and post-traumatic stress disorder (PTSD) and were more likely to drink alcohol when experiencing negative emotion.[25] Further, among

U.S. military veterans with AUD, women report more co-occurring mental health and substance use disorders than do men.[26]

Mood and coping factors

Among individuals with AUD, women are more likely than men to experience alcohol cravings in response to daily negative emotion and stress.[20,21,25] In a sample of adults with PTSD and AUD, drinking to enhance positive emotions was associated with alcohol use in both men and women, whereas drinking to cope with negative affect was associated with higher alcohol consumption in women but not men.[27] Another study reported a positive association of negative affect with alcohol cravings for men at the beginning of alcohol detoxification, but for women the association persisted throughout detoxification.[28] Additionally, for women, more depressive symptoms at the beginning of detoxification were associated with more alcohol cravings at the end of detoxification. A third study also found that women were more likely to report high anxiety and depression at alcohol detoxification admission and discharge compared to men.[29] In that study, both genders showed increased anxiety and depression symptoms at 6-month follow-up, with more anxiety symptoms predicting men's relapse at 12-month follow-up and more depression symptoms predicting women's relapse at 12-month follow-up.[29]

Trauma exposure

There are high rates of trauma among women receiving treatment for any substance use, and an estimated 25% to 55% of women in substance use treatment have PTSD.[30] Trauma and acute stressors are causally associated with the development of AUD in women, via the effects of stress and trauma on biological processes and the likelihood of women with AUD to drink to cope with negative emotion and stress.[20] One study examining childhood maltreatment and lifetime odds of AUD found that, for both genders, having a history of physical, sexual, and/or emotional abuse and/or physical and/or emotional neglect was associated with higher odds of having a lifetime AUD.[31] For women, the strength of the relationship between lifetime AUD and all types of childhood maltreatment, except emotional abuse, was stronger than for men. In addition, Heffner and colleagues found that, for women, severity of current trauma symptoms and number of lifetime traumas predicted relapse over the course of the study.[32] No association between trauma and relapse was found for men.

Social networks

Research has found gender differences in the relationship between social networks, social support, and alcohol use. For example, compared to men, women with AUD are more likely to have a family history of AUD and a spouse with a history of AUD.[33] Women also are less likely than men to have social support in their recovery.[15] This may be at least partly due to greater stigma related to women's alcohol use compared to men, or to women's fear of interpersonal consequences related to their drinking.[34] Indeed, women tend to be more isolated in their excessive alcohol use and recovery.[15] Men report greater social pressure to change their drinking behaviors than women.[35] However, a study using data from the National Alcohol Study between 1984 and 2010,[36] with data from more than 32,000 people, showed changes over time for women. Although results did show that men displayed overall greater incidences of pressure to change across the years, there was also a significant cohort effect for women, with younger cohorts of women (i.e., born after 1964) reporting greater social pressure to change drinking. Such results coincide with gender convergence in rates of AUD and suggest that there also may be an emerging convergence of social pressure to change drinking. The role of social networks in drinking is evident in predicting treatment outcomes, reviewed below, and is an important risk and maintenance factor for AUD in men and women—albeit in different ways.

Summary

Research has illuminated gender differences in the biopsychosocial factors contributing to the development of, and recovery from, AUD. The physical effects of alcohol are more pervasive for women than men, and sex-specific factors, such as sex hormones, have been associated with alcohol use. In terms of psychosocial differences, stress, trauma, and negative affect are particularly relevant contributors to alcohol use and development of AUD among women. Relatedly, there are gender differences in terms of rates of co-occurring mental health conditions, the rates of major depressive disorder among women with alcohol abuse being particularly high. These differences provide a context for understanding potential gender differences in AUD treatment and recovery and can be used to guide future research.

GENDER DIFFERENCES IN TREATMENT ENTRY, RETENTION, AND OUTCOME

Treatment Entry

A small percentage of individuals with AUD ever receive treatment, with past-year estimates of 7% of men and 5% of women with AUD receiving treatment[37] and lifetime estimates of 22% to 23% for men and 15% for women.[38,39] There are several female-specific barriers to accessing AUD treatment, such as external and internalized stigma, lack of childcare, and systemic barriers.[6] Women are more likely than men to believe their alcohol problem will resolve on its own.[6] Additionally, women who are of minority racial or ethnic groups, of different sexual orientations, in the criminal justice system, living in rural areas, and/or of older age and women who speak languages other than English represent intersectional identities that add barriers to treatment entry.[40]

Among individuals who do enter AUD treatment, there are gender differences in clinical presentation. Women tend to have more severe alcohol and drug use histories, lower education and income, higher unemployment and housing needs, more children living at home, and higher parental stress, and they tend to be younger in age.[15] Primary care settings are a useful portal for AUD treatment access, and for women even more so.[41] Research consistently has found that women access AUD treatment via portals other than specialty AUD options, tending to receive AUD care in mental health and primary care settings.[6,15,16,42-44]

Treatment Retention

Data on gender differences in treatment retention are mixed, and most studies have been completed among samples with substance use disorder (SUD), meaning the results are not specific to AUD. For example, a review by Greenfield and colleagues reported no overall gender differences in SUD treatment retention but hypothesized that there would be different predictors and mediators of retention among men and women.[42] Among both genders, treatment retention has been associated with higher financial resources, fewer mental health problems, less severe substance use problems, more employment, and older age. Female-specific factors related to SUD treatment retention include referral source, personal stability, number of children, and availability of childcare.[42] A separate study found that type of care setting (i.e., detoxification, residential, ambulatory) also may moderate care retention, with women more likely than men to leave a detox facility prematurely.[45]

Treatment Outcome

The following review on outcomes of psychosocial treatments for AUD focuses on empirically supported treatments identified by American Psychological Association Division 12.[46] The pharmacotherapy section focuses on medications approved by the U.S. Food and Drug Administration for treatment of AUD. Search terms included the treatment name (e.g.,

"motivational interviewing" or "naltrexone") + "gender" or "sex" + "alcohol." The authors also searched ClinicalTrials.gov for clinical trials on these AUD treatments, and reviewed publications from large clinical trials for AUD, to determine whether gender differences were analyzed and reported. Lastly, the authors searched for and reviewed reports of clinical trials, literature reviews, or meta-analyses on specific treatments to identify commentary or results regarding sex or gender. This was done to address the fact that analyses not yielding any significant gender differences may not have been identified using the search terms. Thus, for some treatments the authors were able to comment on null gender difference findings. Despite the NIH mandate to include females in biomedical research,[1,2] relatively few AUD treatment outcome studies have reported on gender as a moderator of treatment outcome. The more recent NIH policy mandating analysis and reporting of gender differences in treatment outcomes[3] should result in deepened knowledge of gender differences in response to treatment and in gender-specific mechanisms that help explain treatment effects.

Psychotherapy

Motivational enhancement therapy, cognitive behavioral therapy for AUD, and twelve-step facilitation

Motivational enhancement therapy (MET) is a psychotherapy that helps patients resolve their ambivalence about engaging in treatment and reducing or stopping their substance use. Cognitive behavioral therapy (CBT) is an approach that focuses on the reciprocal effects of cognitions, emotions, and behaviors that maintain problem drinking. In treating SUD, CBT also focuses on identifying and resolving factors that reinforce or punish the substance use behavior and teaching both general coping skills and coping skills to negotiate drinking triggers. Twelve-step facilitation (TSF) treatment for AUD is based on the traditional Alcoholics Anonymous (AA) 12-step model and focuses on AA attendance, personalized spirituality, and guided introspection ("step work").

MET and CBT are among the most widely researched treatments for AUD;[47] however, there has been limited research examining gender differences in the effects of these treatments. Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity) generated studies on gender differences in treatment efficacy, although the samples of the three conditions (CBT, MET, and TSF) were between 70% and 80% male.[48] Project MATCH had a gender matching hypothesis, positing that women receiving CBT would have better outcomes than women in the TSF condition, a difference that would be greater among women than men. This hypothesis was based on the expectation that CBT would better address secondary issues (such as mood and stress) and that TSF could exacerbate stigma and guilt among women.[49] This hypothesis was not supported, with women in the TSF aftercare arm attending more AA meetings and reporting more AA involvement than men. CBT was ultimately not found to improve secondary issues to a greater extent than TSF.[49]

Witkiewitz, Hartzler, and Donovan tested whether matching patients' motivation level to CBT or MET was associated with better outcomes in the aftercare arm of Project MATCH.[50] Men with lower baseline motivation and above-average alcohol dependence severity were found to drink more frequently in the MET than in CBT condition; the authors proposed that this more severe group may not have done as well in the lower-intensity MET treatment. Women with low motivation (regardless of severity, but who had overall fewer AUD symptoms than men), as well as low-motivated men with below-average AUD severity, reported less frequent drinking in MET compared to CBT. Another study on the outpatient arm of Project MATCH found that, compared with women, men showed greater increases in abstinence self-efficacy over time and across all treatment conditions.[51]

A meta-analysis on controlled trials of brief motivational interventions examined gender as a moderator of treatment effect.[52] The study was able to generate aggregate effect sizes only

for two studies, which did not show evidence of differential response between genders. In a meta-analysis of 22 studies on motivational interviewing, only one study reported on gender effects, with no differences between men and women observed on treatment outcomes.[53] A meta-analysis of 53 randomized controlled trials (RCTs) testing CBT for SUD found that the percentage of female participants in each study was positively associated with effect size, suggesting that women may benefit more from CBT than men, but these results must be interpreted with caution, as women comprised only 29% of the total sample.[54]

Alcohol behavioral couples therapy

Couples-based approaches to the treatment of AUD are based in the assumptions that partners engage in malleable behaviors that reinforce and/or punish the client's drinking behaviors, and that enhancing intimate relationships can improve problem-solving, enhance relationship functioning, and reduce likelihood of relapse. Behavioral couples therapy (BCT) and Alcohol BCT (ABCT) have been shown to be effective at increasing rates of abstinence from alcohol, decreasing alcohol-related problems, and improving relationship functioning.[55,56] Only one study to date has directly compared BCT outcomes by gender: O'Farrell et al. compared treatment outcomes among men and women with AUD and their partners receiving BCT in a naturalistic setting (not a clinical trial).[57] Results revealed few differences between genders, with large treatment effects in drinking reduction and small to medium effects in improved relationship satisfaction across the entire sample.

Several studies have tested ABCT separately among samples of men and women. An early study among men with alcohol dependence and their female partners compared three conditions: (1) ABCT, in which the spouse attended all sessions that included both alcohol- and marital-focused treatment; (2) full spousal attendance but alcohol-focused treatment only; and (3) minimal spousal involvement in alcohol-focused individual treatment.[58] Participants in the ABCT condition showed greater drinking reductions and improvements in relationship functioning compared to those in the other conditions. A second study randomized men with AUD and their partners to either ABCT, ABCT and relapse prevention, or ABCT and AA facilitation; this study found no differences in outcome across treatment conditions but high rates of abstinence across all three conditions.[59]

ABCT also has been tested among women with AUD, and one study compared ABCT to a treatment arm in which women received individual CBT for AUD.[60] In that study, however, 31% of the women refused the couples' study arm due to the need to bring their male partner.[61] The women who did participate in ABCT had slightly more days abstinent and fewer heavy-drinking days at follow-up than did women in the individual CBT arm. In response to women's preference for individual treatment—yet recognizing the positive results of ABCT and the role significant others play in women's drinking—a separate study compared ABCT to a "blended-ABCT," in which women with AUD attended five sessions individually and seven with their male partner.[62] Results showed equal outcomes across conditions. Thus, ABCT yielded excellent outcomes for men and women with AUD in separate studies, but gender differences in the effects of, and engagement in, ABCT have yet to be directly tested.

Pharmacotherapy

Three medications are currently approved by the U.S. Food and Drug Administration for the treatment of AUD: acamprosate, naltrexone, and disulfiram. There are important gender differences in their bioavailability, distribution, metabolism, elimination,[63] and side effects,[64] highlighting the importance of examining sex as a moderator of medication treatment efficacy for AUD.

Acamprosate

A meta-analytic study examined acamprosate for AUD treatment separately for men and women from a total of 22 studies,[65] some of which included women and some of which did not.

Patient data were accessed from 1,217 women and 4,794 men across the studies. Results showed no gender differences in any measure of acamprosate efficacy, safety, or tolerability (including percentage of abstinent days, heavy drinking, study completion, and medication compliance). Another study examined gender differences in treatment outcomes of the Combined Pharmacotherapies and Behavioral Interventions (COMBINE) study.[66,67] Participants in COMBINE received medication management with 16 weeks of placebo, naltrexone, acamprosate, or their combinations, with or without a combined behavioral intervention (a combination of empirically supported interventions from different therapies). Analyses showed that acamprosate was no more effective than placebo when separately analyzed in both men and women.

Naltrexone

One of the first studies on naltrexone for AUD was a multicenter, placebo-controlled RCT of injectable naltrexone,[68] with each condition comprising 32% women. Results showed that naltrexone was efficacious for men, but not women, in terms of reducing heavy drinking. Another study tested outcomes of psychotherapy with either oral naltrexone or placebo and found that naltrexone was not efficacious compared to placebo for female participants in reducing drinking, but it did delay the onset of drinking after an initial lapse.[69]

A third study tested high-dose naltrexone in men and women with co-occurring cocaine use disorder and AUD in a double-blind placebo RCT.[70] Participants were randomized to receive either naltrexone (150 mg) or placebo (58 men and 24 women in each condition), combined with either CBT or medication management. Women taking naltrexone used more cocaine and alcohol than did men and the placebo group, whereas men in the naltrexone group used less cocaine and alcohol compared to women and the male placebo group. The authors hypothesized that side effects of naltrexone (e.g., nausea, vomiting) for women may account for this effect. Indeed, women have been shown to have more negative side effects from naltrexone than men, which may be related to women's greater sensitivity to the endogenous opioid system.[71] Women's sensitivity to the effects of naltrexone also may vary across the menstrual cycle, with greater sensitivity in the luteal phase (i.e., post-ovulatory, late phase of the cycle) compared to the early follicular phase (i.e., pre-ovulatory, early phase of the cycle).[72]

Thus, early studies suggested naltrexone for AUD was not as effective for women as for men, or that women may experience worse side effects, contributing to worse outcomes. However, more recent research has suggested that these effects may be due to study characteristics such as sample size or outcomes assessed. Baros, Latham, and Anton used data from two RCTs comparing a naltrexone plus CBT group and a placebo plus CBT group and found effect sizes favoring naltrexone in men compared to women on some outcomes (drinks per drinking day), but not others (percentage of days abstinent, percentage of heavy drinking days).[73] A review of naltrexone RCTs among women suggested that the medication may have modest effects for women in drinking quantity and time to relapse, but not on drinking frequency.[74] However, the number of studies reviewed was small, and additional research is needed.

A secondary analysis of COMBINE data tested treatment effects separately in men and women and found that both genders had better treatment response when they received naltrexone with either medication management or combined behavioral intervention (a combination of empirically supported interventions), in comparison to placebo and any other combination of treatments.[66] The authors concluded that naltrexone is effective among women, and that studies showing noneffectiveness among women may be due to inadequate sample sizes.

Disulfiram

In 2016, Agabio et al. cited the low number of women in clinical trials on disulfiram that preclude evaluation of sex differences in efficacy and safety.[75] A search for any additional trials since 2016 (search terms "sex" or "gender" or "women" + "disulfiram") did not yield new information

on sex differences in the effect of disulfiram for alcohol use.

Digital and Mobile Treatment Technologies

Emerging digital and mobile models of treatment delivery include platforms such as telehealth sessions via videoconference; direct access computer programs such as CBT4CBT;[76] smartphone applications (apps) such as the Addiction—Comprehensive Health Enhancement Support System (A-CHESS)[77] to help patients track their drinking and provide real-time assistance with coping skills; and therapist text-messaging protocols.[78]

The preliminary research on access and use of AUD treatment via digital and mobile technologies suggests gender differences. For instance, a survey of members of an online social network site for women trying to resolve alcohol problems revealed that 47% of the site's members had never tried any other form of support related to their drinking.[79] A large survey study in the United Kingdom showed that women were more likely than men to use online recovery groups (but not recovery websites or apps).[80] A separate study examining use of one social network site for SUD recovery also found a higher proportion of women than men using the site.[81] Secondary analyses of an effectiveness trial testing a computer-assisted behavioral intervention (compared to treatment as usual) did not find gender to moderate the effect of treatment condition; however, results did show that acceptability of the computerized intervention was positively associated with abstinence among women, but not men.[82] Digital and mobile treatment technology for AUD is a burgeoning area of research, which should include analysis and reporting of gender differences in both access and outcomes going forward.

Summary

Existing research suggests no major gender differences in terms of overall outcome in psychosocial or pharmacological treatments for AUD. However, this finding is qualified by the small number of studies that directly test gender differences and the low enrollment of women in clinical trials. Additionally, as demonstrated by secondary analysis of Project MATCH, moderating factors such as AUD severity and motivation may be differentially associated with outcomes for men and women.

SEX AND GENDER DIFFERENCES IN LONG-TERM RECOVERY

Gender Differences and the Broader System of Recovery Care

Recovery is a complicated construct, ill-defined and historically confined to a mutual care, 12-step "disease model" system that considers abstinence as the only viable outcome.[12] AUD is now conceptualized as a chronic, relapsing medical condition and is thought to require a continuum of care, ranging from acute stabilization to ongoing, post-treatment monitoring and maintenance of recovery, and in need of clear benchmarks of disease resolution.[12] In this complicated context, gender differences in recovery historically have been understudied, but there are some limited findings, for instance, on AA use and clinical outcomes. As more sophisticated treatment approaches and definitions of target outcomes (including "recovery") are developed in the field, there will be an accelerated need to identify moderating variables (including gender and other demographic variables) that predict treatment outcomes. The following sections highlight aspects of the intersection between gender differences and recovery research.

Gender Differences and Mutual Help Groups

Alcoholics Anonymous, the largest and most popular mutual help organization available, offers primarily mixed-gender meetings, but also some single-gender meeting options (i.e., men-only, women-only). However, AA meeting content is

consistent across groups and does not necessarily include gender-specific content.[83] One gender-specific and secular mutual help organization is Women for Sobriety, which provides coping skills and reciprocal support for participants.

Outcomes of single-gender versus mixed-gender AA meeting attendance have not been studied; however, studies on gender differences in treatment outcomes among attendees of mixed-gender AA have shown some significant results, including different moderators of attendance for men and women. One longitudinal study followed 466 men and women for 16 years who were initially untreated for problem drinking.[84] Women were more likely to participate in AA, had longer stays in inpatient treatment for alcohol in the year after baseline, achieved better outcomes than men at 1 and 8 years, and benefited more from AA attendance during years 2 through 8. At 16 years post-baseline, women were more likely than men to participate in treatment and in AA, to be free of drinking problems, to consume less alcohol, to have fewer DSM-IV dependence symptoms, and to report less drinking to cope and higher abstinence self-efficacy;[85] women were also more likely to report improvements in depression, friendships, problem-solving, self-confidence, and family relationships and social functioning, compared to men.

Witbrodt and Delucchi followed participation in AA for 7 years and found that men were more likely to stop attending over the 7-year period.[86] Women with higher co-occurring drug severity were less likely to participate in AA than were women with lower drug severity. Women with more severe psychiatric symptoms were more likely to attend AA than women whose symptoms were less severe. Lastly, men who were less religious and those with networks supportive of drinking were less likely to attend AA treatment. Another study that followed 96 women and 180 men for up to 3 years found that AA membership increased participants' odds of achieving a year of abstinence, an association that was stronger for women than for men.[87] Comparing men and women in the United States and Sweden, the odds of AA attendance was greater for women who were both alcohol and drug dependent (versus just alcohol), and for women, the odds of AA attendance increased with the number of friends with whom to talk about personal problems.[83]

In sum, research on gender differences in outcomes of AA attendance are mixed, but the most consistent findings suggest women are more likely to stay in AA longer than men, and there may be different moderators (e.g., drug use, psychiatric comorbidity, religiosity, social networks) of the efficacy of AA for men and women.

Gender Differences in Response to Continuing Care Interventions

In line with contemporary notions of AUD and SUD as chronic, relapsing diseases requiring a continuum of care, McKay and colleagues developed and tested stepped and continuing care interventions with various levels of intervention, including telephone counseling.[88,89] The continuing care approach has implications for women with AUD, for whom social networks supporting abstinence may be particularly relevant for maintenance of recovery.

In a sample of participants who used cocaine, most of whom were also alcohol dependent, McKay and colleagues found that women but not men benefited from telephone continuing care.[89] Further study of gender moderators revealed lower rates of cocaine-positive urine for women at 24 months, but not men, if receiving telephone continuing care versus treatment as usual.[90] More work is encouraged in this area for AUD; sample sizes of women need to be sufficiently large to test for gender differences, and social support for abstinence and emotional support should be incorporated.

Precipitants to Relapse

Sliedrecht and colleagues conducted a review of 321 articles, published between 2000 and 2019, to examine the evidence for precipitants of relapse in AUD.[91] The review focused on 37 potential determinants of relapse in AUD, including gender,

and identified the number of studies that found evidence for (or against) each relapse determinant. The review showed mixed results in terms of rates of relapse among men and women. Specifically, most studies (59%) included in the review found no gender differences in participants' likelihood of relapse after treatment, but 41% of the studies did find gender differences and collectively suggested that women were less likely to relapse.[91]

In another review, Walitzer and Dearing indicated that rates of alcohol relapse did not differ among men and women, but evidence did indicate different predictors of relapse by gender.[92] For women, being married, marital stress, interpersonal conflict, and negative affect were risk factors for alcohol relapse whereas for men, risk factors included isolation and both negative and positive affect. Being married was identified as a protective factor for alcohol relapse in men, and having more children in the home was protective for women. The gender difference in marital status in relation to alcohol relapse (protective for men, risk factor for women) is worth noting, given that women are more likely to be married to a spouse who drinks and men are more likely to be married to a light or non-drinker.[92] Women also are more likely to drink to cope with marital conflict whereas men are more likely to report that their drinking contributes to marital conflict.[92]

Various Forms of Recovery: Abstinence and Moderated Drinking

Gender differences in empirical studies on viability of non-abstinent forms of recovery have recently been studied. Analysis of gender differences in such studies needs to attend to different thresholds for risky or heavy drinking for men and women.[14] Using Project MATCH data (30% female), four recovery profiles were generated at 3 years post-treatment: poor-functioning frequent heavy drinkers, poor-functioning infrequent heavy drinkers, high-functioning occasional heavy drinkers, and high-functioning infrequent non–heavy drinkers. No gender differences in profile assignment were found.[93]

In a study of three clinical trials for AUD—including data from Project MATCH, the COMBINE study, and the United Kingdom Alcohol Treatment Trial—several baseline variables were tested as predictors of low-risk drinking; gender was not found to be predictive.[94] In a large epidemiological sample (41% female), gender differences in past-year likelihood of falling into one of six drinking patterns (ranging from abstinent recovery to five types of non-abstinent recovery) were examined. Women were more likely than men to be in the abstinent recovery or asymptomatic, low-risk drinking categories than in the persistent AUD category. Additionally, women were less likely than men to fall into the symptomatic, high-risk drinking category. These results persisted after adjustment for daily amount of alcohol used, severity of AUD, illicit drug use, SUD, and anxiety/depression.[95]

One study examined men and women with AUD between ages 55 and 77 in a private outpatient program.[96] At 6-month follow-up, 79% of women reported abstinence from alcohol and drugs in the prior 30 days, compared to 54% of men. Among those not abstinent, no women reported heavy drinking in 30 days prior to follow-up, whereas non-abstinent men reported an average of 4 heavy-drinking days (a significant gender difference).

Quality of Life During the Recovery Period

Issues such as co-occurring mental health conditions, social environment, sleep, and physical health are directly affected by problem drinking and are important independent outcomes reflecting quality of life (QoL). Literature reviews have shown that heavy drinking is associated with reduced QoL, which improves with reductions in drinking.[97] There is some evidence that the association between drinking, recovery, and QoL may be moderated by sociodemographic constructs, including

gender.[97] Among women with AUD, both abstinence and moderate consumption of alcohol were associated with improved QoL over a mean follow-up of 46 months.[98] Among 82 patients with AUD admitted for inpatient detoxification and assessed at baseline and 12 weeks later, women with AUD reported lower QoL (general health, psychosocial impairment) than men with AUD.[99] These studies suggest that QoL be examined in gender differences to continue to address the relationship of QoL among women vis-à-vis reduction in drinking.

Summary

Attention to gender differences among various forms of recovery (both in the 12-step model and in the treatment outcome literature)—including examination of abstinence, reduction of drinking, and/or secondary outcomes—has yielded some interesting results, but research is sparse so far. Predictors of relapse appear to differ between men and women, with women being more likely to relapse in response to interpersonal conflict and negative affect whereas men are more likely to relapse in response to isolation and both positive and negative affect. Also, although being married is a protective factor for men, it can act as a risk factor of relapse for women. Having at least one close friend to discuss drinking with is differentially helpful for women. Also, gender differences in treatment outcome and maintenance may depend on the outcome of interest (drinking or secondary outcomes) and the "form of recovery" studied.

SEX AND GENDER DIFFERENCES IN AUD MECHANISMS OF BEHAVIOR CHANGE

There are several behavioral treatments now known to be efficacious for AUD, but there is almost no examination of gender differences in the AUD psychotherapy process and mechanisms of behavior change in this research literature. For example, the authors of this paper found 49 articles published between 2000 and 2012 (26 published since 2010) studying mechanisms of change in CBT, Motivational Interviewing, or MET or examining general therapeutic alliance as a mechanism of change. Of these 49 articles, 22 were review or non-empirical papers and did not mention gender. Of the 27 empirical studies, seven (26%) provided no sample breakdown by gender, one study (4%) had an all-female sample, and 17 (63%) had mixed-gender samples (albeit 11 of the 17 had samples that comprised at least two-thirds men). Furthermore, of these 17 mixed-gender studies, only five (29%) mentioned gender at all, typically as a statistical covariate. Since 2012, researchers have continued to examine mechanisms of change but generally have continued to ignore gender or used single-gender samples.

The Women's Recovery Group (WRG), a treatment for women with SUD (including AUD), examined mechanisms of change between men and women. WRG was compared to a traditional mixed-gender Group Drug Counseling (GDC) treatment in Stage I[100] and Stage II[101] trials. The pilot study and RCT results indicated that WRG was at least comparable to a mixed-gender, traditional drug counseling group. Secondary analyses of the pilot study and/or RCT data tested affiliative (supportive, positive, or empathic) statements as WRG mechanisms of change. Women in WRG emitted more affiliative statements compared to both genders in the GDC condition. Affiliative statements were made more in WRG than GDC and were associated with better drinking outcomes during and 6 months after treatment for women, especially in WRG.[102]

Litt et al. studied Network Support Treatment (NST) for AUD, which is designed to help patients build social support networks for sobriety.[103] Main treatment effects showed that men had a better treatment response than women. NST effects were mediated by changes in abstinence self-efficacy and number of abstinent friends for both men and women. Among those receiving NST,

women reported less improvement in abstinence self-efficacy and fewer abstinent friends. Kelly and Hoeppner explored gender moderation of purported mediators, assessed at 9-month follow-up, of the effects of AA on drinking at 15-month follow-up among Project MATCH participants.[104] Social self-efficacy and pro-abstainer social networks mediated AA's effects on abstinence for both men and women, but a larger proportion of AA's effect on treatment outcome was accounted for by these mediators for men (91%) than for women (57%). Additionally, although self-efficacy in positive social situations at 9-month follow-up was a mediator of the effect of AA on drinking at 15-month follow-up for men, it was not for women. Alternatively, self-efficacy not to drink in negative affect situations was a significant mediator for women, but not for men.

Recent studies have investigated potential mechanisms of behavior change among female-only samples receiving CBT for AUD (see McCrady, Epstein, and Folkus[6] for review). For instance, using times-series network analysis to examine concurrent and sequential relationships among several putative mechanisms of change, Holzhauer et al. examined mechanisms of change in an RCT comparing a gender-neutral to a female-specific CBT for women with AUD.[105] Higher self-confidence to abstain from drinking and increased use of alcohol-related coping skills were associated with less drinking in women in both CBT conditions. Women receiving female-specific CBT also reduced their drinking through decreased sociotropy (reactivity to others) and increased social support for abstinence. Changes in autonomy (importance of one's independence and personal rights) were associated with higher self-confidence in abstinence, use of coping skills, and less drinking in both conditions, suggesting that increasing autonomy may be a treatment mechanism specifically for women.

Identifying mechanisms of behavior change in treatments for AUD is a critical research effort, as it provides an understanding of the active ingredients of effective treatments. Such an understanding provides clinicians information about the critical elements that should be provided for different populations and will aid dissemination of empirically based treatments.[106,107] However, identifying such mechanisms has been difficult,[106] and moderating factors, including sex and gender, may play an important role in how people change.

DISCUSSION

Literature on gender and sex differences in AUD has grown exponentially since 1994. This has been particularly true regarding research on biopsychosocial risk and maintenance factors of AUD and treatment entry and gender-specific barriers to treatment for AUD. However, there is room for improvement regarding analysis and reporting of gender differences in treatment response for AUD and in mechanisms of drinking behavior change. Past reviews of gender differences in treatment outcomes have found mixed results and little evidence for systematic gender differences.[11,42] However, many of the studies covered in these reviews were completed among patients in treatment for other substances or for alcohol and other substances, not AUD alone. Additionally, many of the studies reviewed were set in naturalistic settings rather than in randomized and/or controlled trials, and most studies simply did not recruit enough females and did not present data on gender differences even when there was a subset of female participants.

A recent review conducted by the RAND National Defense Research Institute examined 24 AUD RCTs to examine gender differences in outcome and found mixed results, with little evidence for systematic gender differences in treatment effects across studies.[108] However, the authors of that review also stated: "Most notably, despite an extensive search and thorough screening procedure, we found very few studies reporting on gender differences, which hindered our analyses. . . . The review showed a profound lack of information on presence and absence of gender differences. We contacted authors and scrutinized numerous U.S. RCTs for differential

effects for men and women but found very few relevant studies."[108 (p54)]

Our review and those by Greenfield and colleagues[42] and Epstein and Menges[15] all concur with this assessment—that there is not enough research on the topic of gender differences in treatment outcomes (psychotherapy or pharmacotherapy). There is not enough research on gender differences regarding the efficacy of specific treatments or enough research that examines secondary outcomes, aside from alcohol use, that are especially relevant to long-term recovery (e.g., co-occurring psychological disorders or symptoms, physical health, QoL, moderated drinking). Although some research suggests women may have better outcomes than men in recovery from AUD, multiple factors—including but not limited to sample size/percentage of women, severity of AUD, and motivation to change—may contribute to such findings and preclude conclusions at this point.

As suggested by Moyer and colleagues,[52] future work would be enhanced by clearly delineated hypotheses about why gender differences might be expected in specific treatments—both in terms of treatment efficacy and in terms of mechanisms of behavior change. There has been substantial research on gender differences in risk and maintenance factors for AUD, and there is expanding research on female-specific treatment needs and approaches.[6] The field of AUD treatment development may be well positioned to use this research on gender differences to propose hypotheses about and, perhaps more important, men and women might respond differentially to a given treatment. For example, Project MATCH formulated a priori gender matching hypotheses; although these were not confirmed in the direction expected, gender differences did emerge that were then available to inform continued research.

It is also important to note that even among the studies that examined sex and gender differences, the sample sizes of women were often small, and analyses were likely underpowered. Given the historical differences in prevalence of AUD among men and women, this may have been justifiable in the past. However, the convergence of prevalence rates for lifetime AUD among men and women no longer justifies such small samples of women in treatment. Although studies may recruit men and women, women often comprised less than 50% of the sample, which makes it difficult to examine gender differences. If gender is considered a moderating factor, there must be enough men and women to statistically power the examination of interaction effects. Thus, in conducting clinical trials it may be important to enroll comparable numbers of men and women, with sufficient power to properly examine gender differences.[108] This includes using gender as a variable in randomization and examining gender-related co-occurring conditions and other secondary outcomes. The literature highlighted in this review provides substantial evidence that sex and gender differences impact the factors that are integral to AUD recovery—such as frequency and intensity of drinking, social functioning, physical health, risk for relapse, and possibly mechanisms of change—and therefore deserves to be considered in recovery research as the field moves forward.

Another consideration is single-gender treatment options, with female-only treatment most often a focus of research. This area of research has examined the delivery of treatment in a women-only setting, with or without including female-specific content (see McCrady et al.[6] for a review). There is evidence for differential, positive outcomes for treatment delivered in women-only versus mixed-gender settings,[6,42] but only when female-specific programming (i.e., content) also is provided. Thus, some argue that women-only treatment settings are not necessary, compared to mixed-gender settings, and at least one study of women in a residential treatment setting indicated that female-only treatment is not, at least initially, preferred by all female patients.[109] However, consistent findings have suggested that women express satisfaction and preference for female-specific format and treatment content.[6] Additionally, even if mixed-

gender treatments were shown to be as good as or better than single-gender treatments, women-specific treatments are likely to enhance treatment access for many women.

SUMMARY AND RECOMMENDATIONS FOR FUTURE RESEARCH

Gender differences in AUD treatment and recovery is an area in need of accelerated research. Specific areas of investigation are recommended:

- An overarching factor is the low engagement of men and women with AUD treatment. Gender differences may play important roles in understanding how, when, where, and why individuals seek care for AUD.
- Emerging research on digital and mobile technologies needs to include equal numbers of female and male participants and to analyze data by gender.
- Additional research is needed to test treatment access, retention, and outcomes for women versus men in primary care settings.
- Further research on gender-differentiated use of AA and other mutual help groups, and differences in treatment outcomes and mechanisms of change, is indicated.
- Rigorous, randomized trials for AUD on single-gender versus mixed-gender group settings with gender-specific programming are lacking.
- Another important contextual factor is a clarified definition of "recovery." Variations in treatment goals and non-abstinent outcomes need to be examined, including gender as a moderating variable.
- Gender differences in secondary outcomes (such as co-occurring symptoms, interpersonal functioning, and quality of life) should be reported in AUD treatment outcome research.
- Research suggests gender differences in relapse precipitants. Furthering our understanding of biological, social, and psychological determinants of relapse based on gender has implications for personalized or tailored relapse prevention approaches.
- Clinical trials are mandated to recruit men and women, as well as analyze and report gender differences; however, the field needs to adhere more stringently to these mandates in future research. This involves consistent changes to methods such as intentional oversampling of women, randomization based on gender, and gender-specific analyses.

The research reviewed here provides ample reason to believe that men and women recover from AUD differently. It is important to test and report gender differences when studying mechanisms of change—mediators, moderators, and active therapeutic ingredients—in AUD treatments.

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Women and Alcohol-From The Editors

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Recent epidemiological research has identified alarming trends in drinking patterns of girls and women in the United States. In recent years, the amount and frequency of alcohol use are increasing in White and Hispanic girls and young women in contrast to decreasing patterns of heavy alcohol use in boys and young men.[1,2] Similarly, current and binge alcohol use is rising among older women,[3,4] resulting in increased morbidity and mortality in this growing segment of the U.S. population. For example, emergency room visits associated with both acute and chronic drinking[5] and alcohol-related inpatient diagnoses in U.S. middle-aged adults[6] have accelerated more rapidly in women than men. Overall, these changes have narrowed the long-established gender gap in alcohol consumption and associated problems, with women's drinking patterns across the life cycle approaching those of men.

These epidemiological trends have increased the urgency of sex-specific, gender-focused research on alcohol.[7] Historically, because they were underrepresented among heavy/problem drinkers, women often were omitted from a wide range of alcohol studies, including basic science on alcohol effects in women, alcohol-related medical morbidities, social/behavioral consequences of drinking, and treatment intervention studies. With this topic series on women and alcohol, *Alcohol Research: Current Reviews (ARCR)* seeks to close these knowledge gaps and identify important areas for future research directions.

"Gender Differences in the Epidemiology of Alcohol Use and Related Harms in the United States" provides an update on the diminishing sex differences in alcohol consumption, related health problems, hospitalizations, emergency department visits, and death across the life span.[8] Of particular concern, White highlights the reversal in historical alcohol consumption patterns of underage drinkers, such that adolescent girls now report higher rates of monthly alcohol use and binge drinking compared with adolescent boys.[8] Findings have important implications for prevention of fetal alcohol spectrum disorders.

As illustrated in articles throughout this *ARCR* topic series, many alcohol-related sex differences—including development and maintenance of alcohol misuse, alcohol-driven cognitive and medical problems, and even psychiatric comorbidities—derive from key differences in the neurobiology of men and women. In "Sex Differences in the Neurobiology of Alcohol Use Disorder," Flores-Bonilla and Richardson explore preclinical and human research on neural differences using a three-stage framework of addiction.[9] Specifically, they examine how neurobiological differences contribute to initial development of binge/intoxicated drinking, the transition into withdrawal, negative affect and dysfunctional behaviors associated with continued heavy drinking, and finally development of preoccupation with or craving for alcohol and compulsive drinking, and relapse.[9]

In "The Endocrine System and Alcohol Drinking in Females," Finn extends this neurobiological review by examining the multidirectional interactions of alcohol, stress, and key gonadal sex steroid hormones and stress steroid hormones.[10] Findings suggest promising directions for development of novel pharmacological treatments for alcohol use disorder (AUD).

In "Alcohol's Unique Effects on Cognition in Women: A 2020 (Re)view to Envision Future Research and Treatment," Fama, Le Berre, and Sullivan provide a wide-ranging update on the interrelationships between alcohol and cognition, including effects of acute and chronic alcohol consumption across the drinking continuum.[11] Although current research indicates many overall similarities in structural and functional effects of alcohol in women and men, the authors bring focus to factors that may influence sex-specific differences, such as age, drinking patterns, abstinence duration, and medical history and psychiatric comorbidities.[11] One area of particular relevance for women is the effects of alcohol on social and emotional cognition; this relatively young area of cognitive research has important implications for both development and consequences of AUD. Overall, it is clear that women who are chronic heavy drinkers experience cognitive deficits relative to age-matched women who are social drinkers or do not drink. These findings should be used to inform development and adaptations of alcohol treatment interventions and recovery programs for women.

It is well established that women experience higher prevalence of mood and anxiety disorders[12] and more frequent interpersonal trauma associated with higher prevalence of post-traumatic stress disorder[13] compared with men, and that these negative factors have a role in the development and maintenance of heavy drinking and associated problems in women. In "The Role of Stress, Trauma, and Negative Affect in the Development of Alcohol Misuse and Alcohol Use Disorder in Women," Barros Guinle and Sinha examine the sex-specific neurobiological underpinnings of the biological, psychosocial, and psychiatric factors that may be contributing to the accelerating drinking patterns recently observed in girls and women.[14] Of particular concern is the growing evidence of a sex-related, chronic negative feedback cycle in which childhood maltreatment and trauma lead to the development of a maladaptive, blunted stress response in girls and women.[14] In turn, this blunted neurobiological response escalates alcohol consumption, further blunting neuroendocrine responses, and contributing to the progression from alcohol misuse to AUD.

Given differences between women and men in risk factors, developmental course, and health and psychosocial consequences of alcohol misuse and AUD, tailored approaches to alcohol identification, prevention, and intervention for girls and women may be necessary to maximize treatment outcomes. Indeed, specialized screening instruments that are more sensitive and specific to women are available to improve case identification.[15] Although evidence suggests that women and men have comparable outcomes in mixed-gender, nonspecialized alcohol treatments,[16] women cared for in specialized, women-specific programs may experience greater improvements in key areas such as pregnancy outcomes, psychiatric health, HIV risk reduction, and psychosocial well-being.[17] These areas are reviewed in several key articles in this topic series.

In "Maternal Substance Use: Consequences, Identification, and Interventions," Chang reviews prevalence and addresses the importance of early identification and intervention for substance use among pregnant women, with emphasis on alcohol, tobacco, cannabis, and opioid exposure.[18] She reviews strengths and shortcomings of available screening tools specific to pregnant women, legal and social barriers to implementation of universal screening, and available prevention intervention strategies, particularly for fetal alcohol spectrum disorders.[18]

In "Alcohol Screening, Brief Intervention, and Referral to Treatment (SBIRT) for Girls and Women," Hammock, Velasquez, Alwan, and von Sternberg provide a comprehensive review of

the effectiveness of this evidence-based, public health approach to identifying and intervening in heavy/harmful alcohol use across the life span, specifically examining SBIRT for girls, women of childbearing age, and older women.[19] This clinically relevant, evidence-based article offers information on age-appropriate screening tools and intervention approaches.[19] It also summarizes facilitators and barriers to SBIRT implementation in social service and health care settings,[19] including recently identified unanticipated consequences of state-level policies related to alcohol use during pregnancy.[20]

"Treatment Interventions for Women With Alcohol Use Disorder" examines women's barriers to treatment seeking and referral, program services to address these barriers, and efficacy of women-specific services relative to traditional mixed-gender care.[21] Importantly, McCrady, Epstein, and Fokas address mechanisms of change, which often are overlooked but highly relevant to successful development of strategies to tailor treatment to women more effectively.[21] Finally, the article considers the effects of women-specific substance abuse services on a breadth of outcomes, ranging from the primary targets of alcohol and drug use to secondary outcomes such as psychosocial well-being, psychiatric health, pregnancy outcomes, and HIV risk reduction.[21]

Although much of the research discussed in this topic series addresses sex-specific findings, it is critical to bear in mind that this literature often obscures important differences among women as a group. In "Alcohol-Related Disparities Among Women: Evidence and Potential Explanations," Mulia and Bensley address key foci of diversity research, including race, ethnicity, socioeconomic and social status, and sexual orientation.[22] Although the research to date is quite limited, these factors have been shown to influence not only effects of acute and chronic alcohol consumption, but also alcohol-related health disparities and access to care. The article highlights the "alcohol harm paradox"[23]—that certain racial/ethnic minority groups, particularly African Americans, and lower socioeconomic groups experience greater harm despite comparable or lower alcohol consumption. The authors consider possible explanations and interventions for these disparities.[22]

Finally, we have known for decades that women are more vulnerable to many of the negative health consequences of alcohol consumption, in part, due to their higher blood alcohol levels achieved at comparable alcohol doses compared with men. Now, research is providing system-specific findings of the interplay of alcohol and health in women. Indeed, this topic series addresses sex-specific health effects of alcohol in four key areas. In "Alcohol and Liver Function in Women," Maddur and Shah address the increasing rates of liver disease in women, the key role that estrogen plays in the greater vulnerability and more rapid progression to alcohol-related liver disease in women compared with men, and sex differences in liver transplant availability and outcomes.[24]

In "Alcohol's Effects on Breast Cancer in Women," Freudenheim highlights the compelling evidence that any alcohol use increases breast cancer risk and that risk increases as total consumption increases, emphasizing the importance of targeting this modifiable risk factor for public education and intervention.[25] Current findings suggest that these effects are independent of alcohol beverage type or age at alcohol exposure. The author reviews possible mechanisms for this increased risk including direct carcinogenic effects of alcohol and acetaldehyde, changes in hormones associated with drinking, and alterations in DNA methylation.[25]

Cardiovascular (CV) diseases (e.g., hypertension, coronary heart disease, stroke) are the leading cause of death in women.[26] In "Effects of Alcohol on the Cardiovascular System in Women," Piano, Thur, Hwang, and Phillips address the sex-specific findings about the contribution of alcohol consumption to CV morbidity and mortality.[27] Unlike the generally linear relationship between drinking and CV disease in men, there appears to be a J-shaped function for women, with no or lower CV risk at one or two drinks per day and increased risk at and above three or four drinks per day.[27] The

authors examine the contributions of estrogen to these relationships.[27]

Women are more likely to experience insomnia and other common forms of sleep dysregulation compared with men and, in turn, sleep disruption has more severe health consequences for women compared with men.[28] Despite the fact that sleep disturbance is one of the most frequent complaints among persons with AUD,[29] sex differences in sleep have been understudied and underreported in alcohol research. In "Sleep and Alcohol Use in Women," Inkelis, Hasler, and Baker consider important bidirectional effects of alcohol and sleep disruption, examining both how poor sleep quality may contribute to alcohol consumption and how acute and chronic alcohol consumption can lead to sleep dysregulation.[30] The authors review biological, psychological, and social factors that contribute to these bidirectional relationships as well as their treatment implications.[30]

All of the articles in this topic series highlight critical, ongoing, sex-specific knowledge gaps in our understanding of the epidemiology of alcohol use, the interplay of physiology and alcohol, and best approaches to prevention and treatment. This research supports the importance of the National Institutes of Health mandate not only to include female subjects in research, but also to include them in sufficient numbers to permit sex-specific analyses of findings. As evidenced by these articles, the National Institute on Alcohol Abuse and Alcoholism has successfully targeted many of these areas for support in recent years, yet much remains to be learned as we confront the rapidly changing characteristics of women's alcohol misuse and harms.

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Gender Differences in the Epidemiology of Alcohol Use and Related Harms in the United States

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Over the past century, differences in alcohol use and related harms between males and females in the United States have diminished considerably. In general, males still consume more alcohol and experience and cause more alcohol-related injuries and deaths than females do, but the gaps are narrowing. Among adolescents and emerging adults, gaps in drinking have narrowed primarily because alcohol use among males has declined more than alcohol use among females. Among adults, alcohol use is increasing for women but not for men. Rates of alcohol-related emergency department visits, hospitalizations, and deaths all have increased among adults during the past two decades. Consistent with the changing patterns of alcohol use, increases in these outcomes have been larger for women. Recent studies also suggest that females are more susceptible than males to alcohol-induced liver inflammation, cardiovascular disease, memory blackouts, hangovers, and certain cancers. Prevention strategies that address the increases in alcohol consumption and unique health risks for women are needed.

KEY WORDS: alcohol use disorder, sex, brain, development, stress, mental health, alcohol

INTRODUCTION

Alcohol consumption has long been a male-dominated activity. Globally, men consume more alcohol and account for more alcohol-related harms to self and others than women do. In 2016, 54% of males (1.46 billion) and 32% of females (0.88 billion) age 15 and older worldwide consumed alcohol.[1] Alcohol caused roughly 3 million deaths (5% of all deaths) that year, including 2.3 million deaths for men (8% of deaths) and 0.7 million deaths for women (3% of deaths). Although gender gaps in alcohol use seemingly are universal, the size of the gaps varies between countries and their respective cultures, from a male to female ratio for

current drinking of 1:1 in New Zealand and Norway to 12.3:1 in India.[1-3] Large variations between countries suggest that culturally prescribed gender roles, above and beyond physiological sex differences, are central in shaping gender-specific drinking patterns.[4]

In the United States, more males than females drink each year (68% males, 64% females). Males drinkers tend to drink more often and more heavily than females do,[5] consuming nearly three times as much pure alcohol per year (19.0 liters for males, 6.7 liters for females).[1,6] Males also are more likely to be arrested for driving under the influence of alcohol (DUI),[7] treated in emergency departments and hospitals for alcohol-related harms,[8-10] and to die from alcohol-related causes.[11] In addition, more males (7%) than females (4%) are diagnosed with an alcohol use disorder (AUD) each year. Among those with AUD, roughly similar percentages of males (9%) and females (9%) receive treatment.[6] Research examining harms experienced due to another person's drinking suggests women are more likely than men to suffer consequences as a result of alcohol use by a spouse/partner/ex-partner (4.2% vs. 1.8%) or a family member (5.6% vs. 3.7%).[12,13]

NARROWING GENDER GAPS

Although males still outpace females for most alcohol-related measures, the gaps are narrowing[5,14] (see Figure 1). In the 85 years since the end of Prohibition, drinking habits of males and females have converged. For cohorts born near 1900, males outnumbered females roughly 3:1 for measures of alcohol consumption (e.g., prevalence, frequency) and problematic drinking (e.g., binge drinking, early-onset drinking). Many of these ratios are closer to 1:1 today, and the differences continue to become smaller (see the box **Summary Statistics on Female and Male Alcohol Use and Outcomes in the United States** and Figure 1).[14] An analysis of six different national surveys between 2000 and 2016 suggests that the number of women age 18 and older who drink each year increased by 6% but decreased by 0.2% for men, and the number of women who binge drink increased by 14% but by only 0.5% for men.[15] As this article explores, gender gaps are narrowing for different reasons among adolescents and emerging adults relative to adults. Specifically, alcohol use is declining faster for adolescent and emerging adult males than for females, whereas gaps are narrowing among adults because of increases in drinking by women but not by men.[15,16]

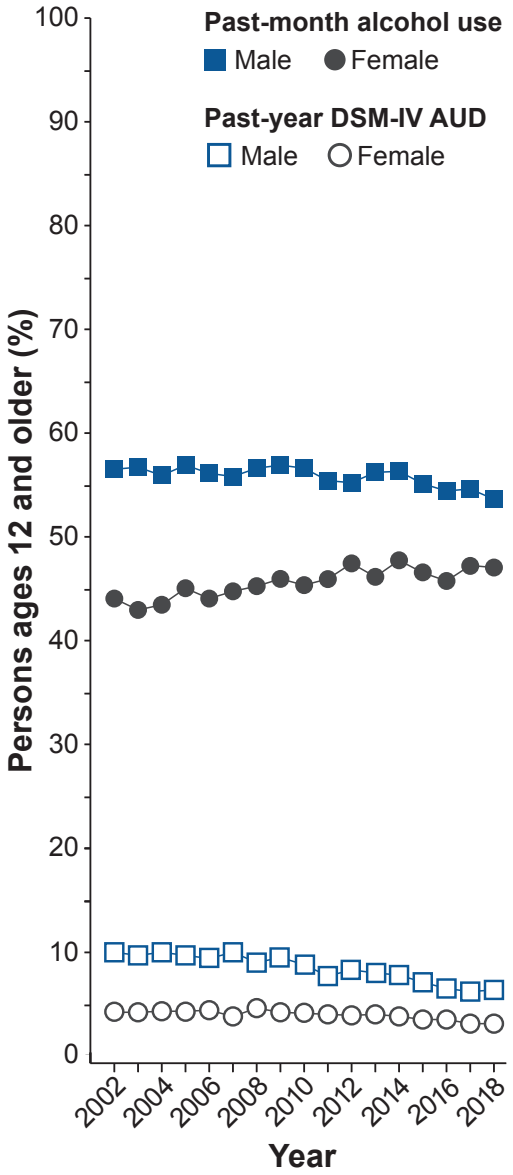

Figure 1 Narrowing gender gaps in the prevalence of past-month alcohol use and past-year DSM-IV AUD between females and males age 12 and older using data from NSDUH 2002–2012. Gender gaps narrowed for both measures, primarily due to increases in alcohol use among females and smaller declines in AUD among females than males. *Source:* White et al., 2015.[5]

Summary Statistics on Female and Male Alcohol Use and Outcomes in the United States

Drinking patterns

- Female drinkers consume about one-third as much total pure alcohol per year as male drinkers (6.7 liters for females, 19.0 liters for males).[1]
- Alcohol use among people age 12 and older: *Lifetime*—82% male, 78% female; *Past year*—68% male, 62% female; *Past month*—55% male, 46% female; *Binge* (4+/5+)* *past month*—29% male, 20% female[28]

DSM-IV AUD† (alcohol abuse or dependence) age 12 and older

- Past-year AUD—males, 9.2 million (7%); females, 5.3 million (4%)[28]
- Percentage who needed and received treatment for DSM-IV alcohol abuse or dependence—males, 9%; females, 9%[28]

Overall deaths

- In 2017, 72,558 death certificates listed alcohol as a factor (18,072 females and 54,486 males).[64]
- Using death certificates and estimates, the Centers for Disease Control and Prevention calculated that 93,296 people died from alcohol-related causes each year between 2011 and 2015 (26,778 females and 66,519 males).[11]
- The World Health Organization reported that excessive drinking accounted for roughly 3 million deaths (5% of all deaths) worldwide, including 2.3 million deaths for men (8% of deaths) and 0.7 million deaths for women (3% of deaths).[1]

Cirrhosis deaths

- In 2017 there were 44,478 deaths due to cirrhosis and 50% (22,246) were caused by alcohol (15,470 deaths among males; 6,776 deaths among females).[10]
- Overall, the rate of death from alcohol-related cirrhosis is more than twice as high for men (9.7 per 100,000) than for women (4.1 per 100,000).[10]

Driving under the influence

- More men (10%) than women (5%) reported driving under the influence of alcohol (DUI) in the past year in 2017.[19]

Gender gaps are narrowing

- Differences are shrinking in drinking patterns, AUD, hospitalizations, emergency department visits, DUI, liver disease, and deaths.[5,14-16,31]

***Binge drinking:** Defined as four or more drinks on an occasion for females and five or more drinks on an occasion for males (4+/5+).

†**AUD:** According to criteria for alcohol abuse and alcohol dependence in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

ADOLESCENTS

Alcohol use, like other drug use, becomes more likely as young people enter and progress through adolescence, which encompasses the second decade of life or more.[17] Data from the 2018 National Survey on Drug Use and Health (NSDUH) suggest that, by age 12, approximately 1 in 100 (1%) adolescents report consuming alcohol in the previous month.[6] The prevalence increases to nearly 1 in 4 (23%) by age 17. Racial, ethnic, and gender differences in alcohol use also emerge during this period (see Table 1). Among students ages 12 to 17, past-month alcohol use is reported by 12% of White students, 9% of Hispanic or Latino students, 8% of American Indian or Alaska Native students, 6% of Black or African American students, 6% of Asian students, and 11% of students of two or more races.[6] Although more boys (19%) than girls (13%) start drinking before age 14, girls who begin drinking in early adolescence have a shorter time period between first drink and first episode of binge drinking.[6,18]

Table 1 Percentage of Past-Month Alcohol Consumption and Binge Drinking (4+/5+) and Past-Year DSM-IV AUD Among Female and Male Adolescents and Young Adults by Race/Ethnicity, NSDUH 2018

	Females						Males					
	Ages 12-17			Ages 18-25			Ages 12-17			Ages 18-25		
Race/ Ethnicity*	Drink	Binge†	AUD‡	Drink	Binge†	AUD‡	Drink	Binge†	AUD‡	Drink	Binge†	AUD‡
Overall	9.6	5.3	1.9	55.5	34.9	8.8	8.8	4.6	1.5	54.4	35.0	11.1
Hispanic	8.0	3.9	1.6	49.3	33.0	8.5	6.9	3.8	1.8	49.6	21.3	10.7
NH Asian	5.6	3.7	1.8	45.1	23.4	8.0	3.7	2.0	0.0	43.0	32.1	10.8
NH AI/AN	5.8	2.1	1.1	45.1	31.1	15.5	4.7	2.9	0.7	49.8	33.0	7.0
NH Black	6.3	2.9	0.5	43.7	23.0	4.4	3.6	1.7	0.9	41.2	23.6	5.8
NH Multiple	13.3	9.2	6.7	55.7	36.3	12.5	8.4	3.4	1.2	58.9	36.9	9.7
NH H/OPI	14.9	11.1	4.5	24.7	17.3	18.4	1.8	1.8	0.4	54.7	46.3	15.9
NH White	11.5	6.6	2.2	62.8	40.3	10.0	11.6	6.2	1.8	61.0	30.6	12.7

***Race/ethnicity:** Hispanic, non-Hispanic (NH) Asian, NH American Indian or Alaska Native (AI/AN), NH Black, NH more than one race (NH Multiple), NH Hawaiian or other Pacific Islander (H/OPI), NH White.
†Binge drinking: Defined as four or more drinks on an occasion for females and five or more drinks on an occasion for males (4+/5+).
‡AUD: Either DSM-IV alcohol abuse or alcohol dependence.
Source: SAMHSA, 2019.[19]

In contrast, when drinking starts at age 15 or later, males progress more quickly to binge drinking.

Data from the 2018 NSDUH (see Table 1) suggest that 5% of adolescents (5% of females and 5% of males) ages 12 to 17 engage in binge drinking each month, defined as having four or more drinks on an occasion for females or five or more on an occasion for males.[19] The National Institute on Alcohol Abuse and Alcoholism defines binge drinking as reaching a blood alcohol concentration (BAC) of 0.08%, the legal limit for operating a motor vehicle for adults age 21 and older, which takes about four drinks in 2 hours for women or five drinks in 2 hours for men (https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking). It should be noted that, for most teens, drinking four or five drinks can produce a BAC well beyond 0.08%. When typical body weights of adolescents are taken into consideration, the number of drinks needed to reach a BAC of 0.08% is closer to three standard drinks within a 2-hour period for girls ages 9 to 17 and boys ages 9 to 13, four drinks for boys ages 14 to 15, and five drinks for boys ages 16 to 17.[20] Thus,

it is likely that studies that assess binge drinking among adolescents by using the criteria of four or more drinks for girls and five or more for boys, or in some cases a five-drink threshold for both males and females,[21] underestimate the extent of potentially dangerous alcohol consumption, particularly among young females.

Alcohol consumption, including binge drinking, declined significantly among adolescents since the beginning of the new millennium. Between 2002 and 2018, past-month alcohol use by adolescents ages 12 to 17 decreased from 18% to 9% and binge drinking declined from 11% to 5%.[19] The declines in drinking were much larger for young males than for young females, leading to significant narrowing of long-established gender differences in alcohol use among adolescents. Until recently, by 10th grade, young males reported higher levels of alcohol use and binge drinking than females. By 12th grade, the differences were quite large and remained so throughout adulthood. These gender differences are disappearing and have reversed for some measures. According to data from the Monitoring the Future (MTF) study, in 1991, 46% of males and 40% of females in 10th grade reported drinking in the past month. By 2018, levels declined significantly for both and the gender gap reversed, with 22% of females reporting alcohol use in the past month compared to 17% of males.[22] Among 12th graders, in 1991, 58% of males and 49% of females drank in the month before the survey. In 2018, past-month alcohol use was equally prevalent among males (30%) and females (30%). Gender differences in self-reported past-month drunkenness among 12th graders also narrowed considerably between 1991 (37% males, 25% females) and 2018 (19% males, 16% females), as shown in Figure 2.

Smaller declines in alcohol use and drunkenness by girls are troubling for several reasons. Evidence suggests that levels of anxiety and depression are increasing among adolescents, particularly females,[16,23] and it appears that females, in general, are more likely than males to drink to cope.[24,25] Drinking to cope is associated with faster progression of alcohol use and a higher incidence of alcohol-related harms.[26] The percentage of adolescents who report drinking alone on their last drinking occasion also is increasing, and more so for girls than boys.[6] In a longitudinal study, more episodes of drinking alone during adolescence predicted a larger number of AUD symptoms during emerging adulthood.[27]

Roughly 1 in 9 students, including 10% of females and 13% of males, drop out of school by 12th grade. Compared to teens who stay in school, those who drop out are more likely to drink and/or use other drugs. In 2014, approximately 1 in 3 (32%) students who dropped out (37% males, 26% females) reported binge drinking compared with 1 in 5 (26% males, 16% females) 12th-grade students in school.[28] Males and females who drop out also are more likely to smoke cigarettes, use marijuana, and misuse prescription medications.[6] Effective prevention strategies are needed to address alcohol and other drug use in this population.

EMERGING ADULTS

Over the past few decades, alcohol use declined among emerging adults, although the declines were smaller than those seen among adolescents.[21] Gender gaps narrowed as well. Roughly 40% of people ages 18 to 24 are enrolled in college. Historically, male college students were more likely to drink and did so more heavily than female college students, and college students drank far more than their peers not enrolled in college. Gender differences among college students have disappeared for some measures. For instance, in 1953, 80% of males and 49% of females in college reported having been drunk at some point in their lives.[29] In 2014, 69% of both males and females in college reported having been drunk at some point in their lives.[30] Differences in alcohol use among college students and their non-college peers are shrinking as well. According to data from the MTF study, between 1980 and 2018, the prevalence of binge drinking—in this

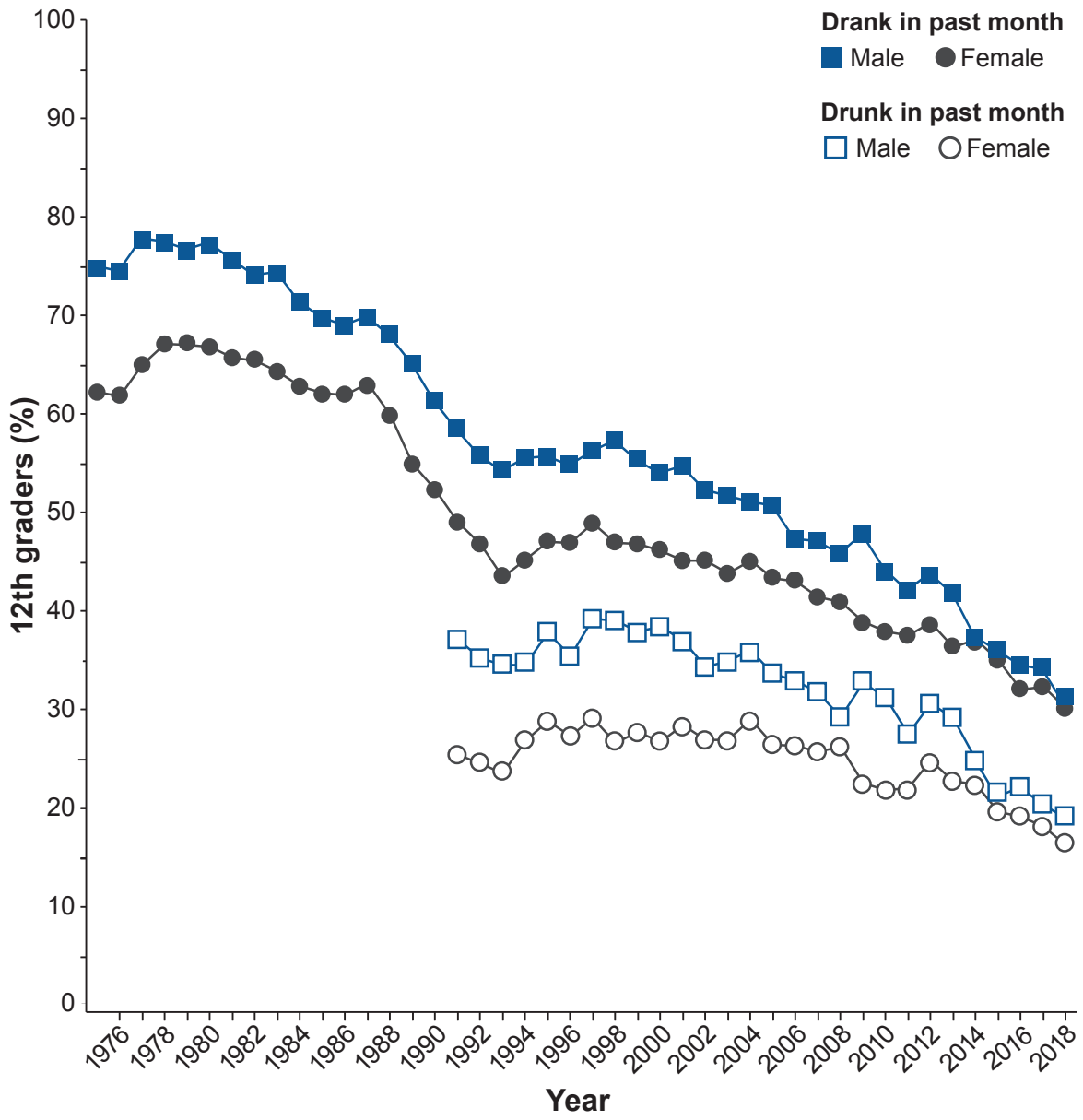

Figure 2 Past-month alcohol use from 1975 to 2018 and past-month drunkenness from 1991 to 2018 among 12th graders. Alcohol use and drunkenness declined more for young males than for young females, leading to disappearing gender gaps in 12th grade. *Source:* Adapted from Johnston, 2019.[22]

case having five or more drinks on an occasion in the previous 2 weeks for both males and females—declined among males in college from 52% to 32% and among males not in college from 54% to 25%.[21] The declines were smaller for females. The prevalence declined for females in college from 36% to 27% and for females not in college from 29% to 25%. For past-month alcohol use and reports of being drunk, the gender gaps reversed, with females both in and outside of college exceeding the levels among their male counterparts (see Figure 3).[22] In 2018, 61% of females in college and 51% of females not in college reported past-month drunkenness, compared to 58% of males in college and 50% not in college. These shifts are remarkable given the long history of heavier alcohol use among young adult males than females.

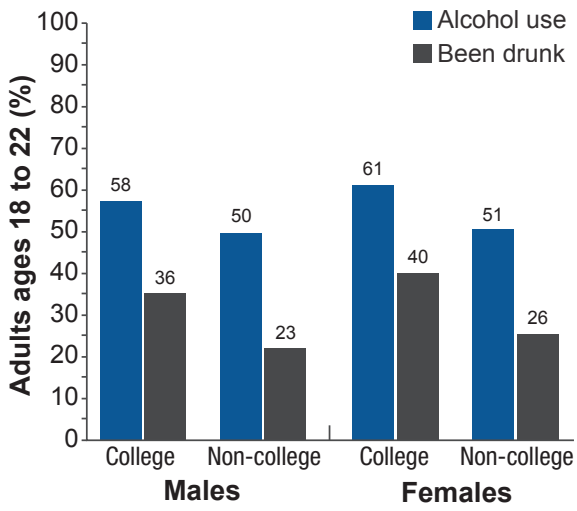

Figure 3 Past-month alcohol use and drunkenness among emerging adults (ages 18 to 22) based on college status. Both measures are declining more for emerging adult males than for emerging adult females, leading to disappearing gender gaps. *Source:* Adapted from Schulenberg et al., 2019.[21]

ADULTS

Despite declines in alcohol use among adolescents and emerging adults, the prevalence of alcohol use, binge drinking, and the number of drinking days in the past month increased among all females age 12 and older between 2002 and 2012.[5] These measures did not increase among males, leading to narrowing gender gaps. Figure 1 shows narrowing gender gaps in past-month alcohol use and past-year AUD—according to criteria for alcohol abuse and alcohol dependence in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). An examination of alcohol measures among adults age 18 and older in six national surveys showed increases in past-year alcohol use and binge drinking among females between 2000 and 2016, with no increases for males.[15] The prevalence of alcohol consumption and binge drinking did not increase for young adults ages 18 to 29, but increased for all adults age 30 and older, with the biggest increases occurring among people beyond age 50.

Several studies suggest that alcohol use and related harms are increasing among older people as the baby boomer cohort (now ages 55 to 75) ages. As with adults as a whole, the increases in alcohol use among older drinkers have been larger for women than for men.[14,31,32] Between 2005 and 2014, past-month binge drinking among adults age 50 and older increased more for women (6% to 9%) than for men (20% to 22%).[31] During that time period, the prevalence of past-year AUD also increased more for women age 50 and older (1.3% to 2.4%) than for men in that age group (5.0% to 5.1%). Similarly, data from the National Health Interview Surveys suggest that, between 1997 and 2014, the prevalence of past-month drinking among adults aged 60 and older increased more for women than for men, and the prevalence of binge drinking in this age group increased for women only.[32] Consistent with narrowing gender gaps in alcohol use among older drinkers, between 2006 and 2014, the rates of emergency department (ED) visits related to both acute and chronic alcohol consumption increased more for women than men among those ages 55 to 64.[8]

SEXUAL ORIENTATION

Sexual orientation influences drinking patterns and alcohol-related outcomes for males and females.[33-35] In the 2018 NSDUH, past-month binge drinking (four or more drinks for females and five or more drinks for males) was reported by 26% of respondents who identified as heterosexual, 33% who identified as lesbian or gay, and 37% who identified as bisexual.[6] Data from the National Epidemiologic Survey on Alcohol and Related Conditions III suggest that lesbians and bisexual women are twice as likely as heterosexual women to engage in binge drinking each year (lesbian 49%, bisexual 59%, heterosexual 26%)[35] (see Table 2). Lesbians and bisexual women also are more likely than heterosexual women to consume 12 or more drinks on an occasion—three times the standard binge threshold for women—in the past year (lesbian, 8%; bisexual, 8%; heterosexual, 3%). Consuming 12 or more drinks is potentially lethal.

Table 2 Binge Drinking Levels in the Past Year Among Women and Men Based on Sexual Identity, National Epidemiologic Survey on Alcohol and Related Conditions III, 2012–2013

	Women (%)			Men (%)		
Binge Level*	**Heterosexual**	**Lesbian**	**Bisexual**	**Heterosexual**	**Gay**	**Bisexual**
4+/5+	26.3	48.6	58.5	39.3	46.5	47.0
8+/10+	7.2	20.7	21.1	18.4	17.8	26.4
12+/15+	2.9	8.2	7.8	7.1	8.2	11.0

***Binge drinking:** Defined as four or more drinks on an occasion for females and five or more drinks on an occasion for males (4+/5+).
Source: Adapted from Fish, 2019.[35]

In a study based on data from the 2000 National Alcohol Survey, lesbians were nearly 11 times more likely, and bisexual women eight times more likely, than heterosexual women to report negative social consequences from drinking.[34,36] Among emerging adults ages 18 to 25, 8% of heterosexual women reached criteria for DSM-IV AUD in the previous year, compared to 15% of lesbians and 10% of bisexual women.[6] Alcohol use does not decline as much with age among sexual minority women relative to heterosexual women.[37] Overall, the influence of sexual orientation on alcohol use and related outcomes appears to be greater among women than among men.[38,39]

PREGNANCY

In 1973, a paper by Jones and Smith detailed a syndrome involving facial dysmorphology, growth retardation, and central nervous system dysfunction in children exposed to alcohol in the womb.[40] Since then, our understanding of the effects of alcohol on embryonic and fetal development has advanced greatly, yet alcohol use during pregnancy remains a significant public health concern. An examination of data from the Behavioral Risk Factor Surveillance Survey suggests that from 2015 to 2017, 12% of pregnant women drank alcohol and 4% engaged in binge drinking in the previous month.[41] The average frequency of binge drinking was five times per month and the average number of drinks per binge was six.

A report using data from NSDUH suggests that past-month alcohol use did not decline between 2002 and 2017 for non-pregnant women ages 18 to 44 (from 57% to 58%) but did decline for pregnant women in this age group (from 13% to 10%).[42] Between 2002 and 2014, past-month binge drinking—in this case, five or more drinks on an occasion—increased for non-pregnant women (24.9% to 26.6%) but declined for pregnant women (4.7% to 2.9%).[42] Risk factors associated with alcohol use or binge drinking during pregnancy include the use of other substances, meeting DSM-IV criteria for AUD, depression, and being unmarried. An examination of NSDUH data averaged between 2001 and 2011 suggests that alcohol use during pregnancy tends to decline abruptly after the first month as women discover they are pregnant. Among pregnant women, 42% reported drinking in the first month, declining to 17% in the second month and 8% in the third month. For binge drinking, prevalence declined from 20% in the first month of pregnancy to 9% in the second month and 3% in the third month.[43] Monthly declines were much smaller for women

who met criteria for DSM-IV alcohol dependence in the previous year.

Despite declines in drinking during pregnancy, the fact that roughly 1 in 10 pregnant women still drink each month is concerning.[44] A recent estimate suggests that the prevalence of fetal alcohol spectrum disorder (FASD) in the United States is 1% to 5%.[45] A prospective study of roughly 31,000 women found that birth weight in newborns was reduced even when the mother's alcohol intake was limited to an average of one drink per day (14 grams of alcohol).[46] Drinking even 3.5 standard U.S. servings of alcohol (14 grams each) per week is associated with lower IQ scores in offspring at age 8, particularly if they have one of four genetic variants in alcohol-metabolizing genes.[47] Alcohol exposure during the first trimester appears to be particularly detrimental, but even low to moderate levels of alcohol exposure throughout pregnancy are associated with morphological, cognitive, and motor deficits.[44,48] It should be noted that recent studies raise the possibility that alcohol use by the father before conception also might influence fetal development and later alcohol use.[49]

HEALTH EFFECTS

As patterns of alcohol use by girls and women changed over the past few decades, so did our knowledge about the potential health consequences faced by female drinkers. Research suggests that, although women tend to drink less than men, a risk-severity paradox occurs wherein women suffer greater harms than men at lower levels of alcohol exposure.[50] For instance, men in the military drink more heavily than women in the military, yet women are at greater risk of DSM-IV alcohol dependence and lost productivity.[51] The number of drinks needed to feel drunk is one-third lower among women (four drinks) than men (seven drinks), probably relating to lower average body weights and less total body water in women.[52] Despite drinking less often and less heavily than males, roughly similar percentages of female and male drinkers in college report having experienced at least one alcohol-induced memory blackout in the past 2 weeks (10% females, 9% males),[53] in the past 6 months (22% females, 17% males),[54] and in the past year (29.2% females, 28.8% males).[55] Females with AUD perform more poorly than males with AUD on a variety of cognitive tasks, even with fewer years of AUD.[56] Research suggests that women have faster progression of AUD than men and are at greater risk than men for alcohol-induced hangovers, liver inflammation, cardiovascular diseases, and certain cancers.[11,57-60] Compared with their male counterparts, women with alcoholic liver disease have a more rapid progression to fibrosis that persists after abstinence from alcohol.[61] The Million Women Study in the United Kingdom, which included more than 28,000 women with breast cancer, suggests that every 10 grams of alcohol consumed per day (less than one standard 14-gram U.S. serving) was associated with a 12% increase in the risk of breast cancer.[62] Because women reach higher blood alcohol levels than do men of comparable weight, their body tissues are exposed to more alcohol and acetaldehyde, a toxic metabolite of alcohol, with each drink.[63]

MEDICAL EMERGENCIES AND DEATHS

Long-standing gender differences in alcohol-related medical emergencies and deaths are narrowing. Alcohol-related hospitalizations and ED visits increased over the past few decades, and rates increased more for women.[8,10,64] Although men still account for the majority of these events, women are catching up. For instance, between 2006 and 2014, the number of ED visits involving alcohol increased from 2,132,645 to 3,366,477 for men (a 58% increase) and from 947,173 to 1,609,320 for women (a 70% increase).[8]

Between 1999 and 2017, nearly 1 million people died from alcohol-related injuries, overdoses, and diseases in the United States.[64] The number of such deaths more than doubled from 35,914 per

year to 72,558 per year, and the rate increased 51%, from 17 to 26 per 100,000. Males accounted for the majority (76%) of alcohol-related deaths over the years (721,587 males, 223,293 females). However, a steeper increase was observed for females (136% in numbers, 85% in age-adjusted rates) than for males (93% in numbers and 39% in rates). Over the years, rates of alcohol-related deaths were highest for males and females in the age range of 45 to 74, but the biggest increase in rates occurred among young adults ages 25 to 34 for both genders. Deaths related to injuries and overdoses increased significantly for females ages 16 to 20 but did not change for males. Although alcohol-related mortality increased each year for non-Hispanic White males and females, there were initial declines early on for several groups. By the end of the study period, deaths were increasing in all racial and ethnic groups for both males and females in nearly every age group.

DRIVING UNDER THE INFLUENCE

Driving under the influence of alcohol (DUI) declined over the past few decades, but the rates of decline were greater for males than females.[65] For instance, Schwartz and Davaran reported that, between 1990 and 2007, rates of arrests for DUI declined by 32% for males (from 2,019 to 1,033 per 100,000) but by only 5% for females (from 306 to 275 per 100,000).[66] The authors suggested that the smaller decline among females might be partly related to changes in DUI enforcement practices. Schwartz observed a similar narrowing of the gender gap in DUI arrests due to steeper declines for males than females between 1982 and 2004.[67] Reilly et al. reported that the percentage of DUI arrests involving female drivers increased in California from 11% in 1989 to 24% in 2012.[68] Further, the percentage of female clients attending a DUI program in southern California increased from 28% in 2009 to 31% in 2014. Among male drivers who died in car crashes, the percentage of crashes in which the driver had a BAC of 0.08% or greater decreased from 25% in 2008 to 21% in 2017. In contrast, there was a small increase in the percentage of female drivers in fatal crashes with BACs greater than 0.08%, from 13% to 14%.[69] Overall, it appears that differences in the prevalence of DUI arrests and fatalities between males and females are becoming smaller.[70]

HARMS TO OTHERS

Alcohol consumption by an individual often leads to harms to others, also known as secondhand harms.[12,71,72] Traffic crash injuries and fatalities are well-known secondhand harms caused by another person's alcohol use, but there are more. A recent study by Nayak and colleagues utilized data from the 2015 National Alcohol's Harms to Others Survey, which asked respondents about secondhand harms such as having property vandalized or damaged, being harassed or assaulted, or experiencing financial troubles.[12] The findings suggest that roughly 1 in 5 adults in the United States experiences harm due to someone else's alcohol use each year. This includes 21% of adult women and 23% of adult men. Women and men under age 25, those who were unmarried, and those who drank excessively, were more likely to report experiencing secondhand harms. Women more often than men reported harm related to aggression on the part of an alcohol-consuming spouse, partner, ex-partner, or family member. Men were more likely to report harm because of a stranger's drinking. Additional research on secondhand harms from alcohol use could be helpful for elucidating gender differences in the risk for alcohol-related consequences.

SUMMARY

For at least a century, differences in the prevalence and amount of alcohol consumption between males and females in the United States have been narrowing.[73-76] As a result, so have rates of alcohol-related harms, including DUIs, ED visits, hospitalizations, and deaths. Although men still

account for more total alcohol consumption and the negative outcomes that follow, the gaps are slowly disappearing. In fact, among adolescents and emerging adults, females are now more likely to report drinking and getting drunk in the past month than their male peers for the first time since researchers began measuring such behaviors.

Importantly, it is not the case that women in the U.S. are simply drinking more like men. Instead, women and men appear to be moving toward one another in terms of drinking patterns and harms. Among adolescents and emerging adults, narrowing gaps are being driven primarily by faster declines in alcohol use by males than females. Among adults, gaps are narrowing primarily because women are drinking more while men are either drinking less or maintaining their levels.

Knowledge of the unique risks that alcohol poses for women—including an increased likelihood of memory blackouts and hangovers and a faster progression of liver disease and AUD—makes recent increases in alcohol use by women more concerning.[77] Although alcohol use by pregnant women has declined, research regarding the impact of prenatal alcohol exposure has accelerated and suggests that relatively small amounts of alcohol can produce detectable changes in morphology and deficits in cognitive and motor function. It is important to consider the unique factors that might influence alcohol use among women, and the unique direct and secondhand health effects that alcohol poses for women, when developing prevention strategies to address alcohol use and related harms.

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The author declares no competing financial interests.

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Sex Differences in the Neurobiology of Alcohol Use Disorder

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Sex differences may play a critical role in modulating how chronic or heavy alcohol use impacts the brain to cause the development of alcohol use disorder (AUD). AUD is a multifaceted and complex disorder driven by changes in key neurobiological structures that regulate executive function, memory, and stress. A three-stage framework of addiction (binge/intoxication; withdrawal/negative affect; preoccupation/anticipation) has been useful for conceptualizing the complexities of AUD and other addictions. Initially, alcohol drinking causes short-term effects that involve signaling mediated by several neurotransmitter systems such as dopamine, corticotropin releasing factor, and glutamate. With continued intoxication, alcohol leads to dysfunctional behaviors that are thought to be due in part to alterations of these and other neurotransmitter systems, along with alterations in neural pathways connecting prefrontal and limbic structures. Using the three-stage framework, this review highlights examples of research examining sex differences in drinking and differential modulation of neural systems contributing to the development of AUD. New insights addressing the role of sex differences in AUD are advancing the field forward by uncovering the complex interactions that mediate vulnerability.

KEY WORDS: alcohol use disorder; animal models; sex differences; stress; adolescence; alcohol; brain

BACKGROUND

Addiction is a chronic relapsing disorder characterized by continued substance misuse despite harmful consequences. Alcohol use disorder (AUD) is specific to the maladaptive consumption of alcohol.[1,2] The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), published by the American Psychiatric Association, describes AUD by mild, moderate, and severe subclassifications depending on the number of criteria met for the diagnosis.[3] These criteria

include symptoms of (1) compulsive excessive drinking; (2) persistent desire to consume alcohol and unsuccessful efforts to quit; (3) increased time spent in activities necessary to obtain, consume, and recover from alcohol; (4) craving or strong desire to consume alcohol; (5) recurrent use of alcohol that disrupts obligations such as work, school, or home; (6) continued use of alcohol despite persistent social or interpersonal problems; (7) important social, recreational, or occupational activities are reduced; (8) drinking persists in situations that cause harm to the individual or others; (9) consumption persists despite knowledge of the detrimental effects caused by alcohol; (10) tolerance for alcohol by having a diminished effect with the same amount or needing increased amounts for the same effect; and (11) symptoms of alcohol withdrawal. Mild AUD meets two or three of the criteria, moderate AUD meets four or five of the criteria, and severe AUD meets six or more of the 11 total criteria. The severity diagnosis for AUD could be useful for determining distinct neurobiological profiles that may be associated with mild, moderate, and severe AUD. Importantly, preclinical and clinical studies that include sex as a biological factor in experimental design will be essential to fully understand these complex neurobiological mechanisms.

OVERVIEW

The goal of this review is to discuss AUD using the three-stage framework of addiction—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation[4]—to highlight examples of sex differences in drinking and related behaviors and to describe some of the neurobiological systems underlying AUD. There has been a recent upsurge in clinical studies in humans and experimental studies in animals in which females are included in the experimental design to elucidate the role of sex in the transition from alcohol use, to alcohol misuse, and ultimately to AUD. Sex differences may influence the three phases of addiction and consequently impact AUD risk differently in men and women.[5] The approach of considering sex as a biological factor in study design has gained even more traction because the gap between men and women in the prevalence of AUD has been closing in the past few years.[6,7]

This review focuses primarily on preclinical animal studies using self-administration procedures to elicit alcohol exposure and/or to measure drinking behaviors to allow for more direct comparison to key findings about drinking behaviors in humans. Preclinical drinking models are summarized in other reviews.[8-12] This article also considers the implications of sex on the onset of drinking, the exacerbation of the negative consequences of drinking, and the increased cue-induced relapse in more advanced stages of AUD. Overall, by presenting examples of studies that address sex differences within these stages, this review aims to show the dynamic role sex differences may have on vulnerability to the development of AUD, to generate enthusiasm for studying sex differences in preclinical and clinical alcohol research, and to advance our understanding and treatment of AUD.

BINGE/INTOXICATION STAGE

In this phase, individuals consume enough alcohol to induce intoxication and cause impairment of physical and mental abilities. An example of this is binge drinking—the excessive consumption of alcohol that results in blood alcohol levels of 0.08 gram percent (g/dL) or higher—typically reached by consumption of five or more drinks in men and four or more drinks in women within a 2-hour period.[12-15] When individuals first start binge drinking, they may not experience any physiological or emotional changes of withdrawal when the alcohol wears off; however, this changes over time.

AUD Prevalence and Age at Drinking Onset

The lifetime prevalence of AUD is 29% in the United States, with a higher prevalence in men than women.[2] In the United States, 33% of men and 17% of women binge drink at least once a month, and longitudinal studies suggest that this gap is narrowing due to a decline in frequency

among men.[15] Sex differences in AUD prevalence may relate to the age at drinking onset or an individual's first experiences with drinking alcohol—especially if alcohol consumption is high enough to elicit intoxication.[16,17] The lifetime risk of AUD quadruples when drinking begins on or before age 14 versus age 18,[18] and the factors motivating individuals to first start drinking and to drink heavily differ with sex.[16,17]

Higher risk-taking tendencies can lead to early-onset use and subsequent alcohol misuse—especially in males.[17] Adolescent boys reported "risk taking" and "curiosity" as motivators for drinking alcohol, whereas this was not the case in adolescent girls.[17] Adolescent boys also have higher levels of impulsivity and sensation seeking compared to adolescent girls.[19] Likewise, men have lower aversion to risk in a social context compared to women, which may lead men to engage in more risk-taking behaviors.[20] Interestingly, a significant positive relationship between sensation seeking and alcohol-related risks such as driving under the influence has been observed in women, but not men.[19] This suggests that women with high sensation-seeking tendencies may have an increased chance of causing harm to themselves and others after drinking alcohol compared to men with the same sensation-seeking tendencies. Alcohol-induced increases in risk-taking behavior also have been shown to differ by sex in rodents, with adolescent male rats engaging in higher risk-taking behavior after drinking alcohol compared to adolescent female rats.[21]

Another reason that individuals may drink alcohol is for its acute anxiolytic, or anxiety-reducing, properties. Experimenter-administered alcohol intoxication can temporarily reduce anxiety-like behavior in rodents.[22] Adolescent girls are more likely than adolescent boys to report drinking alcohol to alleviate stress, social isolation, and psychological distress.[23] Similarly, female mice are more sensitive to the anxiolytic effects of experimenter-administered alcohol compared to males, indexed by increased time spent in the open arms of an elevated plus maze.[24] Notably, the anxiety-reducing properties of alcohol are short-lived, experienced only during and immediately following alcohol drinking. As discussed later, and previously reviewed,[25] there is a rebounding effect during the withdrawal phase after alcohol wears off, and the degree of negative affect and altered stress hormone levels experienced at that time differs with sex.

Overall, these studies suggest that sex plays a distinct role in the motivating factors leading to drinking initiation. Risk-taking behaviors are more likely to influence adolescent boys to consume alcohol, whereas adolescent girls are more likely to consume alcohol due to its anxiety-reducing properties. Understanding the factors underlying early alcohol drinking onset may produce better strategies to prevent and dissuade alcohol consumption in adolescence and may help create specialized alternatives to alleviate the need for this coping mechanism.

Frontal Lobe Development and Early-Onset Drinking

Drinking during adolescence has been shown to lead to higher levels of drinking in adulthood in both male and female mice.[26] Heightened levels of risky behavior, such as binge drinking, during adolescence is thought to occur, at least in part, because the frontal lobes are still undergoing significant development during this time. Through its connections to other cortical regions and subcortical limbic structures, the prefrontal cortex coordinates higher executive function and behavior including decision making, stress responses, working memory, and attention.[9,27-29] The anterior cingulate cortex is one of the medial prefrontal regions that is negatively impacted by alcohol drinking, with more pronounced effects in adolescent male rodents and young men compared to adolescent female rodents and young women.[30-32]

Imaging studies in humans show other prefrontal regions are also altered with alcohol drinking in adolescence and early adulthood. The dorsolateral prefrontal cortex is thinner in younger adults who frequently engage in heavy drinking (≥5 drinks) compared to controls, and the magnitude of this effect is more robust in young

adult men compared to young adult women.[32] Binge drinking is associated with lower cortical volume and thickness in adolescent boys versus higher cortical volume and thickness in adolescent girls.[33-35] Notably, alcohol-naïve adolescent boys and girls with a family history of AUD have thinner orbitofrontal cortices compared to age-matched adolescents without a family history of AUD, indicating that some cortical differences precede alcohol misuse.[36] Considering these findings altogether, it is conceivable that an underdeveloped prefrontal cortex may promote early-onset of alcohol drinking, which could further delay or perturb this development—especially in boys and young men—and increase their lifetime risk of developing AUD.

Gonadal Hormones and Dopamine

Reward comprises learning (cue associations), hedonic ("liking"), and motivational ("wanting") components.[37] Conditioned stimuli are initially associated with a reward, but can become motivational cues on their own, incentivizing both appetitive approach and consummatory behavior.[37,38] Female rats show more appetitive approach, measured by the total number of head entries into a dipper access area (dipper approaches) and have higher levels of lever presses (active lever approaches) to obtain the alcohol reward.[39] Consummatory behavior, measured by the number of dipper presentations into the access area (reinforcers delivered) is also higher in female rats compared to male rats.[39] This is consistent with other rodent studies showing that females consume more alcohol relative to body weight and engage in higher levels of cue-mediated alcohol-seeking behaviors compared to males.[40-42]

The mesocorticolimbic dopamine pathway may contribute to sex differences in appetitive and consummatory behaviors, given its essential role in conditioning and associative learning of environmental and physiological cues that predict alcohol reward availability.[39,43-45] Alcohol binge drinking activates cells in the ventral tegmental area (VTA) of the mesocorticolimbic dopamine pathway.[45-47] This midbrain structure is the origin of dopaminergic cells that project to the ventral striatum (nucleus accumbens), frontal cortex, and amygdala. Rats will press a lever to self-administer alcohol directly into the VTA, but a higher dose of alcohol is needed for reinforcement of this behavior in males compared to females.[48,49] Moreover, a prior history of adolescent intermittent alcohol exposure leads to heightened sensitivity to the rewarding properties of alcohol in both sexes, indexed by a leftward shift in alcohol dose-response curves in rats.[48] In humans, a familial history of AUD is associated with an exaggerated ventral striatum dopamine response to the expectation of alcohol.[50] Although this study did not find a sex difference in this dopamine response, perhaps a larger number of subjects would be needed to detect a subtle, but statistically significant, difference in this measure in men and women.[50] Nevertheless, it is important to consider how dopamine contributes to sex differences in AUD vulnerability, given the role dopaminergic cells in the VTA play in reinforcement learning and in expectation of alcohol availability.

The interaction between gonadal hormones and dopamine may provide insight into the molecular mechanisms underlying sex differences in the rewarding properties of alcohol.[51,52] Estradiol enhances the stimulating effect of alcohol on VTA dopamine neurons.[51] In vitro extracellular recordings of dopaminergic neurons have been conducted using VTA slices obtained from female mice under the following hormonal conditions: no estradiol (ovariectomized and vehicle-treated) or low circulating levels of estradiol (gonadally intact mice in estrus) versus moderate (gonadally intact mice in diestrus II) or high (ovariectomized mice treated with proestrus-like levels of estradiol benzoate) circulating levels of estradiol.[51] Alcohol increased excitation of VTA dopamine neurons in brain slices from mice of all hormonal conditions, but the effects were most robust when estradiol levels were moderate or high.

Lastly, in vitro treatment with ICI 182,780—an antagonist of estrogen receptor subtypes alpha and beta (ERα and ERβ, respectively)—attenuated alcohol-induced excitation of VTA dopamine

neurons in mice with moderate levels of estradiol (diestrus II); this suggests that estradiol's modulation of dopamine sensitivity to alcohol may be occurring through its acute interaction with ERα and/or ERβ subtype in the VTA slice. The acute interaction between estradiol and its receptors appears to depend on moderate or high estradiol levels, as the ERα/ERβ antagonist did not measurably attenuate alcohol-induced increases in dopamine firing under conditions of low estradiol (estrus).

Through its effects on mesocorticolimbic dopamine, estradiol appears to mediate association-based learning and the rewarding properties of alcohol in context, which could ultimately promote drinking. Indeed, estradiol-treated ovariectomized mice show both increased dopamine signaling in the VTA in response to alcohol and increased preference of an alcohol context compared to vehicle-treated ovariectomized mice.[53] The preference for an alcohol-paired context suggests that estradiol enhances the rewarding effects of alcohol.[53] Estradiol also increases alcohol consumption in these mice and inhibition of either ERα or ERβ blocks this effect, suggesting that co-activation of both receptor subtypes is dependent on estradiol.[53]

Progesterone and its metabolites also have been implicated in the modulation of mesocorticolimbic dopamine neurons in response to alcohol.[54] A study in male rats showed that progesterone increases the dopamine extracellular concentration in the medial prefrontal cortex after an experimenter delivered administration of alcohol, inducing a 55% increase compared to controls.[54] Alcohol intake also increases brain concentrations of allopregnanolone (3a-hydroxy-5a-pregnan-20-one)—a neuroactive metabolite of progesterone.[55] Nonhuman primate research in females shows that drinking levels increase when serum levels of estradiol and progesterone and its metabolites are higher (i.e., during the luteal phase compared to the follicular phase of the menstrual cycle).[56] Within the luteal phase the highest drinking occurred on the declining phase of the progesterone peak, with a trend of a positive correlation between serum allopregnanolone levels and alcohol intake.[56] Progesterone and neuroactive steroids could be modifying drinking behavior through effects on mesocorticolimbic dopaminergic neurons involved in reward processing, but more research is needed to understand sex differences in these effects.[54]

Sensitivity to the Aversive Consequences of Drinking

Binge drinking can cause injuries and other adverse outcomes, with high-intensity (extreme binge) drinking (10 or more drinks in men, eight or more drinks in women) resulting in more severe consequences such as blackouts, alcohol overdose, and even death.[57] Some of the short-term aversive consequences of alcohol intoxication can help curtail continued alcohol consumption; yet, these are more subdued during adolescence, and in males in particular.[57] Adolescent boys are less prone to the negative effects of alcohol after a binge-drinking episode, taking less time to recover from alcohol intoxication compared to adolescent girls.[23] Similar trends of decreased sensitivity to the aversive properties of alcohol have been reported in male rodents, but this varies with age, species, and other factors.[58-61] Nevertheless, reduced sensitivity to the aversive properties of alcohol may contribute to higher levels of binge and extreme binge drinking in adolescent boys compared to adolescent girls, which ultimately could lead to differential risk of AUD in adulthood.[57]

WITHDRAWAL/NEGATIVE AFFECT STAGE

After repeated episodes of binge drinking, individuals can begin to experience a negative affective state when alcohol is withdrawn voluntarily or involuntarily. This includes dysregulated stress hormone levels, dysphoria, anxiety, depression, and irritability—a symptomology thought to be due in part to adaptations in stress-related neural pathways.[9,62,63] Experiencing these aversive symptoms when alcohol wears off can set up a strong cyclical pattern of negative reinforcement in

which individuals learn that if they consume alcohol again, they can "feel normal"—at least temporarily.

Negative Affective State During Alcohol Withdrawal

Chronic heavy alcohol consumption eventually can lead to severe AUD. A hallmark feature of AUD is the negative emotional and physiological state that arises when alcohol wears off.[64] Individuals may experience a combination of various symptoms ranging from dizziness to headaches, irritability, anxiety, dysphoria, sleep disturbances, and hypersensitivity to pain.[3] As mentioned above, it has been proposed that alcohol dependence arises because individuals go through repeated cycles in which alcohol consumption serves to mediate the effects of withdrawal, acting as a negative reinforcer.[5,25,45,65,66] A negative reinforcer is a driving force that—with the removal of an aversive stimulus such as negative affective state during withdrawal—promotes a specific behavioral response such as drinking relapse.[65]

Individuals with AUD report having negative and unpleasant feelings during withdrawal, such as low self-concept, neuroticism, depression, and hostility—all of which predict alcohol craving.[67,68] Behavioral assays also have been developed to assess a negative affective state experienced during withdrawal in animals. In addition to the traditional assays such as the elevated plus maze and open field, the frequency of ultrasonic vocalizations also can be measured to assess anxiety-like symptoms of negative affect that are experienced early after withdrawal from chronic alcohol exposure in rodents.[69,70] A recent study used this measure to examine sex differences in withdrawal-induced negative affect in rats that were exposed to 6 weeks of intermittent alcohol.[71] The researchers found that male rats increased the frequency of vocalizations during acute withdrawal, whereas female rats did not.[71] A difference in withdrawal sensitivity may incentivize continued heavy alcohol use to a greater degree in males compared to females, thus putting them at a higher risk of AUD.

Male rats and mice show a more pronounced display of negative affective-like behaviors and neuroactivity after withdrawal from chronic alcohol exposure compared to female rats and mice.[71-75] Alterations in glutamate signaling from the stria terminalis projecting into the basolateral amygdala are thought to mediate these behavioral differences.[73,76] Shorter duration of exposure to chronic intermittent alcohol vapor intoxication and withdrawal cycles was sufficient to detect these synaptic alterations in male rats versus female rats.[73] Furthermore, a translational study using magnetic resonance spectroscopy showed that rats exposed to chronic intermittent alcohol vapors and people diagnosed with AUD have increased glutamatergic neurotransmission during acute alcohol withdrawal compared to their respective controls.[77]

Dysregulation of Stress Hormones

Withdrawal from alcohol is associated with a dysregulation of stress hormones. The hypothalamic pituitary adrenal (HPA) axis governs the neuroendocrine response to stress by releasing corticotropin-releasing factor (CRF) from the hypothalamus, which activates the release of the adrenocorticotropic hormone (ACTH) from the anterior pituitary, resulting in the release of the glucocorticoids from the adrenal glands (cortisol in primates and corticosterone in rodents).

Studies in humans show that, compared to men, women had lower ACTH and cortisol levels under baseline (resting) conditions in the morning, but were more sensitive to peripheral stimulation of the HPA axis as indexed by the dexamethasone/CRF test.[78] In contrast, men showed a greater response than women to the centrally acting citalopram stimulation test.[78] This test measures the extent to which a selective serotonin-reuptake inhibitor acts specifically on the hypothalamus to initiate a stress response. Compared to women, men also exhibited greater activation in response to stress of corticolimbic structures including the medial prefrontal cortex, the extended amygdala and posterior insula, and the hippocampus.[79] In rodents, HPA activity is higher in females under basal (stress-free) conditions and in response

to an acute stress challenge.[25,80-82] In rodents, stress experienced in utero can exaggerate these sex differences even more by enhancing HPA responses in females and dampening it in males.[83]

In male rats, dampened HPA responsivity has been observed after withdrawal from chronic intermittent alcohol vapor exposure, and to a lesser extent following chronic alcohol drinking alone.[84] Although sex differences in corticosterone responsivity were not directly tested, corticosterone responsivity appears to differ 24 hours into withdrawal from chronic alcohol drinking and following predator order stress in male and female mice.[81] Studies in nonhuman primates and rodents have confirmed that alcohol drinking acutely elevates blood levels of ACTH and glucocorticoids.[81,84-86] It is thought that repeated cycles of intoxication and withdrawal eventually desensitize this system, resulting in neuroendocrine tolerance to alcohol.[9,87]

Dysregulation of the HPA axis is thought to result from alcohol-induced neuroadaptive changes within this neuroendocrine axis itself.[84] Glucocorticoid receptor signaling is required for the development of dependence, but it remains unknown whether the accompanying neuroendocrine tolerance contributes functionally to escalated drinking after dependence.[9,88] In addition to the HPA axis, there are neuroadaptive changes in other stress regulatory pathways as well such as the prefrontal cortex, bed nucleus of the stria terminalis, and central amygdala.[9,47,88-91]

Stress can increase alcohol drinking, but this depends on sex, age, and the type of stress exposure.[81,92] Adult female rodents show higher drinking compared to adult males, relative to body weight, and predator odor stress has been shown to elevate drinking in male rodents to the level of drinking observed in females.[40,80] In one study, adult mice had 3 weeks of intermittent binge drinking using the scheduled high alcohol consumption (SHAC) procedure, followed by 1 month of abstinence, and then were tested for alcohol drinking before and following 2 weeks of intermittent predator odor stress (dirty bedding from rats).[81] Among male mice with a prior history of binge drinking, 2 weeks of stress elicited the greatest increase in drinking relative to baseline. This stress effect was found in female mice only when the baseline drinking was stratified into two subgroups: low versus high levels of drinking. Only females that had originally exhibited low drinking levels showed the increase in drinking in response to stress.[81] Female mice that initially exhibited high drinking did not show a further elevation, possibly due to a ceiling effect.

Another study of mice used the "Drinking in the Dark" (DID) binge drinking procedure for 2 weeks followed by 11 days of unpredictable, chronic, mild stress.[93] Afterwards, alcohol drinking was measured with a two-bottle choice of 20% versus 40% v/v alcohol test. Stress increased alcohol binge drinking in both sexes, but this effect was exacerbated even more in male mice with a previous history of drinking prior to stress.[93]

The studies discussed above and others[94] suggest that males may be more susceptible to alcohol withdrawal; however, early-onset drinking can interact with these factors and drive up vulnerability in females. Five days of exposure to restraint stress increased alcohol drinking in adolescent female rats, but decreased drinking in adolescent male and adult female rats.[92] This suggests a heightened sensitivity to stress in adolescence that may have a particularly detrimental impact in females. In support of this, adolescent-onset binge drinking increased anxiety-like behavior early in withdrawal in female mice, and this persisted into abstinence.[95] Likewise, acute stress elicited a negative affective state in the novelty-induced suppression of feeding task in adult female mice with a history of adolescent alcohol exposure.[76] A history of adolescent binge drinking and intermittent alcohol vapor exposure led to a negative affective-like state in the elevated plus maze task and fear conditioning response in male mice, but it did not emerge until later in abstinence.[96]

The neural systems implicated in the interactive effects of stress and alcohol include not only structures of extended amygdala, but also brain regions thought to be involved in the third stage of AUD (preoccupation/anticipation).[73,86,97-100] For

example, a history of prior binge drinking and exposure to predator odor stress dysregulates protein levels of stress-related receptors, and does so in a sex-specific manner.[81] After chronic drinking, there is a measurable increase in glucocorticoid receptors in the prefrontal cortex and hippocampus, and CRF receptor 1 in the hippocampus of female mice, but not male mice.[81] These neuroadaptive changes in stress-regulatory circuits could persist well beyond withdrawal and underlie some of the psychological components that predict craving and relapse.[67]

PREOCCUPATION/ ANTICIPATION STAGE

Prolonged heavy alcohol use leads to a state of a constant preoccupation with alcohol and compulsive drinking despite negative consequences.[88,101,102] This craving can continue into abstinence for months or years, making it difficult to abstain from alcohol altogether or to shift to a healthier level of drinking.[103]

Sensitivity to Alcohol-Related Cues

After long bouts of abstinence, alcohol-related cues can trigger incentive salience, which heightens cravings and precipitates relapse.[37,104,105] Men in particular exhibit higher levels of alcohol craving than do women,[106] and cravings are associated with increased activity in the striatum in men, but not in women.[79] Cue-induced reinstatement procedures are useful for studying the underlying neurobiological mechanisms by which alcohol-related cues promote craving and relapse during abstinence.[107] Like humans, male rodents appear more susceptible to relapse than females.[108] Brain-derived neurotrophic factor (BDNF) may play a role in mediating this sex difference.

In mice, male offspring of alcohol-exposed fathers have high *Bdnf* gene expression in the VTA and low alcohol drinking behavior; this effect was not observed in female offspring.[109] Conversely, genetic manipulation to reduce BDNF protein levels to 50% in female rats resulted in a heightened, male-like, response to alcohol cues.[108] This genetic manipulation had no effect in males. Others have found a sex difference in tropomyosin receptor kinase B (TrkB) signaling in *Bdnf* +/– mice, with males showing higher TrkB phosphorylation than females in the prefrontal cortex and striatum.[110] Consequently, BDNF signaling is presumed to mediate cravings in response to alcohol cues and this increased sensitivity to alcohol-related cues could put males at higher risk of relapse even after long periods of abstinence.

Compulsive Alcohol Drinking After Chronic Use

As discussed earlier, multiple cycles of binge intoxication followed by withdrawal can transition individuals from light to moderate drinking to severe AUD.[5,25,45,66] At this point, heavy drinking can become more compulsive.[111] Compulsive alcohol use is inflexible and persists despite negative consequences or despite devaluation of the rewarding effects of alcohol. This type of drinking is characteristic of physical and motivational/emotional dependence on alcohol.[88,112]

One strategy used to measure inflexible drinking is the assessment of a persistent motivation to drink despite increasing the response requirement to obtain alcohol. In animal studies, this can be tested by training subjects to press a lever or nose poke for alcohol in operant boxes.[9] The number of responses to get the reward can be changed using fixed ratio or progressive ratio schedules of reinforcement in operant alcohol self-administration studies. Fixed ratio is the number of presses necessary for reward delivery, increasing the response requirement for the reward. This challenge measures compulsive-like behavior that is characteristic of addiction, in which individuals go to extreme lengths to obtain the drug on which they are dependent. Progressive ratio takes this a step further and increases the response requirement for reward delivery. In humans, a progressive ratio trial of intravenous alcohol self-administration showed that women increased their work effort to obtain alcohol after resumption following 2 weeks of abstinence, whereas men decreased this effort.[113] Male rats exposed to alcohol vapors to produce

dependence display increased compulsive-like behavior and increased intake on both fixed and progressive ratio schedules.[88] However, progressive ratio tests in Long Evans rats suggest there is no sex difference in motivation for alcohol, at least following extinction and reinstatement of alcohol self-administration.[114] Comprehensive studies are needed to assess compulsive drinking behaviors and relapse after prolonged abstinence in both nondependent and dependent animals to better understand sex differences in AUD.

Alcohol solutions also can be manipulated to devalue reward and to test for signs of inflexible drinking. One approach to devaluing alcohol is the addition of an unpleasant substance to change the flavor of alcohol by adding the bitter taste of quinine hydrochloride dihydrate or lithium chloride.[111] Female mice have been shown to be more resistant to devaluation by quinine than males, and this sex difference was not attributable to differences in sensitivity to quinine.[115] Nevertheless, sex differences in sensitivity to alcohol reward devaluation may be temperament- or species-specific, as male and female Long Evans rats reduce drinking levels to the same extent following alcohol devaluation.[114,116] In addition to alcohol adulteration, more sophisticated procedures derived from behavioral economics can be used to manipulate the value of the reward by changing the alcohol reinforcer magnitude, availability of alternative reinforcers, and delay discounting.[117,118]

Another approach used to test for inflexible drinking is to measure shock-resistant alcohol intake.[112,119] Rodent and human studies use these procedures to measure compulsive alcohol drinking despite negative consequences (e.g., foot shock or electric shock to the wrist, respectively). In rats, when one of eight alcohol-seeking responses are paired with foot shock, half of the alcohol-dependent male rats exhibit shock-resistant alcohol intake.[120] Male alcohol-preferring rats that received an intermittent foot shock in response to alcohol seeking separated behaviorally into three distinct subgroups: (1) compulsive rats that continued alcohol seeking despite punishment, (2) noncompulsive rats that diminished their alcohol-seeking responses, and (3) an intermediate group that only partially suppressed their alcohol-seeking behavior.[119] These two studies did not elucidate a sex difference as neither included female rats in the study design.[119,120] Heavy alcohol use in men and women is associated with risky and inflexible drinking, with men and women with AUD making more attempts to obtain aversion-paired rewards compared to individuals without AUD.[121,122] Furthermore, higher connectivity between the anterior insula and the nucleus accumbens is associated with increased compulsive-like behavior.[122]

Altogether, these studies suggest that inflexible drinking promotes heavy and continued use of alcohol and, consequently, may lead to further neuroadaptations in the brain. However, some of the devaluation strategies show limited evidence of sex differences. The inclusion of female subjects in these studies to directly compare the effects is vital to evaluate the role of sex in compulsive-like drinking under these different paradigms.

Chronic Alcohol Use and Corticolimbic Circuitry

Deficits in executive function can result from early-onset drinking or chronic heavy use, and this may lead to a higher chance of relapse following abstinence.[123] Some of these effects may be due to alterations in connectivity between prefrontal cortices and subcortical structures that are involved in reward processing.[5,124] The medial prefrontal cortex, anterior insula, and striatum are more active and have stronger connections in men and women with AUD compared to controls.[125] This could result in more subcortical control over decision-making processes based on reward reactivity rather than executive control.[125]

With long-term abstinence in both men and women, there is increased resting-state connectivity to brain regions that control executive function and decreased connectivity within reward processing regions.[126] Connectivity between the nucleus accumbens and the orbitofrontal cortex has been observed to be stronger in individuals with a familial history of AUD compared to individuals without this predisposition.[127] These studies suggest that chronic

exposure to alcohol leads to reduced function of the prefrontal cortex, which, when combined with a stronger influence of striatal control over decision-making, can increase the risk of relapse.[125,127]

Animal studies have advanced our understanding of neural connectivity at the axonal and microstructural level, giving insight into the mechanisms by which prefrontal function improves across development and can be impaired after alcohol exposure. During adolescent development in rats, prefrontal axons undergo robust increases in myelin ensheathment, which corresponds with a twofold increase in neuronal transmission speed.[128] Binge drinking during adolescence is also associated with altered neurodevelopmental trajectories including poor frontal white matter integrity in adolescent boys and girls.[129,130]

Longitudinal studies show that white matter growth is attenuated in the frontal lobes in humans who started drinking during adolescence—an effect that was comparable in both sexes.[131,132] The abnormal microstructural development of white matter in the frontostriatal region relates to binge drinking during adolescence and poorer cognitive function.[133,134] Likewise, animal studies show that voluntary alcohol exposure during adolescence decreases the density of myelinated axons in the anterior cingulate subregion of the medial prefrontal cortex, with higher adolescent drinking levels predicting lower working memory performance later in adulthood.[30] Reduced myelin density was not observed in female rats after adolescent binge drinking,[31] which corresponds with another study in mice showing that high doses of alcohol reduce myelin genes to a lesser extent in adolescent females compared to males.[135]

Despite more robust effects in males, examination of myelinated axons at the microstructural level shows that alcohol alters the nodal domain in both male and female rats.[31] The nodes of Ranvier are the ion channel–rich gaps between myelin sheaths on the prefrontal axons, and reduced length-to-width nodal ratios were detected in male and female rats following adolescent binge drinking.[31] In males, the decrease in nodal ratio was due to an increase in nodal diameter after the exposure, whereas in females it was due to a decrease in the nodal length. In both cases, these microstructural alterations have potential to negatively impact the speed and integrity of neural transmission, which is essential for effective communication within and between cortical and subcortical structures.[31] Altogether these studies show alcohol affects cortical circuits that are important for executive functioning and behavioral control, and does so to a greater extent in males than in females.

Administration of extreme binge-like doses of alcohol damages the hippocampus and prefrontal cortex, and impairs memory in rats.[136-138] While damage within the prefrontal cortex was similar in both sexes[138] the severe damage to the dentate gyrus of the hippocampus was greater in females compared to males.[136] The dentate gyrus is a subregion of the hippocampus where new granule neurons are normally produced for the formation of new memories; however, alcohol impairs cell proliferation and reduces the number of granule neurons in this region and does so to a greater extent in females.[136] This damage is associated with a reduction of trophic support molecules and the heightened vulnerability in female rats appears to be due to more robust downregulation of BDNF, insulin-like growth factor 1 (IGF-1), and cyclic adenosine monophosphate (AMP) response element-binding protein (CREB) signaling cascades.[136] These results are consistent with human studies in which the hippocampus was shown to be particularly vulnerable to the effects of alcohol binge drinking.[124,139] Self-administration studies in rodents suggest that even much lower levels of alcohol (low-binge) can decrease neurogenesis and hippocampal size,[140] with reports of alcohol drinking reducing neurogenesis to a greater extent in females compared to males[141] or similarly in both sexes.[142] Hippocampal damage after alcohol drinking in rodents corresponds with significant cognitive and memory dysfunction, especially when the alcohol exposure occurs during adolescence.[26,137,143] Thus, early-onset drinking and chronic heavy alcohol use may eventually lead to sustained hippocampal damage

to a greater extent in female rodents, which in conjunction with prefrontal dysfunction, could interfere with the ability to regulate reactivity to stress and alcohol-related cues that promote craving and relapse.

CONCLUSIONS AND CLINICAL IMPLICATIONS

The preclinical and clinical studies outlined in the current review show sex differences in behavioral risk factors and neural systems implicated in AUD, as summarized in Table 1 and Figure 1. This approach of incorporating sex differences in research studies has enhanced understanding of the complex mechanisms driving alcohol-related behaviors that lead to AUD. An increasing body of evidence shows sex differences in factors contributing to AUD vulnerability during the onset of alcohol drinking and later in the development of severe AUD and relapse following abstinence (see Table 1 for details).

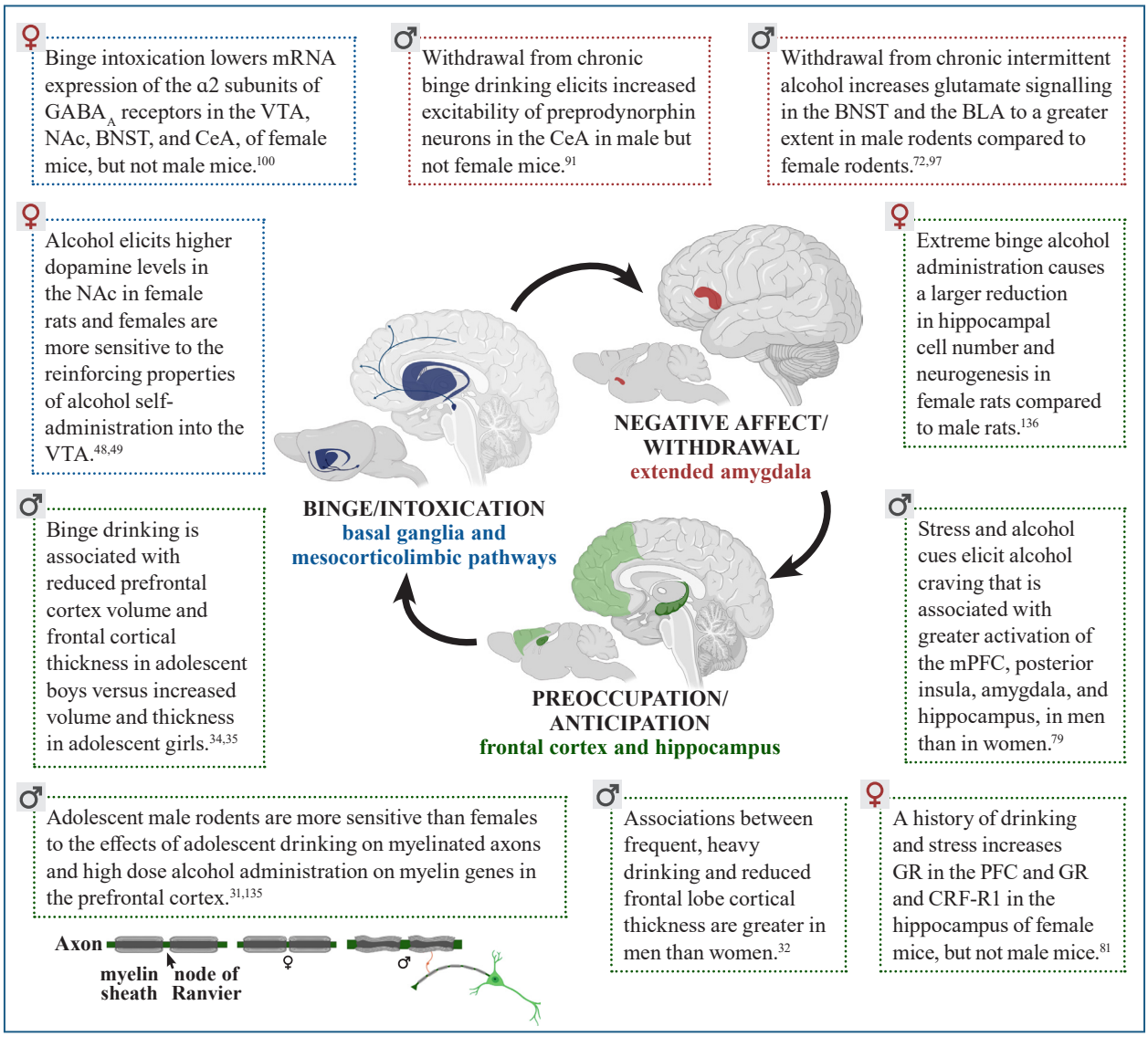

Figure 1 Sex differences in the effects of alcohol on the interacting brain systems associated with the three stages of addiction. *Note:* BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; CRF-R1, corticotropin-releasing factor receptor 1; GABA$_A$ receptors, gamma-aminobutyric acid type A receptors; GR, glucocorticoid receptors; mPFC, medial prefrontal cortex; mRNA, messenger RNA; NAc, nucleus accumbens; PFC, prefrontal cortex; VTA, ventral tegmental area. Created with BioRender.

Table 1 Sex Differences in Behaviors Associated With the Three Stages of Addiction

Binge/Intoxication	
Risk factors that promote early-onset drinking	Impulsivity, a risk factor for adolescent drinking, is higher in adolescent boys compared to girls.[19]
	Drinking to alleviate psychological distress is higher in adolescent girls compared to boys.[23]
Alcohol drinking behavior	Prevalence of binge drinking is higher in adolescent boys compared to girls.[15]
	Appetitive approach in response to a dipper presentation is greater in female rats than male rats.[39]
	Acute alcohol injection increases preference to a large/uncertain reward (a measure of risk-taking behavior) in males, with no preference shown in females.[21]
Withdrawal/Negative Affect	
Alcohol drinking behavior	Restraint stress increases drinking in adolescent female rats, but decreases drinking in adolescent male rats.[92]
	A prior history of adolescent binge drinking augments drinking levels later in adulthood in female mice, but not in male mice.[81]
	Female mice drink more alcohol under baseline conditions in adulthood, but a history of binge drinking and chronic unpredictable stress or predator odor can elevate drinking in male mice to the level of females.[81]
Effects of alcohol withdrawal on negative affect	Adolescent girls report more negative mood states following recent heavy episodic drinking than do adolescent boys.[23]
	A history of adolescent binge drinking elicits active coping responses to stress in female mice vs. passive coping responses to stress in male mice (indexed by less time vs. more time immobile in the forced swim test).[95,96]
	Frequency of ultrasonic vocalizations, a measure of anxiety-like behavior, is increased following withdrawal from chronic intermittent alcohol vapors in male rats, but not females.[69-71]
Preoccupation/Anticipation	
Alcohol drinking behavior	Men exhibit higher levels of alcohol craving in response to cues than women do.[106]
	Women increased work effort in a progressive ratio trial following resumption after 2 weeks of abstinence. Men showed a decrease in effort.[113]
	Relapse-like behavior in response to alcohol availability is higher in male rats compared to female rats.[108]
	Female mice have a higher degree of aversion-resistant drinking than male mice.[115]

Adolescent drinking in the context of stress, negative affect, and increased cue-reactivity is greater in females. Males show vulnerability with regard to higher levels of impulsivity and, compared to females, they are less sensitive to the aversive effects of intoxication, making males less likely to stop drinking. Sex also was found to be a predictor of the negative impact that chronic alcohol use has on the brain (see Figure 1 for details). Males show more severe reductions in cortical thickness and reduced myelinated fiber density in the prefrontal cortex, whereas females show more robust decreases in neurogenesis in the hippocampus in response to alcohol. Sex can specifically influence the effects of alcohol in the brain in the context of intoxication, withdrawal, and cravings, leading to a robust vulnerability to AUD. Overall, these findings show that sex differences in humans and animal models of AUD are also dependent on the unique physiological characteristics of the stages of addiction. Effects of alcohol can be mediated by sex in different directions, by increasing or decreasing vulnerability to AUD depending on

the specific factor being considered. This complex shifting of vulnerability mediated by sex calls for a comprehensive approach toward studying AUD and other addictions.

A number of other health consequences endured after chronic heavy alcohol use are greater in women compared to men. Women with AUD experience higher risks of developing cancers, alcohol-related liver injury, and cardiovascular disease compared to men with AUD despite comparable levels of drinking.[7,25,144-150] Specifically, binge drinking shows an increase of mortality, including cancer-related mortality, and people with AUD have a threefold increase of death and a higher risk of digestive diseases, dementia, cancer, and liver disease. Women with AUD show higher risk of liver disease-related mortality, with 71% of mortality in women compared to 64% in men.[146] Sex differences in the effects of alcohol drinking may be explained in part by the role of gonadal steroid hormones in modulating a variety of functions in the brain. These functions include regulation of hypothalamus-driven social behavior;[151] cognition, memory, and learning driven by the hippocampus and the prefrontal cortex;[152] amygdala-mediated stress responses;[25,153] dopamine-mediated reward;[51] and synaptic plasticity.[154] Moreover, alcohol binge drinking in women can dysregulate the menstrual cycle,[155] which can affect endogenous steroid hormone levels.[156-159]

New diagnostic neuroimaging approaches are being explored to improve the assessment of AUD severity and circumvent limitations of the more traditional methods such as the Alcohol Use Disorders Identification Test (AUDIT) self-report questionnaire. A metabiological study recently reported that resting state connectivity functional magnetic imaging can be useful for assessing AUD.[160] Specifically, differential functional connectivity between the prefrontal cortex and the reward-related areas predicted the severity of AUD with accuracy that surpassed other functional magnetic resonance imaging, structural magnetic resonance imaging, combined magnetic resonance imaging features, or demographic features. The usefulness of these new diagnostic approaches exemplifies the great urgency for more inclusion of female subjects in preclinical AUD studies in humans and animal models. With heightened attention to detail in experimental design and increased consideration of sex/gender differences in interpretation of research findings, we can enhance our understanding of the neurobiological mechanisms underlying AUD to improve diagnosis and treatment in the future.

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Alcohol's Unique Effects on Cognition in Women: A 2020 (Re)view to Envision Future Research and Treatment

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Alcohol use and misuse is increasing among women. Although the prevalence of drinking remains higher in men than women, the gender gap is narrowing. This narrative review focuses on the cognitive sequelae of alcohol consumption in women. Studies of acute alcohol effects on cognition indicate that women typically perform worse than men on tasks requiring divided attention, memory, and decision-making. Beneficial effects of moderate alcohol consumption on cognition have been reported; however, a number of studies have cautioned that other factors may be driving that association. Although chronic heavy drinking affects working memory, visuospatial abilities, balance, emotional processing, and social cognition in women and men, sex differences mark the severity and specific profile of functional deficits. The accelerated or compressed progression of alcohol-related problems and their consequences observed in women relative to men, referred to as "telescoping," highlights sex differences in the pharmacokinetics, pharmacodynamics, cognitive, and psychological consequences of alcohol. Brain volume deficits affecting multiple systems, including frontolimbic and frontocerebellar networks, contribute to impairment. Taken together, sex-related differences highlight the complexity of this chronic disease in women and underscore the relevance of examining the roles of age, drinking patterns, duration of abstinence, medical history, and psychiatric comorbidities in defining and understanding alcohol-related cognitive impairment.

KEY WORDS: alcohol; women; cognition; acute consumption; AUD; recovery

INTRODUCTION

Alcohol use and misuse have increased among women over the past 2 decades,[1] with an estimated 5.3 million women age 18 and older meeting criteria for alcohol use disorder (AUD) in the United States in 2018 (https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-use-disorders). The rate of AUD in women increased 84% over the past decade in comparison with a 35% increase in men.[2] Although the prevalence of men who drink is still higher than that of women, the gender gap is narrowing.[2-4] Of note, prevalence of drinking and binge drinking, defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as four or more alcoholic beverages on the same occasion for women, rose in older women (age 60 and older)[5,6] compared with previously reported levels.

Commensurate with the rising rates of women with AUD should be enhanced efforts to examine sex differences related to consequences of alcohol consumption. Most of the earliest reports of the untoward consequences of alcohol focused on men and suffered from lack of statistical power to identify sex-related differences because of small numbers of female participants or unequal sample sizes between the sexes, raising limits on generalizability to women.[7] Despite this bias, appreciation of sex differences in alcohol-related factors and consequences is not new. Indeed, Lisansky addressed the importance of examining alcohol factors uniquely related to women more than a half century ago.[8] What is new, however, is greater insistence in research studies and clinical applications for systematic investigations to address sex-related differences in alcohol consumption, antecedent factors of drinking, and alcohol-related consequences. As a result of this mandate, work over the past decade has made it amply apparent that men and women differ in alcohol-related risks, health and cognitive consequences, and factors related to successful abstinence and sobriety.[9]

This narrative review focuses on the cognitive sequelae of alcohol use in women, including deficits associated with acute consumption, moderate drinking, at-risk or hazardous drinking, and chronic excessive drinking. (See the box **Effects of Alcohol Consumption on Women and Factors That Influence Research Outcomes**.) Over the years, nomenclature regarding alcohol misuse has changed based on scientific understanding of the disease—for example, "alcohol abuse" and "alcohol dependence" in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) evolved into "alcohol use disorder" by the fifth edition (DSM-5). Although anachronistic for studies predating DSM-5 nomenclature, the term "AUD" is used throughout this review when referring to individuals who met criteria for an alcohol misuse-related diagnosis at the time of assessment.

SEX DIFFERENCES IN ALCOHOL METABOLISM AND THE CONSTRUCT OF "TELESCOPING"

Alcohol is metabolized at different rates in men and women,[10] and these sex differences in the pharmacokinetics of alcohol are biologically founded. Particularly notable is sexual dimorphism of body composition. Compared with men, women generally have less body water and a higher proportion of fat, which does not absorb alcohol, resulting in higher blood alcohol concentration (BAC) levels, even when the amount of alcohol consumed is adjusted for body weight. In addition, women tend to have lower levels of gastric alcohol dehydrogenase, the enzyme that breaks down ethanol into its metabolites. Thus, BAC levels rise faster and stay elevated longer in women than men.[3] It has been speculated that these sex-related pharmacokinetic differences underlie why women can develop health-related consequences, including cirrhosis of the liver, earlier in their disease and after lower total lifetime alcohol consumption than men.[7,11]

"Telescoping" describes the accelerated or compressed progression of the landmark events of AUD (e.g., age at first drink, age when started

Effects of Alcohol Consumption on Women and Factors That Influence Research Outcomes

What We Know

Acute alcohol consumption

Deficits reported in women

- Divided attention
- Psychomotor speed
- Working memory
- Short-term memory
- Set-shifting
- Decision-making

Moderate drinking

Modest beneficial effects

- Better overall cognitive ability
- Slower rate of cognitive decline in aging

Increased risk of

- Breast cancer
- Gastrointestinal disorders
- Infectious diseases

Chronic excessive alcohol consumption

Telescoping

Compared with men:

- Women have shorter intervals between landmark events from the inception of drinking to entering treatment.
- Women experience medical and health-related problems earlier, even when duration and amount of alcohol consumed are comparable between the sexes.
- Women exhibit different patterns and severity of cognitive compromise, some modulated by sex-related emotional and social factors.

Factors That Influence Research Outcomes

* Differences in task demands
* Heterogeneity of response to alcohol
* Small sample sizes
* Differences in study inclusion and exclusion criteria
* Cross-sectional vs. longitudinal study
* Important to control for variables such as
  - Age
  - Education
  - Socioeconomic status (SES)
  - Depression/anxiety symptoms
  - Smoking status
  - Drinking patterns
  - Alcohol-related pharmacokinetics
  - Hormonal differences
  - Nutritional status
  - Comorbid medical conditions
    - HIV
    - Hepatitis C
    - Non-alcohol substance misuse
    - Psychiatric conditions
    - Chronic pain

having problems related to alcohol, age when first entered treatment) in women compared with men.[12,13] Initial studies addressing telescoping focused on duration of time from onset of drinking to time to enter alcohol treatment or time to develop medical problems (e.g., hepatic disease). Early studies reported that women initiate hazardous drinking—drinking that puts a person at heightened risk of developing AUD—at a later age than men, although they enter alcohol treatment earlier in their disease than men.[14,15] Women also were reported to be more susceptible and to experience alcohol-related medical problems after a shorter time of chronic heavy drinking[12] and lower lifetime consumption compared with men.[16] Indeed, there is evidence that women are at heightened risk of alcohol-related heart disease.[3] Taken together, there is increasing support for this phenomenon as it pertains to the physiological and health-related consequences of alcohol in women.[3,17]

Telescoping has been invoked in studies examining the timing and severity of cognitive deficits associated with chronic heavy drinking in women compared with men.[7,18] Demonstration of a shorter duration from drinking to detectable cognitive deficits in women, however, has received mixed support, with some studies supporting the concept of telescoping of select cognitive processes,[18] whereas other studies do not.[19,20] Additional research is needed to examine the temporal sequencing, pattern, and severity of cognitive deficits in women and men in relation to landmark events associated with alcohol consumption. Inconsistency among studies examining the temporal sequence of events related to AUD in men and women could be due in part to methodological or even geographical factors, including accuracy of self-report and factors that mediate and moderate a woman's decision to seek sobriety-related or health-related treatment, such as ease or availability of treatment and help with family responsibilities.[21]

ALCOHOL'S EFFECTS ON COGNITION IN WOMEN

Acute Alcohol Consumption

An early study directly compared the acute effects of alcohol on men and women who were social drinkers without an alcohol misuse diagnosis and reported that, after moderate levels of alcohol consumption (BAC = .04%), women scored lower than men on a short-term memory task.[22] In a study examining divided attention and balance (sway) in light drinkers (12 men—average absolute ethanol intake in the 30 days prior to testing was 7.9 g/kg (range: 5.6-10.0 g/kg), 12 women—7.38 g/kg (range: 5.01-10.23 g/kg); ages 18 to 24), it was reported that the women scored significantly lower on divided attention than the men only at higher alcohol levels (BAC = .06%) and not lower levels (BAC = .03%) or for placebo.[23] Sex-related differences were not observed in sway at any BAC level. Data summarized from seven experiments examining the effects of moderate alcohol dose (0.65 g/kg) in participants with no self-reported history of substance use disorder (ages 21 to 35) on driving performance indicated that these young social drinking women showed greater deficits in memory recall, divided attention, and motor skills than did young social drinking men who did not have AUD.[24] In that review, all driving-related measures were impaired for both men and women after alcohol consumption compared with their nondrinking performance, with women demonstrating a larger decline in performance after drinking than men. These studies provide support for the notion that women may be more vulnerable than men to the cognitive effects of acute intoxication.[16]

By contrast, other studies have failed to find sex differences in relation to acute alcohol consumption. Accordingly, a study assessing 11 men and 13 women found no significant sex differences in performance on cognitive tests including assessment of divided attention, short-term memory, and rotary pursuit at moderate levels of acute consumption, blood alcohol levels (BALs) of .054% for men and .062% for women. BALs were measured at 20-minute intervals after the first drink by using a gas chromatographic intoximeter, and BALs were statistically controlled for in between-group analyses.[25] Additionally, although both men and women were impaired, no sex differences were reported in a study that assessed flight simulation performance in general aviation pilots ages 21 to 40 at moderately high BALs (12 women = .084%, 11 men = .087%), levels exceeding legal limits of intoxication in the United States (BAL = .08%).[26]

Age can moderate the effects of acute alcohol consumption on cognition.[27,28] A double-blind, placebo-controlled factorial design study assessing psychomotor, set-shifting, and working memory processes in community-dwelling social drinkers who had never met criteria for an alcohol misuse diagnosis (15 men, 24 women; ages 55 to 70) at low (breath alcohol concentration [BrAC] = .04%) and moderate (BrAC = .065%) levels of acute alcohol administration reported age-related deficits compared with 51 younger community-dwelling moderate drinkers (31 men, 20 women; ages 25 to 35). Both the younger and older adult groups exhibited some beneficial effect of low-dose alcohol compared with placebo on a simple psychomotor sequencing task (Trail Making Test, Part A). At the higher dose level (BrAC = .065%), however, only the older adults were impaired on a more complex psychomotor task requiring sequencing and working memory (Trail Making Test, Part B).[28] Cognitive efficiency, the ability to perform quickly and accurately, was most compromised in the moderate-dosage group of older adults, regardless of sex.[28]

An examination of acute alcohol effects on cognition failed to identify sex differences in tests of set shifting, psychomotor speed, or working memory in non-problem drinking older adults (26 men, 36 women; ages 55 to 70) randomly assigned to one of three dose conditions: placebo; low dose (BrAC = .040%); and moderate dose (BrAC = .065%).[29] The authors concluded that sub-intoxicating doses of alcohol do not differentially affect healthy, older, moderate-drinking men and women.

Taken together, studies that find sex-related differences on cognitive effects of acute alcohol consumption report that women tended to perform worse than men on higher-order cognitive tasks requiring divided attention, working memory, and decision-making, as opposed to less complex tasks such as reaction time or psychomotor measures.[9] Inconsistency of findings across studies is likely due to a number of factors including subject selection, task demands, and heterogeneity of response to alcohol.

Acute Cognitive Effects of Binge Drinking and Blackouts

Binge drinking can produce blackouts, defined by periods of amnesia (the inability to transfer information from short-term to long-term memory) experienced while an individual is apparently conscious and able to engage in activities such as walking, talking, and driving.[30-32] Rapid increase of BAC is a major risk factor for a blackout, with BAC levels of .22% having upward of a 50% chance of producing a blackout.[33] In young adults, blackouts are a common consequence of binge drinking.[34] Of 2,140 young adults 1 year post high school, 68% reported consuming alcohol at some point in their lifetime, and 20% of that group reported a blackout in the past 6 months.[34] The occurrence of blackouts was as prevalent among young women (17%) as men (22%) in this cohort. Blackouts have been associated with poor decision-making and impulsivity, and they increase the vulnerability of both women and men to unlawful, regrettable, and dangerous interpersonal and social situations. It has been speculated that blackouts could be more predictive than level of consumption of alcohol-related harms.[34]

AUD and Chronic Excessive Consumption

DSM-5 conceptualizes AUD as a chronic relapsing disease, where an individual continues to drink despite knowing that one's current drinking pattern is likely to lead to untoward medical, personal, and social consequences.[35] The diagnosis of AUD is based on a severity continuum ranging from mild to moderate to severe, depending on the number of diagnostic criteria met, which include but are not limited to drinking more than intended, having difficulty refraining from drinking, drinking that interferes with work and family responsibilities, cravings, tolerance, and withdrawal. The AUD continuum differs from the previous diagnostic classification system, DSM-IV-TR,[36] which made a categorical distinction between alcohol abuse and alcohol dependence. Studies investigating the effects of chronic heavy drinking on cognitive processes in women with an alcohol-related diagnosis defined by either DSM system often have reported deficits in line with those in men with an alcohol-related diagnosis, but a number of studies also have reported differences in the cognitive effects of alcohol based on sex, described next.[37-39]

Based on rigorous, quantitative assessments, cognitive deficits associated with chronic heavy drinking in women have been reported since the early 1980s.[19,40] One of the earliest studies compared 33 recently sober women (10 to 23 days since last drink) with 44 age- and education-matched control women on a number of cognitive and motor domains. Impairments were observed in visuospatial processing (block design), psychomotor speed (trail making), information processing (digit symbol substitution), and memory (verbal and visual recognition and recall).[18] The authors of this study noted that the women with AUD displayed significant cognitive and motor deficits, yet had a notably shorter drinking history than participants in previously reported studies that included men with AUD.[18] Indeed, even after statistically controlling for differences in drinking histories between men and women—duration of hazardous drinking in men was more than twice that of women (13 years vs. 6 years, respectively)—and then separately matching men and women on age and years of problem drinking, the study found that women still scored significantly lower than men on tests of memory recall and psychomotor speed.[14] However, it has been cautioned that, given the cross-sectional

nature of the study, it could not be determined whether cognitive deficits in the women were a risk factor for or a consequence of drinking.[14]

The pattern and extent of cognitive and motor deficits across six domains (i.e., executive functions, short-term memory and fluency, declarative memory, visuospatial abilities, upper-limb motor ability, postural stability) were examined in 43 recently sober (average duration, 3.6 months; range 2 to 15 months) women with AUD ages 28 to 63.[41] Compared with 47 no- to low-drinking control women matched on education and scores standardized on age, the women with AUD demonstrated deficits in verbal and nonverbal working memory, visuospatial abilities, and postural stability (balance and gait), with relative sparing of executive functions, declarative memory, and upper limb strength and speed.[41] By comparison, an earlier study examining the pattern and extent of cognitive deficits in 71 recently (1 month) sober men with AUD—compared with 74 healthy control men—reported deficits in executive function, visuospatial abilities, and gait and balance in men with AUD.[42] Taken together, these studies demonstrated that both women and men with AUD showed impairment on visuospatial processes; however, compared with nondrinking, sex-matched control participants, only the women were impaired on tasks of short-term memory, and only the men exhibited executive function deficits.

In a more recent cross-sectional study of 164 older DSM-IV alcohol-dependent participants (62 women, 102 men; age 62.6 ± 6.4 years), women performed better than men on mental flexibility as assessed by the Trail Making Test.[43] By contrast, men performed better than women on a test of visual processing assessed with a figure recognition task. Despite impairment in men and women, sex differences were not forthcoming on ability to overcome cognitive interference assessed with the Stroop Color and Word Test.[43]

Taken together, chronic excessive drinking in women is associated with myriad cognitive deficits, overlapping but not identical to the pattern of deficits observed in men. Although some evidence indicates that women develop cognitive deficits earlier in their disease or at lower lifetime consumption rates than men, its generalizability has not been clearly established.

POTENTIAL BENEFITS ASSOCIATED WITH MODERATE DRINKING

Despite the association of chronic excessive drinking with cognitive and motor deficits, much has been made about the potential beneficial health effects associated with moderate drinking—notably decreased risk of cardiovascular disease, better overall cognitive ability, and a slower rate of cognitive decline associated with normal aging.[44-47] Moderate drinking is generally defined as no more than one standard drink (14 grams of 95% alcohol) per day for women and two standard drinks per day for men. The pattern of performance from no drinking to excessive drinking has often been denoted as a U-shaped curve[48,49] or a J-shaped curve[50] with amount drunk modifying performance level.

Even moderate levels of alcohol consumption, however, have been associated with an increased risk of breast cancer, liver-related diseases, and cardiomyopathy in women (https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/women-and-alcohol), as well as infectious diseases, gastrointestinal disorders, and alcohol-related injuries.[51] In addition, for older women (particularly those age 60 and older), interactions between alcohol consumption at any level and aging, age-related disease, and drugs commonly prescribed to older people (including antibiotics, antidepressants, anxiolytics, and warfarin) can be hazardous.[52] Indeed, in addition to comorbid use of other drugs and medical comorbidities, AUD in older women often presents with complex clinical issues including untreated or undertreated depression and anxiety, which can exacerbate problems related to consumption and consequences of alcohol, family responsibilities, and feelings of guilt and shame surrounding their drinking. Although concern for older women in relation to

alcohol consumption is not new,[53] there remains a dearth of literature addressing the complexity of the factors associated with AUD in the elderly. With such a range of medical and mental health problems in this subpopulation, personalized treatment plans taking into account the entire picture and not just problem drinking are needed if abstinence and recovery are to be successful.[52]

An early study examining sex differences in 1,389 low to moderate drinkers (574 men, 815 women; ages 59 to 71) reported that women who were light (fewer than two drinks daily) to moderate (two or three but fewer than four drinks daily) drinkers performed better on set shifting, as assessed by the Trail Making Test, Part B, than women who reported abstaining from alcohol.[48] This beneficial effect of light to moderate drinking was not observed for men. These authors reiterated the importance of controlling for variables such as age, education, income, depressive symptoms, and smoking status in studies examining sex-related cognitive differences in relation to alcohol.

More recently, a longitudinal study of 818 older adults (age 65 and older; 139 moderate drinkers and 679 nondrinkers) found that although moderate alcohol use (defined as one to 14 drinks per week; average number of drinks per week in this cohort = 5.02 $\pm$ 3.79 *SD*) was related to higher baseline cognitive performance, no relation was observed on rate of change over time (spanning 7 years) across cognitive domains.[54] These authors highlighted the importance of future research focusing on the influence of demographic, genetic, and lifestyle factors on the variability observed in moderate drinking in relation to cognition. Indeed, another study cautioned that studies reporting beneficial effects of moderate drinking may have included an inappropriate selection of reference groups and little control for confounders.[55] The authors of this study found a beneficial dose-response relation only for women drinkers age 65 and older, with no measurable benefit of moderate drinking in other age-sex groups.

Another longitudinal study examined the relation between cognitively healthy longevity—defined as living to age 85 without cognitive impairment, as assessed by the Mini-Mental State Examination—and amount and frequency of alcohol intake in 1,344 older community-dwelling adults (728 women and 616 men; ages 55 to 84) and found a beneficial effect of regular, moderate drinking.[44] Indeed, individuals who reported drinking at moderate to heavy levels—up to three standard drinks per day for women on a near-daily basis—had twofold higher odds of living to age 85 without cognitive impairment compared with nondrinkers.[44] Nonetheless, another study of nondemented autonomously living octogenarians reported that older women who drank moderately did not appear to benefit at the same level as older men who drank moderately when it came to cognitive performance.[56] Indeed, only a relatively modest benefit in verbal memory for short stories was observed in women compared with men with moderate-level drinking. Sex differences were speculated to be due to myriad factors including drinking patterns and alcohol-related pharmacokinetics.

ALCOHOL CONSUMPTION AND RISK OF DEMENTIA

It is projected that the U.S. population age 65 and older will nearly double, from 48 million currently to 88 million by 2050 (https://www.nih.gov/news-events/news-releases/worlds-older-population-grows-dramatically). With an ever-increasing aging population, it is imperative to understand the effects of chronic excessive drinking on the structure and function of the aging brain and the moderating and mediating effects of age-related medical and psychiatric conditions, interactions with medications, and life-related stressors.

A meta-analytic study assessing risk of dementia in relation to alcohol consumption reported a modest U-shaped relation.[57] Results highlighted that moderate alcohol consumption, defined as fewer than 12.5 g/day (about one standard drink), was associated with a reduced risk of dementia, whereas drinking to excess (defined as $\geq$ 23 standard drinks per week) was associated with a significantly greater risk of dementia

compared with light drinking. The lowest risk of dementia was associated with drinking 6 g/day of alcohol, and wine was reported to be selectively associated with protective effects.

Another study—which included 2,874 women (of 9,087 total participants) with an average length of follow-up of 23 years—reported that abstainers and those who drank heavily (defined as more than 14 standard drinks per week) had a greater risk of dementia, determined from electronic health records.[58] These authors speculated that nondrinkers and those who drink excessively may be at higher risk of cardiometabolic disease including diabetes and hypertension, which, in turn, is associated with an increased risk of dementia.

At-risk drinking in the elderly is a timely issue. One study noted that 12% of older women (age 60 and older) reported drinking in excess of the recommended guidelines of no more than one standard drink a day or seven standard drinks per week but without meeting diagnostic criteria for AUD.[52] Without proper screening and intervention, these older adult women may be at particular risk for alcohol-related health and cognitive problems including dementia.

EMOTIONAL PROCESSING AND SOCIAL COGNITION IN WOMEN WITH AUD

Over the past decade, emotional processing and social cognition have become a focus of addiction research, highlighting the relevance of one's abilities to identify and respond to emotional and social cues in interpersonal interactions at home, at work, and with friends. Sex differences outside of AUD typically note better performance in women than men in decoding emotional facial expression and in performing tasks of social cognition such as the Reading the Mind in the Eyes Test or the Faux Pas Recognition Test.[59-63] Taken together, these findings suggest a potential resilience to social cognition disorders in women. This section reviews whether AUD disrupts this protective factor as a whole or interferes with selective processes.

AUD is associated with difficulties in components of emotion processing and social cognition, notably alexithymia, issues in decoding others' emotions, inferring others' mental states or feelings (i.e., Theory of Mind [ToM] deficit), and experiencing empathy.[64] Factors contributing to deficits in emotional processing and social cognition include an increased risk of personal, social, and work problems as well as poor initiation of action to achieve abstinence in AUD.[65] Vulnerability to emotional decoding and social cognition impairment in women with AUD may trigger an additional burden in their emotional and interpersonal interactions, thereby increasing relapse risk. Despite known sex differences in the severity of brain compromise and cognitive impairment in AUD,[66] the literature on sex differences in emotional processing and social cognition in AUD is scant.

Alexithymia is a multidimensional personality construct that comprises four core characteristics: (1) difficulty identifying feelings in oneself and differentiating feelings from the physical sensation of emotional arousal, (2) difficulty describing feelings to others, (3) restricted imaginative processes featured by limited fantasy life, and (4) an externally oriented style of thinking.[67] Alexithymia is commonly assessed by the Toronto Alexithymia Scale-20 (TAS-20), a self-report questionnaire, exploring three factors: difficulty identifying feelings, difficulty describing feelings, and externally oriented thinking (i.e., tendency to focus attention outside of oneself).[68] Higher prevalence of alexithymia in women with AUD than in men with AUD has been observed, especially on the global TAS-20 score and its "difficulty identifying feelings" factor.[69] Interestingly, alexithymia factors can play a moderator role in the relations between depressive mood and craving for alcohol in recently detoxified individuals with AUD.[70] In particular, women with AUD who reported difficulty describing feelings were at higher risk for craving when experiencing depressed mood, which is

consistent with the hypothesis that relapse would be more frequently associated with negative affect in women than men.[71]

Emotion decoding skills are crucial when assessing one's immediate social environment, providing valuable information regarding others' internal affective state, enabling behavioral adaptation according to others' thoughts and intentions, and facilitating social interactions in daily life. Contradictory findings on sex differences have been reported in studies that assessed decoding of emotional facial expressions (EFE) in AUD. Although no evidence of sex differences was found in recently detoxified individuals,[72,73] vulnerability to alcohol-related EFE recognition deficits was reported in recently detoxified women.[74,75] Lack of consistency between studies could be related to the small sample sizes of women (fewer than 15 women), which may not be representative of the population of women with AUD. Elsewhere, assessment with the social cognition module of the Wechsler Advanced Clinical Solutions revealed significant impairment in recognizing affect from facial expression in long-term abstinent men but not in long-term abstinent women.[76] Although the women did not differ from their sex-matched controls, better identification of emotional facial expressions was related to longer length of abstinence.

ToM refers to the ability to attribute mental states to oneself and others, and to understand that others' mental states might differ from those of oneself.[77] ToM enables individuals to predict, anticipate, and interpret the behavior of others and facilitates appropriate social interactions.[78] Large effect sizes were identified in two recent meta-analyses for deficits in ToM in AUD.[79,80] In support of the vulnerability hypothesis of emotional and social functioning impairment in women with AUD, a meta-analysis indicated that the effect size was modulated by sex, such that increasing the percentage of men in the treatment group decreased the effect size—results suggesting that "AUD is more likely to be associated with affective ToM deficits in females."[80(p 413)]

SEX DIFFERENCES IN ALCOHOL EFFECTS ON BRAIN STRUCTURE AND FUNCTION

Three decades of magnetic resonance imaging (MRI) studies describe patterns of brain structural abnormalities characteristic of chronic, heavy drinking.[81,82] Despite the rich literature on neuroimaging in AUD, the mainstay of studies does not address sex differences. The focus of this section is on the research in women with AUD and starts with studies using conventional structural MRI to quantify regional brain volumes; also summarized are studies using magnetic resonance diffusion tensor imaging to assess the microstructural integrity of white matter fibers and finally functional MRI done in the task activation state.

Structural MRI

Individuals with AUD but without neurological complications generally show ventricular expansion and shrinkage of selective cerebellar lobules and regions of the cerebral cortex. Volume deficits in cerebellar and cortical regions generally extend to gray and white matter macrostructure and microstructure. Whole-brain analyses support the profile of widespread damage to gray matter structures, including the frontal cortex, thalamus, insula, hippocampus, and cerebellum, as well as white matter regions including the cerebellar peduncles, pons, corpus callosum, and periventricular area.[83-87] The exploration of specific brain damage in women with AUD has been limited by an inclusion bias of men in most studies and by the lack of methodological consideration of sex differences with respect to an appropriate control group matched in sex and other relevant factors to the clinical group. The few neuroimaging studies considering differences between men and women on alcohol-related brain structural changes have generated conflicting results.

A number of cross-sectional studies investigating brain macrostructural abnormalities and alcohol misuse have reported no sex differences in brain volumes.[85,88] However, other

studies have reported inconsistent findings including greater vulnerability in men than women,[89,90] greater susceptibility to structural abnormalities in women than men,[91,92] and sex-related differences in the pattern and severity of regional brain volumetric deficits.[66] A study using a longitudinal design tested for, but did not find, sex differences on brain volumes related to chronic heavy drinking.[93]

Hippocampal volume deficits were identified in individuals with moderate alcohol consumption (fewer than 14 standard drinks per week for women, fewer than 21 standard drinks per week for men) in a study of 527 community-dwelling men and women who did not have AUD (mean age = 43 $\pm$ 5.4 years). This dose-dependent relation between alcohol consumption (i.e., alcohol units/week) over 30 years and hippocampal shrinkage, however, was significant only for men and not for women.[49] A lack of effect in women may be attributed to inadequate statistical power given the smaller number of women (n = 103) than men (n = 424) in the study and the fact that few women in the study were categorized as unsafe drinkers (n = 14 women reported drinking more than 14 standard drinks per week). In addition, no demonstrable beneficial effect was observed with light alcohol consumption compared with abstinence on brain structure and function. The authors cautioned that the protective effect reported in association with moderate drinking in other studies may be due to confounding variables, such as socioeconomic status or IQ. Beneficial effects, defined as a reduction of age-related decline in brain volume, also were not observed in a study of nondependent (DSM-IV) drinking men and women, with a relation between greater amount of alcohol consumed and smaller total brain volume, which was more pronounced in women than men.[94]

Diffusion Tensor Imaging (DTI)

This neuroimaging approach enables examination of the integrity of the microstructure of white matter, which comprises linearly organized fiber tracts that connect proximal and distal gray matter regions (that is, brain structures composed of neurons). Fiber integrity is measured in terms of fractional anisotropy (FA), typically higher in fibers with a homogeneous or linear structure such as healthy white matter, and bulk mean diffusivity of water movement for which higher values reflect diminished integrity or edematous tissue. In men with AUD, the greatest microstructural white matter abnormalities are reported in the corpus callosum, but for women with AUD, these abnormalities are greatest in the centrum semiovale.[95] In other cross-sectional DTI studies, when matched for alcohol history variables, women with AUD showed more signs of white matter degradation than men with AUD in several fiber bundles, suggesting an enhanced risk for alcohol-related degradation in selective white matter systems.[96] By contrast, no evidence for alcohol-related sex differences was forthcoming in DTI metrics for six anatomically defined transcallosal white matter fiber bundles.[97]

Potential sex differences in brain structural recovery with abstinence require further investigation. Contradictory results based on relations with length of abstinence[66,98] showed stronger positive association between length of sobriety and white matter volumes in women with AUD than in men with AUD within the first year of abstinence.[66] By contrast, positive associations between length of sobriety and white matter volumes were observed in men with AUD but not in women with AUD after 1 year of abstinence, suggesting faster white matter recovery in women.

Another DTI study reported relations between longer duration of abstinence and higher FA of the callosal white matter in men with AUD, but not in women with AUD.[98] The authors suggested better callosal white matter recovery with abstinence in men, especially when men with shorter length of abstinence showed lower FA than recently abstinent women, but the opposite pattern was observed for longer duration of abstinence. Moreover, recent neuroimaging investigations found sex interactions displaying opposite patterns. Compared with control men, men with AUD had smaller volumes in the reward network

and lower FA in select white matter tracts. By contrast, women with AUD had larger volumes in the reward system and higher FA in the same white matter tracts compared with control women.[98-100] These authors suggested that this opposite pattern in brain structural abnormalities between men and women with AUD might reflect a sex-specific phenotype related to dissimilarities in neuroanatomical and neurobehavioral expressions as risk factors or in sex-based motivation to seek alcohol.

Functional MRI

The literature investigating sex-related effects on brain functioning in AUD with functional MRI (fMRI) is scarce and is sampled next. A task-activated fMRI study revealed lower brain activation in the prefrontal and parietal cortices during a spatial working memory task in 10 women with AUD compared to 10 healthy women controls.[101] During high-risk decisions to drink, control women activated the default mode network, whereas women with AUD simultaneously activated the reward, cognitive control, and default mode networks. These results suggest that risky decisions to drink could be associated with difficulties to switch between different neural networks in women with AUD, potentially due to dysfunction in the anterior insula.[102]

A small fMRI study of airplane pilots—individuals with AUD (8 women, 6 men) and healthy controls (9 women, 5 men)—revealed an interactive effect of AUD and sex on brain activation during negative and positive facial affective processing, such that men with AUD demonstrated higher brain activation than control men, whereas women with AUD showed lower brain activation than control women.[103] By contrast, an fMRI study conducted in long-term abstinent individuals with AUD reported sex-related differences in the pattern of brain responsivity to emotional stimuli, with lower activation in the rostral middle and superior frontal cortex, precentral gyrus, and inferior parietal cortex in men with AUD than in control men, whereas higher activation in superior frontal and supramarginal cortices were observed in women with AUD compared to control women.[104] As suggested, these specificities in brain reactivity between men and women during emotional processing may reflect sex-related differences in the emotional mechanisms leading to the development of AUD.

Taken together, these studies demonstrate the relation between chronic heavy drinking and structural and functional brain abnormalities in men and women; however, due to their cross-sectional nature, these studies cannot determine whether AUD-related brain dysmorphology was caused by drinking, was pre-existing, or both. Prospective longitudinal studies—such as the National Institutes of Health/NIAAA-supported National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA)[105] and the Collaborative Studies on the Genetics of Alcoholism (COGA)[106]—study adolescents before they initiate appreciable drinking. Assessing children as young as age 8, the Adolescent Brain Cognitive Development (ABCD) Study is a longitudinal prospective study[107] that aims to identify the antecedent and resultant effects of alcohol and to track the drinking patterns that contribute to deviations from normal neurodevelopmental growth trajectories in cerebral[108] and cerebellar[109] volumes starting in preadolescence. These studies also will provide information that can address questions of specific sex-related risk factors that contribute to excessive drinking behavior and underlie differential prodromal brain abnormalities between men and women with AUD.

RECOVERY OF COGNITIVE ABILITIES WITH SUSTAINED ABSTINENCE

On an optimistic note, potential for recovery of selective cognitive deficits including memory and psychomotor abilities can occur with sustained abstinence. Functions that appear more resistant to recovery include visuospatial skills and gait and balance stability, which often endure

even with long-term abstinence.[110-113] Cognitive impairment has been associated with higher rate of relapse and lower motivation to initiate and maintain abstinence.[114]

One of the earliest studies examining recovery of cognitive function with abstinence included both short-term abstinent (1 month, $n = 40$) and long-term abstinent (4 years, $n = 40$) women.[115] This study indicated differential recovery among cognitive processes, with long-term sober women showing improvement on complex tasks of abstraction, assessed with the Halstead Category Test, whereas perceptuomotor ability, assessed with the Digit Symbol Test and the Trail Making Test, Part A, was more resistant to recovery. Critically, it was the subset of women who resumed drinking after baseline assessment that accounted for the greatest deficits at baseline compared with the subset of alcoholic women who remained sober. These authors highlighted the possibility that heterogeneity within their cohort could partly be explained by difference in posttreatment drinking (resumers vs. abstainers) and by differential premorbid "at-risk" variables in women compared with men with AUD.

Follow-up of a cohort of women with AUD at 3 to 6 years post–baseline testing after an average of 3 months of sobriety[41] reported recovery of nonverbal short-term memory and psychomotor speed.[111] Postural instability, however, was still noted, even after this extended length of abstinence. These studies highlight the selectivity of dissociable cognitive and motor processes in terms of time course and extent of recovery with abstinence.

An investigation of cognitive recovery after 6-week sobriety in a controlled environment after being in a residential treatment unit reported that a slightly lower percentage of women than men (41% vs. 46%) showed recovery on a general cognitive measure.[116] These authors speculated that the timeline of recovery and factors promoting recovery may differ between men and women and highlighted the relevance of examining the effect of sex on remediation and extent and the timeline of recovery of component cognitive processes.

FACTORS THAT MODERATE OR MEDIATE COGNITIVE AND MOTOR PERFORMANCE IN WOMEN WITH AUD

Hormonal differences between men and women and within cohorts of women have been hypothesized to at least partially underlie sex differences reported in AUD, although studies to establish this relation have been inconsistent and inconclusive.[9,117] Only limited evidence suggests that phase of menstrual cycle accounts for a significant amount of the variability in behavioral response to alcohol, with a number of studies finding that phase of menstrual cycle had no significant effects on alcohol consumption in women.[117,118] In addition, no differences among menstrual phases in alcohol pharmacokinetics have been forthcoming.[119]

Other factors speculated to moderate or mediate cognitive performance between alcoholic men and women or to underlie the heterogeneity among women with AUD are (1) age and aging effects and their interaction with alcohol; (2) alcohol consumption variables including age of AUD onset, amount drunk in one's lifetime, quantity and pattern of binge events, family history of alcohol misuse, and number and severity of withdrawals; (3) nutritional status including thiamine and other vitamin B deficiencies; (4) existence of comorbid medical and health conditions including HIV, hepatitis C, and chronic pain; (5) other drug use (including prescription and illicit); and (6) psychiatric symptoms and disorders.[37,65,120]

Research strongly supports the notion that whether one maintains sobriety or relapses into drinking, even when drinking does not meet AUD criteria, may moderate the extent and rate of cognitive and motor recovery in AUD. Attention has been paid recently to the history of trauma and chronic pain and their relation to initiation and maintenance of hazardous drinking in women and bidirectional effects of alcohol on these factors.[120,121]

Pain, for example, may be both a risk factor and a consequence of excessive drinking.[121,122] Although alcohol can reduce and even quell pain in some individuals when alcohol is initially used, over time increasing amounts of alcohol are needed to achieve pain relief, with the paradoxical effect that alcohol consumption exacerbates pain intensity. In a study of 451 treatment-seeking participants with an alcohol misuse diagnosis in residential treatment, women were more likely to report significant recurrent pain, more concurrent chronic pain conditions, and greater pain severity than men.[122] Taken together, these studies highlight the relevance of including effective pain management in initiation and maintenance of abstinence, particularly in women.

LIMITATIONS OF STUDIES

Limitations commonly noted in studies on the cognitive effects associated with chronic excessive drinking include the fact that most of the data pertaining to alcohol consumption variables, including pattern, severity, and amount, are obtained through self-report. Structured follow-back interviews likely aid accuracy of documentation but are subject to memory distortion. Differences in subject inclusion and exclusion criteria and task demands make it difficult to generalize across studies; standardization of participant characteristics and tests would allow meta-analyses across data. Additionally, the dearth of longitudinal reports limits the ability to determine whether a deficit was pre-existing or caused by alcohol misuse or to document the temporal sequence of cognitive declines and recovery in relation to the dynamic nature of alcohol use.

Additional limitations relevant to review of studies on moderate alcohol consumption and cognition and women include inclusion of "sick quitters" in the group of abstainers—that is, individuals who no longer drink because of previous alcohol misuse.[51] Efforts were taken to include studies where this was not a clear issue. Further, this review only included studies assessing sex differences and not gender differences, per se.

TREATMENT IMPLICATIONS AND CONCLUSION

There is a growing appreciation of direct comparisons between men and women in the examination of alcohol's effects on brain structure and function and the identification of factors contributing to alcohol-related cognitive impairment, including those that affect personal, social, and professional lives. Of course, regardless of sex, assessment of cognitive deficits is relevant to treatment plans, as it has been documented that efficacy of treatment with a heavy cognitive behavioral therapy component may be best delayed until recovery of the cognitive processes relevant to task demands.[123]

Highlighting the cognitive effects of acute, moderate, at-risk, and excessive drinking in women speaks to the urgency of screening, treating, and monitoring women who report patterns of possible alcohol misuse, even if diagnostic criteria for AUD are not met.[124] Young adults should be educated on the cognitive effects of binge and intensive drinking for both the short term and the long term.[125] Older adult women need to be educated on how alcohol interacts with age-related biological changes, comorbid medical conditions related to aging, and medications.

Longitudinal studies that examine the pattern and extent of cognitive and motor deficits associated with chronic heavy drinking and the factors that play a role in initiation and maintenance of alcohol misuse will continue to have both theoretical and clinical implications, steering specialized treatment for women with AUD and informing practice and policy. Heterogeneity among women with AUD highlights the complexity of this chronic disease and underscores the relevance of examining the effects of demographic factors, especially age and aging factors, and disease-related variables, notably

pattern of drinking and duration of abstinence, in identifying the cognitive effects of alcohol and its biological underpinnings.

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Alcohol-Related Disparities Among Women: Evidence and Potential Explanations

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Although research on alcohol-related disparities among women is a highly understudied area, evidence shows that racial/ethnic minority women, sexual minority women, and women of low socioeconomic status (based on education, income, or residence in disadvantaged neighborhoods) are more likely to experience alcohol-related problems. These problems include alcohol use disorder, particularly after young adulthood, and certain alcohol-related health, morbidity, and mortality outcomes. In some cases, disparities may reflect differences in alcohol consumption, but in other cases such disparities appear to occur despite similar and possibly lower levels of consumption among the affected groups. To understand alcohol-related disparities among women, several factors should be considered. These include age; the duration of heavy drinking over the life course; the widening disparity in cumulative socioeconomic disadvantage and health in middle adulthood; social status; sociocultural context; genetic factors that affect alcohol metabolism; and access to and quality of alcohol treatment services and health care. To inform the development of interventions that might mitigate disparities among women, research is needed to identify the factors and mechanisms that contribute most to a group's elevated risk for a given alcohol-related problem.

KEY WORDS: alcohol problems; health disparities; minorities; cumulative disadvantage; life course; alcohol

INTRODUCTION

Although women consume less alcohol and drink less often than men,[1] women's drinking warrants serious attention from alcohol researchers and health care providers, in part because women are more susceptible to certain alcohol-related problems at a given level of consumption[2] and because women are less likely to receive help for problems with alcohol use.[3] While women may share many experiences and risk factors relevant to their alcohol use and associated problems, women are not a monolithic group. Multiple dimensions of social location (e.g., race/ethnicity, socioeconomic status, and sexual identity) profoundly shape women's lived experiences.[4] These can affect health and a wide range of health-related factors over the life course, such as social and environmental risk and health-promoting exposures, health behavior, resources that enhance health and help to manage disease, care-seeking, and the quality of health care received. Thus, unsurprisingly, among women there is heterogeneity of risk for problems related to drinking.

This article briefly reviews what is known about alcohol-related disparities among women and discusses mechanisms that could give rise to inequities in alcohol outcomes. In this article, disparity refers to social group differences in which groups that have greater social or economic advantages have more desirable health outcomes than groups without those advantages.[5] Research on alcohol-related disparities has focused on racial/ethnic and socioeconomic groups[6-8] and often has not been stratified by gender to examine disparities among women or men separately, as doing so would require very large samples for low-prevalence outcomes. Thus, this review reflects a predominant focus in the extant literature on race/ethnicity (often White, Black, and Latinx groups, with rare analysis of Latinx subgroups), socioeconomic status, and the limited study of disparities among women. Far less research has been conducted on sexual minority groups (defined by sexual orientation). Reflecting the work to date, unless otherwise stated, this review defines women based on physiological sex. Finally, this review focuses on problems associated with personal alcohol consumption and does not include the many secondary harms experienced because of other people's drinking.

DISPARITIES IN ALCOHOL-RELATED PROBLEMS

Identifying racial/ethnic and socioeconomic disparities in alcohol-related problems is not always a straightforward task, partly because of differential abstinence rates across racial/ethnic and socioeconomic groups. For example, in the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), the percentage of people who drank alcohol in the past year ranged from 62% to 75% across racial/ethnic groups and 56% to 81% across levels of education.[1] The National Alcohol Survey (NAS) reported 64% of heterosexual women and 78% of bisexual women drank alcohol in the past year.[9] In addition, race, ethnicity, and socioeconomic status are deeply intertwined in the United States.[10] In light of the above, the detection of alcohol-related disparities can be affected by the inclusion of abstainers in analyses and also by how investigators handle socioeconomic status when analyzing racial/ethnic differences. Although analytic decisions depend on research objectives (e.g., to establish general population rates, understand risk relationships, estimate residual racial/ethnic differences, or recognize the role of socioeconomic status in racial/ethnic differences), sensitivity analyses are always a useful option to gauge the effects of such decisions on study results and enhance

interpretation. Effort was made in this review to be attentive to such decisions.

Alcohol Use Disorder and Negative Consequences of Drinking

The following section provides a review of research on the prevalence and risk of alcohol-related problems in different subgroups of women defined by race/ethnicity, socioeconomic status, and sexual minority status. Problems examined in this literature include alcohol use disorder (AUD) and negative consequences of drinking. In nearly all of the studies reviewed, AUD was defined according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),*[11] which includes and distinguishes alcohol abuse and alcohol dependence. In 2013, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*[12] was released, which replaces DSM-IV alcohol abuse and dependence diagnoses with a single AUD diagnosis that is classified as mild, moderate, and severe.

Race and ethnicity

National survey data show greater prevalence of DSM-IV AUD among White women compared to other racial/ethnic groups. For example, in Wave 1 of the NESARC, which was conducted from 2001 to 2002, age group–specific rates of DSM-IV alcohol abuse and dependence among women (including abstainers) were consistently higher in White women compared to Black, Latina, and Asian/Pacific Islander women in nearly all of four age groups examined.[13] The exceptions were American Indian/Alaska Native (AIAN) women, whose prevalence of DSM-IV alcohol abuse and dependence was greater than that of White women in three of four age groups, and Black women, whose DSM-IV alcohol dependence prevalence was higher than that of White women at midlife (ages 45 to 64) and older (ages 65 and older). However, many of these differences did not appear to be statistically significant. Taking into account standard error, the clearest differences were observed among White, Black, and Latina women, the three largest groups. DSM-IV alcohol abuse prevalence was higher in White women compared to Black women before midlife (younger than age 45), and higher than DSM-IV alcohol abuse prevalence of Latinas in all but the oldest age group (ages 65 and older).

In the same NESARC survey, the prevalence of DSM-IV alcohol dependence was significantly higher only in young-adult, White women (ages 18 to 29) at 6% vs. 4% in young Black women and 4% in young Latina women.[13] At 9%, the prevalence of DSM-IV alcohol dependence among young AIAN women was highest of all, but it had a wide confidence interval. By contrast, in 2000, 2005, and 2010 NAS data, White, Black, and Latina women (including abstainers and not stratified by age) showed statistically nondistinguishable prevalence and odds of having DSM-IV alcohol dependence and two or more negative consequences of drinking.[14]

Because these studies were based on older data that, in some cases, were collected nearly 20 years ago, data from the 2017 National Survey on Drug Use and Health (NSDUH)[15] were analyzed to provide updated national estimates for women. As shown in Table 1, most of the significant racial/ethnic differences in DSM-IV alcohol dependence prevalence were no longer apparent when abstainers were excluded. When compared with White women who drink alcohol, only Asian women who drink had significantly lower rates of DSM-IV AUD, and AIAN women who drink had higher rates of DSM-IV AUD.

Table 1 2017 NSDUH 12-Month Prevalence of DSM-IV Alcohol Dependence and AUD Among Women

Category	Alcohol Dependence, % (Standard Error)		Alcohol Dependence or Abuse, % (Standard Error)	
	All Women (*N* = 22,567)	Drank in Past Year (*N* = 16,042)	All Women (*N* = 22,567)	Drank in Past Year (*N* = 16,042)
Race/Ethnicity				
White†	2.70 (0.14)	3.70 (0.20)	4.44 (0.15)	6.07 (0.22)
Black	1.86 (0.24)*	3.11 (0.41)	3.12 (0.31)**	5.21 (0.50)
AIAN	8.04 (1.26)**	16.21 (2.64)**	9.10 (1.32)**	18.35 (2.75)**
Native Hawaiian/Pacific Islander	2.11 (1.54)	4.46 (3.27)	2.90 (1.71)	6.11 (3.62)
Asian	1.29 (0.42)*	2.68 (0.85)	1.79 (0.46)**	3.71 (0.88)*
More Than One Race	4.91 (1.70)	7.44 (2.63)	6.70 (1.76)	10.15 (2.75)
Latina	1.72 (0.23)**	2.93 (0.42)	3.20 (0.28)**	5.46 (0.52)
Education				
Less Than High School	1.58 (0.24)**	3.92 (0.61)	2.11 (0.32)**	5.24 (0.79)
High School Graduate	1.60 (0.15)**	2.80 (0.27)	2.63 (0.19)**	4.61 (0.34)*
Some College	3.05 (0.27)	4.23 (0.39)	4.84 (0.32)	6.72 (0.45)
College Graduate†	2.69 (0.22)	3.38 (0.27)	4.74 (0.27)	5.96 (0.33)
Sexual Identity				
Heterosexual†	2.14 (0.11)	3.18 (0.17)	3.61 (0.12)	5.36 (0.19)
Lesbian	5.12 (1.33)**	6.31 (1.62)*	8.21 (1.69)*	10.12 (2.10)**
Bisexual	8.63 (1.02)**	10.68 (1.25)**	12.23 (1.11)**	15.12 (1.35)**

Note: Data are for women ages 18 and older. Percentages are weighted for sampling, and sample size (*N*) represents unweighted totals. Pairwise significance tests involve comparisons to the reference category using Pearson's chi-square test. *$p < 0.05$, **$p < 0.01$, † = reference category. *Source:* Data from Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, October 2018.[15]

In studies excluding lifetime abstainers, there is some evidence of greater alcohol problems among racial/ethnic minority women who drink compared with White women who drink. For example, Grant and colleagues conducted a longitudinal analysis of NESARC Waves 1 and 2 from the early 2000s and found that at Wave 2, young White women had the greatest risk for DSM-IV alcohol dependence onset compared with young Black and Latina women.[16] However, the risk for young White women was lower than that for older minority women. Both Black and U.S.-born Latina women ages 40 and older had greater risk of DSM-IV alcohol dependence onset than young White women (adjusted *OR* = 1.71 and 2.08, respectively).[16] In addition, older Black and U.S.-born Latina women had more persistent alcohol dependence (adjusted *OR* = 2.73 and 1.36, respectively), and older U.S.-born Latina women had greater recurrence of dependence (among those with lifetime dependence prior to Wave 1). This elevated risk among older minority women was in marked contrast to similarly aged, White peers, whose risk for alcohol dependence onset, persistence, and recurrence was much lower than that of young White women. The racial/ethnic patterning of risk was the same when DSM-IV AUD was the outcome, except that disparities were also evident among younger minority women ages 30 to 39. In this age group, Black women had greater AUD onset, and U.S.-born Latinas had greater AUD persistence than young White women.

Notably, this NESARC study did not control for socioeconomic status indicators.[16] In a 2005 and 2010 combined NAS study of women who drink, which adjusted for demographics, education, and income and also rigorously controlled for heavy drinking, the only disparities found between Black and White women were in DSM-IV alcohol dependence (adjusted *OR* = 3.3), and this disparity held across the range of heavy drinking.[17] There was no significant disparity between Latina and White women in either negative consequences of drinking (an outcome similar to alcohol abuse) or DSM-IV alcohol dependence. (Due to sample size limitations of the study,[17] U.S.-born Latina women were not analyzed separately as they were in the NESARC study by Grant and colleagues.[16])

As noted, all of the research on AUD in demographic subgroups reviewed above, including the 2017 NSDUH data on AUD,[15] is based on the DSM-IV diagnostic criteria rather than the DSM-5 criteria. Thus, it is not clear whether these findings (especially those based on data collected from the early 2000s) accurately reflect DSM-5 AUD patterns among women, as the latter have not yet been examined. However, results from two recent NESARC-III studies of women and men combined suggest that the patterning of AUD prevalence across racial/ethnic, socioeconomic, and other demographic subgroups may be similar across DSM-IV and DSM-5 criteria.[18,19] For instance, AUD prevalence among White, Black, and Latinx study participants based on DSM-IV criteria was 13%, 13%, and 12%, respectively,[18] and the prevalence based on DSM-5 criteria was 14%, 14%, and 14%, respectively.[19] Similarly, for educational levels, the DSM-IV AUD prevalence was 10% for less than high school, 13% for high school, and 13% for some college or more,[18] and the prevalence based on DSM-5 criteria was 12%, 15%, and 14%, respectively.[19] These results suggest that the presence or absence of disparities in women's prevalence of DSM-5 AUD might reasonably be gauged by recent research that uses DSM-IV AUD criteria (for instance, as captured by the 2017 NSDUH). But confirmation is needed, as the NESARC-III analyses were not restricted to women.

Socioeconomic status

Similar to the findings for race/ethnicity, the 2017 NSDUH data show significant differences in DSM-IV alcohol dependence and AUD by educational attainment, but when abstainers are excluded, nearly all differences become nonsignificant (see Table 1).[15] Importantly, in a recent systematic review, Collins concluded that although groups with greater socioeconomic advantages (defined by income, education, and other indicators at the individual, family, or neighborhood levels) had similar or greater levels of alcohol consumption than those with fewer advantages, the groups with fewer socioeconomic advantages were at greater risk for alcohol-related problems.[8] This finding has been referred to as the "alcohol harm paradox"[20] and is similar to the phenomenon among some U.S. racial/ethnic minority groups, particularly Black persons, of having greater risk for alcohol-related problems than White persons despite drinking less.[21]

This socioeconomic status paradox has been studied mostly outside of the United States and has been observed for a variety of alcohol outcomes. A meta-analysis by Grittner and colleagues, drawing upon survey data from 25 countries, found that in several high-income countries, women who drink alcohol and who have less education were at greater risk for external drinking consequences (e.g., consequences affecting finances; work, school, or employment; close relationships; and risk of injury/fights).[22] In the full sample of countries, an inverse educational gradient was found when controlling for age and drinking pattern, as well as country-level, socioeconomic development factors.

The socioeconomic conditions of residential neighborhoods also are relevant. Analysis of the 2000 and 2005 combined NAS data found that women who drink alcohol and live in disadvantaged neighborhoods have twofold greater risk for alcohol problems (adjusted *OR* = 2.07 for two or more drinking consequences or DSM-IV alcohol dependence) than women who drink and live in more advantaged neighborhoods.[23]

This study controlled for individuals' education, income, unemployment status, and demographics.

A different study that used 2000 and 2005 combined NAS data further showed that among White women who drink alcohol, neighborhood disadvantage was associated with increased risk for negative consequences of drinking.[24] The authors noted that White women who drink and reside in disadvantaged (as compared to more advantaged) neighborhoods were challenged by greater family histories of alcohol problems, co-occurring drug use, and drinking to cope with stress, which are risk factors for alcohol problems.

Providing a context for such findings, a longitudinal study of women in poverty highlighted the distinctive stressors faced by women who drink and have low incomes.[25] Stressful life events and neighborhood stressors (e.g., crime, drug trafficking, and shootings) were common, and these in addition to economic stress, contributed to psychological distress and increased women's risk for developing problematic alcohol use.

Sexual minority women

In this article, sexual minority women, including bisexual women and lesbians, are defined based on sexual orientation. In a study by Wilsnack and colleagues, the investigators compared data collected from sexual minority women in the 2001 to 2002 Chicago Study of Health and Life Experience of Women (CHLEW) study with data collected from exclusively heterosexual women in the 2001 National Study of Health and Life Experiences of Women.[26] The investigators found higher prevalence of lifetime alcohol-related problems, alcohol dependence symptoms, and hazardous drinking among sexual minority women. Bisexual women were most likely to report alcohol problems, with 70% reporting lifetime problems in contrast to 29% of heterosexual women.

Similar disparities in hazardous drinking were found in a more recent wave of the CHLEW study (2010 to 2012) and in a 2000 to 2015 NAS analysis.[9] Additionally, a separate study by Drabble and colleagues that used 2000 NAS data found that lesbians had 7.1 times higher risk of meeting criteria for DSM-IV alcohol dependence (bisexual women had 6.4 times higher risk) than heterosexual women.[27] A recent study that used 2015 to 2017 NSDUH data indicated disparities in DSM-IV AUD rates as well.[28] In that study, bisexual women had 2.2 times higher odds than heterosexual women and 1.5 times higher odds than lesbian women of having past-year AUD after adjusting for demographic characteristics.[28]

Although this review focuses on sexual minority women, the newly emerging literature on alcohol use among gender minority women (i.e., noncisgender and nonbinary women) should be noted. A systematic review of transgender individuals (including gender minority women) by Gilbert and colleagues found estimates of binge drinking among transgender individuals ranging from 7% to 65%, with estimates of lifetime and past-year DSM-IV AUD prevalence at 26% and 11%, respectively.[29] More research is needed on these groups. As noted by Gilbert and colleagues, to facilitate research on alcohol use disparities among gender minority women and transgender individuals, new methods will be needed, as many of the current alcohol use measures to assess unsafe drinking rely on physiological sex-specific cut points.

Health, Morbidity, and Mortality

Disparities in alcohol-related health outcomes, morbidity, and mortality are studied less commonly than disparities in AUD and the negative consequences of drinking alcohol. Few studies focus on women; instead, studies typically include women and men and control for gender. Nonetheless, in analyses restricted to women, racial/ethnic and socioeconomic disparities in risk have been reported for some alcohol-related health conditions and outcomes. For example, based on suicide decedent data from the National Violent Death Reporting System, AIAN women had approximately twice the odds of acute alcohol intoxication relative to White women at the time of death.[30] Also, increased alcohol use is known to be associated with

mortality among people with HIV.[31] This risk disproportionately affects Black women, whose incidence rate for HIV far exceeds that of White women (estimated at 783.7 and 43.6 per 100,000 for Black and White women, respectively).[32]

Research also indicates socioeconomic differentials in alcohol-related morbidity and mortality. An English study of hospital admissions from 2010 to 2013 that examined wholly and partially alcohol-attributable conditions found the greatest socioeconomic disparities among women with wholly alcohol-attributable chronic and acute conditions.[33] These results suggest that socioeconomic status differences in harmful drinking patterns contribute to differential morbidity.

Applying a similar comparative approach, Probst and colleagues conducted a meta-analysis of 15 studies from 7 countries and found greater socioeconomic disparities in women's alcohol-attributable mortality than in their all-cause mortality.[34] Across different measures of socioeconomic status (e.g., individual-level education, occupation, employment status, or income), socioeconomically disadvantaged women had 1.8 times the relative risk of alcohol-attributable vs. all-cause mortality when compared to more advantaged women. Similarly, a Scottish study of women and men combined found that socioeconomically disadvantaged participants who drink moderately had much greater risk for alcohol-attributable harms (i.e., hospital admissions or deaths) compared to socioeconomically advantaged participants who drink moderately or even heavily, regardless of the socioeconomic status measure used and even after controlling for differences in binge drinking, obesity, smoking, and other risk factors.[20]

Other research has investigated disparities in the protective health effects of moderate drinking. Although protective effects for cardiovascular disease mortality and for diabetes onset have been found,[35,36] some studies indicate health benefits for Whites but not for racial/ethnic minorities.[37-39] Race/ethnicity differences in the protective effects of alcohol have also been observed in two studies of all-cause mortality. One study used NAS data[40] and the other was a gender-stratified study based on data from the National Health Interview Survey.[41] The latter study found that moderate drinking was associated with the lowest mortality among White women (a mortality rate of 40.1 per 1,000 person-years). In Black women, moderate drinking was associated with a mortality rate of 93.8 per 1,000 person-years), more than double the rate of White women with a similar drinking level and also higher than the mortality rate associated with high-risk drinking among Black women (67.6 per 1,000 person-years), although confidence intervals for Black women's rates were widely overlapping.[41]

In contrast to these disparities, the United States has seen a racial/ethnic crossover in liver cirrhosis mortality rates for women. Although rates for Black women were highest in 2000, they have since dropped, and rates for White, non-Latina women and for White, Latina women have risen, exceeding the rates for Black women.[42] These results are consistent with reports of increased consumption and alcohol problems among White women based on the 2000 and 2010 NAS survey series.[14,43]

POSSIBLE EXPLANATIONS FOR DISPARITIES

An obvious potential explanation for these disparities is that they reflect population differences in harmful drinking patterns. Sexual minority women, for instance, are more likely to drink alcohol, to drink to intoxication, and to drink heavily compared to exclusively heterosexual women (adjusted *OR* = 1.8 and 2.0 for intoxication and heavy drinking, respectively).[27] Yet, it is unlikely that consumption patterns alone account for disparities. Indeed, the finding of greater harm despite lower or similar levels of drinking lies at the heart of the alcohol harm paradox. As noted, the latter refers to socioeconomic disparities in alcohol outcomes but is similar to the phenomenon observed for some racial/ethnic minority groups of disparities in alcohol problems at the same level

of heavy drinking among both women and men. Related to this, it is important to note that previous research finding elevated alcohol consumption among AIAN relative to White individuals has been based on specific AIAN tribes or geographic-area subgroups, whose prevalence of alcohol use varies.[44] Recent analyses of the 2009 to 2013 NSDUH and the 2011 to 2013 Behavioral Risk Factor Surveillance System indicate that, nationally, AIAN and White participants had similar odds of binge drinking and heavy drinking (i.e., drinking five or more drinks on 5 or more days). Moreover, White participants had lower abstinence relative to AIAN participants, with an adjusted odds ratio for abstinence among White participants relative to AIAN participants of 0.64 (95% CI: 0.56, 0.73).[45]

Thus, consideration of other ways that disparities in alcohol-related problems can arise is needed. Recent research calls attention to potential explanations involving the life course, differential vulnerability, and access to care. As noted earlier, this review reflects a predominant focus in the literature on racial/ethnic and socioeconomic disparities. Future studies are needed to assess relevance to other disadvantaged social groups.

Harmful Drinking Patterns Over the Life Course

Reflecting core concepts of life-course developmental theory,[46] both the age at which heavy drinking occurs and the duration of heavy drinking across the life course are relevant to disparities in alcohol-related problems. This makes sense intuitively, as the longer a person engages in health risk behaviors, the greater the chances of experiencing related problems. Also, certain age periods are likely to pose more or less risk for different kinds of alcohol-related problems. Bouts of heavy drinking, for instance, are likely to be tolerated less and to have more consequences when coupled with greater responsibilities to others, such as family and employers.

Notably, three recent studies based on National Longitudinal Study of Adolescent to Adult Health data examined racial/ethnic differences in the heavy-drinking trajectories of young women, with somewhat mixed results (possibly reflecting methodological differences, such as adjustments for socioeconomic status).[47-49] Two studies showed that heavy drinking of young White women consistently exceeded that of Black women.[47,48] One study indicated that the rapidly declining trajectory of White women converged with the trajectory of Latina women by age 30,[47] and another showed a convergence of White, Latina, and Black women's trajectories by their early 30s.[49]

A fourth study based on the 1979 cohort of the National Longitudinal Study of Youth (NLSY) examined women's heavy-drinking trajectories from ages 21 to 51.[50] This study also found that heavy drinking among White women exceeded that of Black and Latina women in their early and mid-20s, but the trajectories of all 3 groups declined thereafter, with no significant racial/ethnic differences in heavy drinking between ages 30 to 51. However, sensitivity analyses excluding lifetime abstainers and women who never drank heavily showed a crossover in the heavy-drinking trajectories of Black and White women.[50] The trajectory for Black women rose during their early 20s, a period when White women's trajectory declined, thus causing a crossover at age 30. Thereafter, Black women's trajectory declined and reconverged with the flattening trajectory for White women at age 40. Consistent with these results, a 2010 NAS analysis of heavy drinking trajectories among women who reported ever drinking in their lifetime found that Black women, compared to White women, had twofold greater odds of persistent, frequent, heavy drinking (vs. declining heavy drinking) beyond their 20s and into their 40s (adjusted $OR = 2.65$, $p < .01$).[51]

Taken together, these life-course drinking studies highlight racial/ethnic differences in the heavy-drinking trajectories of women in their early and mid-20s, which are consistent with the greater DSM-IV AUD risk observed during this period among young White women. Importantly, early adulthood is a time when health is relatively robust, and many women have yet to take on large, adult responsibilities. Drinking trajectory studies

that extend beyond the 20s are rare, but there is some evidence of Black–White disparities in the age and duration of heavy drinking among women who reported ever drinking in their lifetime. These disparities were found for women in their 30s, possibly extending to their 40s.

Prospective studies beyond young adulthood are needed, especially for younger cohorts, as racial/ethnic differences in heavy drinking may be changing.[1,52] Nonetheless, the observed Black–White disparity in heavy drinking after young adulthood is consistent with the findings from a NESARC study of women who drink (described earlier), showing greater DSM-IV AUD onset among Black women in their 30s and 40s, as well as greater AUD persistence among Black women in their 40s and older, compared to White women in these same age groups as well as younger (ages 18 to 29).[16] These disparities are particularly significant when juxtaposed with other life-course findings. Namely, by midlife, there are striking racial differences in cumulative lifetime exposure to socioeconomic disadvantage,[53] and disparities in health become more pronounced.[5,54]

Cumulative Disadvantage

Population differences in exposure to health risk factors and their cumulative effects are an important mechanism in health disparities.[5] Cumulative disadvantage refers to the notion that social status positions such as race/ethnicity and socioeconomic status profoundly influence opportunities and resources over the life course and, thus, also affect exposures to health risk factors.[55]

Growing up in poverty in neighborhoods with inferior schools, greater crime and violence, and limited economic opportunities can lead to poor quality and low-paying jobs, a lack of health insurance, and ongoing exposure to stressors. Black women and men with low incomes are particularly affected by these factors due, in part, to racial residential segregation[56] and geographic inequalities of opportunity.[57] Consistent with this, research has indicated that a large majority of Black children who were raised in poor neighborhoods continue to reside in similar neighborhoods as adults.[58]

In an early articulation of the effects of cumulative disadvantage and its relationship to health disparities, Geronimus proposed the "weathering hypothesis" to account for the accelerated health deterioration of Black persons relative to White persons.[59] This is exemplified by high rates of chronic disease found in young and middle-aged Black women residing in low-income, urban areas, which contribute to their early mortality rates. According to the hypothesis, the widening racial health disparity seen through middle adulthood reflects the cumulative effect of adverse exposures from conception onward. These adverse exposures include chronic social stressors (e.g., discrimination), environmental hazards, inadequate health care access and treatment, and unhealthy behaviors. Notably, greater alcohol availability, targeted advertising, and less access to healthy food in low-income and minority neighborhoods can contribute to and aggravate unhealthy behaviors.[60-62]

Research has since shown that chronic, enduring stress affects the body's physiological stress response, with adverse effects on the cardiovascular, metabolic, and immune systems.[63] Moreover, the physiological consequences of chronic stress, which are referred to as allostatic load and assessed via biomarkers, have been found to be greater among poor and non-poor Black women than White women, and have been associated with accelerated aging.[64,65] Consistent with these findings, data from the 2017 National Health Interview Survey showed that 14% of Black women (and 13% of Latina women) reported fair or poor health, in contrast to 8% of White women.[66] Even when the sample was stratified by poverty status (i.e., poor, near poor, and not poor, with poor defined as having income below the federal poverty threshold), Black women and men tended to report worse health than White women and men.

As suggested, cumulative disadvantage can also affect health indirectly through risky health behaviors that people use to cope with stressors.[67]

A longitudinal study based on NESARC data found that the effect of poverty on heavy drinking incidence was worse for Black women who drink than for their Latina and White counterparts.[68] A different longitudinal study based on the 1979 NLSY cohort data reported that cumulative poverty across the life span was positively associated with onset and persistence of alcohol dependence symptoms after young adulthood (in a combined sample of women and men who drink).[69] Further, a study based on 2010 NAS data found that cumulative socioeconomic disadvantage partly explained the disparity in persistent heavy drinking until midlife between Black and White women.[51]

This confluence of disparities in cumulative disadvantage and health in middle adulthood provides an important backdrop for understanding disparities in alcohol problems after young adulthood. It raises the question of differential health vulnerability—the idea that certain social groups are more susceptible to health-related consequences when they are exposed to risk factors such as, in this case, heavy drinking.[70] To the extent that health "weathering" begins to accelerate after young adulthood and at a faster rate for demographic groups that have more enduring chronic stress, heavy drinking beyond young adulthood may contribute to alcohol-related health disparities at midlife and later. In keeping with this, a recent NLSY study by Kerr and colleagues found that among Black and Latina women, but not White women, diabetes onset was associated with a history of heavy drinking in the previous 10 years, even when controlling for health risk behaviors, socioeconomic status, and other demographics.[71]

Differential health vulnerability may reflect various mechanisms that require future study. It may be rooted in biological interactions with alcohol that affect health. For example, heavy drinking can exacerbate certain health conditions such as hypertension, type 2 diabetes, and chronic kidney disease, which are more prevalent among Black Americans. Also, as discussed by Jackson and colleagues, differential vulnerability may reflect unmeasured health risk behaviors like smoking and unhealthy eating, which may co-occur with heavy drinking and are thus potentially confounding variables.[41]

Alternatively, unhealthy behaviors could, in some instances, be effect modifiers that interact with alcohol to alter risk for health conditions. For instance, the aforementioned NLSY study by Kerr and colleagues found an interaction between alcohol and obesity for diabetes risk for women.[71] Bensley and colleagues' study of male, Veterans Health Administration patients who had HIV provides further illustration of this complexity.[31] Black patients with low-risk drinking (defined as a score of one to three on the Alcohol Use Disorders Identification Test consumption questions [AUDIT-C]) had greater mortality than White patients who had similar drinking levels, indicating differential vulnerability. The disparity was attenuated after adjusting for the greater presence of hypertension, hepatitis C, tobacco use, and other drug use among Black patients. To better understand alcohol-related disparities and the epidemiologic paradox of greater problems despite lower levels of drinking for some groups, research is needed to examine population differences in health and health behaviors and potential interactions with alcohol consumption patterns.

Other Social and Biological Factors

Studies have documented gene variants that are more prevalent among Black persons[21] that affect the metabolism of alcohol, leading to a buildup of acetaldehyde in the bloodstream. While the gene variants have been associated with lower rates of alcohol dependence and heavy drinking, experimental research by Pedersen and McCarthy has found that the variants also are associated with more intense subjective responses to alcohol.[72] Specifically, they found that Black participants experience greater stimulating effects from alcohol than White participants, even after controlling for differences in past-month alcohol use. Further, greater increases in stimulation are associated with more alcohol-related problems among Black participants. As the researchers suggested, this acute stimulation could contribute to disparities in

the negative consequences of drinking alcohol at a given level of consumption.[72]

In addition, Black women in this study experienced greater sedating effects from alcohol than White women. In view of the greater cumulative and chronic stress experienced by Black women compared with White women,[51,65] this finding of greater sedating effects of alcohol might be a factor in Black-White disparities in persistent heavy drinking and AUD among older women who drink.

Social position and sociocultural context also affect the likelihood of experiencing alcohol problems, particularly negative social consequences, at a given level of consumption. For years, researchers have called attention to the greater negative consequences of drinking borne by racial/ethnic minority groups who have less permissive drinking norms and are subject to greater societal scrutiny and stigmatization.[73,74] People with greater resources and higher status are better able to shield themselves from the negative consequences of drinking that others experience.[75] For example, negative consequences could be minimized at work (because of greater flexibility and autonomy and less scrutiny), in family duties (by paying for childcare or home-delivered meals and groceries), and when going out for the night (by hiring a driver).

These differential standards and consequences of drinking may be seen among women, perhaps more now than in the past when gendered roles and drinking norms were more similar across women. Reflecting on recent decades, Schmidt observed that social and economic changes resulting in greater freedoms for women have led to the "equal right to drink" only for women in the middle and upper classes.[76] By contrast, women with low incomes and women who receive welfare benefits, particularly racial/ethnic minority women, arguably have been more surveilled, stigmatized, and penalized for alcohol and other drug use.

Finally, stress experienced due to being a member of a stigmatized minority group may help to explain alcohol-related disparities between sexual minority women and exclusively heterosexual women. Minority stress theory applied to drinking behavior suggests that the heavy drinking patterns of sexual minority women (relative to heterosexual women) are related to the stress of holding one or more minority identities.[77,78]

Minority stress theory has been used in many studies. Research shows that sexual minority women experience stressors such as discrimination and harassment because of their sexual orientation, and that these women are more likely to report psychological distress than heterosexual women.[74] A study of sexual minority women and sexual minority stressors associated with substance use and mental health outcomes (e.g., unfair treatment, events of prejudice, and victimization) has provided further empirical support of this theory.[79] In this study, sexual minority stressors mediated the adverse effects of more masculine gender expression (i.e., a set of culturally assigned qualities to the category of masculine) on mental health and substance use outcomes. Other studies have found that sexual minority women experience additional stressors associated with increased alcohol use. In comparison to exclusively heterosexual women, sexual minority women are more likely to have experienced child sexual abuse, depression in their lifetime or in the past 12 months, and early onset of alcohol use.[26,80]

Together, this varied literature suggests that social and biological factors may contribute to alcohol-related disparities among women in several ways. These factors may increase exposure to high levels of stress and discrimination (and drinking in response), they may increase sensitivity to the physiological effects of alcohol, and they may increase exposure to punitive societal responses to an individual's own alcohol use.

Differential Access to and Quality of Care

Differences in access to care and in the quality of care received constitute another important explanation for disparities in alcohol-related problems. Although health care access and quality account for a relatively small percentage of the

variation in life expectancy in the United States—estimated at 10%[81]—health care is a valuable resource. Indeed, having a regular source of primary care has been associated with reduced racial/ethnic and socioeconomic disparities in health.[54]

The Institute of Medicine's report, *Unequal Treatment*, famously documented racial/ethnic disparities in the quality of health care received in the United States, even after accounting for differences in socioeconomic status, insurance, disease stage, comorbidities, and facility type.[82] Such findings have motivated the national goal of ensuring equitable access to high-quality care to mitigate disparities in early or delayed diagnosis, types of treatment, and care outcomes.[83] Part of the problem of health care disparities is structural, related to income, insurance, and the type and quality of care that is affordable and geographically accessible. Another part of the problem is social, related to implicit (unconscious) bias on the part of health care providers and how this bias affects patient-provider communication and interaction, treatment decisions, and health care outcomes.[84,85] Related to both structural and social factors, health care utilization also reflects patient perceptions, attitudes, and willingness to seek care. In the case of racial/ethnic disparities in alcohol-related care or treatment, cultural acceptability (including language compatibility) and perceived stigma toward people with AUD may be particularly relevant.[86,87]

Whereas considerable research has investigated racial/ethnic and gender disparities in the receipt of alcohol-related care, far less is known about disparities among women specifically. In a rare, gender-stratified analysis of alcohol treatment utilization, Zemore and colleagues' analysis of NAS data found racial/ethnic disparities in treatment use among women with a lifetime AUD.[88] When compared with White women, Latina and Black women were significantly less likely to obtain specialty alcohol treatment, even after controlling for survey year, age, socioeconomic status (i.e., education and income), and insurance status (adjusted $OR = 0.31$ and 0.38 among Latina and Black women, respectively; $p < .05$). Moreover, this disparity was also observed for Alcoholics Anonymous use (adjusted $OR = 0.38$ and 0.37 for Latina and Black women, respectively).[88] Other studies (using samples of women and men combined) have further shown disparities in treatment completion, which is an important predictor of post-treatment substance use and health outcomes.[89,90]

A variety of factors might contribute to racial/ethnic disparities in treatment use specifically among women. One factor is the stigma of AUD, which may be a particularly salient deterrent for social groups that have more conservative drinking norms and that might already be socially marginalized. Notably, there is evidence of more conservative drinking norms for Black women compared to those for White women[91] and less permissive attitudes toward Latina women's drinking, which tend to be held by less-acculturated Latina women.[92] The stigma of AUD could lead to concealment or denial of alcohol problems and to family concerns about privacy and pressure to not seek treatment. All of these issues may be magnified for women due to the more intense social control of women's drinking.

Other potential treatment barriers are a lack of childcare and concerns that children could be taken away. These concerns are not unfounded, given research showing that Black mothers who use alcohol or other drugs are reported to child protective services more often than similar White mothers.[93] In addition, women generally are more likely than men to experience treatment barriers because of transportation difficulties and inadequate insurance.[94] The latter may be particularly relevant to racial/ethnic minority women, as studies have found that Latinx and Black individuals are more likely than White individuals to report logistical and structural barriers.[95,96] Considering the pronounced racial/ethnic disparities in alcohol problems among women after young adulthood, additional disparities in alcohol-related care and treatment compound the problem. This large unmet need among minority women, which may reflect a variety of causes, must be addressed.

CONCLUSION

This review provides evidence of alcohol-related disparities among women. The research in this area is relatively sparse, but disparities in AUD prevalence, the negative consequences of drinking, and alcohol-related health, morbidity, and mortality outcomes are apparent. This review also highlights the importance of a life-course perspective for understanding disparities in alcohol problems. By examining what happens within and between social groups across the life span, the widening of social group differences in cumulative socioeconomic disadvantage, health, and alcohol-related problems—especially after young adulthood—becomes more noticeable. Future research is needed to examine how these various disparities may be interrelated.

Importantly, a life-course lens also requires attending to social roles and health as these change with age. Attention to such changes can help to advance understanding of how alcohol consumption results in negative consequences and why some groups are affected more than others. Finally, social position and sociocultural context remain important considerations because they can affect internal and external responses to drinking. Social position and sociocultural context also influence access to, use of, and the quality of alcohol-related and general health care. All these factors can affect the persistence of alcohol-related problems and the progression of disease.

In thinking about potential remedies, education emerges as one important factor. Some research has found that education, compared with income, is more strongly and negatively associated with the onset of disease (i.e., the likelihood that an individual will develop a chronic health condition). By contrast, income is a stronger predictor than education of how a disease progresses once an individual has the condition.[97] In light of the benefits of education for health and health behavior,[50,98] improving access to quality education at an early age and supporting higher educational attainment is an important strategy for improving health and addressing health disparities among racial/ethnic minorities and socioeconomically disadvantaged persons.

In addition, increasing insurance coverage and access to affordable, quality health care for underserved groups, a goal of the Patient Protection and Affordable Care Act, represents another crucial path to reducing health disparities. However, efforts devoted to improving health care access and quality will yield limited gains so long as stress and social stigmatization among minority populations persist, and profound differences in neighborhood conditions and available opportunities remain. These are the fundamental causes that need to be addressed to truly eliminate alcohol-related and general health disparities.

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The Role of Stress, Trauma, and Negative Affect in Alcohol Misuse and Alcohol Use Disorder in Women

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Recent evidence indicates that the United States is facing a public health crisis of alcohol misuse and alcohol use disorder (AUD), which has been fueled in part by dramatic rises in binge and heavy drinking and prevalence of AUD in women. Historically, alcohol misuse and AUD have been more prevalent in men than in women. However, recent evidence on data from the past decade shows increases in AUD prevalence rates that are associated with substantially higher binge and heavy drinking and AUD prevalence in women compared to men. This paper first addresses the key roles of stress, trauma, childhood maltreatment, negative affect, and mood and anxiety disorders; sex differences in the presentation of these psychosocial and psychological factors; and their contributions to alcohol misuse, escalation to binge and heavy drinking, and transition to AUD in women. Also examined are potential central and peripheral biological mechanisms by which stressors and traumatic experiences, as well as chronic stress states—including depression and anxiety—may facilitate differential pathways to alcohol misuse, escalation, and transition to AUD in women. Finally, this paper discusses major gaps in the literature on sex differences in these areas as well as the need for greater research on sex-specific pathways to alcohol misuse and transition to AUD, so as to support a more comprehensive understanding of AUD etiology and for the development of new strategies for prevention and treatment of alcohol misuse and AUD in women.

KEY WORDS: girls and women; sex differences; early trauma; child maltreatment; alcohol craving

INTRODUCTION

There has been a global increase in alcohol misuse and rates of alcohol use disorder (AUD) over the last two decades.[1] Recent substantial increases in the United States come from dramatic rises in the prevalence of alcohol misuse and AUD in women relative to men (women, 84% increase; men, 35% increase).[2] This dramatic rise stems from increases in hazardous and binge drinking in girls during adolescence as well as in women.[3] Even though alcohol misuse and AUD are more prevalent in men than in women, there are no sex differences in prevalence of alcohol use during adolescence.[4] These increases are especially alarming given the fact that women tend to experience greater alcohol-related health problems than do men.[5] This article focuses on the roles of stress, trauma, childhood maltreatment, negative affect, and mood and anxiety disorders and their contributions to the increases in alcohol misuse, escalation of binge and heavy drinking, and transition to AUD in women. Although there are likely additional genetic and social factors and related mechanisms that may contribute to specific risks of binge drinking and AUD in women, a review of this literature is beyond the scope of this review. Rather, this article focuses on the psychosocial and biological processes by which stress, trauma, negative affect, and mood and anxiety disorders increase the risk of binge and heavy drinking, AUD, and relapse.

PSYCHOSOCIAL FACTORS INVOLVED IN THE ONSET AND PREVALENCE OF AUD IN WOMEN

Women in the United States are largely overrepresented in stress-related psychopathology rates,[6] and stress along with drug-related environmental cues are among the most important risk factors driving alcohol seeking, maintenance, and relapse.[7] Studies suggest that men and women differ in risk trajectories for the development of AUD and in AUD-related health consequences.[8] For example, women are more likely than men to experience certain types of stressors, such as sexual trauma,[9] and higher levels of stress have been shown to increase alcohol misuse and AUD vulnerability.[10] Also, women demonstrate a significantly "more rapid and risk-oriented path to compulsive drug seeking,"[11] pointing to a significant need to understand sex differences in risk for AUD development and maintenance in order to develop novel prevention and treatment approaches for AUD in women.

Psychosocial Factors of Early Trauma, Maltreatment, and Adversity

Early trauma, maltreatment, and cumulative adversity are psychosocial stress factors that have long been associated with alcohol misuse, development of AUD, AUD maintenance, and relapse.[10] Both boys and girls face physical and emotional abuse and neglect, sexual abuse, and cumulative adversity stemming from specific adverse childhood experiences such as substance use and mental health problems in the home, parental discord, and divorce, which are each associated with greater alcohol initiation in childhood.[12] However, girls and women face significantly higher rates of childhood sexual abuse and violent victimization.[13] Notably, higher rates of sexual abuse and violent victimization, especially in girls and women, are factors that produce the highest odds ratios for association with heavy drinking, drinking to cope with negative affect, and development of AUD.[10,12,14]

Sex Differences in Stress Factors, Early Onset Alcohol Misuse, and AUD

An extensive number of studies point to a positive association between negative affect, trauma, adversity, and chronic stress and vulnerability in developing AUD. Recent studies have shown that girls who report a history of abuse before adulthood are more vulnerable to developing AUD.[15] Other studies have found that adolescents who face a number of negative life events show increased levels of drug use (and misuse)

compared to those who do not face these adverse events.[7,10] Exposure to early life stress may be especially harmful for women, who are exposed to more high-impact trauma (e.g., sexual abuse) than men are, and at a younger age.[16] Thus, early trauma and chronic adversity both may increase vulnerability to alcohol use initiation, as well as maintenance, especially in girls. However, it is important to consider estimation biases, as women may be more likely to endorse stressful life events; thus, the contribution of these factors to binge drinking and AUD risk among women may be influenced by such estimation biases.

A study by Cheng and Anthony conducted between 2006 and 2014 assessed the dates of first full drink and first heavy drinking episode in around 33,000 females and males (ages 12 to 21) in the United States who had their first heavy drinking episode within the past 24 months.[15] Their findings revealed that, among adolescents who started to drink between ages 11 and 14, females progressed to a heavy drinking episode more quickly than males. This suggests that when drinking starts before age 15, females are at greater risk than males of progressing to a heavy drinking episode. When considered with the information that girls are more likely than boys to suffer sexual abuse before age 18, these findings raise the possibility that sexual abuse and other trauma, and victimization-related increases may contribute to increased risk of alcohol misuse and development of AUD in women.[17] However, the specific contribution of these factors to the development of AUD in women needs to be further explored.

PSYCHOLOGICAL ASPECTS OF STRESS AND TRAUMA EFFECTS ON AUD IN WOMEN

Experiencing stress, trauma, and adversity activates psychological processes of cognitive, affective, and behavioral emotion regulation and self-control to cope with and adapt to such negative life circumstances. During adolescence and young adulthood, emotion regulation becomes particularly relevant because of the rapid brain changes in regions associated with regulating emotion, stress, reward, and higher-order cognitive functioning; such changes underlie the significant biological and psychological changes that boys and girls undergo throughout adolescent development.[18] Alcohol experimentation occurs frequently during adolescence and young adulthood, and there is a higher risk for the development of AUD or substance use disorder during this time.[19] Findings indicate that exposure to early trauma and life stressors is associated with greater difficulties in emotional experiences, behavioral control, executive function, and decision-making, which contribute to behavioral control of alcohol intake, and thus could be one pathway that contributes to early onset of alcohol intake and risk of alcohol and substance use disorders.[12,19] Discussed below are the sex differences and impact of negative affect, mood and anxiety symptoms, and post-traumatic stress disorder (PTSD) and their contribution to development of binge and heavy drinking and AUD in women.

Negative Affect and Alcohol Intake

Negative affect is broadly defined as a state of emotional distress, and is associated with unpleasant feelings, such as anxiety, fear, anger, irritability, and sadness. Repeated and cumulative exposure to stress, trauma, adversity, and maltreatment is associated with greater levels of negative affect, anxiety, and depressed mood. Past literature suggests that women report more negative affect compared to men,[20] and higher negative affect has been linked to greater emotion dysregulation and associated with affective, anxiety, and substance use disorders.[10,21] A previous experimental study exposed healthy social drinkers to emotional stress, alcohol cues, and a control neutral relaxing cue using a personalized guided imagery method that individually calibrates stress imagery so as to

remove any provocation-related bias between men and women.[22] Results indicated that men and women were similar in cue-induced craving ratings. However, women reported greater stress-provoked sadness, anxiety, and body sensations compared to men (see Figure 1). These data indicate sex differences in stress and negative affect responses in women versus men, separate from alcohol motivation.

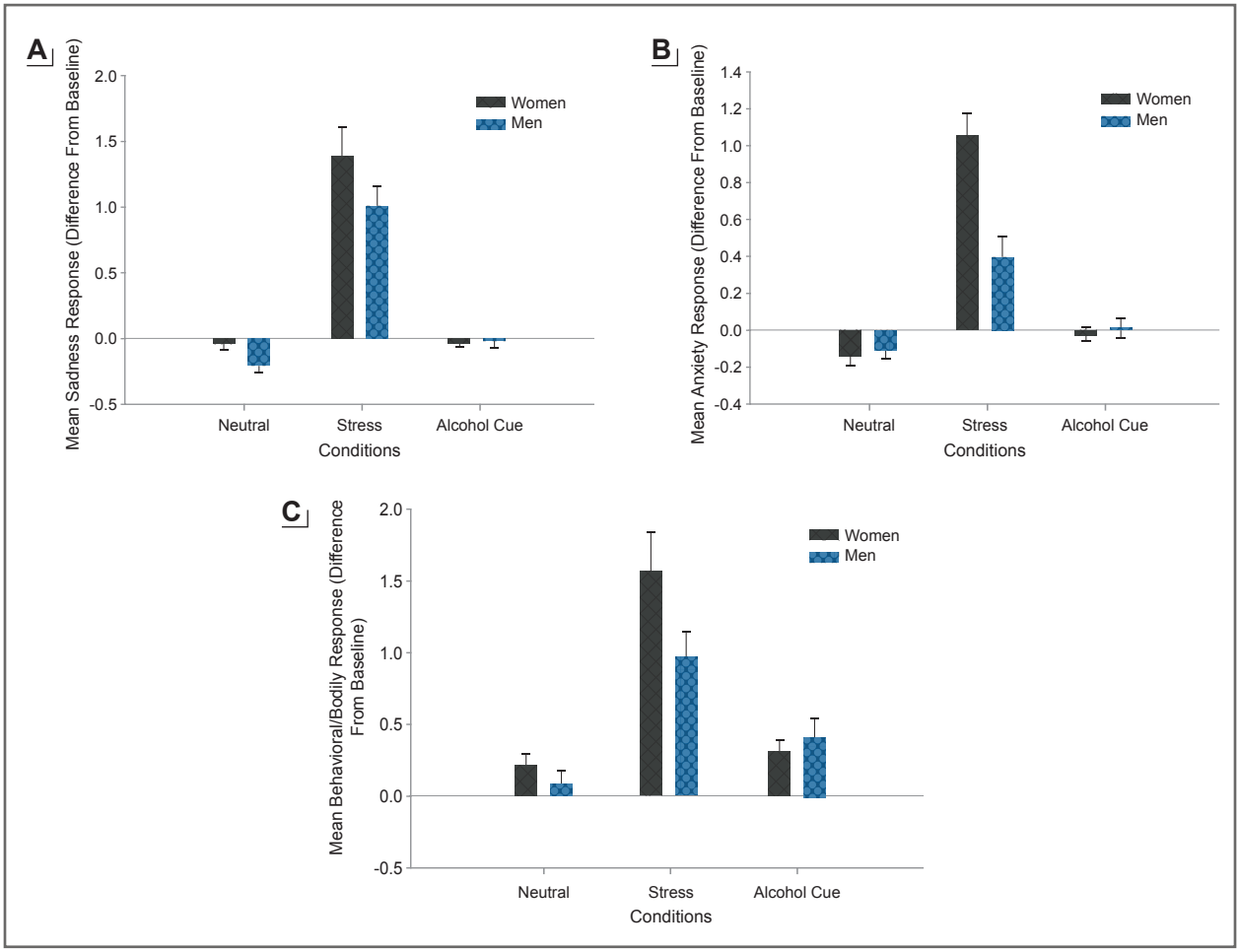

Figure 1 Gender differences in socially drinking volunteers' average subjective responses to individually calibrated exposure to stress, alcohol cue, and neutral-relaxing control provocation conditions, assessed repeatedly over time in an experimental study. *Figure 1a:* Average subjective sadness response over time to neutral, stress, and alcohol cue conditions by gender (in stress: women > men, $p = .01$). *Figure 1b:* Average subjective anxiety response over time to neutral, stress, and alcohol cue conditions by gender (in stress: women > men, $p < .0001$). *Figure 1c:* Average observed nonverbal behavioral and body responses to neutral, stress, and alcohol cue conditions by gender (in stress: women > men, $p = .04$). *Source:* Reproduced with permission from Chaplin et al. 2008.[22] Copyright © 2008 Research Society on Alcoholism and the International Society for Biomedical Research on Alcoholism. Published by Wiley-Blackwell. All rights reserved.

Higher levels of negative affect have specifically been linked to initiation and relapse in alcohol and other substance use disorders.[23] In adolescents, negative affect is strongly associated with the onset of drinking and alcohol misuse, and higher levels of negative affect are also associated with greater child maltreatment, victimization, and adversity.[23] Girls show greater negative affect such as sadness in response to early life stress than boys,[19] similar to findings for adults (and as shown in Figure 1). A number of studies have shown that emotional stress and negative

affect also elicit significant alcohol craving,[10] and negative affect and anxiety are key symptoms of alcohol withdrawal that are further exacerbated by exposure to alcohol cues.[7] Such a link between stress and negative affect and alcohol motivation highlights the need to assess sex differences and women-specific vulnerability in processes underlying the association between stress and negative affect and alcohol intake, alcohol misuse, and risk of AUD.

Negative affect becomes an important component in the development of AUD in women because past literature has documented that, while men tend to consume alcohol to enhance positive feelings,[24] women more frequently consume alcohol in response to negative emotions.[11,25] Much like the association between early trauma and substance use, negative affect, such as temperamental negative mood, has also been associated with the development and maintenance of substance use disorders.[11] Negative emotions, drinking to regulate negative affect, and stress are among the factors associated with increasing rates of AUD in women.[11] Furthermore, studies have also shown that, in addition to trauma, abuse, and chronic stress, negative affect is predictive of alcohol misuse and addiction vulnerability.[10] Thus, temperamental negative emotionality, which is often documented as higher in women and is linked to substance use vulnerability, may place women at a higher risk of subsequent alcohol and substance misuse, but its specific role in women's substance misuse needs further investigation.

Sex Differences in Anxiety and Depression

Gender gaps in rates of mental illnesses tend to emerge and/or widen during puberty and have been associated with the rise of different sex steroid hormones in boys and girls that occurs during this period. Before puberty, boys and girls have similar rates of depression; however, soon after puberty, depression becomes twice as prevalent in girls than in boys until late adulthood.[26] This is also true of other mental conditions such as anxiety disorders.[18] Adult women report more mental health problems than men,[21] with women with AUD reporting greater mental health problems than women without AUD. In fact, affective disorders have been shown to be the most commonly comorbid psychiatric disorders in individuals with substance use disorder, including AUD.[10] Even though there exists a representation and estimation bias of women in epidemiological mental health studies, a better understanding of sex-based differences in mental health is crucial to understanding specific risk factors in the development of AUD in women.

Stress is significantly associated with affective and anxiety disorders, raising the issue of whether these disorders contribute to the association between stress and AUD.[11] Research has shown that individuals with anxiety disorders who reported drinking to cope with their anxiety symptoms drank more alcohol and had a higher rate of DSM-IV alcohol dependence than those who did not report drinking to lessen their symptoms.[27] There are higher rates of AUD in those with PTSD than in those without PTSD,[28] and PTSD precedes AUD more often in women than in men.[29] Both stress and trauma exposure experimentally increase alcohol craving,[30] and women with both PTSD and AUD report higher levels of trauma, anxiety, and mood symptoms than men.[31] Furthermore, studies have found that co-occurring AUD, mood and anxiety disorders, and PTSD are associated with higher relapse rates than AUD without such comorbidity.[32,33] Women present different biological, psychological, and physiological effects of alcohol misuse that are crucial to the maintenance of their alcohol use.[5,11] For this reason, sex differences in mental health not only are relevant in the development of AUD, but also need further consideration, especially with regard to prognosis and treatment outcome. Due to the differential physiological and subjective effects of alcohol use in women,[5] AUD symptoms and progression of disease are accelerated in women, including progression to comorbidities of AUD with other psychopathology such as depression, phobias, and other anxiety and affective illnesses.[11,21]

BIOLOGICAL FACTORS INVOLVED IN THE ONSET AND PREVALENCE OF AUD IN WOMEN

Exposure to stressful and traumatic events as well as chronic adverse environments trigger a biological stress response characterized by neural, physiological (autonomic), hormonal (hypothalamic-pituitary-adrenal [HPA] axis), and immune response changes to support resilient, adaptive coping.[10] However, uncontrollable events, repeated or chronic stress, and trauma disrupt these responses, thereby breaking down the adaptive nature of stress responses.[10] This results in allostasis and maladaptive psychological and behavioral responses that put an individual at risk for neuropsychiatric illnesses, including AUD.[10] Well-documented sex differences start in childhood and continue throughout the life span in these physiological, hormonal, and immune responses, and in the disruption and adaptations that occur as a result of childhood trauma, chronic adversity, and repeated stress experiences.[10,11,21] Findings from the authors of this paper and other studies have shown that repeated stress and childhood trauma result in sex-specific adaptations in the autonomic, HPA axis, and immune responses, which have not been well addressed in the literature on risk of AUD.[10,11] For example, girls and women with childhood maltreatment show a blunted HPA axis stress response,[10] but those without trauma histories and with high negative affect and mood disorders have a hyperreactive HPA axis response to stress.[10] Changes such as a hyporeactive HPA axis response to acute stress are associated with greater risk of alcohol misuse and AUD, as documented in large longitudinal studies tracking adolescents through young adulthood.[14] Thus, these youth may seek out substances to normalize their lower basal level of arousal.

Other studies document the highly sexually dimorphic stress response, represented by girls and women showing a higher autonomic, catecholaminergic, and immune response to stress, whereas boys and men show greater glucocorticoid and HPA axis responses to acute stress.[11] Recent findings also document that increased exposure to childhood victimization results in higher C-reactive protein levels in girls but not boys,[34] suggesting more stress-related immune compromise and susceptibility in girls relative to boys. In addition, the HPA axis and the autonomic pathways—including the sympathetic and parasympathetic components that coordinate the peripheral biological stress response—show significant dysregulation associated with early life trauma as well as childhood maltreatment, with sex differences in the extent and nature of dysregulation.[10,35] However, specific data on sex differences are not entirely clear. Chronic stress and comorbid mood and anxiety disorders are also associated with altered stress responses,[21] with higher stress responses in women with mood disorders and without childhood maltreatment, but also blunted stress responses in women who misuse alcohol or who have AUD.[11,36] These findings highlight that a critical aspect of the biological stress response is the associated plasticity in peripheral and central stress biology associated with repeated stress, trauma, and adversity. The sex-specific nature of the stress response also results in sex-specific adaptations and allostatic responses to repeated or chronic stress, adversity, and early life trauma and maltreatment.[35] The effects on alcohol motivation and intake of such changes in the stress response are discussed below.

Alcohol Effects on Stress, Negative Affect, and Motivation for Drinking

Alcohol consumption dramatically affects human physiology, and repeated high-intensity use and misuse is associated with significant neuroadaptations and breakdown of the brain and peripheral systems that coordinate stress, emotion, and reward regulation.[36] Growing evidence suggests that these adaptations promote a feedforward development of compulsive motivation for alcohol use and misuse.[10,21,33] Not only does alcohol stimulate striatal dopaminergic pathways, but it also directly stimulates the HPA axis and affects glucocorticoid receptors in extrahypothalamic, limbic, forebrain, and medial

prefrontal cortex (mPFC) circuits associated with the development and progression of AUD.[36] Alcohol-associated neuroadaptations in HPA axis responses to stress and alcohol cues may serve as psychobiological markers of the cycle of recurring alcohol consumption.[36] Sex differences in individuals with AUD in the phasic response to stress and in basal tonic levels of HPA axis and the peripheral catecholamines have also been documented.[11] For example, women with AUD show lower tonic adrenocorticotropic hormone (ACTH) levels but higher norepinephrine (NE) levels relative to men, but also higher relative stress-induced ACTH response and more blunted stress-induced NE response relative to men[11] (see Figure 2). Thus, neuroadaptations resulting from alcohol consumption (acute and chronic) may facilitate the risk for AUD susceptibility and maintenance in a sex-specific manner.

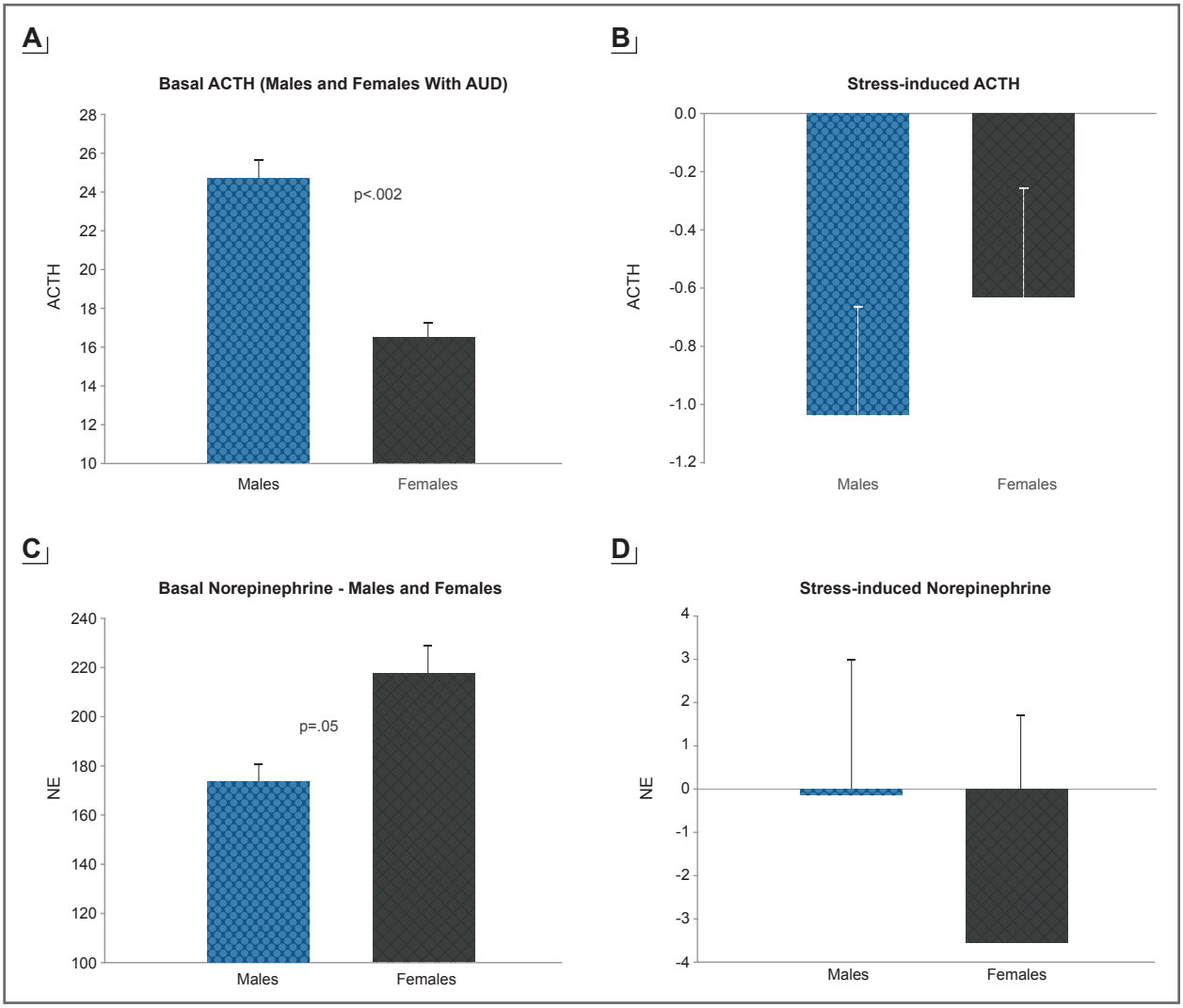

Figure 2 Gender differences in ACTH and NE in men and women with alcohol use disorder (AUD) participating in a laboratory experiment with exposure to individually calibrated stress, alcohol cue, and neutral relaxing imagery on 3 separate days, one condition per day. *Figure 2a and Figure 2b:* ACTH differences between males and females with AUD at baseline (a) and following stress exposure (b) relative to their neutral response. Attenuation of the diurnal drop is shown in females (Stress > Neutral, $p = .0009$) but not in males. *Figure 2c and Figure 2d:* NE differences between males and females with AUD at baseline (a) and following stress exposure (b) relative to their neutral response. Attenuation of the diurnal drop is shown in males, but not in females (Neutral > Stress, $p < .0001$). *Note:* ACTH, adrenocorticotropic hormone; NE, norepinephrine.

Following acute, moderate exposure to alcohol or stress, dopaminergic, hypothalamic autonomic, and catecholaminergic pathways have the opportunity to return to their basal states after activation. With alcohol misuse, binge or heavy drinking, and chronic alcohol use, large-scale adaptations and allostatic overload to neuroendocrine regulation circuits occur. These physiological changes have been associated with the transition from controlled to compulsive alcohol seeking in humans.[36] In fact, in binge and heavy drinkers, a neuroendocrine tolerance to stress and alcohol consumption is observed. For example, a blunted cortisol response to alcohol is observed among individuals with a history of binge or heavy drinking relative to moderate drinkers.[37] This blunted response to alcohol in those with a history of binge or heavy drinking is identified as neuroendocrine tolerance. Recent findings indicate that, in binge or heavy drinkers, blunted cortisol responses and higher subjective craving are each associated with greater amounts of alcohol intake in the laboratory.[37] It is important to note that the sample had a majority of men, and sex differences in these effects have yet to be explored. Thus, although binge and heavy alcohol use and associated adaptations in stress biology appear to be involved in the development of neuroendocrine tolerance and in the resulting increases in compulsive motivation,[36,37] neither sex differences in the alcohol-related neuroendocrine tolerance nor the possible sex differences on its effects on alcohol motivation and intake have been explored thus far.

Alcohol and Stress Interactions on Peripheral and Central Nervous System Responses and Sex Differences

Sex differences have been found in pharmacokinetics and pharmacodynamics of alcohol[38] as well as in neuroanatomy and chemistry.[24] Blood alcohol levels rise faster and stay elevated for longer in women than in men. Sex hormones affect the neural pathways and influence neurotransmitter activity, which affects an individual's physiological and behavioral responses to drugs.[24] For example, even though men show stronger activation of the brain reward system in response to alcohol than do women,[24] the female brain suffers more damage and inflammation from alcohol withdrawal.[39] Important to the current discussion, alcohol stimulates the biological stress pathways in similar ways to psychological stress and trauma.[36] Similarly, significant adaptations and changes occur as a function of repeated and binge alcohol use in these biological stress pathways, and stress and alcohol misuse may act synergistically to modify HPA as well as autonomic and neural responses to stress and alcohol, which may in turn drive greater craving and compulsive seeking for alcohol.[10,36]

A number of studies have linked greater stress reactivity in plasma/salivary cortisol responses as a risk factor for comorbidity of mood disorders and AUD.[40] Research has also shown that blunted salivary cortisol response to stress is a risk factor for AUD development in at-risk children with a family history of substance misuse or substance use disorder.[41] There also may be significant variation in these responses as assessed by concentrations in plasma/serum for ACTH, plasma/serum and saliva for cortisol, salivary alpha-amylase (a measure of autonomic adrenergic arousal), and physiological assessments of heart rate and heart rate variability, as a function of extent of chronic stress or trauma exposure.[10,42] Specifically, one study evaluated at-risk prepubertal boys (ages 10 to 12) with fathers with substance use disorder and found that high-risk boys secreted significantly less salivary cortisol in response to an anticipated stressor compared to controls.[41] These findings were corroborated by another study using a stress task in adolescents, which documented that blunted physiological and emotional responses to stress in adolescents were related to greater risk of alcohol and substance use.[43] In a larger cohort that also evaluated sex differences in adolescents ages 14 to 17 who were prenatally exposed to cocaine relative to nonexposed youth, elevated basal salivary concentrations of cortisol were found in the at-risk group relative to nonexposed youth.[44] In contrast, at-risk youth exhibited a blunted salivary cortisol response to a social stressor compared to controls.[44] Furthermore, sex differences were

found in prediction of future substance use: for girls, self-reported sadness in response to the social stressor predicted future drug use, whereas for boys, blunted salivary alpha-amylase (an autonomic nervous system measure) in response to the same social stressor predicted future drug use.[44] These results suggest that distinct physiological and emotional stress responses among boys and girls are associated with different risk profiles for future drug use.

In another series of studies, impaired neuroendocrine responses to alcohol and to stress have also been associated with an increased motivation for binge or heavy drinking, thereby serving as a potential risk marker for the progression from heavy drinking to DSM-IV alcohol dependence.[45] In a large population-based study where children were followed longitudinally between ages 14 and 20, the age at which the first alcoholic drink was consumed varied as a function of cortisol levels, and blunted cortisol responses to stress were associated with greater risk of alcohol misuse.[46] Furthermore, among heavy- and light-drinking adults who were exposed to an oral alcohol challenge and followed for 6 years, heavy drinkers showed greater sensitivity to stimulating effects and lower sensitivity to the sedative effects of alcohol compared to light drinkers.[45] Moreover, heavy drinkers demonstrated lower salivary cortisol release in response to the alcohol challenge and, 6 years later, presented with a greater number of AUD symptoms than did light drinkers.[45] These findings suggest that alcohol and stress significantly impact the psychological and biological stress responses—altering affect, mood, and anxiety as well as biological stress responses. However, a significant gap remains in understanding sex differences in these effects given that differences by gender have not been well studied in the literature.

One of the effects of acute administration of alcohol is the activation of both reward and stress pathways in the brain. The mesocorticolimbic dopaminergic system, involved in reward processing, is activated alongside the corticotropin-releasing factor (CRF)-HPA axis and the autonomic nervous system pathways involved in stress responses. Activation of these central pathways results in increased levels of ACTH and cortisol, as well as changes in heart rate, blood pressure, and skin conductance responses.[10] Withdrawal and abstinence following chronic alcohol use also are associated with dysfunctional sympathetic and parasympathetic responses, highlighting the effect of alcohol misuse on these peripheral stress pathways; as shown in Figure 2, there are sex differences in these alcohol-related adaptations of the stress pathways.

Even though acute administration of drugs, such as alcohol, may increase mesolimbic dopamine levels, sustained alcohol misuse downregulates the mesolimbic dopamine pathways and thus decreases basal dopamine levels.[10] Using brain imaging, research has shown that there are fewer dopamine D2 receptors and less dopamine transmission in frontal regions and in the ventral striatum area of individuals with AUD during withdrawal.[10] Furthermore, dopamine response to drugs is sex-specific, with men showing greater dopamine release than women.[47] Prolonged exposure to drugs, such as alcohol, results in altered and blunted neurochemical responses to drugs as well as to stress. Behavioral sensitization to drugs and stress can also be observed and is associated with CRF and noradrenergic effects on dopaminergic (and non-dopaminergic) pathways and with synaptic alterations in the ventral tegmental area, amygdala, nucleus accumbens, and mPFC.[10] More importantly, sex differences in both stress and reward circuitry have been reported using functional magnetic resonance imaging (fMRI) research, where responses to stress and to alcohol cues relative to neutral cues show a differential profile in men who drink socially versus women who drink socially[48] (see Figure 3). Furthermore, although striatal activation during alcohol cue exposure was associated with alcohol craving, this effect was seen in men only and not in women, and different prefrontal regions were associated with stress-induced anxiety in men and women (see Figure 4). These data suggest that central brain pathways differentially modulate stress and alcohol motivation responses in men and women who drink socially and point to a significant need to

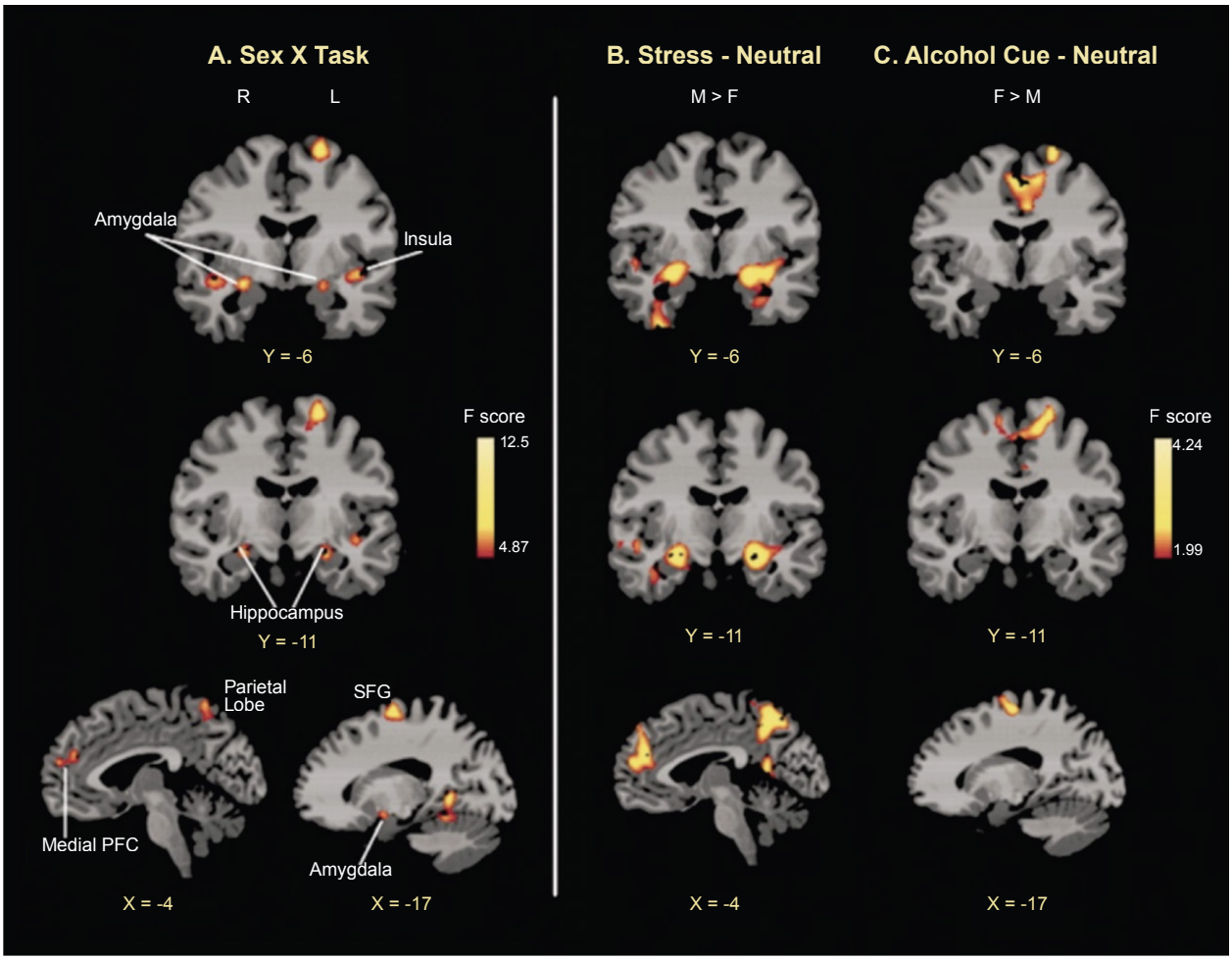

Figure 3 Whole-brain voxel-based functional magnetic resonance imaging (fMRI) showing a sex × condition interaction and corresponding activations in the stress-neutral and alcohol cue-neutral contrasts for males (M) and females (F) who drink socially. **A**: The sex × condition interaction effect was significant in regions of the superior and middle frontal gyrus (SFG/MFG), medial prefrontal cortex (mPFC, dorsomedial and ventromedial), rostral anterior cingulate cortex, emotion limbic regions (posterior insula, putamen, amygdala, hippocampus, and parahippocampal gyrus), temporal lobe, and visuomotor perception areas (parietal lobe, occipital lobe, and cerebellum) ($p < 0.01$ whole-brain familywise error [FWE] rate corrected). To elucidate the source of the interaction, male versus female contrasts were conducted for (**B**) stress relative to neutral, and (**C**) alcohol cue relative to neutral brain responses at the $p < .05$ whole-brain FWE corrected. Significantly, greater M > F stress-induced activity in the mPFC and limbic regions was observed. Alcohol cue-induced activity in the SFG/MFG was significantly higher in women than in men. No differences in F > M for the stress-neutral and in M > F contrast for the alcohol cue-neutral survived whole-brain correction. Coordinates are given in Montreal Neurological Institute space. *Note:* F, female; L, left; M, male; mPFC, medial prefrontal cortex; R, right. *Source:* Reproduced with permission from Seo et al., 2011.[49]

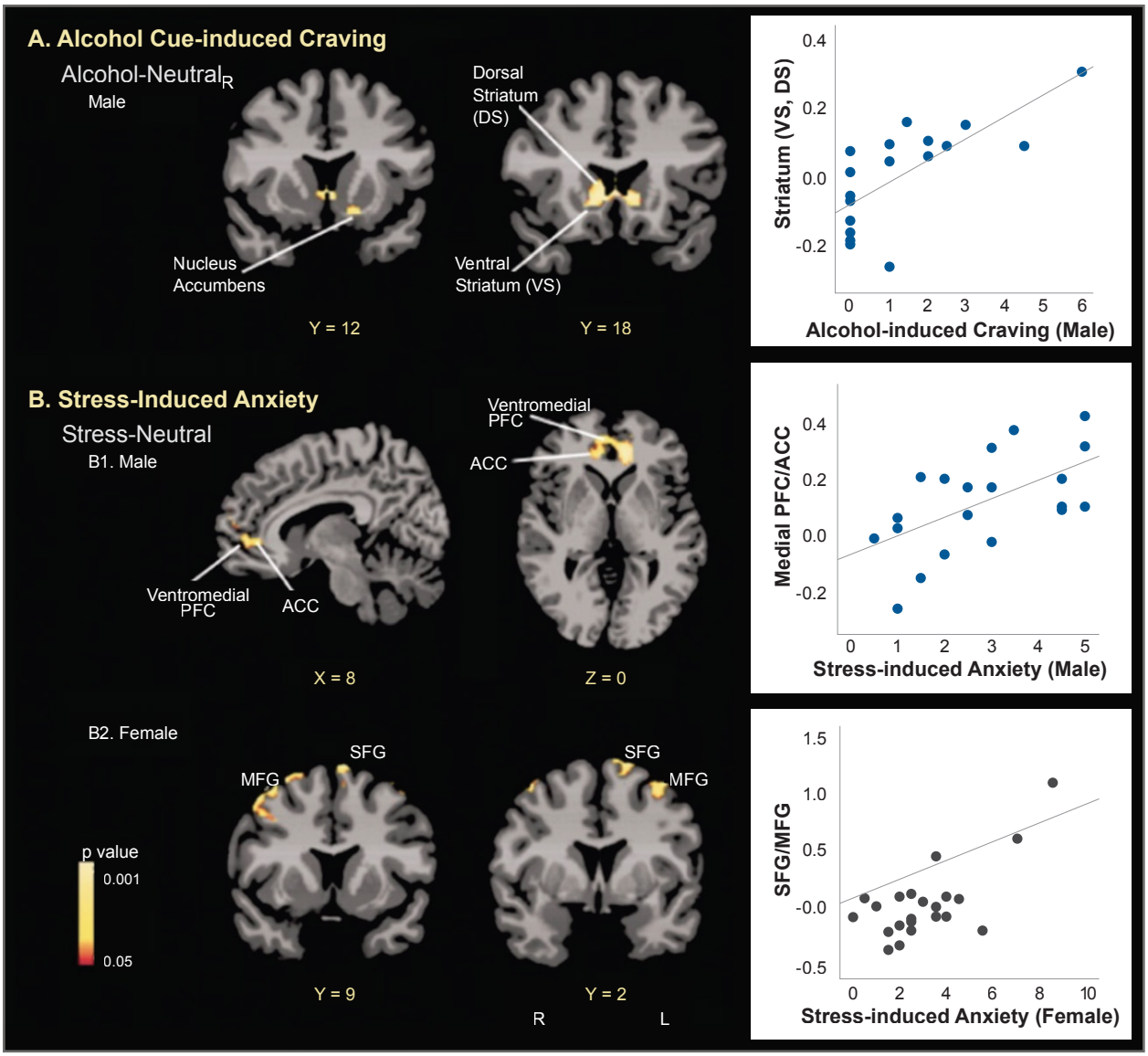

Figure 4 In men and women who drink socially, whole brain voxel-based correlation and corresponding scatter plots for (A) alcohol cue-induced craving ratings with neural responses during alcohol cue versus neutral cue exposure in males as well as (B) stress-induced anxiety ratings with neural response during stress versus neutral cue exposure in males and females ($p < .05$, whole-brain familywise error rate [FWE] corrected). **A**: In males, elevated alcohol craving ratings were associated with increased activity in the striatum cluster ($r = .74$) that encompassed ventral and dorsal striatum, including the left nucleus accumbens (X = −13, Y = 12, Z = −12). **B1**: In males, enhanced stress-induced anxiety ratings were associated with increased brain activity in a medial prefrontal cortex cluster that included the ACC, ventromedial PFC, and medial PFC ($r = .59$). **B2**: In females, stress-induced anxiety ratings were positively correlated with bilateral brain activity in superior/middle frontal gyrus (winsorized $r = 0.62$). Coordinates are given in Montreal Neurological Institute space. *Note:* ACC, anterior cingulated cortex; L, left; MFG, middle frontal gyrus; PFC, prefrontal cortex; R, right; SFG, superior frontal gyrus. *Source:* Reproduced with permission from Seo et al., 2011.[49] Copyright © 2010 Wiley-Liss, Inc. All rights reserved.

understand the neurobiology of binge drinking and chronic alcohol misuse in women.

STRESS NEUROCIRCUITRY, EMOTION REGULATION, AND ALCOHOL CRAVING

Previous human research indicates that trauma, adversity, and chronic stress alter the activity and structure of the prefrontal cortical, limbic, and striatal brain networks involved in regulating stress and emotions as well as reward and higher cognitive or executive control functions.[10] These brain circuits also show significant sexual dimorphism, suggesting a need to explore the role of sex differences in their structure and function in critical regulation and coping functions for stress, trauma, and self-control over alcohol intake. These functions can include the regulation of distress and emotions, such as controlling and inhibiting impulses, refocusing and shifting attention, employing working memory, monitoring conflict and behavior, linking behaviors to possible future consequences, and demonstrating flexible consideration of alternatives for response selection and decision-making.[10]

Recent evidence from human brain structural and magnetic resonance imaging shows that recent life stressors (e.g., death in family, divorce, relationships ending, being assaulted, financial crises, robberies), trauma (physical, emotional, or sexual abuse), and chronic stress (subjective experience of continual stressors or ongoing life problems) are associated with lower gray matter volume in medial prefrontal, amygdala, hippocampus, and insula regions of the brain.[50,51] Similarly, recent life stress and acute stress exposure (such as those listed above) may decrease responses in the prefrontal regions (such as the dorsolateral prefrontal cortex and ventromedial prefrontal cortex) associated with working memory, reward processing, and resilient coping.[52] Such changes in the neural circuits underlying emotion and reward dysregulation may promote risky alcohol use (e.g., binge drinking), emotional eating, and frequency of arguments and fights.[52] Furthermore, these circuits are sexually dimorphic in their responses to stress and anxiety, where differential brain regions are associated with stress-induced anxiety in men versus women[52] (see Figure 5). As anxiety and stress responses are associated with alcohol motivation and increased alcohol use, sex differences in the neurocircuits that respond to and regulate stress and anxiety suggest that there are also sex differences in the brain regions that drive stress-induced alcohol craving and intake. However, there is a need for examining this association in a sex-specific manner in future research.

Across at-risk children and adults with exposure to stress, trauma, or in utero substance use, sex-specific brain changes in emotion and reward regions are associated with risk of alcohol misuse and AUD.[53] A study of prenatally cocaine-exposed and non-exposed adolescents (ages 14 to 17) found lower gray matter volume in limbic and frontal regions of the brain as assessed by MRI and whole-brain voxel-based morphometry in the at-risk prenatally exposed relative to non–cocaine-exposed adolescent controls.[53] In addition, lower gray matter volume in these brain regions was associated with initiation of tobacco, alcohol, and cannabis use.[53] Furthermore, sex-specific effects were found in adults who misuse cocaine and alcohol, with women showing lower gray matter volume in emotional-limbic regions of the insula, amygdala, and hippocampus, and men showing lower gray matter volume in the midcingulate and frontal regions.[54] These data suggest that changes in brain volume may serve as biological risk markers for alcohol misuse, AUD, and substance use. Indeed, low behavioral and cognitive control are linked to lower prefrontal and insular cortex volume, and high activation of limbic-emotional and striatal-motivation brain regions under stress suggest one specific pattern underlying risk of addictive behaviors where there is a decreased ability to control rewarding behaviors.[10] Thus, cortico-striatal reward and motivational brain pathways appear to be key targets of disrupted

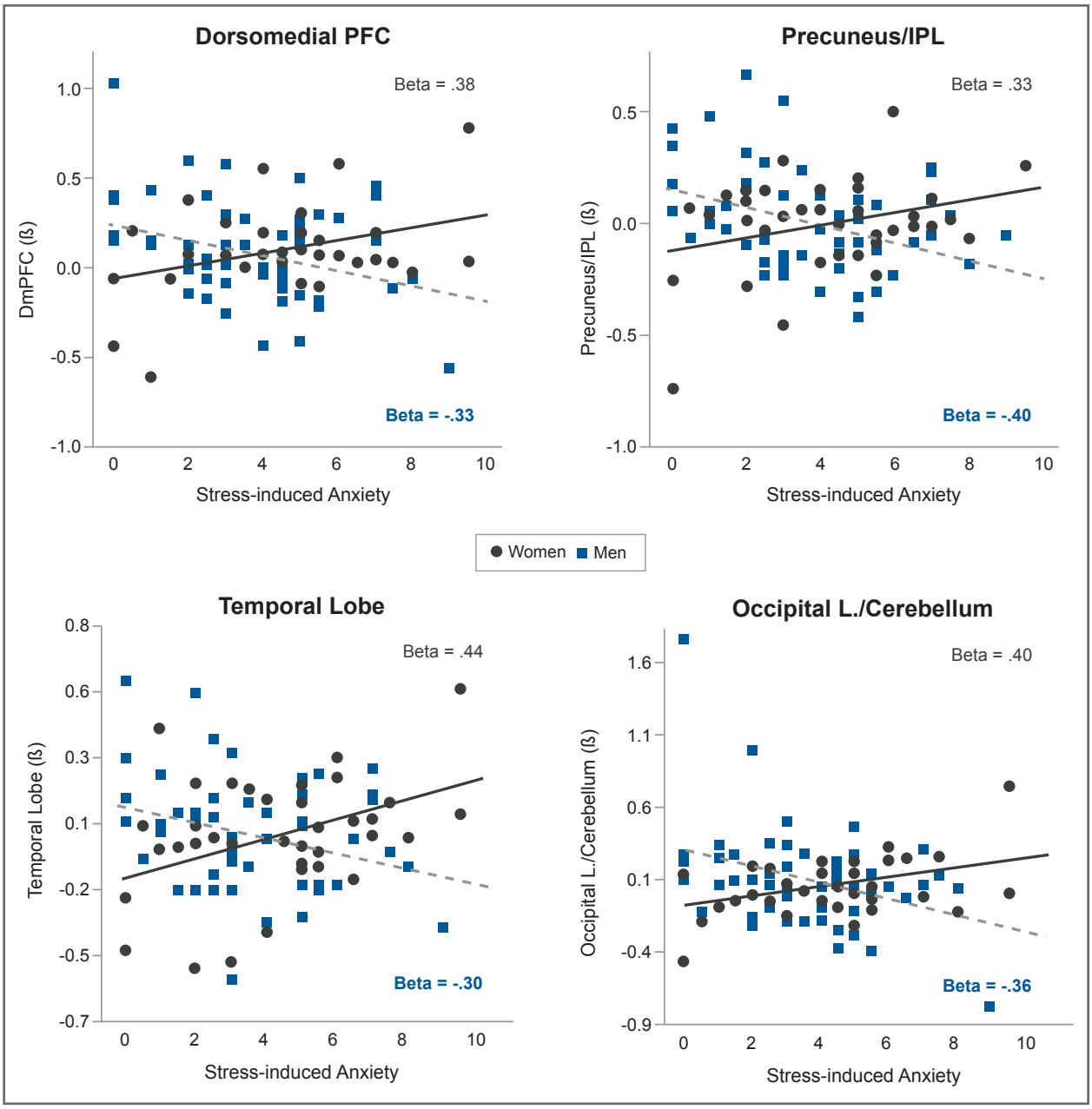

Figure 5 Scatter plots and regression lines for stress-induced anxiety ratings with neural responses during stress relative to neutral-relaxing exposure for specific regions of interest (ROIs). Simple effects in ROIs from whole-brain regression of significant regions from the gender-by-anxiety interaction effects analyses are shown separately in men and women. Stress-induced anxiety predicted brain responses to stress differentially by gender. The plots show (A) positive (women [W]) and negative (men [M]) associations between stress-induced anxiety ratings and activity in the dorsomedial prefrontal cortex (PFC) (W: β = .38; M: β = −.33), precuneus and inferior parietal lobe (W: β = .33; M: β = −.40), middle/inferior temporal gyrus (W: β = .44; M: β = −.30), and occipital lobe and cerebellum (W: β = .40; M: β = −.36). Beta (β) indicates the standardized coefficient. There were no outliers in any of these brain regions for both men and women. *Note:* DmPFC, dorsomedial prefrontal cortex; IPL, inferior parietal lobe; Occipital L., occipital lobe. *Source:* Reproduced with permission from Seo et al., 2017.[48] Copyright © 1999-2020 Wiley-Liss, Inc. All rights reserved.

central stress and emotional responses, suggesting a potentially important sex-specific mechanism by which stress may affect susceptibility to alcohol misuse and AUD vulnerability. As these pathways are sex-specific, the stress- and alcohol-related adaptations also occur in a sex-specific manner, resulting in sex differences in the biological pathways of risk for AUD. However, there is a desperate need for research to elucidate these sex-specific changes and risk factors for AUD.

TRANSITION TO ADDICTION

Women report different motives for alcohol use than men,[10,11] and are more likely to self-medicate their emotional distress, negative affect stemming from high stress, and mood and anxiety disorders.[10,11] As outlined above, sex differences in addiction vulnerabilities set women at a disadvantage related to exposure to and risk of alcohol misuse, maintenance, and relapse.[11] As described in the previous sections, some research has documented sex-based differences in neuroendocrine stress and reward pathways with chronic alcohol use.[11]

The cross-sensitization process of stress and alcohol effects suggests that sex-specific adaptations occur with alcohol misuse and chronic use, which may contribute to alcohol craving, continued use, and relapse. The progression from alcohol misuse to AUD often includes overpowering cravings seen as a physiological need rather than a hedonic desire.[10] This craving is associated with compulsive seeking of alcohol, which becomes stronger in the context of alcohol cues or stress exposure, increasing the chances of relapse. Sex differences in stress assessment and cue reactivity in social drinkers and in patients with AUD have been reported. For example, findings in social drinkers indicate that the incentive value of alcohol may be less sensitized by negative mood and stress in female social drinkers compared with male social drinkers.[55,56] However, findings show that, compared to men with AUD, women with AUD demonstrate greater alcohol cue reactivity following negative mood induction.[57] Furthermore, HPA-axis hyporeactivity to social stress, alcohol cue exposure, and alcohol intake, as well as a blunted cortisol response to stress in women with AUD have been reported concurrently with enhanced emotional distress and greater craving, which, in turn, have been shown to increase the risk of relapse and return to alcohol use in early treatment.[11] Although conducted using separate stress- and cue-reactivity paradigms, this research consistently reflects robust sex-specific dissociations between participants with and without AUD in relation to stress system function and alcohol cue reactivity, supporting the notion that there are sex differences in the mechanisms that drive the transition to AUD, its maintenance, and the relapse to alcohol use. However, the specific link between the robust sex-specific stress and cue reactivity responses and actual binge and heavy alcohol intake in women are not clear and needs greater study in future research.

IMPLICATIONS FOR ONSET AND MAINTENANCE OF AUD IN WOMEN AND FUTURE DIRECTIONS

Sex differences in the onset of alcohol misuse and the development of AUD have been reported. The effects of greater exposure to and experience of stress, trauma, victimization, negative affect, and mood and anxiety disorders in women represent a specific risk pathway for the onset and development of AUD in women. However, estimation bias in occurrence of mood and anxiety disorders needs specific consideration in assessing these associations to alcohol misuse and AUD. Also, although this paper has not focused on genetic mechanisms and epidemiological and sociocultural factors that may explain sex differences, these areas also need further attention. Nonetheless, sex differences in the psychological and biological response to both stress and alcohol intake are well known. Animal studies have revealed that sex steroid hormones interact with

the HPA axis to influence stress regulation, and these sex hormones also modulate brain limbic, striatal, and frontal circuits to influence alcohol seeking in sex-specific ways.[11] However, research in humans assessing interactions between stress, reward, and sex steroid hormones has lagged behind. For example, fluctuations in sex hormones across the menstrual cycle may impact neuroadaptations in stress response and alcohol craving[11] as described below, and, in doing so, may point to specific prevention and treatment efforts.

Although not specifically examined in risk of AUD or in women with AUD, some evidence in other substance use disorders indicates that during the follicular phase of the menstrual cycle, positive rewarding drug effects may be potentiated in women to the same levels as men.[11] Similarly, increased levels of progesterone and decreased estrogen/progesterone ratio have been shown in women who misuse substances relative to healthy controls.[11] Such changes across the menstrual cycle may then alter brain responses to stress and cues as well as affect intensity of emotional responses and craving states in women with AUD relative to men with AUD.[11] As the hypothalamic-pituitary gonadal (HPG) axis modulates sex steroid levels during the menstrual cycle and influences stress responses in women, adaptations in the HPG and HPA axes with the transition to AUD may lead to altered levels of estrogen, progesterone, and their related neuroactive steroids. This could further predispose women to increased anxiety, negative emotion, and lowered tolerance to stress, which in turn may increase vulnerability to craving and compulsive alcohol use in women.

At a time when alcohol misuse is on the rise among girls, and binge drinking and AUD rates have substantially increased in women, there is a major gap in understanding the mechanisms and processes that specifically increase risks for the onset and development of AUD in girls and women and for the maintenance of AUD in women. Greater specific, targeted future research on risk pathways for girls and women can address the need for focused development of targeted prevention and early treatment efforts in females. Prevention and early treatment may reduce the prevalence rates of AUD—as well as the much higher rates of alcohol-related health problems and morbidity in women compared to men—and such efforts may increase alcohol recovery rates among women.

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Alcohol Screening, Brief Intervention, and Referral to Treatment (SBIRT) for Girls and Women

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Females ages 12 and older are the fastest growing segment of alcohol consumers in the United States, with the past decade showing a 16% increase in alcohol use per 12-month period and a 58% increase in high-risk drinking (i.e., > 3 drinks in a day and/or > 7 drinks in a week) per 12-month period. The increase in alcohol use and risk drinking poses unique and serious consequences for women. Women have a more rapid progression to alcohol-related problems and alcohol use disorders (AUD) than men, and if pregnant, women can potentially expose the fetus to alcohol. Screening, brief intervention, and referral to treatment (SBIRT) is an evidence-based, integrated public health approach used to identify and address risky alcohol use among women in a variety of health and social service settings. This article presents the current status of SBIRT among girls ages 12 and older, women of childbearing age, and older women. Screening instruments, brief interventions, and implementation issues specific to women of all ages are described. Through this review of the current literature, care providers can determine best practices for the prevention and treatment of risk drinking in women of all ages presenting in health care settings.

KEY WORDS: brief intervention; risk; alcohol; SBIRT; screening; women; female adolescents

INTRODUCTION

Alcohol is the most commonly consumed substance among Americans ages 12 and older, and women are the fastest growing segment of alcohol consumers in the United States.[1,2] Female alcohol consumption that meets criteria for risk drinking, defined as more than three drinks in a single day or more than seven drinks per week, has the potential to negatively affect the health and well-being of women across their life spans.[3] Evidence indicates converging patterns of alcohol consumption between men and women resulting from recent increases in female alcohol

use behaviors.[2,4,5] For instance, data collected in the past decade reveal that among U.S. women, alcohol use increased by 16% per 12-month period, high-risk drinking increased by 58% per 12-month period, and diagnoses of alcohol use disorder (AUD)—as defined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*—increased by 84% per 12-month period.[2] These increases have unique and serious consequences for women given that they experience a more rapid progression—at lower consumption levels—to alcohol-related problems and AUD than men.[6,7]

This recent increase in female alcohol consumption underlines a need for additional research and clinical efforts to address alcohol use among girls and women.[2,4] Because risky drinking poses unique and detrimental consequences to all women, age and life circumstances should not preclude any subset of girls or women from research or clinical efforts to address this growing public health concern. Indeed, risky alcohol use is prevalent among young girls;[8,9] pregnant and postpartum women;[10,11] victims of child abuse,[12] sexual trauma,[13] and intimate partner violence;[14] female veterans;[15] incarcerated girls and women;[16] sexual-minority women;[17] and older women.[5] Due to alcohol's nondiscriminatory nature towards varying groups of women, universal screening, brief intervention, and referral to treatment (SBIRT) appears to be an appropriate, evidence-based public health approach capable of identifying and addressing risky alcohol use among females in a variety of health and social service settings.[18] This article presents a review of the literature regarding the role of SBIRT in addressing risky alcohol consumption among girls (ages 12 to 18), women of childbearing age (i.e., ages 18 to 44), and older women (i.e., ages 65 and older). There is a general lack of currently available research data specific to women ages 45 to 64, but other than risk of pregnancy associated with women ages 18 to 44, the role of SBIRT is similar for women ages 45 to 64 to that for younger women. Databases used for this review include PubMed, Cochrane Library, Google Scholar, and Academic Search Complete. The reference lists of selected articles and texts were also explored.

SBIRT

The current SBIRT model is based on a recommendation from the National Academy of Medicine (previously called the Institute of Medicine) to develop integrated service systems that bridge the gap between primary prevention and treatment services for individuals with problematic alcohol and/or illicit drug use.[19] In 2003, the Substance Abuse and Mental Health Services Administration (SAMHSA) established an initial SBIRT grant program, with the intent of integrating behavioral health services into settings where individuals who engaged in risky substance use behaviors could be identified and offered an appropriate level of intervention and care.[20] Findings from this initiative suggest that SBIRT is associated with improvements in alcohol use outcomes.[20,21]

The U.S. Preventive Services Task Force (USPSTF), an independent entity consisting of experts in preventive medicine, recently updated its recommendation for care providers. This update recommends that care providers screen all adults ages 18 and older, including pregnant women, for risky alcohol use and provide brief behavioral counseling interventions, when appropriate, to reduce unhealthy alcohol use.[22] Screening adolescents younger than age 18 was not included in the updated recommendation; the USPSTF concluded that there is insufficient evidence to properly assess the benefits versus risks for alcohol screening and brief interventions (BI).[22] The American Academy of Pediatrics (AAP), however, has recommended the practice of screening and providing BI to adolescent alcohol users, citing low cost, minimal potential for harm, and emerging evidence of the benefit that SBIRT may have among adolescent alcohol users.[23]

SBIRT is intended to identify, reduce, and prevent problematic alcohol use behaviors and is made up of three key components: screening, brief intervention, and referral to treatment. Ideally, the first step of the SBIRT process is to administer a validated prescreen

instrument to all presenting individuals in a practice setting, as part of the routine intake procedure, to identify those who are drinking at or above risky levels.[24,25,26] When prescreen instruments detect consumption at risk levels, measured by standard drinks (14 grams or 0.6 fluid ounces of pure alcohol) consumed, a more comprehensive assessment can be conducted to gauge the severity of alcohol use and inform BI and/or treatment options.[3] For example, the National Council for Behavioral Health recommends that a symptom checklist or other validated assessment be used to obtain alcohol-related symptoms from individuals whose prescreen indicates risky consumption.[26] If it is determined that an individual is consuming alcohol at moderate risk levels (i.e., above NIAAA threshold for low-risk consumption but not at a level indicative of AUD), then the second step in the SBIRT process is to complete a BI protocol. BIs are often based on principles of motivational interviewing (MI) and aim to increase awareness of alcohol-related risks and consequences and to encourage motivation for change. If an individual is identified to be drinking at levels that are suggestive of AUD, then referral to specialized treatment for further assessment and care is recommended.[27]

SCREENING

SBIRT begins with universal screening, the goal of which is to identify individuals who have, or are at risk of developing, alcohol-related problems.[27] Universal screening that is adherent to SBIRT standards, and described in multiple SBIRT practice guides, involves the administration of a validated prescreen instrument that has been limited to a few questions needing only simple responses.[24,26,28,29] Ideal screening instruments have high sensitivity and specificity ratings, with cutoff scores designed to maximize both ratings in order to minimize false positives and false negatives.[30] However, for prescreen instruments that are intended to be universally administered, priority is often given to sensitivity over specificity so that individuals in large clinical populations (e.g., women in primary or reproductive care settings who consume alcohol while pregnant) are appropriately identified for further assessment.[30,31]

This article classifies screening instruments into prescreen and screen categories. The purpose of prescreening is to assess an individual's frequency and quantity of alcohol use to determine whether the person is drinking at age-specific risk levels, whereas the purpose of screening is to elicit alcohol-related symptoms from those that have been identified as drinking at risk levels. Prescreens and screens should work in succession, and because many instruments are capable of serving both screening purposes, this dual process is sometimes consolidated into a single step within clinical practice settings.

Universal prescreening and screening efforts must be conducted using valid, age-appropriate instruments with cutoff scores that are tailored to a population's sex and age (see Table 1).[32] Following is an overview of screening practices and instruments that have been validated for use within specified age groups of girls and women.

Adolescents

NIAAA, SAMHSA, and AAP recommend that care providers screen all adolescents and young adults ages 12 to 21 for alcohol and substance use behaviors using validated screening instruments on a yearly basis and, as needed, during acute care visits.[33] There are currently three prescreen options that are applicable to adolescents: the two age-specific questions found in NIAAA's *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*;[29] the first three questions of the Screening to Brief Intervention (S2BI); and the three-item Alcohol Use Disorders Identification Test–Concise (AUDIT-C).[33] The two age-specific questions found within NIAAA's guide ask about an adolescent's personal alcohol use as well as that of their friends and is appropriate for children and adolescents between the ages of 9 and 18. This AAP-endorsed guide includes elementary, middle, and high school age-appropriate variations of these two questions, which allow for accurate correlation of patient responses to current or potential risky alcohol consumption.[29] The S2BI instrument screens

for alcohol, tobacco, marijuana, and illicit drug use by asking a single frequency-of-use question per substance. This screener is highly sensitive and specific at discerning among various risk categories, from no use to severe substance use disorder (SUD). Although not a formal diagnostic instrument, the S2BI has been shown to closely correspond with the likelihood of current SUD.[34] The AUDIT-C, validated for use with young people ages 12 to 19, has three questions to identify the quantity and frequency of alcohol consumption.[32,35,36]

When adolescents score positive on a prescreen instrument, indicating some level of risky alcohol consumption, they are asked to respond to additional, more specific screening questions to determine whether a BI or referral to treatment is appropriate. Screening instruments that have been validated for use with adolescents and can be used to inform next steps include the 10-item Alcohol Use Disorders Identification Test (AUDIT); the Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD); and the Car, Relax, Alone, Forget, Friends, Trouble (CRAFFT) screening instrument.[23,32,37] The AUDIT is the most widely tested alcohol screening instrument and is commonly used to assist in the early identification of individuals engaging in risky drinking behaviors.[22] Furthermore, the AUDIT has been validated for use among young people,and evidence suggests a lack of gender bias between female and male adolescents.[32,35] The BSTAD, an adaptation of the questions found within NIAAA's guide includes questions on alcohol, tobacco, and drugs, and has been shown to be highly sensitive and specific at identifying risky past-year alcohol use among adolescents ages 12 to 17.[38] Recommended by both NIAAA and AAP, the CRAFFT has been validated across pediatric settings to identify risky substance use behaviors among adolescents.[18,39] Interestingly, the CRAFFT was able to detect preconception substance use in a small cohort of pregnant adolescents and young women between ages 17 and 25.[33,40] The CRAFFT has many advantages, including a short administration time and high sensitivity and specificity.[33] It also shows no evidence of gender bias.[36]

Screening adolescents for risky alcohol use can be incorporated into psychosocial approaches. For example, the home environment, education and employment, eating, peer-related activities, drugs, sexuality, suicide/depression, and safety from injury and violence (HEEADSSS) and the strengths, school, home, activities, drugs/substance use, emotions/depression, sexuality, safety (SSHADESS) tools are interview frameworks specifically designed for use with adolescents in health care settings.[23,33] The HEEADSSS interview is a practical, complementary strategy that establishes rapport by asking less threatening questions at the beginning of the encounter before transitioning to more personal or potentially intrusive topics such as substance use.[33] The SSHADESS interview covers the same life areas as the HEEADSSS, but it also underscores adolescents' resiliency by identifying their perceived and realized strengths before asking questions related to environmental context or risky behaviors.[23]

A caveat is that an assurance of confidentiality is needed to improve the accuracy of adolescent screening responses. Because most adolescents are not comfortable discussing topics like alcohol use and sexual activity in the presence of a parent or guardian, clinicians are encouraged to create scripts or other procedures to excuse the accompanying adult from a portion of the health exam.[33] For example, asking the adult to leave the room during the physical exam portion validates the adolescent's developmental need for privacy and creates space for a confidential discussion concerning alcohol and other potentially risky behaviors.[33] Federal and state privacy laws entitle adolescents to privacy regarding substance use treatment, so adolescents may further benefit from a script ensuring that what is disclosed to the provider will not be shared with their caregiver unless an immediate risk of injury to oneself or another is divulged.[33]

Women of Childbearing Age

For women of childbearing age, the USPSTF supports the use of brief prescreening instruments for alcohol with 1 to 3 items—such as the

AUDIT-C or the NIAAA-recommended Single Alcohol Screening Question (SASQ), also referred to as the "single binge drinking question"—to quickly identify women who may be at risk.[22,41,42] The use of a single binge drinking question has also been recommended as a first step to effectively and efficiently identify women who are likely to be at risk of an alcohol-exposed pregnancy (AEP).[43] For example, a single binge drinking question was found to correctly identify 99% of women, from two countries and cultures, who had been identified as at risk of an AEP.[43] The Quick Drinking Screen (QDS) is another brief instrument that is efficacious at initially identifying women at risk of an AEP.[44] Items from the QDS were measured against data collected from a 90-day timeline followback (TLFB) assessment among a sample of women already determined to be at risk of an AEP. The results found that the women's answers to QDS items were highly similar to their 90-day TLFB responses.[43]

Once a brief prescreening measure identifies a woman who is likely to be at risk for alcohol misuse and/or an AEP, it is recommended that a more comprehensive instrument be administered.[22,43] For example, the 10-item AUDIT is an efficacious measure that has been validated for use with this population.[45] There are also several assessments designed specifically for women of childbearing age, including pregnant women and women at risk of an AEP. It is recommended that universal prescreening among women of childbearing age be used to identify and assess women at risk of an AEP.[45,46] Screening this population provides the opportunity for early intervention among women who may have consumed alcohol prior to becoming aware of their pregnancy. Screening also alerts care providers of consumption levels indicative of AUD so that they can refer these women for specialized treatment.

The Tolerance, Annoyed, Cut Down, Eye-Opener (T-ACE) questionnaire was the first validated screening instrument developed to identify drinking among pregnant women. It is often used in reproductive settings, including maternity care and gynecological clinics.[25,31] In comparison to the AUDIT, the four-item T-ACE has shown slightly higher sensitivity at detecting current alcohol consumption among pregnant women.[31] In addition, the T-ACE accurately identifies varying levels of alcohol consumption and is acceptable for use among culturally diverse obstetric populations.[31] The five-item Tolerance, Worried, Eye-Opener, Amnesia, K/Cut Down (TWEAK) screening instrument is another validated questionnaire for identifying drinking among women, including those who are pregnant and those at risk of an AEP.[25,31,45] Although the TWEAK questionnaire appears to be highly sensitive at identifying heavy patterns of alcohol consumption, primarily among white women, it is less sensitive at detecting lower levels of drinking that could still be considered at risk.[25,47]

In addition to the T-ACE and TWEAK, the USPSTF also recommends the Normal Drinker, Eye-Opener, Tolerance (NET), and the Parents, Partner, Past, Present Pregnancy (4P's Plus) as screening measures capable of assessing alcohol use among pregnant women.[22,47,48] Nonetheless, the T-ACE and TWEAK reportedly perform best among pregnant women and do not appear to have a significant advantage over one another, because both are well-validated screening measures that can be quickly administered in a variety of women's health settings.[18]

Older Women

Older women are often missed by screening efforts because their alcohol-related symptoms are often mistaken for signs of aging.[49] For this reason, systems must be put into place to ensure universal screening on a recurring basis in settings that care for older women.[50] Alcohol screening should take place any time new mental or physical health symptoms arise, before prescribing a new medication, in response to major life changes (e.g., retirement, death of a spouse), and on a yearly basis as part of routine physical and mental health services.[50,51] Providers should be aware that a history of risky alcohol use among older adults often predicts future increases in drinking.[50] Prescreening questions like "During your lifetime,

have you ever used alcohol?" followed by "During the past year, have you had four or more drinks on a single occasion?" help to determine whether more comprehensive assessments are warranted.[51,52] The AUDIT-C and the two-item Substance Use Brief Screen (SUBS) are also prescreen options available for use with this population.[53-55]

Several screening instruments have been validated for use with older adults. Measures like the AUDIT include screening questions on lifetime problems to assess current alcohol-related risk.[54,56] Other screening tools include the Cut Down, Annoyed, Guilty, Eye-Opener (CAGE), the Michigan Alcoholism Screening Test—Geriatric Version (MAST-G), the Short MAST-G, and the Comorbidity Alcohol Risk Evaluation Tool (CARET).[54,57] All of these instruments gather information about the level of consumption and offer decision support for care providers.[50,54] In general, alcohol screening and assessment instruments among older women should contain questions about the frequency and quantity of alcohol use, experiences with drinking-related consequences, medication use, and feelings of depression.[50]

SCREENING RECOMMENDATIONS

There are very few studies on alcohol screening specific to adolescent females and older adult females beyond childbearing age, with a majority of information coming from mixed-gender studies. The largest body of evidence on screening women is for those of childbearing age, likely due to the added risks and harms associated with prenatal alcohol exposure. Nonetheless, universal screening should begin in early adolescence and be repeated at regular intervals across settings that provide health care and social services to girls and women. However, although alcohol screening instruments elicit important information about an individual's level of risk and alcohol-related symptoms, these tools are not a replacement for a complete substance use assessment. Because these instruments are brief and, in many cases, can be self-administered, it is often recommended that care providers use them as decision support aids to guide additional steps based on the preliminary level of risk indicated by these alcohol screening instruments.

The successful implementation of a screening protocol depends on the setting in which it is delivered. For example, settings with access to interdisciplinary professionals may find that longer, more thorough assessment instruments are practical, whereas settings with fewer resources are likely to benefit from utilizing brief instruments like the AUDIT, which has been validated for use across age groups.[32,35,56] Additionally, questions or measures may be added to assessment protocols to identify other factors known to be associated with female alcohol use behaviors (e.g., age of onset, depression and anxiety, childhood and/or intimate partner abuse, co-occurring substance use behaviors) to better inform BI and referral to treatment practices.[13,16,58,59] Moreover, care providers need to remain mindful regarding the language they use to describe alcohol-related concerns so as not to further stigmatize female populations.[60] For example, some women may be sensitive to language such as "alcoholic," "addict," or "abuser"; the use of such language may dissuade women from providing relevant information pertaining to their alcohol use behaviors. Therefore, care providers are advised to use medically accurate terms throughout their discussions regarding alcohol and substance use behaviors.[55,60]

BRIEF INTERVENTIONS

BIs are evidence-based practices that are short, targeted conversations between women and clinicians that follow screening results indicative of risky alcohol consumption. The overall goal of BIs is to help adolescent girls and women who are at risk of alcohol-related consequences by increasing their awareness about the ways alcohol use may put them at risk and encouraging their self-motivation for change.[27,61] Common components of BIs include conversations on standard drink sizes, low- versus high-risk drinking limits, and potential health effects and

social consequences of drinking.[3,62] Another common element of BIs is providing personalized normative feedback, with evidence supporting the use of gender-specific feedback for women.[63,64,65] BIs can be delivered by professionals with different backgrounds and expertise, and they can take place in face-to-face settings, over the phone, or through electronic means.[61,66] How effective BIs are can depend on the number of sessions and length of time allotted for each session. For example, systematic reviews and meta-analyses have found that very brief (i.e., ≤ 5 min) and brief single-contact interventions (i.e., 6 to 15 min) tend to be less effective than brief multicontact interventions (i.e., each contact ≤ 15 min), which evidence shows is the most effective across populations and outcomes.[18,63,67] Additionally, one meta-analysis found that extended BIs (defined by the author as BIs that required several visits, or multicontact interventions) resulted in significant change in alcohol consumption for women but not men.[68]

BIs for risky alcohol use are often based on the principles of MI. Using this collaborative, client-centered approach, providers help females explore and resolve their ambivalence toward changing unhealthy behaviors (e.g., alcohol consumption at risk levels).[69] A core tenet of MI is the use of nonconfrontational techniques to allow individuals to guide themselves toward change without feeling the need to defend their choices.[69]

Adolescents

AAP recommends basing the degree of intervention delivery for youth on the level of risk identified at the time of screening. When no alcohol use is reported, clinicians are encouraged to provide positive verbal reinforcements to motivate continued abstinence. Evidence suggests that even a few positive words from a health care provider may delay alcohol use initiation, and thus extend time for adolescent brain maturation.[23] These positive reinforcements may be critical for female adolescents to receive, especially girls at risk of early alcohol initiation,[7,58] because of the detrimental effects of alcohol on the female developing brain.[70] When infrequent alcohol use is endorsed by female adolescents, such as when an S2BI result indicates alcohol use of one to two times the previous year, it is recommended that care providers advise adolescents to abstain. This advice may combine information on negative health consequences with recognition of personal strengths and positive attributes.[23]

BIs are recommended when an adolescent screens positive for drinking at risky levels. Evidence from a recent meta-analysis of 185 studies examining the effects of alcohol-related BIs for adolescents and young adults found that the interventions effectively reduced drinking and alcohol-related consequences, with effects lasting up to 1 year and showing no demographic variance.[65]

BIs that utilize MI have been found to be effective with substance-using adolescent populations. Much of the research supporting this view falls into the harm-reduction continuum: that is, adolescents do not move directly into abstinence but rather gradually decrease their risky behavior.[71,72] In addition to the effectiveness of MI techniques within this population, a systematic review and meta-analysis conducted by Carney and Myers also found that adolescents showed a preference for individualized interventions (i.e., compared with a group format) conducted over multiple sessions (i.e., compared with a single event).[67]

In alignment with the USPSTF finding of there being insufficient evidence to evaluate the utility of BIs among alcohol-using adolescent populations, evidence specific to adolescent females who receive brief alcohol interventions is also lacking and warrants future investigation. In a recent systematic review and meta-analysis of the literature on brief alcohol interventions for adolescents and young adults, Tanner-Smith and Lipsey found a limited number of studies with boy-only or girl-only samples that reported little to no evidence of differential effectiveness based on gender.[65] There is some evidence, however, suggesting that BIs for alcohol use may be particularly effective for adolescent girls, especially when the provider is also female and the information is delivered in the context of an ongoing provider–patient relationship.[73]

Women of Childbearing Age

There is strong evidence supporting the use of BIs among pregnant and nonpregnant women of childbearing age as a means of reducing levels of alcohol consumption and risks associated with AEPs.[18,62,74] For example, in one large multisite trial, approximately 69% of women who, at intake, were drinking at risky levels and not using effective contraceptive methods reduced their risk of an AEP at the 9-month follow-up after receiving an intervention incorporating MI. The women in this study achieved risk reduction by abstaining from alcohol or drinking below risky levels, by using effective contraceptive methods every time they had vaginal intercourse with a fertile male, or both.[75] A number of randomized controlled trials with pregnant women have also reported significant reductions in alcohol use and improved newborn outcomes following the facilitation of BIs.[62]

In addition to previously mentioned common components of BIs (e.g., personalized normative feedback), interventions with women of childbearing age often also include feedback on the potential effects of alcohol on fetal and child development.[25,64] It is recommended that postpartum women receive information on infant exposure to alcohol through breastmilk and that contraceptive use should be incorporated into BIs with nonpregnant women who are at risk of an AEP.[25,64]

Efficacious prevention and intervention programs have been developed for use with women of childbearing age. One example is the CHOICES program and its adaptations: BALANCE, EARLY, and CHOICES Plus.[76,77,78] CHOICES is an established AEP prevention program based on the principles of MI and designed to provide nonpregnant women of childbearing age with information to help them make informed choices on ways to avoid an AEP.[43] The CHOICES protocol has been widely disseminated across health and social service settings (e.g., primary care facilities, jails, sexually transmitted disease clinics).[75,78,79] Also, as a result of meeting rigorous peer-review criteria, the CHOICES program was included in SAMHSA's Evidence-Based Practices Resource Center (https://www.cdc.gov/ncbddd/fasd/choices-importance-preventing-alcohol-exposed-pregnancies.html).

Older Women

Although limited, studies on BIs with older adults suggest that BIs are effective at reducing risky alcohol consumption, with sustained reductions ranging from 2 to 18 months.[80,81,82] The content and format of most BIs are similar, as are the recommendations, whether delivered to younger or older cohorts. For example, providers are advised to use nonstigmatizing and nonjudgmental language when discussing screening results and any potential alcohol-related health consequences with women.[55] Regarding older women, some experts suggest that providers may find that incorporating the women's family and friends into various parts of the BI process may prove successful.[51]

Other BIs

Multiple BI models have been created to aid in the facilitation of BI conversations.[25,27] A systematic review of BIs for risky drinking in primary care settings reported that a majority are arranged according to the SAMHSA-endorsed Feedback, Responsibility, Advice, Menu of strategies, Empathy, Self-efficacy (FRAMES) model.[33,64] Other BI models that are endorsed by SAMHSA include the Feedback, Listen, Options (FLO) model, the Brief Negotiated Interview (BNI) Steps, and the BNI and Active Referral to Treatment: Provider Training Algorithms.[27] All of these models serve as useful guides for delivering BIs and are presumed to be equally efficacious regardless of age or gender. Practitioners should choose the model that best suits their work setting.

In summary, BIs are valuable tools for reducing alcohol consumption and its associated risks (e.g., AEPs). It is vital to consider that despite a number of randomized controlled trials suggesting similar efficacy for brief alcohol interventions among women and men,[83,84] women have been less likely to receive BIs in practice. As such, lending attention to this issue is critical considering that the prevalence rates for alcohol use among women are rising.[85]

REFERRAL TO TREATMENT

Referral to treatment is a process designed to assist women with accessing specialized treatment, selecting facilities, and navigating barriers that may prevent treatment engagement.[27] Treatment options for women with AUD may include residential treatment, outpatient psychological therapy (e.g., family, group, conjoint, individual), medication-assisted treatment, self-help or support group programs (e.g., 12-step programs such as Alcoholics Anonymous), harm reduction approaches, use of a recovery coach, or any combination of these. There are also treatment options that cater exclusively to women, such as the Women for Sobriety program and women-only Alcoholics Anonymous groups. Specialized alcohol treatment should be personalized to the woman, taking into account her medical, social, and cultural needs. Providers should be aware of local treatment options in order to conduct warm handoffs—referrals facilitated in the presence of the patient to encourage communication and partnership between the patient and treatment team—when needed. Providers should also pay special attention to the treatment selection for pregnant and postpartum women to ensure that appropriate medical care and social support options are available.[25] Providers may also choose to access SAMHSA's online resource guide, which includes samples of scripts, procedures, and links to treatment locator websites.[27] Other referral resources include NIAAA's online Alcohol Treatment Navigator tool (https://alcoholtreatment.niaaa.nih.gov) and NIAAA's publicly available resource guides, with information specific to referrals: *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*[29] and *Helping Patients Who Drink Too Much: A Clinician's Guide*.[28]

Referral to treatment is a critical, yet often overlooked, component of SBIRT. Although some studies have found it effective to link individuals to specialty treatments,[86,87] evidence from many others suggests that it is often difficult to link individuals in need of alcohol-related specialized care to substance use treatment services. For example, a meta-analysis of nine studies found no evidence that brief alcohol interventions were efficacious for increasing the use of alcohol-related services.[88] Referral to treatment is further compounded by gender-specific barriers to treatment that impact women's ability to engage in services. In general, women are less likely than men to initiate alcohol treatment services, and when they do, research suggests that women often contend with stigma, negative staff attitudes, lack of affordable or safe childcare options, and concerns over child custody.[89] When they do access treatment services, more women than men present with histories of trauma and abuse, psychological distress and mental health concerns, interpersonal and family-related issues, and financial constraints.[90] Barriers on a systemic level include lack of treatment options because of geographic isolation and lack of awareness among care providers regarding local treatment options that are capable of addressing the unique needs of adolescent girls and women in treatment settings.[89]

BARRIERS AND FACILITATORS TO SBIRT IMPLEMENTATION

A number of health and social service providers (e.g., physicians, nurses, social workers, psychologists, midwives) are qualified to effectively implement SBIRT across a variety of patient and client settings. However, studies of SBIRT implementation reveal that few providers feel comfortable doing so, with the lowest screening and counseling rates seen among young adult and women's reproductive care providers.[18] For example, one study found that one-third of women who endorsed alcohol consumption in women's health clinics were not asked how much they drank and that a majority of women drinking at risk levels did not receive advice on low-risk limits.[91] Another study concluded that approximately half of women at risk of an AEP did not receive information pertaining to this risk from their health care providers.[91] These findings corroborate national survey data of family planning clinicians, which found that of these clinicians,

approximately one-third used a validated screening measure and one-fifth provided a referral that consisted of more than a list of treatment options.[92]

Qualitative analyses conducted among health care providers have revealed several common barriers to implementing SBIRT, including time constraints, competing priorities, cost, and privacy and confidentiality concerns.[93-96] Barriers that pediatric providers cited include concerns regarding the willingness of adolescents to return for follow-up, limited access to and knowledge of adolescent treatment programs or local expertise, and confidentiality concerns.[94] Additional SBIRT barriers that prenatal care providers identified included lack of rapport between providers and women presenting for an initial prenatal consultation; providers' misperception that there is a low prevalence of alcohol use by pregnant women; providers' lack of skills, training, and follow-up protocol; women's underreporting or false disclosure of alcohol consumption; and providers' concerns over creating guilt and anxiety among pregnant women.[95,96]

Many of these provider-identified barriers should be considered in combination with, and resulting from, U.S. state policies mandating that health care providers report perinatal substance use to child welfare agencies.[97,98] For instance, in 2017, Jarlenski and colleagues conducted a systematic content analysis that identified 24 states with statutes around reporting perinatal substance use by health care providers. Twenty of the states identified had mandatory reporting statutes, while 11 states specified a penalty capable of resulting in a misdemeanor charge for health care providers who failed to report known perinatal substance use.[98] Furthermore, some state statutes allow for involuntary commitment and custody loss solely as a result of prenatal substance use, thus creating an ethical and moral dilemma for prenatal care providers because this violates the principles of patient autonomy and beneficence.[99] This issue was further complicated for prenatal care providers by updated recommendations from the American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention, which advise providers to conduct universal screening at initial prenatal appointments.[46,98]

In addition to the barriers faced by prenatal care providers, pregnant women engaged in substance use behaviors often face their own barriers to receiving care, such as fear of stigmatization and legal consequences. This may result in a lack of engagement in prenatal care altogether, thus eliminating the potential for SBIRT implementation and posing significant risks to the health of both mother and child.[60]

Older women also face unique barriers to alcohol intervention and treatment efforts. These include financial limitations and lack of mobility and transportation. Older women also report higher rates of stigma, shame, and guilt than younger women, which may lead to an increased prevalence of isolation, anxiety, and depression.[51]

Approaches to Facilitating SBIRT Implementation

In response to the many recognized barriers, research has begun to identify approaches that facilitate successful SBIRT implementation. So far, evidence suggests that having a practice champion, utilizing an interprofessional team, communicating the details of each SBIRT step, developing relationships with referral partners, instituting ongoing SBIRT training for sustainability, aligning SBIRT practices with the organization's flow, and integrating SBIRT into electronic health records are all ways to facilitate ongoing SBIRT efforts.[24] Additionally, a study of ongoing SBIRT facilitation compared usual care and two adolescent SBIRT delivery modalities (pediatrician-only and pediatrician with an embedded behavioral clinician) and found that although substance use outcomes did not differ between pediatrician-only and embedded behavioral clinician groups, adolescents in the embedded group reported fewer depression symptoms at follow-up.[100] The inclusion of a

behavioral clinician in pediatric settings may be especially beneficial to adolescent girls in light of recent evidence that higher levels of depression severity among girls ages 13 to 16 predicted alcohol use in the following year.[59]

Technology

The use of technology is an additional option for overcoming SBIRT barriers in clinical settings that lack available staff and time resources for ongoing face-to-face implementation.[101] Technology is increasingly being used to facilitate various SBIRT components, with preliminary evidence observed among adolescent girls and women looking promising.[74,102,103] A recent systematic review of women's experiences with technology-based screening found that the perception of anonymity made it easier to divulge potentially stigmatizing information compared to in-person, face-to-face screening methods. Therefore, technology-based screening has the potential to increase disclosure rates and intervention receipt.[104] Studies also suggest that women feel less embarrassed and less afraid of judgment when they participate in technology-based interventions, and the flexibility offered by some technology-based treatments may also be appealing to women who are not willing or able to participate in more formal treatment programs because of family and societal roles.[104]

Nevertheless, whether electronic SBIRT can be effective as a stand-alone entity has yet to be established. One recent study demonstrated successful implementation of a technology-based alcohol intervention (i.e., sans personnel) among women of childbearing age;[66] however, interaction findings from other studies suggest that various female groups may have other intervention needs.[105] For example, Choo and colleagues reported that although female victims of intimate partner violence were receptive to electronic screening and advice, they also desired empathy and compassion from human interaction provided during intervention delivery.[105] Still, evidence has suggested that electronically delivered SBIRT components are mutually beneficial to both women and providers.[103,106] In the future, the use of electronic approaches could also assist in the translation of research findings into routine care settings by standardizing intervention delivery methods while maintaining wide applicability across health and social service settings.[107]

FUTURE DIRECTIONS

More research is needed to evaluate the effectiveness, efficacy, and feasibility of SBIRT practices among females, primarily those in younger and older cohorts, and those at risk of AEPs.[4,10,59,64] Recent reports showed increases in alcohol use among adolescent girls, with evidence suggesting a reversal from traditional male excess to slight female excess in 8th grade, and by 12th grade, 35% of girls reported past-month alcohol use, corresponding to a 250% increase from 8th grade.[9,102] Age of alcohol use initiation is particularly worrisome among adolescent females, given that early initiating females drink more than all male adolescents from ages 12 to 17.[8] Additionally, the association between depression severity and alcohol use appears to be more salient for early adolescent girls than for boys of the same age, with observations suggesting that alcohol use both predicts and is a consequence of depression.[59] Research is also needed to address alcohol use among older women due to population increases. Given the aging of the baby-boom generation, population projections estimate that by 2040, the proportion of women to men ages 65 or older will be 127 to 100.[51,108]

SBIRT is essential for the ongoing identification and intervention of risky alcohol use behaviors among adolescent girls and women. As the prevalence rate of female alcohol use increases, so too should the implementation of SBIRT. These prevention and intervention efforts can help promote lifelong health and well-being among women, with special attention paid to younger and older cohorts, and those at risk of an AEP.

Table 1 Alcohol Screening Instruments

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
NIAAA *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*[29]	2 to 3 depending on severity	~2	Adolescents ages 9 to 18	Elementary or middle school adolescents (≤ 15 years old) reporting any alcohol use (0.89; 0.91)[33] High school adolescents (≥ 16 years old) reporting ≥ 6 days of past-year alcohol use (0.88; 0.81)[33]	Copyright: N/A Source: N/A Cost: Free online	Publicly available NIAAA guide containing screening questions (page 8): https://www.niaaa.nih.gov/sites/default/files/publications/YouthGuide.pdf
Screening to Brief Intervention (S2BI)[34*]	3 (additional 4 if past-year use indicated)	~2	Adolescents ages 12 to 17	Adolescents reporting alcohol use *once or twice* in the past year (0.96; 0.92) Adolescents reporting alcohol use *monthly* in the past year (0.79; 0.96) Adolescents reporting alcohol use *weekly or more* in the past year (1.00; 0.88)	Copyright: N/A Source: N/A Cost: Free online	Publicly available NIDA link to online version with options for patient or clinician administration: https://www.drugabuse.gov/ast/s2bi/#/
Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD)[38*]	6 (additional 3 to 11 if past-year use indicated)	~2	Adolescents ages 12 to 17	≥ 2 days of past-year alcohol use (0.96; 0.85)	Copyright: N/A Source: N/A Cost: Free online	Publicly available NIDA link to web-based instrument with options for patient or clinician administration: https://www.drugabuse.gov/ast/bstad/#/
Alcohol Use Disorders Identification Test (AUDIT)	10	~2 to 3	Adolescent girls ages 12 to 19, adults,§ pregnant women, older adults	Positive score indicating risk: Adolescent girls: ≥ 5 (0.95; 0.77)[32] Adults: ≥ 8 (0.38–0.73; 0.89–0.97)[18]** Pregnant women: > 0[18] Older adults: ≥ 5 (0.86; 0.87)[54]	Copyright: 1989, Thomas Babor and the World Health Organization Sources: World Health Organization, Division of Mental Health & Prevention of Substance Abuse, 1211 Geneva 27, Switzerland Email: Publications@who.int Thomas F. Babor, Alcohol Research Center, University of Connecticut, Farmington, CT Cost: Core questionnaire can be reproduced without permission; test and manual are free; training module costs $75	Publicly available link to self-report instrument: https://cde.drugabuse.gov/sites/nida_cde/files/AUDIT-SelfReport_v1.0_2014May20.pdf

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
Alcohol Use Disorders Identification Test-Concise (AUDIT-C)	3	~1	Adolescent girls ages 12 to 19, adult women,† pregnant women, older adults	Adolescent girls: ≥ 3 (0.96; 0.65)[32] Adult women: ≥ 3 (0.73–0.97; 0.34–0.89)[18] Pregnant women: > 0 (NR‡)[18] Older adults: ≥ 4 (0.94; 0.80)[54]	Copyright: N/A Source: N/A Cost: Free online	Publicly available SAMHSA link: https://www.integration.samhsa.gov/images/res/tool_auditc.pdf
Car, Relax, Alone, Forget, Friends, Trouble (CRAFFT)[37]*	4 (additional 5 if past-year use indicated)	~2 to 3	Adolescents ages 12 to 21	≥ 1 (0.94; 0.74)[30,39] Optimal cutoff score indicating heightened risk for SUD: ≥ 2 (0.79; 0.97)[39]	Copyright: 2001, Boston Children's Hospital Source: The Center for Adolescent Substance Abuse Research, Children's Hospital, 300 Longwood Ave., Boston, MA 02115 Phone: 617-355-5433 Email: crafft@childrens.harvard.edu Cost: N/A	Publicly available SAMHSA link which states that the CRAFFT may be reproduced in [this] exact form for use in clinical settings courtesy of the Center for Adolescent Substance Abuse Research at the Boston Children's Hospital: https://www.integration.samhsa.gov/clinical-practice/sbirt/CRAFFT_Screening_interview.pdf Link from Boston Children's Hospital with additional information: http://crafft.org/
NIAAA Single Item Alcohol Screening Questionnaire (SASQ)[52]	1	~1	Adults	≥ 1 (0.82; 0.79)[18]	Copyright: N/A Source: N/A Cost: N/A	Publicly available SAMHSA link to NIAAA's *Helping Patients Who Drink Too Much: A Clinician's Guide,* which includes NIAAA SASQ (page 4): https://www.integration.samhsa.gov/clinical-practice/Helping_Patients_Who_Drink_Too_Much.pdf Publicly available USPSTF Final Recommendation Statement: *Unhealthy Alcohol Use in Adolescents and Adults: Screening and Behavioral Counseling Interventions,* includes NIAAA SASQ question: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/unhealthy-alcohol-use-in-adolescents-and-adults-screening-and-behavioral-counseling-interventions

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
Quick Drinking Screen (QDS)[44,109]	3	~1	Adults	Scoring based on presence of NIAAA defined at-risk drinking (i.e., more than 3 drinks on any day or 7 drinks per week for adult women) in past 90 days[43††]	Copyright: 2003, Sobell & Sobell Source: Linda C. Sobell, PhD, ABPP, Center for Psychological Studies, Nova Southeastern University, 3301 College Ave., Fort Lauderdale, FL 33314 Email: sobelll@nova.edu Cost: Free	Publicly available link that states that this screener can be freely used as it is in the public domain: https://www.nova.edu/gsc/forms/quick_drinking_screen.pdf
Tolerance, Annoyed, Cut Down, Eye Opener (T-ACE)[31]	4	~1	Women of childbearing age	≥ 2 (0.69–0.88; 0.71–0.89)[25]	Copyright: 1989, Harcourt Health Sciences; permission needed to publish Sources: S. Martier, Ob/Gyn, 4707 Saint Antoine, Detroit, MI 48201 Permissions Department, Mosby, Inc. (a division of Elsevier), 6277 Sea Harbor Dr., Orlando, FL Phone: 407-345-3994 http://www.us.elsevierhealth.com/ Cost: N/A	Publicly available NIAAA link containing copyright information: https://pubs.niaaa.nih.gov/publications/t_ace.htm Publicly available NIAAA link containing T-ACE questions: https://pubs.niaaa.nih.gov/publications/arh28-2/78-79.htm
Tolerance, Worried, Eye Opener, Amnesia, K-Cut Down (TWEAK)[31]	5	~2	Pregnant women	≥ 2 (0.71–0.91; 0.73–0.83)[25]	Copyright: None Source: Marcia Russell Prevention Research Center, 1995 University Avenue, Suite 450, Berkeley, CA 94704 Phone: 510-883-5703 Email: russell@prev.org Cost: Free	Publicly available NIAAA link with more information: https://pubs.niaaa.nih.gov/publications/assessingalcohol/instrumentpdfs/74_tweak.pdf
Normal Drinker, Eye-Opener, Tolerance (NET)[47]	3	~1	Pregnant women	≥ 2 (0.61; 0.87)[47]	Copyright: 1989, Lippincott Williams & Wilkins Source: Lippincott Williams & Wilkins Permissions Department, 351 West Camden St., Baltimore, MD 21201 Phone: 410-528-4050 Email: permissions@lww.com http://www.lww.com/permissions/index.htm Cost: N/A	Not publicly available
Parents, Partner, Past, Present Pregnancy (4P's Plus)[48]*	5	~1	Pregnant women	≥ 1 (0.87; 0.76)[48]	Copyright: The National Training Institute/NTI Upstream Source: NTI Upstream, 180 N. Michigan Ave., Suite 700, Chicago, IL 60601 Cost: Licensing fees may apply	Publicly available link with more information: https://www.ntiupstream.com/4psabout

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
Substance Use Brief Screen (SUBS)[53*]	4	~1	Adults	Any response other than "never" on alcohol binge question: (0.85; 0.77)	Copyright: N/A Source: N/A Cost: N/A	Publicly available NIH publication with more information: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4475501/
Cut Down, Annoyed, Guilty, Eye-Opener (CAGE)[57]	4	~1	Adults	≥ 2 (0.14–0.39; 0.97)	Copyright: None Source: N/A Cost: Freely available as it is in the public domain and no permission is necessary unless used in a profit-making endeavor	Publicly available SAMHSA link: https://www.integration.samhsa.gov/clinical-practice/sbirt/CAGE_questionaire.pdf
Michigan Alcohol Screening Test–Geriatric Version (MAST-G)[57]	24	~5 to 10	Older adults	≥ 5 (0.70–0.91; 0.81–0.85)	Copyright: 1991, The Regents of the University of Michigan Source: Frederick C. Blow, PhD, University of Michigan Alcohol Research Center, 400 E. Eisenhower Parkway, Suite A, Ann Arbor, MI 48104 Phone: 313-998-7952 Cost: Free online	Publicly available NIH link to SAMHSA's *Substance Abuse Among Older Adults: Treatment Improvement Protocol No. 26* (page 55): https://www.ncbi.nlm.nih.gov/books/NBK64419/pdf/Bookshelf_NBK64419.pdf
Short Michigan Alcohol Screening Test–Geriatric Version (SMAST-G)[57]	10	Not reported	Older adults	≥ 2 (0.52; 0.96)	Copyright: 1991, The Regents of the University of Michigan Source: N/A Cost: N/A	Publicly available link provided by The Hartford Institute for Geriatric Nursing, New York University, Rory Meyers College of Nursing: https://consultgeri.org/try-this/general-assessment/issue-17.pdf
Comorbidity Alcohol Risk Evaluation Tool (CARET)	10	~2 to 5	Older adults	A positive response in any of the seven risk categories (0.92; 0.51)[54]	Copyright: N/A Source: N/A Cost: N/A	Not publicly available

NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIDA = National Institute on Drug Abuse; NIH = National Institutes of Health; SAMHSA = Substance Abuse and Mental Health Services Administration.

* Instrument screens for alcohol and other substances.

† Recommended AUDIT-C cutoff score is different for adult women (≥ 3) and men (≥ 4).[18]

‡ Not reported.

§ Recommended AUDIT cutoff score is the same for adult women and men (≥ 8).[18]

** Several U.S.-based studies show more optimal balances of sensitivity and specificity at lower AUDIT cutoffs (e.g., 3, 4, 5); preliminary findings from the USPSTF 2018 updated evidence report and systematic review indicates that lower cutoffs may be preferred.[18]

†† Sensitivity and specificity are not reported for this instrument.

‡‡ N/A, information was not available or retrievable. None, the instrument explicitly states that no copyright is held. Cost: N/A, no information was found regarding cost. Free/free online, the information pertaining to the instrument explicitly states that it is available to the public.

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Treatment Interventions for Women With Alcohol Use Disorder

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Women with alcohol use disorder (AUD) experience more barriers to AUD treatment and are less likely to access treatment than men with AUD. A literature review identified several barriers to women seeking help: low perception of a need for treatment; guilt and shame; co-occurring disorders; employment, economic, and health insurance disparities; childcare responsibilities; and fear of child protective services. Women entering treatment present with more severe AUD and more complex psychological, social, and service needs than men. Treatment program elements that may reduce barriers to AUD treatment include provision of childcare, prenatal care, treatment for co-occurring psychological problems, and supplemental social services. Research has suggested that outcomes for women are best when treatment is provided in women-only programs that include female-specific content. To date, research on treatments tailored to the individual needs of women is limited, but research on mechanisms of change has suggested the importance of targeting anxiety and depression, affiliative statements in treatment, abstinence self-efficacy, coping skills, autonomy, and social support for abstinence. Future research should focus on early interventions, linkages between primary care or mental health clinics and AUD treatment settings, and integrated treatments for co-occurring AUD and other disorders. Further research should also explore novel treatment delivery approaches such as digital platforms and peer support groups.

KEY WORDS: alcohol use disorder; barriers; mechanisms of change; outcomes; treatment; women

INTRODUCTION

Historically, women with alcohol use disorder (AUD) have been an underserved population. In the United States, more than 5 million adult women, or 4.2% of the adult female population, meet criteria for current AUD.[1] Although this percentage is half that of adult men (8.4%), among adolescents, more females than males meet criteria for current AUD (2.7% vs. 2.3%),[1] and recent research has suggested that the gender gap in alcohol use and alcohol-related harm is narrowing.[2] Heterogeneity in rates of AUD is found among different racial/ethnic groups, with higher rates among Black and Hispanic women than among White women,[3] and rates of AUD among gender minority women also are higher than among heterosexual women.[4]

A smaller proportion of women than men received AUD treatment both in the past year[1] (7.9% of adult women vs. 9.2% of adult men; 4.6% of adolescent females vs. 7.4% of adolescent males) and in their lifetime[5] (15.0% of women and 22.0% of men with AUD who are younger than age 45). Utilization rates for treatment services by women and men do not differ across different racial/ethnic groups.[5] Given the increasing rates of AUD among women and the lower rates of treatment utilization among women, a rethinking of AUD treatment for women is in order. The purpose of this article is to describe the barriers to treatment entry experienced by women with AUD, the unique characteristics and presenting concerns of women with AUD who do seek treatment, and the current knowledge about effective treatments. Sources of information for this review included a comprehensive review published in 2013,[6] articles identified in a search in PsycINFO® using the search terms "women," "alcohol," and "treatment," and articles identified through selective reviews to identify key publications on trauma-informed treatment and substance use disorder (SUD) in female veterans.

WOMEN SEEKING AUD TREATMENT

Women seeking AUD treatment differ from men in their sociodemographic characteristics and psychological profiles. They experience some unique barriers to accessing treatment and present to treatment with some needs that differ from men in AUD treatment.

Characteristics of Women With AUD at Treatment Entry

Women seeking AUD treatment vary along a number of dimensions that may impact their access to treatment, treatment needs, and treatment response.

Sociodemographic characteristics and substance use

Women who present to AUD treatment often have markedly different characteristics and backgrounds than men in these treatment settings. Such distinctions among women include younger age, more severe alcohol and drug use histories, less education, lower income, higher unemployment, more housing needs, more children living at home, and higher parental stress.[6] In terms of substance misuse, rates differ among subgroups. For example, non-Hispanic White and American Indian/Alaska Native women are more likely than women of other racial/ethnic groups to identify alcohol as their primary substance of use when entering treatment for SUD.[7] Among pregnant women entering treatment for SUD, approximately 18% identified alcohol as their primary substance of use.[7] In a study of women veterans with SUD, researchers found that entry into and engagement with treatment were associated with having a co-occurring psychological disorder and receiving services at facilities offering women's treatment.[8]

Psychological co-occurrences

Compared to men, women who enter AUD/SUD treatment generally report higher levels of physical and mental health concerns. Rates of co-occurring disorders vary with the treatment setting and population. Epidemiologic data suggest that compared with men with AUD, women with AUD have a higher prevalence of co-occurring DSM-IV Axis I disorders (84.2% vs. 75.5%),

a similar prevalence of other drug dependence (15.2% vs. 14.3%), a higher prevalence of mood and anxiety disorders (53.1% vs. 29.1% and 44.3% vs. 26.2%, respectively), and a similar prevalence of personality disorders (36.5% vs. 33.3%).[9] A recent nationwide study of veterans with AUD found that women veterans had more psychological and substance use comorbidities than men.[10] In addition, women in SUD treatment have a much higher prevalence (up to 80.0%) of lifetime physical, sexual, and/or emotional abuse and trauma, and concerns about current domestic violence are common.[11] Rates of current post-traumatic stress disorder (PTSD) among women in SUD treatment range from 25.0% to 55.0%.[12]

Barriers to Treatment

Women who do not receive AUD treatment have some sociodemographic difference from women in AUD treatment. For example, a sample of women with AUD who were not in treatment but perceived a need for treatment were less educated, had a family income less than $75,000, and were more likely to use psychotropic medications compared to those who did not perceive a need for treatment.[13] Women experience both internal and external barriers to AUD treatment. These barriers may partially explain the gender discrepancy in treatment initiation rates and include low perception of need for treatment; guilt and shame stemming from the discrepancy between traditional gender expectations and societal views of women with AUD; depression and other co-occurring disorders; greater employment, economic, and health insurance disparities relative to men; childcare responsibilities; and fear of child protective services.[6]

Recent research has suggested that traditional gender expectations and lay beliefs about AUD may contribute to lower AUD treatment utilization among women. Lale and colleagues found that compared to men, women were more likely to attribute AUD to "bad character" and less likely to attribute AUD to genetics.[14] Women also worry that they will be perceived as "bad mothers" and potentially lose custody of their children if they disclose having an alcohol problem.[7] Relatedly, women are more likely than men to experience feelings of embarrassment, to experience fear, to have the belief that no one can help, and to have the belief that their problem is not serious enough to require AUD treatment.[15] In addition to these intrapersonal barriers, women may experience less social support to enter AUD treatment than men do. Women with AUD are more likely than men to be in an intimate relationship with a partner who also has AUD,[16] and women tend to have less spousal and family support for recovery.[17] Further, women generally report more logistical barriers to treatment utilization, including greater difficulties with transportation, lack of available childcare, and inadequate insurance coverage.[17]

Compared to men, women are more likely to seek AUD treatment through a general versus substance use-specific health care sector[18] or in the context of treatment at a general mental health clinical setting,[19,20] and less likely to be court mandated to treatment.[21] Women with AUD also generally report stressful life events and nonsubstance-related mental health concerns as their primary reasons for seeking treatment.[22] Welfare, child welfare, and legal systems provide additional portals through which some women enter AUD treatment.[21] Primary care physicians, gynecologists, and psychiatrists may benefit from focused training in identification and referral of women with AUD to offset the gender discrepancy observed in women's entry into AUD treatment. Relatedly, women have shown a preference for AUD treatment settings that offer childcare.[23] Thus, more easily accessible, children-friendly treatment centers with wide availability are also likely to improve treatment utilization among women with AUD.

AUD TREATMENT SERVICES FOR WOMEN

Treatment Retention

In general, the literature is mixed regarding AUD treatment attrition and gender differences.[6] Previous studies have found that women tend to have longer inpatient stays and that longer inpatient

stays are associated with an increase in sustained abstinence for women but not for men.[22,24] Bravo and colleagues reported that women engaged in outpatient AUD treatment longer and discontinued treatment at a lower rate than men.[25] In a comprehensive review, Greenfield and colleagues concluded that although there are no gender differences in attrition, predictors and mediators of treatment retention differ by gender.[23] Predictors of better treatment retention among women include demographic variables, such as lower psychiatric impairment, higher socioeconomic status, and greater social support and stability,[23] and program variables, such as female-specific treatment and facilities that allow children to stay with their mothers.[6] A recent investigation of 1.8 million individuals who received SUD treatment at federally funded facilities found that, across treatment settings, women and men did not differ in rates of early discharge.[26] However, when treatment settings were stratified by type (detoxification, residential, and ambulatory), women were more likely than men to leave detoxification treatment prematurely. The authors suggested that lower rates of female-specific services and higher rates of psychiatric co-occurring disorders within detoxification settings might have accounted for this gender difference.

Treatment Outcome

In general, studies of mixed-gender treatment programs have found few gender differences in short-term outcomes for AUD across a range of interventions, samples, and sites, despite women at baseline generally presenting with more severe clinical issues.[6] For example, in their analysis of five randomized clinical trials (RCTs) of intensive outpatient contingency management for AUD and SUD, Rash and Petry found no differences between men and women's abstinence rates during the 3-month treatment period, although women initially presented with more financial, family/social, and psychiatric problems.[27] Likewise, a study of a large outpatient AUD treatment cohort in Spain found no differences between men and women in alcohol consumption 1 year posttreatment, despite women presenting with more symptoms of dependence at baseline.[25]

Results have been more mixed regarding women's long-term outcomes compared to men.[6] In the same study from Spain described above, women had superior drinking outcomes compared to men at 5, 10, and 20 years posttreatment.[25] Conversely, Litt and colleagues found that women had worse drinking outcomes than men in the 2 years following outpatient AUD treatment.[28] These poorer outcomes may have been due to the nature of the active treatment, which focused on altering the participant's social network to gain more support for abstinence; women in the study had less abstinence-supportive social networks and more difficulty altering these networks.

Historically, gender has typically not been taken into consideration in psychopharmacologic treatment for AUD, and women have been underrepresented in AUD medication trials.[29] However, research has begun to improve in this area. A review by Agabio and colleagues found that too few studies of disulfiram had included women to test potential gender differences in response to this medication.[30] There were a sufficient number of studies on acamprosate and naltrexone, which showed that both medications were generally efficacious for women; however, results of gender comparisons were too variable to draw firm conclusions. Canidate and colleagues conducted a systematic review of seven studies on naltrexone for the treatment of AUD among women.[31] Among this limited number of studies, naltrexone was found to have a modest effect on drinking quantity and time of relapse but not on the overall frequency of drinking among women. The authors concluded that the effect of naltrexone on women is currently understudied. This Canidate article highlights the need to continue to use rigorous research designs to study differences in the efficacy of naltrexone on women versus men.

Reducing Barriers to Treatment for Women

A comprehensive review identified six major elements of SUD treatment programs for women

that reduce barriers to treatment and/or address women's unique needs.[32] These include the provision of childcare, prenatal care, women-only treatment, treatment for co-occurring mental health problems, a comprehensive approach to treatment, and supplemental services that address women-focused topics. Each of these elements was linked to favorable treatment outcomes. In a qualitative meta-synthesis of programs that included women and their children, several treatment processes were identified by different stakeholders (clients, clinicians, and program administrators) as instrumental to positive outcomes: developing a sense of agency, giving and receiving social support, engaging with program staff, fostering self-disclosure, recognizing self-destructive patterns of behavior, setting goals, and feeling motivated by the presence of children.[33] Although some of these processes are common to any AUD treatment, it is necessary to recognize the unique blend of common and specific treatment processes that are effective for women in treatment with their children. Although studies have repeatedly identified the importance of including children-supportive services in women's SUD treatment programs, a 2018 Substance Abuse and Mental Health Services Administration (SAMHSA) survey found that only 5.8% of SUD treatment facilities provided childcare and only 2.6% of residential programs provided beds for clients' children.[34]

Guiding Principles for Women's AUD Treatment

Recognizing the unique treatment needs of women with AUD and SUD, SAMHSA published a set of evidence-based principles to guide gender-responsive treatment for women.[7] These guidelines include several recommendations. For example, they recommend developing cultural competence to frame women's AUD symptoms and treatment in their socioeconomics contexts (e.g., employment, income, housing). They suggest that providers acknowledge the unique significance of women's relationships and attend to the "caregiver roles that women often assume throughout the course of their lives." Relatedly, the guidelines address stigma by noting the importance of "recognizing that ascribed roles and gender expectations across cultures affect societal attitudes toward women who abuse substances." Other recommendations state that SUD treatments for women adopt a trauma-informed approach, which often emphasizes women's strengths, and address "women's unique health concerns" through "an integrated and multidisciplinary approach." The SAMHSA guidelines conclude that clinical treatment services (e.g., screening, mental health services), clinical support services (e.g., parenting education, job training), and community support services (e.g., childcare, transportation) would work collaboratively to facilitate comprehensive AUD treatment for women of diverse backgrounds.[7]

Advances and Gaps in Treatment Development for Women

With increasing recognition of the unique clinical profiles of women with AUD has come increasing attention to whether AUD treatment programs are serving the needs of women. The 2018 SAMHSA annual survey of substance use treatment programs found that 49% of programs surveyed provided special programs or groups for women and 23% provided services for pregnant or postpartum women.[34] In contrast, data from the Veterans Health Administration (VHA) revealed that most VHA facilities offered SUD services to women but that most of these services were generic rather than female-specific (85% vs. 30%).[35]

The need for specialized services for women has both an empirical and a clinical rationale. As reviewed earlier in this article, compared to men, women are less likely to seek AUD treatment, have different social contexts, present with different profiles of co-occurring disorders, and have a unique and complex set of service needs that may not be addressed in a standard, mixed-gender AUD treatment program.[9,36] Thus, treatment programs and researchers have been seeking to create and evaluate services intended to attract women to AUD treatment and improve

outcomes. AUD services for women vary along two dimensions—whether they are provided in a mixed-gender or women-only treatment setting and whether the content of the treatment is generic or tailored specifically to women's clinical and other service needs.[37] Thus, delivery of AUD treatment to women may occur in (a) mixed-gender programs with no female-specific programming, (b) mixed-gender programs with female-specific programming, (c) single-gender (women-only) programs with no female-specific programming, or (d) single-gender (women-only) programs with female-specific programming.

Mixed-gender versus single-gender treatment

Single-gender treatment services seem appealing because they have the potential to provide an environment in which women may feel more comfortable sharing emotional and personal information. For instance, it is possible that among women who have a history of trauma or abuse from men, single-gender treatment might be preferable because of the possibility that participation in a mixed-gender program could trigger trauma-related symptoms. In addition, given the broader literature on the relative interactional dominance of men in mixed-gender groups, women may have more opportunities to participate when in women-only groups.[38] However, research on women's treatment preferences yields a more nuanced picture. Although some research suggests that women prefer women-only groups,[23] a narrative analysis of interviews with women with a range of SUD treatment experiences found that the women reported concerns and anxiety about being in women-only treatment because of their own history of dysfunctional relationships with women and their greater comfort in being with men.[39] However, women in the study reported positive experiences once they entered women-only services.

Few studies have compared women's outcomes from mixed-gender versus women-only programs that were not adapted with female-specific content. In one early study, Bride compared the outcomes for women who were in a mixed-gender program to the outcomes for women who later participated in the same program that had become a women-only program with no female-specific content.[40] Outcomes were similar between the two samples.

More extensive research has compared mixed-gender to single-gender programs that incorporate female-specific themes, services, or content. For example, interviewed providers of services for female veterans with SUD identified five female-specific themes and services that they viewed as key to treatment: a focus on safety; scheduling that accommodates women's work and family responsibilities; flexibility in the resources provided; staff trained in serving women's clinical needs; provision of on-site childcare; and a positive, supportive, nonconfrontational treatment environment.[41] Although some of these treatment elements may be relevant to treatment for any patient with SUD, the combination of these elements was seen as key to successful treatment for the female veteran population. In addition to treatment elements, female-specific content has focused on clinical issues of particular significance to women, such as trauma, physical abuse, relationships, parenting, assertiveness, and treatment of co-occurring disorders.

One of the earliest studies of women-only treatment with female-specific content was the Early Treatment of Women with Alcohol Addiction (EWA) study.[42] A 2-year follow-up of women found better clinical outcomes in the EWA than mixed-gender treatment, and a long-term study of mortality revealed lower mortality rates for younger women who participated in the EWA program than the mixed-gender treatment.[43] A later study of a large sample of women in women-only versus mixed-gender residential SUD treatment found that women were twice as likely to complete the women-only treatment and that higher retention was associated with higher rates of abstinence posttreatment.[44,45] More recent studies have found that (a) treatment retention and entry to aftercare were enhanced by gender-specific services in an intensive treatment program that also provided transitional housing, particularly for women who completed residential treatment;[46] (b) women-only treatment predicted

better legal and drug outcomes but no differences in alcohol use outcomes;[47] and (c) women in the single-gender treatment had significantly less substance use (participants were primary stimulant users) and less criminal activity than those in the mixed-gender treatment.[48] In contrast, Kaskutas and colleagues found that a mixed-gender, comprehensive, hospital-based treatment resulted in better alcohol abstinence outcomes than women-only treatment and was superior to generic, community-based, mixed-gender treatment.[49]

Single-gender treatment with no female-specific programming

Some empirically supported treatments have been tested in female samples with any adaptation of the treatment to women's treatment needs. Two studies compared behavioral couple therapy to individual treatment for women with AUD and their male partners.[50,51] O'Farrell and colleagues compared behavioral couple therapy to individual treatment for women with SUD and their male partners.[52] All three studies found that the behavioral couple therapy led to positive changes in alcohol or drug use, with better alcohol or drug use outcomes for the women receiving couple therapy. In their study, McCrady and colleagues found that women presenting with higher levels of relationship distress and women with co-occurring Axis I or II disorders had greater improvements in drinking.[50] Note, however, that couple therapy is a modality available to only a small proportion of the population of women with AUD. Notably, when given the choice, even women with male partners indicated a preference for individual rather than couple therapy, stating that they wanted to work on their own problems, did not see their partners as supportive, or thought the logistics of scheduling couple sessions was too difficult.[53]

Chronic care models for persons with serious mental illness and SUD are another empirically supported approach that has been tested in female samples without female-specific programming. These models have been developed and tested with homeless women who have AUD. The chronic care model emphasizes availability of a primary care provider, care management, education about alcohol, and referral to addiction services. Compared to women who received treatment as usual in a health care clinic for homeless women, women who participated in the chronic care program engaged with more SUD treatment services in the 3 months after starting the program.[54]

Single-gender treatment with female-specific programming

There has been substantial research on women-only treatment with female-specific content. For example, Polcin and colleagues compared intensive, nine-session motivational interviewing (MI) for women with standard one-session MI.[55] For the intensive treatment, therapists were trained to use MI to focus on alcohol use as well as female-specific themes—such as personal relationships, issues related to parenting, abuse, and barriers to treatment—and other psychological concerns, such as low self-esteem or co-occurring disorders. Compliance with the treatment was high (80% of heavy drinkers completed at least seven sessions), and women receiving intensive MI reduced their drinking more than women receiving standard MI. Connors and Walitzer developed and tested an intervention to help heavy-drinking, nonalcohol-dependent women reduce their drinking.[56,57] The intervention focused on skills to reduce drinking and other life skills believed to be relevant to women, such as problem-solving, communication and assertiveness, and strategies to enhance their social support system. Compared to treatment focused only on drinking, women who also received the life skills interventions and booster sessions had outcomes that were more positive.

Another single-gender treatment with women-specific programming was developed by Epstein and colleagues. The outpatient, female-specific cognitive behavioral treatment (FS-CBT) was an adaptation of a the gender-neutral cognitive behavior therapy manual-guided treatment for AUD.[58] The FS-CBT manual (a) highlighted two clinical themes meaningful to women, self-care and autonomy; (b) included female-specific

interventions focused on coping with negative emotions and developing/enhancing women's social network supportive of abstinence; and (c) provided women-specific examples throughout to personalize the material to each woman's issues, such as dealing with heavy drinkers in the social network, parenting, life-stage transitions, trauma, self-esteem, and relationships.[59] In an RCT comparing FS-CBT to an evidence-based, gender-neutral CBT for AUD, Epstein and McCrady found that women in both treatment conditions were highly engaged, reported a high level of satisfaction with the treatment, significantly reduced their drinking, and improved in other areas of life functioning such as depression, anxiety, autonomy, and sociotropy.[58] There were no treatment condition effects, and the FS-CBT treatment was equally effective as the gender-neutral one. In a subsequent RCT, Epstein and colleagues tested the individual modality FS-CBT treatment versus a new group therapy format of the same contents in a "pure comparison" design.[60] Both FS-CBT treatment modalities (individual and group therapy) resulted in significant positive changes in drinking, depression, anxiety, coping skills, self-confidence, interpersonal functioning, and self-care even though treatment attendance and therapeutic alliance were greater in the individual FS-CBT condition. Cost-effectiveness analyses favored the group format.[61]

In a pilot study, Greenfield and colleagues tested a women-only Women's Recovery Group (WRG, $n = 16$) for SUD against mixed-gender Group Drug Counseling (GDC, $n = 7$ women, 10 men).[62] WRG included cognitive behavioral and relapse prevention elements, as well as "repair work" relevant for women (repairing SUD-related damage to relationships and self, and learning to enjoy life without substances).[63] GDC was a traditional mixed-gender treatment program focused on substance-related topics with no gender-specific content. During treatment, the groups did not differ in substance[62] or psychiatric improvement;[64] however, women in WRG continued to reduce substance use in the 6 months posttreatment, and also reported higher satisfaction with the treatment they received.

In a subsequent, larger RCT,[65] with a similar design except that the WRG groups offered rolling admission, outcomes of 52 women in WRG were compared with those of 48 women in GDC (with 58 men in GDC). All participants had SUD or AUD. Women in both treatments reduced drinking, and there were no treatment condition differences in within- or posttreatment drinking outcomes. Because WRG had both a women-only group composition and female-specific content compared to GDC, which had both a mixed-gender format and no female-specific content, it is unclear whether study results were linked to group composition, female-specific content, or both, but both the pilot and the larger RCT demonstrated that WRG is at least comparable to a typical "treatment-as-usual" such as a mixed-gender GDC in community settings. The authors also noted that the WRG in the larger trial was delivered on a rolling admissions basis and suggested that the revised format may have diluted the impact of the WRG.

In a series of three studies on putative mechanisms of change in WRG, secondary analyses of the pilot and/or larger RCT data from studies just described here above, showed that more affiliative statements were made in WRG than GDC[66,67] and that more affiliative statements were associated positively with women's drinking outcomes during and 6 months after treatment, particularly in the WRG condition.[68] Sugarman and colleagues created and piloted (for feasibility, acceptability, and satisfaction) a web-based, gender-specific individual psychoeducation intervention based on WRG content.[69] The gender-specific modules might ultimately comprise a female-specific component of care to be delivered in a mixed-gender setting.

Najavits and colleagues reported an RCT comparing the A Woman's Path to Recovery (WPR) model to the gender-neutral 12-Step Facilitation (TSF) model for women veterans with SUD, the majority of whom (i.e., more than 74%) had current AUD.[70] The WPR model is based on cognitive behavioral, interpersonal, and emotive therapy methods, and theory on gender differences in addiction and recovery. The "exploration" phase of the treatment highlights five themes:

"body and sexuality, stress, relationships, trauma and violence, and thrill-seeking."[70(p211)] The "healing" section covers "recovery methods in four domains—relationships, beliefs, actions, and feelings."[70(p211)] Both WPR and TSF were single-gender groups, facilitated by women clinicians, and provided compensation to offset potential childcare costs or other financial barriers to participation. The treatments resulted in similar improvements in alcohol and drug use, coping skills, and psychiatric functioning. The authors noted that female-specific treatment content might be less relevant to veterans than to their civilian counterparts because male-dominated military culture may diminish traditional gender experiences for women.

In summary, several forms of empirically supported treatments have been tested and found to be efficacious with women, and several women-only treatments with female-specific content have been tested in rigorous RCTs. Overall, most of these studies have found limited evidence for superior alcohol use outcomes, but several of these studies have found greater satisfaction with the female-specific format and treatment content. Because these programs are appealing to women, they may increase women's utilization of AUD treatment, and enhance both engagement and retention in AUD treatment.

Treatment for Co-occurring Disorders

Treatment for co-occurring disorders may be indicated for the many women with AUD who present with additional mental health concerns. Interventions that address the co-occurrence of AUD with trauma and PTSD, mood disorders, and borderline personality disorder may be especially relevant for women.

Trauma

Given the highly elevated rates of trauma among women with AUD/SUD, SAMHSA has suggested that treatment for this population may benefit from adopting principles of trauma-informed care.[7] A trauma-informed approach recognizes the prevalence and impact of trauma in women with AUD and adjusts treatment accordingly, even if clients do not meet diagnostic criteria for PTSD. Trauma-informed AUD treatment does not need to target trauma explicitly, but rather may consider trauma in the assessment and planning phases of treatment. For example, SAMHSA recommends that AUD treatment providers should assess women at intake for trauma histories and PTSD symptomatology and refer clients with severe symptomatology to providers who have experience working with traumatized populations (i.e., if they lack such experience themselves). Another recommendation is to "avoid triggering trauma reactions or re-traumatizing women." For example, violating a client's trust or disregarding a client's emotions or experiences may trigger trauma reactions. SAMHSA also recommends that programs should "adjust staff behavior" and modify the treatment environment "to support clients' coping capacities and safety concerns." Specific strategies may include ensuring that urine specimens are collected in a private setting and establishing consistency in the treatment program's routines and enforcement of rules. In addition, AUD treatment providers should "allow survivors to manage their trauma symptoms" in a manner conducive to AUD treatment engagement and success. For example, allowing clients to express strong feelings without facing judgment and explicitly addressing trauma only when a client is ready are considered trauma-informed approaches. Finally, SAMHSA recommends that trauma-informed AUD treatment for women should "emphasize skills and strengths, interactive education, growth, and change beyond stabilization." Specific skills to incorporate into treatment may include assertiveness training and relaxation techniques.

Covington developed the Helping Women Recover program for the treatment of SUD.[71] Following the principles of trauma-informed care, this treatment aims to provide a "healing" (i.e., safe, empowering, relational) environment that emphasizes strengths and is sensitive to cultural and gender issues. Treatment modules include topics hypothesized to be essential to women's recovery: a focus on self and the integration of roles with feelings, thoughts, and attitudes;

healthy interpersonal relationships; sexuality; and spirituality. Covington also developed the Beyond Trauma: A Healing Journey for Women treatment program, which teaches women how to identify trauma and other forms of abuse, helps them understand typical reactions to trauma and abuse, and fosters the development of coping skills.[72] In an RCT with incarcerated women, 77% of whom were primary stimulant users, Messina and colleagues integrated the Helping Women Recover and Beyond Trauma protocols into a gender-responsive treatment (GRT) program.[73] GRT was compared to a standard prison-based therapeutic community (TC), which, like GRT, was single-gender and targeted SUD, but unlike GRT did not focus on gender-specific issues or trauma histories. Both conditions improved women's psychological well-being and alcohol use outcomes, but women in GRT also had more favorable outcomes for drug use, length of aftercare treatment engagement, and rate of reincarceration in the year following release from parole. A subsequent analysis showed that women with physical/sexual abuse histories had significantly better posttreatment depression and substance use outcomes following GRT than TC.[74]

An extension of trauma-informed care is treatment for co-occurring SUD and PTSD. In general, this co-occurrence is complex and difficult to treat because SUD and PTSD are reciprocally functional and often exacerbate each other.[75,76] Drinking or drug use often functions to self-medicate PTSD symptoms and enable avoidance of remembering traumatic events. Reducing substance use may initially intensify PTSD symptoms and thus predispose the client to relapse. An increasing focus has emerged on targeting PTSD and SUD concurrently.[75,76] This integrated focus is particularly relevant to women who present to SUD treatment and often have elevated rates of trauma history and PTSD.[12]

Recently, integrated models of treatment for PTSD and SUD have been developed and tested with mixed results. For instance, Najavits developed Seeking Safety (SS), a CBT-based treatment model that aims to reduce co-occurring PTSD and SUD by enhancing coping skills.[77] SS emphasizes themes of establishing safety, taking back power, being honest, setting boundaries, practicing compassion, healing from anger, grounding, creating meaning, and increasing self-care. Hien and colleagues tested the efficacy of SS and another active treatment condition Relapse Prevention against a treatment-as-usual control condition.[78] Women in SS and relapse prevention had comparable posttreatment reductions in both PTSD and SUD symptoms, and both treatments were superior to the control condition. Likewise, a study conducted through the National Institute on Drug Abuse Clinical Trials Network found no differences in PTSD or SUD outcomes between an abbreviated version of SS and a health education control condition, both delivered as adjuncts to standard SUD treatment.[79]

Morrissey and colleagues studied another integrated treatment approach for women with SUD.[80] The researchers used a quasi-experimental design to examine a large cohort treated across nine sites. Participants were mostly of low socioeconomic status and had serious mental and/or physical health problems as well as an interpersonal trauma history. The integrated treatment was associated with lower substance use and improved general mental health but not with reduced PTSD symptoms. Overall, it remains unclear whether integrated treatments for PTSD and AUD/SUD in women are superior to stand-alone SUD treatments. Widespread methodological limitations in the current literature warrant continued investigation of integrated treatments, including outcomes that may be specific to women with AUD.[75,76]

Mood disorders

Another promising area of treatment development for women is integrated behavioral therapy for SUD and depression. Treating depression and AUD concurrently may be important because negative affect is a particularly salient trigger for drinking among women. In turn, regular heavy drinking may inhibit recovery from mood disorders. Further, more women than men with AUD have a co-occurring mood disorder, and

there is an elevated suicide risk among women with AUD.[6] However, research on integrated AUD and mood disorder treatments for women is limited. For example, in a pilot study, researchers tested 8 sessions of interpersonal psychotherapy as an adjunct to outpatient AUD treatment for 14 women with co-occurring AUD and major depression.[81] The study found that women were highly engaged and satisfied with the adjunct treatment and reported follow-up reductions in drinking, depressive symptoms, and interpersonal problems. A study of men and women with depressive symptoms and hazardous drinking compared the effects of integrated alcohol-depression treatment, alcohol-only treatment, and depression-only treatment.[82] The integrated treatment generally produced the best alcohol and depression outcomes for both women and men. In the nonintegrated treatments, women's drinking and depressive symptoms improved more in the depression-only treatment, whereas men improved more in the alcohol-only treatment. These findings highlight the unique benefit of treating depression among women with co-occurring AUD and suggest the need for more RCTs targeting this co-occurrence in women.

Given that drinking and antidepressant use are generally contraindicated adds to the significance of concurrent treatment of AUD and depression to maximize the effectiveness of psychotropic medications.[6] One RCT tested the effect of citalopram plus naltrexone and clinical case management for men and women with AUD and depression.[83] Compared to placebo, citalopram did not produce greater improvements in drinking or mood with one exception: women (but not men) on citalopram had a higher percentage of abstinent days. These findings point to the potential for tailoring antidepressant treatment to maximize treatment benefits for women with co-occurring AUD and depression.

Borderline personality disorder

Research has demonstrated elevated rates (i.e., of approximately 18%) of borderline personality disorder (BPD) in women seeking treatment for AUD.[84] Dialectical behavior therapy (DBT) is an empirically supported treatment for BPD that has been successfully adapted for co-occurring SUD.[85] A systematic review found that DBT has shown positive potential for the treatment of women with co-occurring SUD and BPD,[86] leading to reductions in substance use, suicidal/self-injurious behaviors, treatment attrition, and social functioning problems. No studies that tested DBT specifically with women who have co-occurring AUD and BPD have been found.

Mechanisms of Change: How Change Occurs

The goal of understanding moderators and mechanisms of change in treatment is to identify how patient characteristics interact with treatments, identify variables key to successful change, and then develop or modify treatments to target those variables more efficiently in treatment. Currently, there are relatively limited data on moderators and mechanisms of change in alcohol use during and after AUD treatment for women. Moderators are defined as "specification variables" that impact the association between two other variables,[87] for instance, the effect of baseline major depressive disorder on treatment outcome of female-specific versus gender-neutral treatment for AUD. A mediator is an "intervening variable" that "transmits the effect of the independent variable on the dependent variable";[87] for instance, cognitive behavioral treatment of AUD has its effect on drinking outcome in part by increased use of effective coping skills among clients.

Research on moderators of outcome has elucidated the need for heterogeneity in samples and helped to refine female-specific treatments.[87] For example, findings that anxiety pretreatment and depression pre- and posttreatment predicted poorer drinking outcomes for women[88] suggest the value of including interventions to alleviate depression and anxiety in female-specific AUD treatment. Recent and more sophisticated research has studied the interaction of moderators and mediators of treatment response. For instance, Holzhauer and colleagues combined a moderator

analysis with testing the intensity and timing of reductions in drinking after specific outpatient treatment sessions that targeted depression and anxiety in female-specific AUD treatment.[89] Three moderators assessed at baseline—depression, anxiety, and self-efficacy to remain abstinent in negative affect situations—predicted sudden gains (i.e., a steep decrease in drinking) after Session 5 or 6, which included interventions to attenuate negative affect. The results suggest that women who enter treatment struggling with negative affect may respond well to very specific, targeted interventions for those problems.

Hallgren and colleagues examined three hypothesized mechanisms of change—abstinence self-efficacy, coping skills, and therapeutic alliance—in outpatient AUD treatment for women.[90] These authors used daily data from the individual versus group female-specific parent study[60] and sophisticated longitudinal statistical modeling to quantify rates of change around initiation of abstinence for each participant in outpatient FS-CBT. They also tested time-linked change in mediators before each of the 12 therapy sessions. Data on daily drinking and craving were available for the baseline, in-treatment, and 12-month follow-up periods. Results focused on two subgroups of women: those who had initiated abstinence before treatment and those who initiated abstinence during treatment. Those who initiated abstinence during treatment showed marked improvements in two key hypothesized mechanisms of change (abstinence self-efficacy and coping skills) during the week that they initiated abstinence. Women who were abstinent at the start of treatment maintained higher abstinence self-efficacy and coping skills throughout treatment. Previously, Hallgren and colleagues had found that daily-rated alcohol craving (a different mediator) decreased in relation to initiation of abstinence in men and women in outpatient CBT for AUD.[91]

Using Network Analysis, a novel statistical approach that uses multilevel vector autoregression estimation for multiple time series data to simultaneously examine change among several hypothesized mechanisms of change, Holzhauer and colleagues compared pathways to drinking reduction among women in gender-neutral versus FS-CBT.[59,92] Across treatments, women changed their drinking via increased coping skills, abstinence self-efficacy, and increased autonomy. For women in FS-CBT, change in drinking also occurred through decreases in sociotropy and increases in social support for abstinence. Surprisingly, change in depression was linked to better drinking outcomes for women in gender-neutral CBT.

Going forward, continuing moderated mediation studies that examine the response of gender-specific moderators of response to medications or behavioral interventions for AUD, and the mechanisms by which these treatments operate for specific subpopulations, will help guide the development of personalized medicine for addiction.[30] A moderated mediation approach can facilitate examination of individual differences and sample heterogeneity that are linked to drinking outcomes and help to identify gender differences in pathways to successful treatment outcomes.

CONCLUSIONS AND RECOMMENDATIONS

Since the National Institutes of Health mandate in 1994 that biomedical research include female participants in clinical research,[93] a substantive body of literature emerged describing the unique aspects of AUD among women, which led to an accelerated development of treatments targeting women's unique clinical presentation. In 2006, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) identified women as an understudied population in treatment research and prioritized research to better understand the mechanisms by which treatments for AUD effect change in drinking.[94,95] Findings that drinking outcomes of female-specific and gender-neutral treatments may be similar does not mean that the development of female-specific treatments should not be pursued. First, there is evidence that mechanisms of women's response to treatment

(i.e., pathways to change) may differ from that of men, and identification of these gender-specific pathways can guide the development of efficient, gender-differentiated active ingredients in treatment. Second, there may be greater benefits of women-specific (vs. gender-neutral) treatment for secondary outcomes, such as psychosocial well-being, psychiatric health, pregnancy outcomes, and HIV risk reduction. Third, further study is needed on whether the availability of women-specific and women-only treatments enhances treatment access and engagement for women with AUD.

Gaps in knowledge remain; however, increasingly sophisticated research approaches are available to continue to tackle the questions of how and which treatments work best for whom. The contemporary focus on personalized medicine[96,97] extends to women with AUD; the end goal is not only to provide an array of specialized treatment options specifically tailored to enhance women's treatment access and engagement but also to provide science-based treatment elements and options uniquely matched to various common clinical presentations among women with AUD.

A critical problem to resolve is treatment access and utilization. Only 15% of women with lifetime AUD ever seek treatment for it, and women experience multiple individual-based barriers to accessing treatment. In addition, systemic barriers to AUD treatment for women need attention, as a minority of substance use treatment services in the United States offer gender-segregated or female-specific programming. Extant literature suggests that women may prefer gender-segregated treatment for AUD but also suggests this treatment offers no added benefit in the absence of female-specific programming content. Thus, widespread availability of female-only treatment settings that include evidence-based female-specific interventions and content is likely to increase treatment utilization and enhance outcomes for women with AUD. In order to populate female-only treatment settings with female-specific programming, we need to develop an array of evidence-based options. A number of RCTs have yielded newly available, evidence-based female-specific treatment protocols for AUD and SUD treatment that are at least equivalent in positive outcomes to evidence-based control treatments.[59,60,62,70,74,79] Outcomes for secondary (non-AUD) patient problems, such as depression and anxiety,[59,60] trauma symptoms,[69] cardiovascular function,[98] health behaviors, drug use, and quality of life[99,100] from these female-specific treatments also have been positive. NIAAA's focus on implementation studies in conjunction with the study of mechanisms of change[101] should accelerate testing the incorporation of female-specific interventions into community settings—not just addiction specialty clinics but also primary care and general mental health settings. These interventions should ultimately lead to algorithms for optimal personalization of treatment components to individuals' clinical presentation. In the meantime, since most women currently receive treatment in gender-neutral settings, it is important to address women's specific needs even in the context of mixed-gender, gender-neutral[102] clinical programming. Research to address unresolved gaps in the knowledge base is needed. For example, does the availability of female-specific programming, whether in female-segregated or mixed-gender settings, increase AUD treatment utilization by women? In addition, there is a dearth of rigorous RCTs comparing female-only versus mixed-gender treatment formats that contain female-specific programming to test differential treatment engagement and positive outcomes.

Notable areas of additional needed research on women and AUD treatment follow.

Prevention

Women who enter treatment for AUD present with greater addiction and more severe psychosocial issues than men. Secondary prevention research has focused on engaging women in treatment as well as on providing alcohol psychoeducation earlier in women's problem drinking careers, which may help arrest the telescoped trajectory to AUD and SUD and the corresponding psychosocial decline.

Setting

Women are more likely to self-identify as having an alcohol problem and enter AUD treatment through a medical or mental health portal than a substance use specialty clinic. For instance, women may obtain AUD treatment in the course of seeking treatment for a co-occurring psychiatric disorder, such as PTSD or depression, in a general mental health setting.[19,20] Also, brief interventions in primary care settings have been found to be promising in reducing drinking among less complex cases of women with low co-occurrence,[103] but no studies have examined the co-location of more intensive outpatient female-specific AUD treatments in primary care or women's medical clinic settings.

Treatment Silos

Increasing rates of drug use among women point to a need for integrated AUD and SUD female-specific treatments. Although some evidence-based treatments are available,[103] the net can be cast even wider to include a range of health behaviors such as nutrition, sleep, exercise, smoking cessation, and use of benzodiazepines. Framing AUD treatment for women in the context of a general health and wellness approach that addresses other health behaviors may increase appeal, reduce stigma, and enhance utilization.

Digital Delivery Platforms

Testing telehealth platforms for individual and group AUD treatments may help reduce barriers to use among women. Likewise, testing ancillary smartphone applications that link women to in vivo coping skills training and social network support could enhance outcomes of existing in-person programs or serve as stand-alone aids for women who face insurmountable treatment entry barriers.

Female-Specific, Coping-Skills-Based, Peer Support Groups

Female-specific, coping-skills-based, peer support groups are not widely available. The evidence base for women's Alcoholics Anonymous meetings needs to be established. In addition, the recent positive development of a recovery coach industry may help with in vivo social support especially for women, but research is necessary to establish an evidence base.

Medications

Research on medications for women with AUD as one treatment element should continue. A precision medicine approach testing gender, genetic profiles, and specific medications is an important avenue to pursue.

Mechanisms of Change Research

Research on mechanisms of change is crucial to untangle whether similar drinking outcomes of women and men with AUD are achieved via gender-specific pathways to change and to identify active ingredients and mediators of treatment change best suited for women with only AUD and for women with specific types of co-occurring disorders. New methodologies in statistics, neuroscience, and research design are helping to clarify these questions; however, additional research is needed to streamline and personalize optimally efficient treatment components for every woman seeking care for AUD.

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The Endocrine System and Alcohol Drinking in Females

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Sexually dimorphic effects of alcohol exposure throughout life have been documented in clinical and preclinical studies. In the past, rates of alcohol use disorder (AUD) were higher in men than in women, but over the past 10 years, the difference between sexes in prevalence of AUD and binge drinking has narrowed. Recent evidence adds to historical data regarding the influence of sex steroids on alcohol drinking and the interaction with stress-related steroids. This review considers the contribution of the endocrine system to alcohol drinking in females, with a focus on the hypothalamic pituitary gonadal axis and the hypothalamic pituitary adrenal axis and their reciprocal interactions. Emphasis is given to preclinical studies that examined genomic and rapid membrane effects of estrogen, progesterone, glucocorticoids, and GABAergic neurosteroids for their effects on alcohol drinking and models of relapse. Pertinent comparisons to data in males highlight divergent effects of sex and stress steroids on alcohol drinking and emphasize the importance of considering sex in the development of novel pharmacotherapeutic targets for the treatment of AUD. For instance, pharmacological strategies targeting the corticotropin releasing factor and glucocorticoid receptor systems may be differentially effective in males and females, whereas strategies to enhance GABAergic neurosteroids may represent a biomarker of treatment efficacy in both sexes.

KEY WORDS: estrogen; ethanol; glucocorticoid; neurosteroid; progesterone; stress

INTRODUCTION

Alcohol use disorder (AUD), a diagnosis that combines criteria for alcohol abuse and alcohol dependence from the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders into a single disorder in the 5th edition,[1] negatively influences health and is the third-leading preventable cause of death in the United States.[2] According to the 2015 National Survey on Drug Use and Health, the prevalence of binge drinking, which is the consumption of an excessive amount of alcohol in a short period of time, and of heavy alcohol use was similar in males and females.[2] Likewise, a recent meta-analysis confirmed a greater increase in alcohol use and binge drinking in women versus men over the past 16 years,[3] representing a narrowing of the historically higher

AUD rate in males. It has been suggested that the increased rate of AUD among women may be due to stress or to drinking to regulate a negative affect.[4-6]

As elegantly reviewed by Rachdaoui and Sarkar, acute and chronic alcohol administration disrupts functioning of the endocrine system, which is a complex system of glands that work in conjunction with the nervous system to maintain homeostasis.[7] Glands of the endocrine system produce and secrete hormones into the circulation, which can have long-lasting as well as rapid actions. Hormones affect physiological functions such as metabolism, reproduction, growth, and development, and they facilitate the ability to respond to changes in the environment and to stress.[7-8] Additionally, gonadal sex steroid hormones exert organizational (permanent) and activational (transient) effects on the brain to regulate sexual differentiation, secondary sex characteristics, and sex differences in behavior.[4,9-11] Gonadal steroids also influence the stress response that is mediated by the hypothalamic-pituitary-adrenal (HPA) axis, and elevated stress hormones affect the reproductive or hypothalamic-pituitary-gonadal (HPG) axis.[8] Finally, sex and stress hormones influence alcohol consumption and behavior in models of addiction.[4-5,10,12] As a result, it should be considered that alcohol consumption can influence the endocrine system and the reciprocal interaction between the stress and reproductive axes and that gonadal and stress steroid hormones can influence alcohol drinking and addiction-related behaviors.

This review highlights preclinical research on the contribution of gonadal and stress steroids to alcohol drinking in females. It focuses on the HPG and HPA axes and describes how endogenous fluctuations in steroid hormones as well as exogenous administration influence alcohol drinking and other pertinent addiction-related phenotypes. In addition to a discussion of how classical steroid responses are mediated by genomic effects via intracellular receptors, this review considers rapid steroid responses via membrane receptors and the interaction with neurotransmitter systems. Relevant comparisons to results in males bolster the emerging evidence for sex differences in steroid hormone and stress effects on alcohol drinking behavior and addiction-related phenotypes. These comparisons emphasize the importance of considering sex in the development of novel pharmacotherapies for the treatment of AUD.

OVERVIEW OF THE HPG AND HPA AXES

The HPG axis is the neuroendocrine axis important for reproduction, whereas the HPA axis is the neuroendocrine axis important for the stress response. As depicted in Figure 1, both the HPG and HPA axes are regulated by steroid hormone feedback and reciprocal interactions between steroids in each axis.

The HPG axis comprises the hypothalamus, pituitary, and gonads. Hypothalamic nuclei (e.g., in the preoptic area) release gonadotropin-releasing hormone (GnRH) into the portal vasculature to stimulate the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary (see Figure 1). Circulating LH and FSH act on the gonads to stimulate the production and release of estrogen and progesterone from the ovary and of testosterone from the testis.[7,13] In females, FSH stimulates follicle development in the ovary and the secretion of estradiol, which promotes a surge in LH and FSH. LH stimulates ovulation and the subsequent secretion of progesterone. These overall effects of estradiol are similar across species, but phases of the 28- to 30-day menstrual cycle in primates and the 4- to 5-day estrous cycle in rodents are not completely analogous (see the box **Phases of Primate Menstrual and Rodent Estrous Cycles**). Additionally, steroid hormone feedback loops regulate HPG axis function at the level of the hypothalamus and anterior pituitary. Testosterone inhibits GnRH, LH, and FSH through negative feedback, whereas estradiol and progesterone can exert both negative (inhibitory) and positive (stimulatory) feedback actions, depending on the stage of the ovarian cycle (see Figure 1).

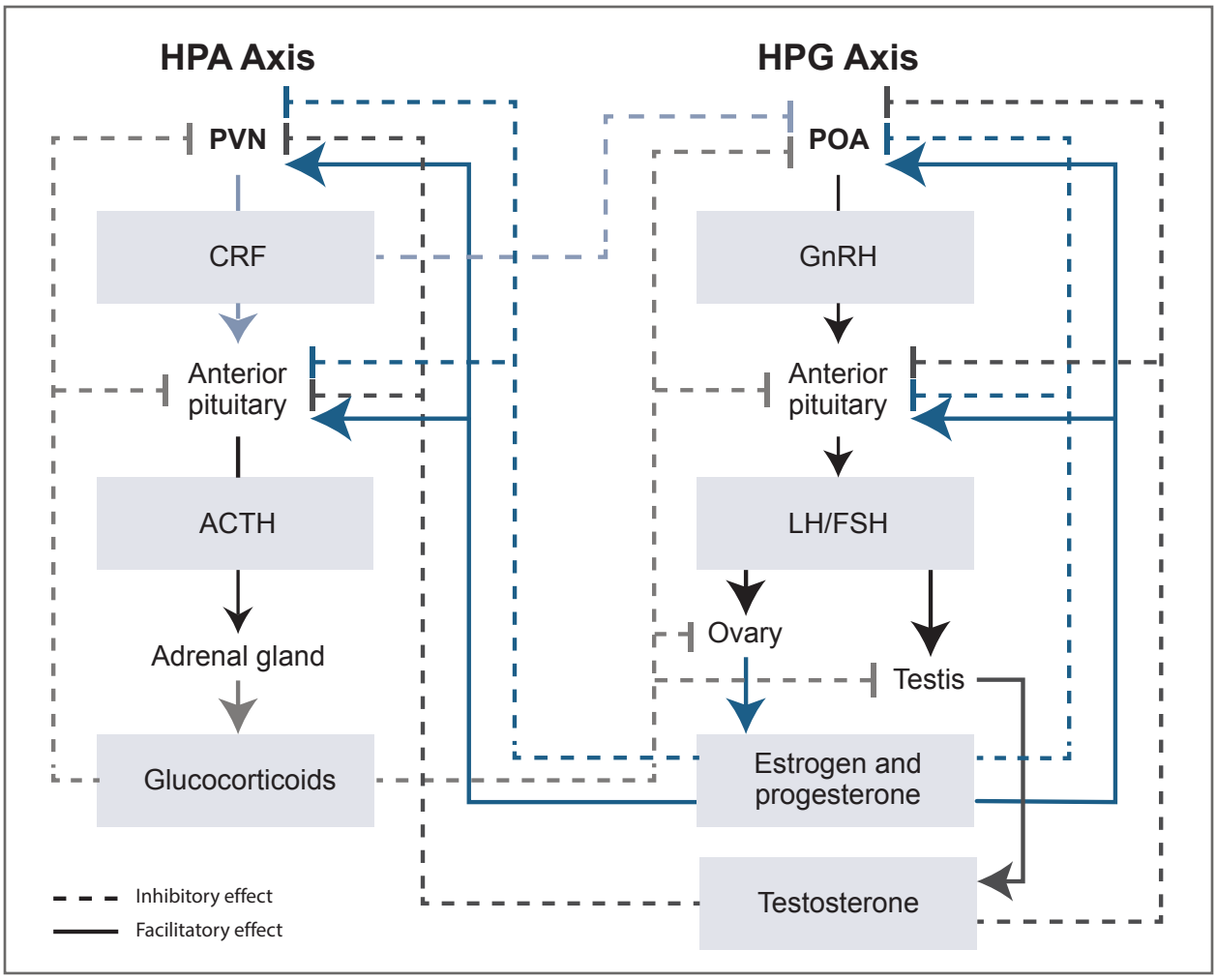

Figure 1 Simplified diagram of the reciprocal interaction between the HPA axis and the HPG axis. Solid lines with arrows depict facilitatory effects. Dashed lines with block symbols depict inhibitory or negative feedback effects. Gonadal steroids are involved in the regulation of the HPA axis at the level of the PVN and the anterior pituitary. Specifically, testosterone has negative feedback effects at the PVN and the anterior pituitary, and estrogen and progesterone can have either a facilitatory or an inhibitory effect at the PVN and the anterior pituitary. Stress steroids can regulate the HPG axis at the level of the hypothalamic POA, anterior pituitary, and gonads (ovaries or testes). Glucocorticoids (corticosterone in rodents, cortisol in humans and monkeys) exert negative feedback at each level of the HPG axis, and CRF exerts negative feedback at the POA. Upstream regulatory centers for each axis are not shown. Also shown is the negative feedback exhibited by glucocorticoids within the HPA axis, the negative feedback exhibited by testosterone within the HPG axis, and the negative and positive feedback exhibited by estrogen and progesterone within the HPG axis. *Note:* ACTH, adrenocorticotropic hormone; CRF, corticotropin releasing factor; FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; POA, preoptic area; PVN, paraventricular nucleus. *Source:* Modified from a figure by Oyola and Handa.[8]

Responses to stress are mediated by the HPA axis and the sympathetic autonomic response. Short-term activation of the HPA axis produces beneficial effects, whereas chronic activation can result in deleterious effects.[14] Neurons in the paraventricular nucleus (PVN) of the hypothalamus are responsible for the secretion of corticotropin releasing factor (CRF) and arginine vasopressin into the portal system, and CRF causes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH stimulates the biosynthesis and release of glucocorticoids from the adrenal cortex.[13] Negative feedback of glucocorticoids at the level of the

Phases of Primate Menstrual and Rodent Estrous Cycles*	
Primate (Human and Monkey)	**Rodent (Rat and Mouse)**
The average length of the menstrual cycle is 28 to 30 days.	The average length of the estrous cycle is 4 to 5 days.
Follicular phase: As the ovarian follicle develops, estradiol is secreted. Menstruation overlaps with the beginning of the follicular phase.	**Metestrus/diestrus phase:** As the ovarian follicle develops, estradiol is secreted.
Periovulatory phase: A rapid estradiol increase triggers an LH surge, which produces ovulation.	**Proestrus/estrus phase:** A rapid estradiol increase triggers an LH surge, which stimulates progesterone release and produces ovulation.
Luteal phase: The corpus luteum releases high levels of estradiol and progesterone. Menstruation occurs at the end of the luteal phase as hormone levels fall.	**No equivalent phase:** Female rodents do not have a functional corpus luteum.

*Adapted from a table by Becker and Koob.[4] *Note:* LH, luteinizing hormone.

anterior pituitary and PVN inhibits CRF, arginine vasopressin, and ACTH production and helps maintain optimal glucocorticoid levels (Figure 1).

An additional consideration is that the HPA and HPG axes have reciprocal interactions in terms of steroid hormone feedback, as depicted in Figure 1.[8] For example, glucocorticoids exhibit negative feedback of the HPG axis at the level of the hypothalamus, anterior pituitary, and gonads. As a result, a chronic elevation of glucocorticoids can result in suppressed HPG axis function. Likewise, gonadal steroids may influence HPA axis function, as evidenced by the effects of testosterone, progesterone, and estrogen at the level of the PVN and anterior pituitary.[13] For example, basal and stress-induced increases in glucocorticoids are greater in female than in male rodents. Evidence from studies that used gonadectomy and hormone replacement suggests that testosterone exerts an inhibitory influence on HPA axis activity in male rodents, whereas estrogen primarily produces a facilitatory effect on HPA axis activity in female rodents. Some of the differing results for estrogen on HPA axis function may be due in part to the opposing actions of two types of estrogen receptors.[13]

STEROID HORMONE RECEPTORS AND CIRCUITRY IMPORTANT FOR STRESS AND DRINKING

Steroid hormones produce effects through several mechanisms. First, steroid hormones bind to their classical intracellular receptors, which act as ligand-activated transcription factors to alter gene expression and produce long-lasting actions.[13] Progestins, such as progesterone and dihydroprogesterone, bind to two progesterone receptor isoforms: A and B.[15] Estrogens, such as 17beta-estradiol, bind to two distinct receptor subtypes: estrogen receptor-alpha and estrogen receptor-beta.[13,16] Androgens, such as testosterone and dihydrotestosterone, bind to androgen receptors.[13] Glucocorticoids, such as corticosterone in rodents and cortisol in humans and monkeys, bind to mineralocorticoid receptors (type I) and glucocorticoid receptors (type II).[13] Endogenous glucocorticoids have higher affinity for mineralocorticoid receptors than for glucocorticoid receptors.[13]

Second, through classical and nonclassical receptors located in the cell membrane, steroids have rapid effects that influence second-messenger

pathways and ion channel function.[16-22] Finally, steroid hormone derivatives can rapidly alter ion channel function via allosteric interactions with ligand-gated ion channels.[23-26] For example, the progesterone derivative allopregnanolone and the deoxycorticosterone derivative tetrahydrodeoxycorticosterone (THDOC) are very potent positive allosteric modulators of gamma-aminobutyric acid$_A$ (GABA$_A$) receptors and can rapidly alter neuronal inhibition. Rapid actions at the cell membrane gave rise to the terms "neuroactive steroids" and "neurosteroids" (Refer to the Finn and Jimenez article on neurosteroid networks for more information about neurosteroid synthesis and pathways.)[24] Thus, steroid hormones and their derivatives can influence brain function and behavior through classic genomic actions and rapid membrane effects.

Neuroanatomical overlap occurs between gonadal and adrenal steroid hormone receptors within the hypothalamic (the PVN) and extra-hypothalamic (e.g., in the amygdala and the bed nucleus of the stria terminalis) stress circuitry (see Figure 2). Overlap also occurs within components of the mesocorticolimbic circuitry (e.g., in the medial prefrontal cortex, nucleus accumbens, ventral tegmental area, and hippocampus). Ultimately, this overlap can affect output of the PVN (i.e., the stress response) and alcohol drinking. Figure 2 shows simplified circuitry of

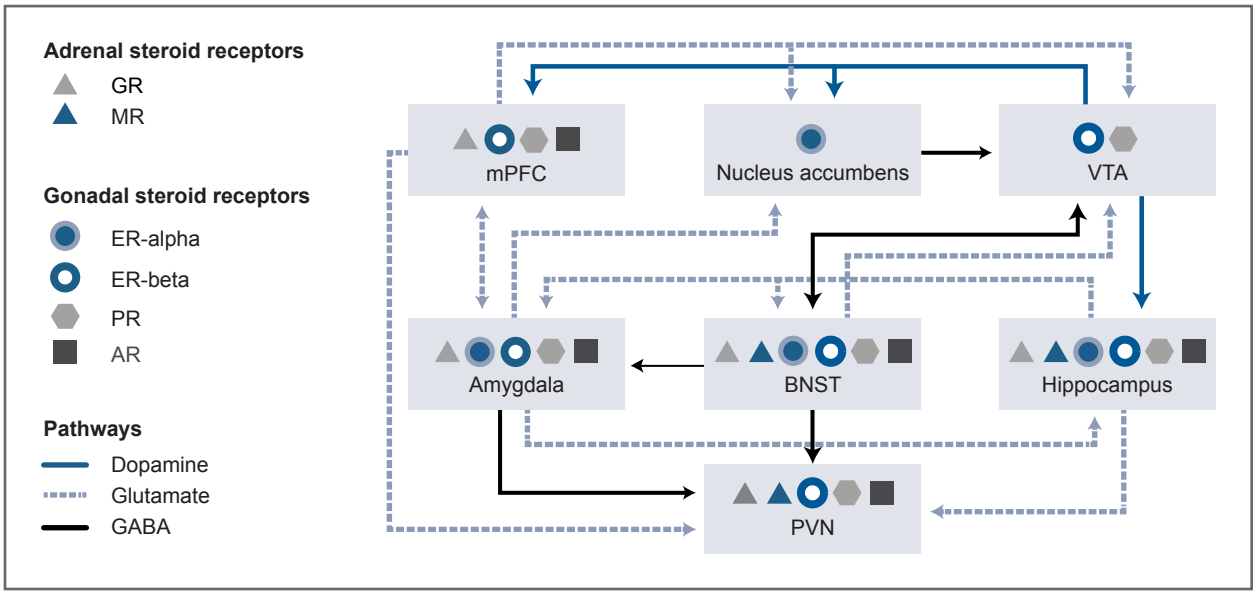

Figure 2 Simplified stress and mesocorticolimbic circuitry, including inputs to the HPA axis and the distribution of gonadal and adrenal steroid receptors. Rapid steroid actions at associated receptors and neurosteroid actions at GABA$_A$ receptors represent additional mechanisms for fine-tuning central nervous system excitability. Gonadal and adrenal steroid receptors have considerable overlap in expression within the hypothalamic (PVN) and extrahypothalamic (e.g., amygdala, BNST) stress circuitry, as well as among components of the mesocorticolimbic (e.g., mPFC, nucleus accumbens, VTA, and hippocampus) circuitry, which ultimately can affect output of the PVN (i.e., the stress response) and alcohol drinking. This simplified circuitry shows GABAergic (red), glutamatergic (green), and dopaminergic (blue) projections within the brain regions that input to the PVN, either directly or indirectly through an inhibitory projection from the peri-PVN (which contains ER-alpha and GR, not shown). The brain regions involved and the overall influence on the output of the PVN (and HPA axis activity) depend on the stressor modality, the level of acute or chronic alcohol consumption, and the various steroid and neurosteroid levels and actions at their associated receptors. *Note:* AR, androgen receptor; BNST, bed nucleus of the stria terminalis; ER-alpha, estrogen receptor-alpha; ER-beta, estrogen receptor-beta; GABA, gamma-aminobutyric acid; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; PR, progesterone receptor (both isoforms); PVN, paraventricular nucleus; VTA, ventral tegmental area. *Source:* Circuitry[13,24] and steroid receptor distribution[13,15,21,33-36] are modified from other sources.

glutamatergic, GABAergic, and dopaminergic projections in brain regions important for responses to stress and alcohol drinking behavior. These responses to stress and alcohol drinking behavior may be modulated by steroid actions at receptors localized within the brain regions.

For example, the brain regions involved and the overall influence on PVN output depends on the stress, on various steroid hormone levels and actions at associated receptors,[8,13] and on $GABA_A$ receptor–active neurosteroid levels and actions at $GABA_A$ receptors.[24] Alcohol's ability to activate the HPA axis relies on activation of the PVN.[27] Synaptic connections within the PVN are primarily GABAergic and glutamatergic.[28,29] As a result, glutamatergic afferents in the forebrain that increase GABA release in the PVN, and upstream GABAergic projection neurons that activate the PVN, produce tonic inhibition of the PVN.[30]

Additionally, stress-induced elevations in $GABA_A$ receptor–active neurosteroids can modulate PVN activity, given that physiological concentrations of allopregnanolone (i.e., 10 nM to 100 nM) inhibit output of PVN neurons (i.e., CRF release) via a potentiation of $GABA_A$ receptors. [31,32] A neurosteroid-induced inhibition of CRF release likely represents another mechanism for terminating the stress response.

Another consideration is that alcohol-induced alterations to neurotransmission within the circuitry depicted in Figure 2 can be modulated by steroid hormone and neurosteroid levels. For instance, estradiol and progesterone can rapidly affect dopamine signaling via actions at their respective steroid receptors, functional coupling between estrogen receptors (both alpha and beta) and metabotropic glutamate receptors (Group I or Group II) can activate distinct signaling pathways, and neurosteroids can rapidly increase $GABA_A$ receptor–mediated signaling.[21,23,24,33-36] Thus, rapid steroid actions at associated receptors and neurosteroid actions at $GABA_A$ receptors are other mechanisms for fine-tuning central nervous system excitability.

STEROID HORMONE EFFECTS ON DRINKING AND OTHER ADDICTION-RELATED BEHAVIORS

Investigations of sex differences in drug misuse and self-administration behavior have gained momentum, particularly after 2015, when the National Institutes of Health announced a policy of including sex as a biological variable. Clinical and preclinical alcohol research offers many examples of sex differences, given that alcohol exposure can produce sexually dimorphic effects throughout life. Discussion of all these studies is beyond the focus of this review, but several excellent reviews describe sex differences in the effects of alcohol exposure across development. Reviews have summarized findings from prenatal[37] and adolescent[38-41] alcohol exposure, as well as from exposure during adulthood.[4,7] Marked sex differences in self-administration patterns have been well-documented and observed at every stage of the course of drug exposure, from acquisition to maintenance to relapse, although more evidence has been reported for psychostimulants than for alcohol.[42,43]

In general, results from preclinical alcohol models indicate that females acquire self-administration of alcohol more rapidly and consume larger alcohol doses during maintenance phases than males, but females exhibit a reduced severity in somatic and negative affective symptoms of alcohol withdrawal than males.[4] Although the potential role of organizational steroid effects in controlling sex differences in alcohol responses cannot be ruled out, this review focuses primarily on the effects, during adulthood, of estrogen, progesterone, and neuroactive metabolites on alcohol drinking and pertinent addiction-related phenotypes in females.

Gonadal Steroids

In a variety of models of alcohol access, preclinical research in rodents documents that females consume larger doses of alcohol than males. This sex difference appears to be partly due to

a facilitatory effect of estrogen in females and an inhibitory effect of testosterone in males.[4,44] In female rodents, the estrous cycle phase had minimal effects on alcohol drinking or operant self-administration.[45] Reduced self-administration of alcohol was observed in females during proestrus and estrus only when their cycles had been experimentally synchronized (the effect was not observed in randomly cycling females that were not synchronized). Likewise, microanalysis of alcohol drinking patterns revealed increased frequency of bouts but less alcohol consumed within each bout during proestrus,[46] suggesting subtle differences in the pattern of alcohol drinking across the estrous cycle. In several models, more recent evidence confirmed that the phase of estrous cycle did not significantly influence alcohol drinking, including binge drinking,[47] escalated drinking among dependent animals,[48] self-administration of alcohol,[49] or cue plus yohimbine-induced reinstatement of alcohol-seeking.[49]

In contrast to studies of rodents, a recent, longitudinal study of female rhesus monkeys with systematic and extensive hormonal monitoring of menstrual cycle phase across 15 months of active alcohol drinking determined that the monkeys drank more alcohol during the luteal versus the follicular phase and drank the most alcohol during the late luteal phase, when progesterone declines rapidly.[50] These results from a nonhuman, primate model of self-administration of alcohol were the first to show that typical menstrual cycle–related fluctuations in progesterone, especially during the late luteal phase, modulated alcohol drinking. Previous studies that used less accurate characterization of menstrual cycles and differing histories of alcohol intake revealed inconsistent effects of the menstrual cycle on alcohol drinking. Therefore, Dozier and colleagues' method of extensive menstrual cycle characterization during periods of active drinking[50] likely was necessary to show the significant menstrual cycle–related fluctuation in alcohol drinking.

The results by Dozier and colleagues are consistent with clinical studies in which increases in premenstrual distress and negative affective states in women were positively correlated with greater alcohol drinking during the late luteal phase.[4,51] Thus, existing data support the conclusion that typical hormonal fluctuations during the menstrual cycle, but not during the estrous cycle, can influence alcohol drinking. These differences may reflect hormonal changes during the menstrual cycle that are distinct from those in the estrous cycle,[51] because rodents have no equivalent luteal phase (see the box **Phases of Primate Menstrual and Rodent Estrous Cycles**).

Despite minimal effects of the estrous cycle phase on alcohol drinking, several lines of evidence in studies of rodents indicate that the hormonal milieu contributes to sex differences in models of alcohol drinking behavior and alcohol reward. First, development of the four core genotype (FCG) mouse model has enabled researchers to examine the sex chromosome complement (XX versus XY) and the gonadal phenotype (testes versus ovaries) and their independent contributions to sex differences.[52] This model produces four different progeny, each with a different combination of sex chromosomes and gonadal sex: XXF (XX gonadal females), XXM (XX gonadal males), XYF (XY gonadal females), and XYM (XY gonadal males). Use of the FCG model determined that gonadal phenotype predicted self-administration of alcohol, independent of the sex chromosome complement.[53] That is, gonadal females consumed more alcohol than gonadal males.

Second, several studies that used gonadectomy and hormone replacement found that when compared with intact female rats, female rats with gonadectomy drank significantly less alcohol.[54,55] After the gonadectomized rats received estradiol replacement, the low levels of alcohol drinking increased significantly to baseline levels. Also, in female mice, gonadectomy significantly reduced binge drinking from the high levels of consumption among intact females to levels of consumption equivalent to that of intact males.[47] The lower levels of binge drinking among female mice with gonadectomy increased significantly following replacement with 17beta-estradiol.[47]

Similarly, gonadectomy in male and female rats produced shifts in operant alcohol self-administration toward the pattern of the opposite sex (i.e., reduced for females and increased for males).[49] In these rats, estradiol replacement in females with gonadectomy significantly increased self-administration of alcohol, and testosterone replacement in males with gonadectomy significantly decreased self-administration of alcohol. However, in rodent males, the suppressive effect of testosterone on alcohol drinking contrasts with fairly consistent clinical reports that found positive associations between blood or salivary testosterone levels and alcohol drinking among human adolescent and adult males.[10]

Third, in studies that used conditioned place preference as a measure of alcohol reward, only intact female rats exhibited conditioned place preference to an intermediate alcohol dose.[56] Intact male rats and female rats with gonadectomy (males with gonadectomy were not tested) did not exhibit the preference for the drug paired side of the testing chamber. Subsequent studies in female mice determined that in females with gonadectomy, 17beta-estradiol facilitated alcohol-induced conditioned place preference due to activation of both estrogen receptor-alpha and estrogen receptor-beta.[57]

The facilitatory effects of estradiol on alcohol drinking and a measure of alcohol reward may be due, in part, to estradiol's rapid enhancement of dopaminergic signaling.[36] In the prefrontal cortex, the ability of a low dose of alcohol (0.5 g/kg) to enhance extracellular dopamine levels in female rats during estrus was eliminated by gonadectomy and restored by estradiol treatment.[58] In the striatum, the well-documented ability of estradiol to enhance dopaminergic signaling in females was hypothesized to be associated with effects of estradiol on membrane-localized estrogen receptor-alpha and estrogen receptor-beta that were functionally coupled to metabotropic glutamate receptors.[34,36] Collectively, research confirms that within each sex, activational effects of gonadal steroids can modulate alcohol drinking behavior.

The organizational effect of testosterone-derived estrogen, which causes sex-specific differentiation of the mammalian brain,[9,52,59] during a critical period of brain development, also influences alcohol drinking. Early work found that neonatal exposure to estrogen among female rats, which conferred a male phenotype on a genetically female brain, produced levels of alcohol drinking that were lower than levels in intact females but similar to levels in intact males.[60]

More recent work has determined that gonadectomy alone in male and female rats shifted self-administration of alcohol toward the pattern of the opposite sex, but it did not eliminate the sex difference.[49] Females with gonadectomy still self-administered more alcohol than males with gonadectomy. Likewise, during tests of alcohol-seeking (cue plus yohimbine-induced reinstatement), intact females engaged in active lever presses more than intact males. Females with gonadectomy still had more lever presses than males with gonadectomy, and lever presses were not altered by steroid replacement (i.e., estradiol in females and testosterone in males). These results suggest that in addition to the contribution of the activational effects of gonadal steroids on alcohol drinking in males and females, permanent factors, such as sex chromosomes and the organizational effects of gonadal steroids, contribute to sex differences in alcohol-drinking and alcohol-seeking behaviors.

Use of the FCG model also determined that independent of gonadal phenotype, the sex chromosome complement mediates habitual responding for alcohol reinforcement after moderate instrumental training.[53] Specifically, XY mice (XYM and XYF) were insensitive to alcohol devaluation, a procedure that established conditioned taste aversion by pairing alcohol consumption with lithium chloride injections. Both valued (no conditioned taste aversion) and devalued (with conditioned taste aversion) XY mice responded similarly, indicating that XY mice were responding in a habitual manner. XX mice (XXM and XXF) were sensitive to alcohol devaluation (devalued XX mice responded less

than valued XX mice), indicating that XX mice retained goal-directed responding.[53]

Given that AUD involves a transition from casual to habitual use, as well as a transition from ventral striatal circuitry including the prefrontal cortex to a more dorsal circuit involving the dorsolateral striatum,[61] the results from Barker and colleagues[53] suggest that sex chromosomes mediate sex differences in habit formation for alcohol, and they may underlie sex differences in alcohol-induced neuroadaptation. Additional studies are necessary to disentangle the contribution of sex chromosomes and the organizational effects of gonadal steroids on alcohol-motivated behavior.

Neurosteroids

Studies have examined whether manipulation in levels of the progesterone derivative allopregnanolone, which is a potent, positive allosteric modulator of $GABA_A$ receptors,[23-26] alters alcohol drinking and alcohol's subjective effects. In general, females have higher endogenous allopregnanolone levels than males. Allopregnanolone levels in females fluctuate across the estrous and menstrual cycles and increase during pregnancy in a time-dependent manner that is related to fluctuations in endogenous progesterone.[25,62,63] The majority of studies, which were conducted in male rodents, consistently have shown that allopregnanolone, after systemic and intracerebroventricular administration, exerts a biphasic effect (i.e., increases with low physiological doses and decreases with supraphysiological doses) on alcohol drinking and operant self-administration.[64]

In contrast, research has shown that allopregnanolone does not alter alcohol drinking in female mice (see Figure 3).[65] Administration of the 5alpha-reductase inhibitor finasteride to mice, which decreased endogenous $GABA_A$ receptor–active neurosteroids such as allopregnanolone,[65] produced a decrease in the acquisition and maintenance phases of self-administration of alcohol in males, with females, again, being less sensitive to these modulatory effects.[66-68] A priming dose of allopregnanolone promoted reinstatement of alcohol-seeking behavior in male mice and rats,[69,70] but similar studies in females have not been conducted.

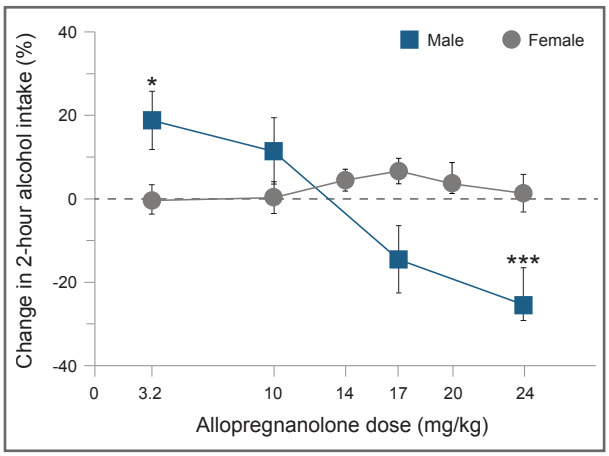

Figure 3 Sex differences in the modulatory effect of allopregnanolone on limited-access alcohol drinking in mice. Dose response is shown as a percentage of change from baseline values (vehicle treatments). The graph depicts the means and standard errors for 18 male and 24 female C57BL/6J mice. The dashed line represents the baseline values. *Note:* $*p \leq 0.05$; $***p \leq 0.001$ versus respective vehicle treatment (20% beta-cyclodextrin). *Source:* Adapted from Finn DA, Beckley EH, Kaufman KR, et al.[64]

Finally, evidence also suggests that allopregnanolone and its 5beta-isomer, pregnanolone, like alcohol, possess positive motivational effects, as demonstrated by conditioned place preference among male mice,[71] preference for drinking steroids versus water in male mice and rats,[72,73] and intravenous self-administration in four rhesus monkeys, with the highest self-administration of pregnanolone in the one female versus the three male monkeys.[74] Both allopregnanolone and pregnanolone produced potent, alcohol-like, discriminative stimulus effects in male and female cynomolgus monkeys.[75] Also, during the luteal phase of the menstrual cycle, when endogenous allopregnanolone levels were highest, female cynomolgus monkeys were more sensitive to the discriminative stimulus effects of alcohol and

to the alcohol-like effects of allopregnanolone.[76] Collectively, these results suggest that GABAergic neurosteroid levels may enhance the reinforcing effects of alcohol, and that in rodents, sensitivity to neurosteroid effects differs by sex.

A comparison of results in female mice and monkeys suggests that female monkeys are more sensitive to allopregnanolone's modulatory effects on alcohol drinking behavior. However, the relative insensitivity in female mice contrasts with the enhanced sensitivity to the anticonvulsant effect of allopregnanolone and THDOC during alcohol withdrawal in female rats and in female mice that have a low withdrawal phenotype.[77-79]

Based on evidence that local allopregnanolone metabolism in hippocampal subregions significantly altered $GABA_A$ receptor–mediated inhibition,[80] a sex difference in allopregnanolone metabolism in discrete brain regions in mice possibly contributes to low sensitivity to allopregnanolone's modulatory effects on alcohol drinking. Belelli and Herd used the 3alpha-hydroxysteroid dehydrogenase (3alpha-HSD) inhibitor indomethacin to inhibit oxidation of allopregnanolone to dihydroprogesterone, which increased local allopregnanolone levels and enhanced $GABA_A$ receptor–mediated inhibition.[80] Early work indicated that female rats, when compared with males, had about twice the activity of 3alpha-HSD from rat-liver cytosol, and that this sex difference was induced by ovarian estrogen.[81] So, in female rodents, more 3alpha-HSD activity within neurocircuitry fundamental to the regulatory processes underlying alcohol intake possibly contributes to insensitivity to the effects of allopregnanolone on alcohol drinking. Consistent with this idea, administration of allopregnanolone and indomethacin in female mice did not alter alcohol drinking when administered separately but produced a significant decrease in alcohol drinking when administered in combination (see Figure 4, DA Finn and MM Ford, unpublished data, May 2013).

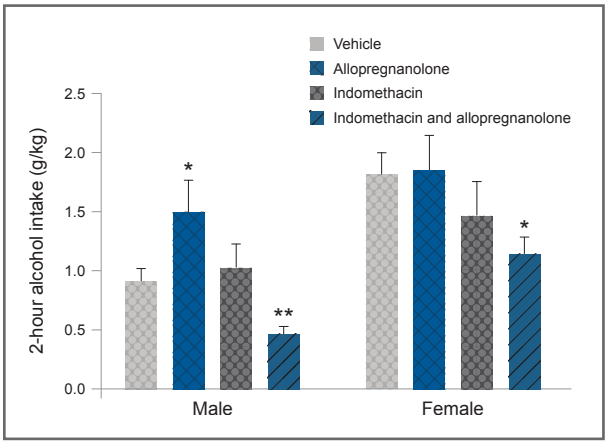

Figure 4 Modulatory effect of a combination of allopregnanolone and indomethacin in male and female mice. Female mouse insensitivity to allopregnanolone's modulatory effect on limited-access alcohol drinking was overcome by administering 0.1 mg/kg indomethacin along with 10 mg/kg allopregnanolone. Indomethacin blocks the oxidation of allopregnanolone and thereby enhances allopregnanolone's effect on $GABA_A$ receptor–mediated inhibition. The graph depicts the means and standard errors for 10 male and 10 to 11 female C57BL/6J mice. *Note*: $*p \leq 0.05$; $**p \leq 0.01$ versus respective vehicle treatment (20% beta-cyclodextrin). *Source:* DA Finn and MM Ford, unpublished data, May 2013.

Another strategy for avoiding potential confounds of rapid allopregnanolone metabolism is use of a synthetic allopregnanolone analog, such as ganaxolone.[82] Ganaxolone has a similar pharmacological profile to allopregnanolone, but it has an additional 3beta-methyl group that protects the steroid from metabolic attack at the 3alpha-position and extends the half-life about three to four times longer than that of allopregnanolone. In male rodents, ganaxolone produced a biphasic effect on alcohol drinking and self-administration when administered systemically[83-85] or bilaterally into the nucleus accumbens shell.[86] Systemic ganaxolone also promoted reinstatement of alcohol-seeking,[87] These effects of ganaxolone on alcohol drinking and seeking were similar to those observed following allopregnanolone administration. Preliminary results suggest that ganaxolone also

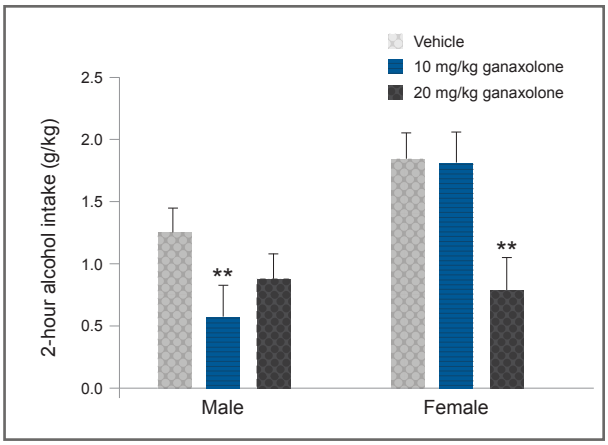

Figure 5 Sex differences in the modulatory effect of the synthetic neurosteroid ganaxolone in mice. Ganaxolone significantly decreased limited-access alcohol drinking in males and females. To significantly suppress alcohol drinking, female mice required a higher dose (20 mg/kg) than male mice (10 mg/kg). The graph depicts the means and standard errors for 10 male and 10 to 11 female C57BL/6J mice. *Note:* **$p \leq 0.01$ versus respective vehicle treatment (20% beta-cyclodextrin). *Source:* DA Finn and MM Ford, unpublished data, April 2013.

significantly reduces alcohol drinking in female mice, although a higher dose was required to produce a comparable reduction to that observed in male mice (see Figure 5, DA Finn and MM Ford, unpublished data, April 2013).

The U.S. Food and Drug Administration recently approved the allopregnanolone analog brexanolone for treatment of postpartum depression. In addition, ganaxolone is in phase 2 clinical trials for treatment of various disorders, such as postpartum depression, treatment-resistant depression, post-traumatic stress disorder (PTSD), and epilepsy. Allopregnanolone analogs and strategies to stabilize allopregnanolone levels also are being examined in clinical trials for the treatment of various central nervous system disorders.[88] Collectively, evidence suggests that targeting neurosteroid synthesis or use of neurosteroid analogs such as ganaxolone may represent innovative therapies for the treatment of AUD in males and females.[26]

EFFECTS OF CHRONIC ALCOHOL USE ON GONADAL STEROID LEVELS

Alcohol misuse and AUD produce significant hormonal disruptions in the endocrine system.[7] For sex steroids, the majority of evidence in rodents and humans suggests that chronic alcohol exposure significantly increases estradiol levels in both males and females, produces a slight or significant decrease in progesterone levels in both males and females, decreases testosterone levels in males, and produces a transient increase in testosterone levels in females. Additional work found that chronic exposure to alcohol vapor to induce dependence significantly increased testosterone levels in female mice and suggested that the increased testosterone levels in dependent female mice contributed to an observed estrous cycle disruption (i.e., prolonged diestrus).[89]

Thus, the HPG dysfunction that occurs in people with AUD can be associated with deleterious effects on reproduction in both males and females. However, some preclinical studies suggest that 6 weeks of binge drinking by female rodents[47] or 15 months of active drinking by female monkeys[50] did not significantly alter the estrous or menstrual cycles, respectively, in terms of overall cycle length or the length of specific cycle phases. Fifteen months of active drinking also did not alter progesterone or estradiol levels in the female monkeys.[50] The method of chronic alcohol exposure and resulting blood alcohol concentrations, which are considerably higher for vapor exposure (e.g., 200 mg%) than for drinking models (e.g., 80 mg% to 100 mg%), may contribute to the differences among studies with regard to whether chronic alcohol exposure disrupted the estrous or menstrual cycle.

EFFECTS OF CHRONIC ALCOHOL USE ON NEUROSTEROID LEVELS

Preclinical models of chronic alcohol drinking and vapor exposure both produce significant alterations in neurosteroid levels. Most of the evidence supports changes to allopregnanolone levels in plasma and in discrete brain regions.[24] The majority of available data are from studies in male rodents and monkeys. The results consistently show that chronic alcohol drinking and vapor exposure significantly decrease plasma allopregnanolone levels during acute withdrawal, a finding in harmony with the limited results reported for males and females with AUD.

In a small cohort of females with AUD, a significant reduction in allopregnanolone, progesterone, and estradiol levels was detected upon detoxification, and levels recovered to baseline values after 4 months of abstinence.[90] In contrast, chronic alcohol drinking did not significantly alter serum allopregnanolone levels in female monkeys,[50] nor did withdrawal from chronic alcohol vapor exposure alter plasma allopregnanolone levels in female mice (DA Finn and JP Jensen, unpublished data, Feb 2019 and Nov 2019).

Regarding brain regional changes, chronic alcohol exposure and withdrawal significantly decreased allopregnanolone levels in the amygdala of male monkeys and in the nucleus accumbens, ventral tegmental area, and medial prefrontal cortex of male rodents, with divergent changes reported in hippocampal subregions in male rodents.[24] However, preliminary results in female mice suggest that withdrawal from chronic alcohol exposure did not significantly alter cortical or hippocampal allopregnanolone levels (DA Finn and JP Jensen, unpublished data, Feb 2020 and Mar 2020).

Collectively, preclinical results in male rodents and monkeys suggest that independent adrenal and brain region regulation of neurosteroid synthesis occurs after chronic alcohol exposure and withdrawal. More preclinical research in females is necessary, but the available preclinical results suggest that females may be protected from chronic alcohol–induced suppression of allopregnanolone synthesis. Given the preclinical evidence that severity of alcohol withdrawal is reduced in females versus males,[4] and that allopregnanolone has anticonvulsant, anxiolytic, and antidepressant properties,[24] females may have the ability to maintain endogenous allopregnanolone levels after chronic alcohol exposure. This maintenance, versus the suppression seen in males, may contribute to the female phenotype for reduced severity and duration of alcohol withdrawal.

STRESS STEROIDS AND ALCOHOL-RELATED BEHAVIOR

Clinical studies provide evidence for a positive association between stress and alcohol drinking and other phases of AUD, including evidence of stress as a trigger of alcohol relapse.[91] Additionally, males and females have different sensitivities to alcohol and stress.[4-6] Acute stress exposure and alcohol intoxication both activate the HPA axis, and the HPA and HPG interact reciprocally (Figure 1).[8] Therefore, sex differences in HPA axis responsivity following acute stress or acute alcohol intoxication (i.e., enhanced elevation in glucocorticoids in females versus males) are not surprising. Discussion of all studies on this topic is beyond the scope of this review, but other reviews provide more detail.[5,8,13,92]

Preclinical studies demonstrate conflicting evidence regarding the influence of various stressors on alcohol drinking in rodents, and sex- and stress-related alterations in drinking vary with the stress model used.[5,93] However, a few examples of results show a sex difference in the relationship between corticosterone levels and alcohol drinking or alcohol-seeking.

First, studies have shown that exposure to predator odor stress (PS), which is considered a traumatic stress and used as a model of PTSD, significantly increases alcohol drinking and self-administration in rodents.[94] Evidence supports greater PS-enhanced drinking among female

versus male mice.[93,95] Plasma corticosterone levels following PS exposure have been shown to be significantly higher in female versus male mice when mice were naïve and also when the mice had a history of alcohol drinking.[93,95] Also, investigators have reported a significant positive correlation between plasma corticosterone levels and alcohol intake on the first day after PS exposure. When all mice were considered, the goodness of fit of the regression line ($R^2 = 0.26$, $p < 0.05$) indicated that the variation in PS-induced corticosterone levels accounted for 26% of the variance in alcohol drinking on the day after PS exposure. The relationship was stronger in females ($R^2 = 0.42$, $p < 0.05$), confirming that the amount of HPA axis activation after PS exposure significantly influenced alcohol drinking the following day.[93]

Second, studies examining cue plus yohimbine-induced reinstatement of alcohol-seeking in male and female rats determined that active lever presses during the reinstatement tests were significantly higher in females versus males.[96] During the reinstatement testing for female rats only, corticosterone and estradiol levels were significantly, positively correlated with active lever presses.[96]

Third, in mice deficient in beta-endorphin (knockout mice), a peptide that regulates HPA axis activity via mu opioid receptor–mediated inhibition, the females had elevated basal levels of anxiety, plasma corticosterone, and CRF in the extended amygdala when they were compared with female wild-type mice.[97] High binge alcohol intake in the female beta-endorphin knockout mice normalized their high levels of basal anxiety, corticosterone, and CRF. This relationship was not observed for the male beta-endorphin knockout mice when they were compared with wild-type mice.

Fourth, in mice with a history of alcohol drinking and exposure to PS, the PS-induced increase in plasma corticosterone was significantly lower in male mice, and tended to be lower in female mice, versus respective naïve mice.[95] This result is consistent with evidence that AUD in humans and alcohol dependence in rodents can lead to a dampened neuroendocrine state in terms of HPA axis responsivity.[7] Collectively, the results suggest that overlapping stress and gonadal steroids, as well as sex differences in HPA axis responsivity, contribute to sex differences in alcohol drinking, alcohol-seeking, and interaction with stress.

Preclinical studies also demonstrate cellular and molecular sex differences in stress response systems.[5,8,13,92] Both glucocorticoid receptors and CRF_1 receptors are being pursued as potential targets for AUD pharmacotherapies, but preclinical data in support of these targets have been generated primarily in males.[98] Recent work in male and female mice found that a history of alcohol drinking and intermittent PS exposure produced sexually divergent and brain region differences in protein levels for glucocorticoid receptors and CRF_1 receptors.[95] Increased cortical glucocorticoid receptor levels and hippocampal CRF_1 receptor levels were only found in female mice. These findings are consistent with evidence for impaired glucocorticoid negative feedback resulting from inhibition of glucocorticoid receptor translocation and evidence for increased CRF_1 receptor signaling and decreased CRF_1 receptor internalization in female versus male rodents.[92]

Collectively, an increased endocrine response to stress and alcohol consumption in females may result from sex differences that occur at the molecular and systems level. The sex differences in CRF_1 receptor and glucocorticoid receptor protein levels described above suggest that sexually divergent mechanisms may contribute to HPA axis dysregulation following a history of alcohol drinking and repeated stress exposure. As a result, pharmacological strategies targeting the CRF_1 receptor and glucocorticoid receptor systems may be differentially effective in males versus females.

EFFECTS OF STRESS ON NEUROSTEROID LEVELS

Exposure to stress[31] and models of acute alcohol intoxication[24,99] also significantly increase levels of $GABA_A$ receptor–active neurosteroids, although some species differences in the effects of alcohol

administration on neurosteroid levels have been reported.[100] In addition, most of these studies were conducted in males. In male rats, alcohol's steroidogenic effect was shown to be regulated by an alcohol-induced increase in ACTH release and by de novo synthesis of adrenal steroidogenic acute regulatory protein.[101] Chronic alcohol exposure blunts alcohol's steroidogenic effect on neurosteroid levels, but administration of ACTH restores the steroidogenic effect.[102] Although comparable studies have not been conducted in females, limited data have indicated that CRF and ACTH tests in women significantly increase serum allopregnanolone, progesterone, and dehydroepiandrosterone levels.[63] Studies also have reported that binge alcohol intoxication in male and female adolescent humans significantly increased serum allopregnanolone levels.[103,104]

Preclinical studies found that exposure to various stressors significantly increased plasma allopregnanolone levels in male and female mice that had been consuming alcohol for weeks,[93] whereas weeks of alcohol consumption alone (i.e., without stress exposure) significantly increased brain allopregnanolone levels in male mice but not in female mice.[62] Thus, data available for females suggest that stress and activation of the HPA axis increases neurosteroid levels, whereas acute alcohol administration produces inconsistent effects. Additional studies in females are necessary to determine whether an alcohol-induced steroidogenic effect can exert a protective effect against further alcohol drinking, as has been proposed for males.[99]

Two studies with small cohorts of male and female patients with co-occurring AUD and cocaine use disorder found that progesterone administration decreased cue-induced craving and cortisol responses.[105] The male and female subjects with the highest allopregnanolone levels after progesterone administration showed the greatest reductions in craving,[106] with no sex differences in these relationships. Consequently, despite no direct data on neurosteroid treatment in patients with AUD, strategies to enhance levels of $GABA_A$ receptor–active neurosteroids, such as allopregnanolone, may represent a biomarker of treatment efficacy among men and women.[5,91]

CONCLUSION

The current review considered the contribution of the endocrine system to alcohol drinking and addiction-related behaviors in females, with a focus on the HPG and HPA axes and their reciprocal interactions. The majority of results from preclinical models indicate that females acquire self-administration of alcohol more rapidly and consume higher alcohol doses during maintenance phases than males. However, aspects of alcohol withdrawal, especially somatic and some negative affective symptoms, are less severe in females than in males. Some of these behavioral differences are due to the organizational and activational effects of gonadal steroids.

Numerous studies that used gonadectomy and steroid replacement documented that gonadal steroids have activational effects and that these activational effects contribute to the higher alcohol drinking, self-administration, and responding during reinstatement tests of alcohol-seeking in females versus males. However, additional studies determined that permanent factors, such as sex chromosomes and the organizational effects of gonadal steroids, also can contribute to sex differences in alcohol drinking and alcohol-seeking. For example, elegant studies that used the FCG mouse model determined that the sex chromosome complement mediated habitual responding for alcohol reinforcement. Additional studies are necessary to distinguish how sex chromosomes and the organizational effects of gonadal steroids contribute to alcohol-motivated behavior.

Sex steroids also influence the stress response, and elevated glucocorticoids can suppress HPG axis function (Figure 1). In addition to the facilitatory and inhibitory feedback mechanisms within and between the HPA and HPG axes, steroid hormones and their derivatives (e.g., neurosteroids) can influence brain function and behavior through classic genomic actions and rapid membrane effects at receptors localized

within brain regions important for stress responses and for alcohol-related behaviors (Figure 2). For example, ovarian steroids can modulate dopamine signaling and distinct signaling pathways through actions at their membrane receptors, and neurosteroids can rapidly increase $GABA_A$ receptor–mediated signaling. These effects represent another way that steroids and neurosteroids modulate alcohol-drinking and -seeking behaviors.

Likewise, sex steroids modulate PVN output (e.g., the stress response). Estrogen has a facilitatory effect, and testosterone has an inhibitory effect. These effects are consistent with enhanced HPA axis responsivity and elevated glucocorticoids in females versus males. In both sexes, a neurosteroid-induced inhibition of CRF release via enhancement of GABAergic inhibition likely is a mechanism for terminating the stress response.

Another consideration is that the well-documented effects of chronic alcohol use and exposure on steroid levels provides another level of complexity toward understanding the influence of gonadal and stress steroids on alcohol-related behaviors.

Evidence for a positive association between stress and alcohol drinking is strong in clinical studies and mixed in preclinical studies. However, stress is a potent trigger of alcohol relapse in clinical studies and of alcohol-seeking in preclinical studies. HPA axis responsivity is enhanced in females versus males. So, it is interesting that only female rodents exhibited positive correlations between corticosterone levels following stress and stress-enhanced drinking as well as between corticosterone and estradiol levels and lever presses during cue- and stress-induced reinstatement tests of alcohol-seeking. In addition to the facilitatory effect of estrogen on the HPA axis, these sex differences could be due, in part, to impaired glucocorticoid receptor negative feedback and increased CRF_1 receptor signaling in female rodents.

Both glucocorticoid receptors and CRF_1 receptors are being pursued as potential targets for treatment of AUD, but most preclinical and clinical data examining medications that target these receptor systems have used male subjects. The few clinical studies that included female subjects were underpowered to examine for sex effects. In the single study conducted with females—who had anxiety and AUD—the CRF_1 receptor antagonist verucerfont reduced HPA responsivity without altering measures of alcohol craving.[91] Considering the preclinical data indicating that CRF_1 receptor antagonists effectively reduce escalation in alcohol drinking in dependent male rodents, it is not known whether verucerfont would reduce measures of alcohol drinking in females with AUD.

Regarding glucocorticoid receptor antagonists, the mixed glucocorticoid receptor and progesterone receptor antagonist mifepristone (also known as RU-486) significantly reduced measures of alcohol craving and alcohol consumption in participants with AUD.[5] These participants were predominantly male (the mifepristone treatment group was 82% male). Because of its progesterone receptor antagonism, mifepristone is used in females to terminate pregnancy. Thus, use of mifepristone in females may be confounded by its mixed pharmacological properties, with the progesterone receptor antagonism producing more serious side effects in females versus males.

More selective glucocorticoid receptor antagonists, such as CORT113176, are being pursued, but data for females are not available. Preliminary data in mice selectively bred for a high binge drinking phenotype determined that CORT113176 significantly decreased binge drinking in both male and female mice, and that female mice were more sensitive to the effect.[107]

Pharmacological strategies targeting the CRF_1 receptor and glucocorticoid receptor systems may be differentially effective in males versus females, and new strategies targeting these systems could have greater specificity for females.[92] For example, inhibiting molecules that facilitate the transport of glucocorticoid receptors to their classical intracellular receptor might normalize high glucocorticoid levels in females. Likewise,

compounds that target the CRF_1 receptor and shift signaling away from pathways that enhance CRF_1 receptor signaling might make females more resilient to stress-induced hyperarousal.[92]

Strategies targeting $GABA_A$ receptor–active neurosteroids or their biosynthesis may represent an approach to effectively treat AUD in males and females. Results from preclinical models suggest that chronic alcohol drinking or the induction of dependence in females does not significantly alter allopregnanolone levels, as is seen in males. These results are consistent with the idea that the ability of females to maintain endogenous levels of a GABAergic neurosteroid following chronic alcohol exposure may contribute to the reduced severity of their alcohol withdrawal phenotype. Alternately, strategies to enhance neurosteroid synthesis may exert a protective effect against further alcohol drinking in females, as has been proposed for males.[99]

Neurosteroid analogs with a longer half-life than allopregnanolone show promise as another effective strategy. For instance, brexanolone was recently approved for the treatment of postpartum depression. Currently, ganaxolone also is in clinical trials for treatment of postpartum depression, as well as for treatment-resistant depression, PTSD, and epilepsy. Preclinical results indicate that ganaxolone significantly reduces alcohol drinking in male and female mice (Figure 5, DA Finn and MM Ford, unpublished data, April 2013). Thus, neurosteroid analogs may be effective at reducing alcohol drinking in individuals with co-occurring AUD and depression or co-occurring AUD and PTSD, or in individuals with AUD who drink to alleviate stress and negative affect.

Finally, use of progesterone as a "prodrug" to increase allopregnanolone levels has been an effective strategy to decrease cue-induced craving and cortisol responses in small cohorts of male and female patients with co-occurring AUD and cocaine use disorder.[105,106] The greatest reduction in craving was observed in male and female participants who had the highest allopregnanolone levels after progesterone administration.[105,106] Thus, strategies to use allopregnanolone analogs with longer half-lives, or to stabilize or enhance levels of $GABA_A$ receptor–active neurosteroids such as allopregnanolone, may represent new efficacious treatments for both males and females with AUD.

Collectively, the importance of arriving at a more complete understanding of the neuroendocrine mechanisms underlying sex differences is clear, as treatment strategies and their effectiveness may revolve around sex differences in the endogenous steroid and neurosteroid environments and in sexually divergent downstream signaling mechanisms. In addition, variations in neurosteroid physiology also may help explain individual differences in susceptibility to AUD, vulnerability to relapse, and the negative health consequences of alcohol intake.

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Sleep and Alcohol Use in Women

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Sleep disturbance is common among individuals with alcohol use disorder (AUD). Insomnia not only is a pathway toward alcohol consumption but also is related to increased risk of relapse, psychosocial impairment, decreased quality of life, and suicidal ideation in individuals with AUD. Few studies examining sleep disturbance and alcohol use have explored how this relationship differs between men and women. Historically, studies of AUD have included few, if any, women in their samples. However, women are increasingly consuming alcohol at an earlier age and at higher rates, and the effect of alcohol on women's mental and physical health is expected to rise. This narrative review consolidates findings from studies that have reported the effects of acute and chronic alcohol use on sleep among women. Additional research is needed to investigate sex differences in this area. Such research should consider the modifying effects of age, lifetime alcohol use, and psychiatric co-occurrence, as well as the effectiveness of combined interventions for AUD and sleep disturbance.

KEY WORDS: adolescence; alcohol use disorder; circadian; sex differences; slow wave sleep; substance use

INTRODUCTION

Sleep disturbance is one of the most common complaints of individuals with alcohol use disorder (AUD), with prevalence estimates ranging from 36% to 91%.[1] Insomnia in particular has been associated with multiple aspects of AUD: relapse to drinking, psychosocial impairment (e.g., employment problems, social conflict, and impulse control), decreased quality of life, suicidal ideation, and insufficient sleep duration. (For

definitions of insomnia and other technical terms, see the box **Glossary of Sleep Terms.**) Sleep disturbance can serve as a pathway to increased alcohol use, in part because alcohol can be used as a sleep aid to reduce time to sleep onset. However, even acute alcohol consumption increases sleep disruption throughout the night, and tolerance to the sedating qualities of alcohol accumulates quickly.[2] In people with AUD, chronic alcohol use is related to changes in sleep structure that persist into abstinence. For abstinent individuals with AUD, this persistent sleep disturbance is a risk factor for relapse.[1] Once relapse occurs, the cycle repeats, as continued consumption of alcohol perpetuates sleep disturbance.

Historically, studies of AUD and sleep have mostly included men. Although women with AUD have been recruited for a handful of studies,[3-7] women have largely been underrepresented in the research that examines the relationship between sleep and alcohol use. Sex differences in the effects of alcohol are dependent on the interaction of many biopsychosocial factors. Sleep intertwines with several of these relationships: alcohol disrupts sleep, and sleep disturbance relates to increased risk of psychiatric co-occurrence, alcohol misuse, and relapse to AUD. In addition, sleep is a modifiable behavior.[8,9] Thus, understanding how sleep problems relate to problematic alcohol use and the extent to which this relationship differs between men and women can inform the development of targeted methods for prevention and treatment of AUD.

This narrative review aims to stimulate new research in this area by consolidating findings from studies that have reported effects of acute and chronic use of alcohol on sleep among women. First, an overview of sex differences in sleep disorders is provided, followed by considerations for how sex may modify the relationship between alcohol use and sleep. (For consistency, both biological and psychological/sociological/cultural factors are referred to as "sex"-related throughout the review.) The review concludes by providing treatment considerations and directions for future research.

SEX DIFFERENCES IN SLEEP

Sleep is a universal process across species and is a behavioral state that is essential to physical and mental health in humans. Changes in brain activity throughout the night demarcate different stages of sleep. This neuronal activity, along with muscle activity and eye movements, can be measured via polysomnography (PSG) to provide an objective measure of sleep. Sleep is divided into stages (N1, N2, and N3) of non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep.[10] Throughout the night, sleep follows a cyclical pattern. Each cycle begins with stage N1, and the majority of time is spent in stage N2 before progression to stage N3 (deep sleep) and eventually to REM sleep. Each cycle lasts approximately 90 minutes. More detailed analysis of the sleep electroencephalogram (EEG) is possible with spectral analysis to determine activity during sleep within a specific frequency band (e.g., slow wave activity).

PSG provides a detailed, objective measure of sleep architecture and quality but is mainly confined to the laboratory. Actigraphy (usually measured with devices worn on the wrist) relies on an accelerometer to measure patterns of activity from which sleep–wake states can be estimated.[11] Actigraphy is useful for objective assessments of sleep outside the laboratory environment. Self-perception of sleep quality is also valuable and can be measured over many nights with questionnaires or sleep diaries.

Glossary of Sleep Terms

Actigraphy: An objective measure of sleep quantity and circadian patterns that uses an accelerometer (generally worn like a wristwatch) to detect sleep–wake activity over several days or weeks.

Apnea-hypopnea index: An index used to indicate the severity of sleep apnea that is represented by the number of apnea and hypopnea events per hour of sleep.

Circadian period: The amount of time for a cyclical process to return to the same phase (e.g., from one day's waking to the next day's waking).

Circadian preference/ chronotype: An individual's tendency towards relatively earlier or relatively later sleep and activity patterns, typically measured via preferred timing (i.e., morningness versus eveningness) or self-reported actual timing (i.e., early versus late chronotype).

Circadian rhythm: An endogenous 24-hour rhythm, typically measured via levels of melatonin or by core body temperature.

Circadian timing: The timing of biological processes that follow a circadian rhythm (e.g., sleepiness, wakefulness, melatonin, body temperature).

Hypopnea: The partial blockage of air, resulting in decreased airflow and oxygen saturation.

Insomnia: A sleep disorder characterized by difficulty falling asleep or staying asleep, causing distress or impairment in daytime functioning.

K-complex: A high-voltage delta frequency EEG event seen in NREM sleep that occurs when large numbers of healthy neurons fire in a synchronized manner.

Non–rapid eye movement (NREM) sleep: The sleep stage characterized by slower, higher amplitude EEG activity, regular breathing and heart rate, muscle tone (i.e., low-level contraction), and a lack of eye movement; consists of stages N1, N2, and N3.

Polysomnography (PSG): A test conducted to study sleep and diagnose sleep disorders using a multitude of physiological measures, including measures of brain activity, blood oxygen levels, heart rate, breathing, and muscle movements.

Rapid eye movement (REM) sleep: The sleep stage characterized by low-amplitude, high-frequency EEG activity, rapid eye movement, irregular respiration and heart rate, and muscle atonia.

Sleep apnea: A sleep disorder in which breathing is repeatedly interrupted during sleep.

Sleep architecture: The structural organization of sleep, such as cyclical alternation of NREM and REM sleep stages.

Sleep behavior: Self-report measures from questionnaires that typically ask about sleep over a period of weeks or months.

Sleep-disordered breathing: An umbrella term that encompasses breathing disorders and respiratory abnormalities that occur during sleep, including sleep apnea and snoring.

Sleep efficiency: The total number of minutes of sleep divided by the number of minutes in bed.

Sleep electroencephalogram (EEG): A recording of brain activity during sleep.

Sleep onset latency: The number of minutes to fall asleep after the lights are turned off.

Sleep timing: The times of day an individual goes to sleep and wakes up.

Slow wave activity: EEG activity in the delta (slow wave) band (0.5 Hz to 4.0 Hz), typically averaged separately for NREM and REM sleep for the entire night.

Slow wave sleep: The deepest stage of NREM sleep (stage N3), characterized by more than 20% delta wave EEG activity.

Stage N1: The lightest stage of sleep, which occurs right after falling asleep; characterized by low-voltage, fast EEG activity.

Stage N2: The intermediate stage of sleep that follows stage N1; characterized by theta activity (4-7 Hz), K-complexes, and bursts of faster activity on EEG.

Stage N3: The deepest stage of sleep; characterized by high-amplitude slow waves on EEG.

Total sleep time: The total number of minutes asleep.

Total wake time: The total number of minutes awake during the sleep period.

Wake after sleep onset: The number of minutes awake after falling asleep.

Differences in Sleep Measures

Women tend to have better sleep quality, as measured by PSG, than men. Women have less total wake time, shorter sleep onset latency, better sleep efficiency, and a larger percentage of slow wave sleep and slow wave activity (for definitions of these sleep measurements, see the box **Glossary of Sleep Terms**).[12] The prevalence of sleep-disordered breathing is 9% among women versus 24% in men. However, women with sleep-disordered breathing are more likely to present with initial symptoms of insomnia or fatigue rather than the typical symptoms associated with sleep-disordered breathing, such as snoring, daytime sleepiness, and witnessed apneic events.[13]

Although PSG is considered the gold standard of sleep measurement, it has limitations. PSG cannot capture habitual sleep duration under naturalistic settings and may miss subcortical brain activity (particularly in regions shown to be involved in conscious awareness) that may be more prominent in individuals with insomnia than in those who sleep well.[14] Although not yet examined, possible sex differences in subcortical brain activity during sleep may explain the finding that women report poorer subjective sleep quality than men despite having better PSG-based sleep quality.

When using subjective measures, women report more sleep problems than men, including disrupted and insufficient sleep, poor sleep quality, difficulty falling asleep, frequent night awakenings, and time awake during the night.[15,16] Women also have a 40% greater risk of insomnia[12] and report earlier sleep timing (i.e., bedtime and wake time) than men.[17] Potential reasons for sex differences in sleep are described briefly in this review. For more detailed discussions, see the reviews by Mong and Cusmano[12] and Krishnan and Collop.[13]

Biological Differences

Sex steroids (i.e., testosterone in men and estrogen and progestins in women) modulate sleep differently. Generally, women's sleep is more sensitive to changes in ovarian steroids.[12] For example, sex hormones modulate the orexin/hypocretin system, which plays an important part in regulating sleep and wake states.[18] Therefore, fluctuations in ovarian steroids in women (e.g., puberty, menstrual cycle, menopausal transition) are associated with changes in sleep and circadian rhythms[19] and increased prevalence of sleep disturbance.[20,21] In addition, among men and women with similar sleep timing and duration, women have a shorter circadian period and earlier circadian timing of endogenous temperature and melatonin rhythms.[12] (For definitions of these circadian terms, see the box **Glossary of Sleep Terms.**) This mismatch in sleep timing and circadian timing can cause sleep disturbance, such as problems with sleep maintenance and/or early morning awakening, which, in part, may underlie women's increased risk for insomnia.

Psychosocial Differences

Among women, those with more anxiety and more perceived nighttime awakenings also report worse subjective sleep quality, despite a lack of objectively measured sleep disturbance.[12] Anxiety and depression are both more prevalent among women and are strongly associated with insomnia. The risk of affective disorders increases at the onset of puberty, especially among girls.[22]

ALCOHOL AND SLEEP

Sex differences occur in sleep continuity and sleep architecture measures as well as in the prevalence of sleep disorders like insomnia and obstructive sleep apnea. Sex differences also have been reported in alcohol use patterns, biological effects of alcohol, and risk factors for heavy alcohol use. Alcohol use likely affects sleep systems differently in men and women, and pathways that link sleep disturbances with subsequent heavy alcohol use also may differ according to sex. In this section, we review the evidence for sex differences in bidirectional relationships between sleep quality and alcohol use (although directionality is not always clear when based on findings from observational or cross-sectional studies).

Sleep and wake states are regulated by complex patterns of neurotransmitter release and

neural activation, many of which are affected by alcohol.[23] Individuals who have trouble sleeping may initiate alcohol use as a sleep aid. Because alcohol affects the gamma-aminobutyric acid (GABA) neurotransmitter system, alcohol acts as a sedative and reduces time to sleep onset, increases slow wave sleep, and suppresses REM sleep in the first half of the night.

Alcohol has acute neurotoxic effects that affect receptors important for sleep generation. As alcohol metabolizes (at 7 grams per hour, on average), its sedating benefits diminish.[24] Later in the night, sleep becomes more disrupted and awakenings are more frequent. Thus, the effects of alcohol on sleep differ depending on which half of the night is examined. Chronic alcohol exposure damages nerve cells and fibers, reducing the likelihood of synchronized neuronal firing across the cortex, which is necessary for slow wave sleep. With prolonged use, neurotransmitter systems adapt and modulate their release, which can increase sleep disruption and change sleep architecture, sometimes permanently.[23,25]

Studies (mostly among men) indicate that these changes in sleep structure persist during abstinence, and disturbed sleep is a risk factor for relapse.[1] Therefore, sleep disturbance has been suggested as a target for treatment, potentially decreasing the risk of problematic alcohol use while also increasing the likelihood of abstinence.

Sleep Architecture

This section examines studies (which included women participants) of both the acute and chronic effects of alcohol on sleep architecture. To the extent possible, results from experimental studies are emphasized.

Effects of acute alcohol use

First, we present studies that primarily used PSG to examine the acute effects of alcohol on sleep architecture. These experiments provide some evidence of directionality in the relationship between alcohol use and subsequent sleep quality. One of the first studies to investigate the effect of acute alcohol use on sleep, specifically in young women, was conducted by Williams and colleagues.[26] As part of this double-blind trial, 11 healthy women (ages 18 to 21) completed several nights of PSG an hour after consuming a beverage with either 0.00, 0.50, or 0.75 grams of alcohol per kilogram of body weight (g/kg). Results were consistent with previous findings reported for men. As the alcohol dose increased, sleep onset latency decreased. A significant decrease in the percentage of REM sleep was found, which was most apparent in the first 3 hours of the night. Also, a dose-dependent increase in slow wave sleep during the first half of the night was found, followed by a decrease in slow wave sleep in the second half of the night. Furthermore, these women demonstrated a dose-dependent increase in the percentage of stage N1 sleep, with increased minutes spent in stage N1 sleep in the second half of the night.

A later study conducted by Van Reen and colleagues examined the extent that a moderate dose of alcohol (0.49 g/kg), compared to placebo, consumed an hour before bedtime affected the sleep and sleep EEG of 7 women (ages 22 to 25).[27] Similar to the findings reported for men,[23] this study reported that alcohol consumption led to an increase in slow wave sleep (in the first 2 hours) and an overall decrease in REM sleep.[27] Also, frontal EEG power during NREM sleep in the alpha range (9 to 11 Hz) increased relative to placebo following alcohol consumption.

In a direct evaluation of sex differences, Arnedt and colleagues performed PSG for 93 healthy adults (ages 21 to 31, 59 were female) following alcohol intoxication.[28] For this double-blind, randomized trial, all participants received alcohol on one night and placebo on another night, 1 week apart. Participants were given either placebo or alcohol (1.2 g⁄kg for men and 1.1 g⁄kg for women) 1 to 2.5 hours before bed. The alcohol dose was adjusted for weight and sex such that breath alcohol concentration (BrAC) levels were equivalent in men and women. At bedtime on the alcohol night, women reported higher ratings of sleepiness than men. Despite reaching equivalent BrACs, sleep continuity was more disrupted in women than in

men. For women, the total sleep time decreased by 20 minutes relative to the placebo night, and the wake after sleep onset time increased by 15 minutes. In addition, among women participants, the frequency of awakenings increased, and overall sleep efficiency decreased by 4% after alcohol intoxication. In men, no significant differences in sleep continuity measures (i.e., sleep onset latency, total sleep time, sleep efficiency, frequency of nighttime awakenings, and wake after sleep onset) between the placebo and alcohol conditions were reported. For both sexes, sleep architecture variables differed for the alcohol condition compared to the placebo condition—alcohol use increased slow wave sleep and decreased REM sleep.

Chan and colleagues also examined the effects of acute alcohol consumption (a mean dose of 0.828 g/kg an hour before bedtime) on the sleep architecture of 24 older adolescents (ages 18 to 21, 12 were female).[29] They found main effects of alcohol on sleep, dependent on halves of the night. In the first half of the night, participants experienced fewer arousals, less stage N1 sleep, increased slow wave sleep, and reduced REM sleep. In the second half of the night, they experienced less sleep efficiency and more time awake after sleep onset. These researchers did not find evidence for an interaction between sex and alcohol.

Effects of chronic alcohol use

The following studies are observational, such that they examine sleep among individuals with a history of chronic alcohol use in the context of many other variables. Individuals in these studies vary regarding the duration of their abstinence at the time of study, their co-occurring disorders, and their lifetime alcohol use. When participants were examined early (at less than 1 month) during recovery, the effects on sleep may have reflected the effects of withdrawal more than any chronic effects of heavy alcohol use. When participants were examined later during recovery, withdrawal effects would have subsided. Therefore, the associations observed do not prove causality in these relationships, but they provide a starting point to stimulate further research that may better distinguish directionality.

Colrain and colleagues collected sleep architecture and EEG measures from 42 abstinent participants (mean age of 49, 15 were women) with long-term AUD and from 42 control participants (mean age of 51, 23 were women).[5] Overall, women had better sleep efficiency, fewer periods of in-bed awake time, and more slow wave activity during NREM sleep than men. There were main effects of AUD for some sleep measures. For example, individuals with AUD had less slow wave sleep and slow wave activity during NREM sleep and more stage N1 and REM sleep than controls.

Despite a lack of significant interaction between sex and diagnosis, women with AUD and women control participants had similar amounts of NREM slow wave activity, whereas men with AUD had substantially lower NREM slow wave activity than men control participants.[5] Women with AUD had lower levels of lifetime alcohol consumption and longer periods of sobriety when compared with the men who had AUD in this study. Although greater estimated lifetime alcohol consumption was related to a lower percentage of slow wave sleep in men, this measure was not related to the percentage of slow wave sleep in women. This study did not investigate sex interaction effects, and the samples of women and men with AUD were unequal sizes, had varying lengths of sobriety, and had different levels of lifetime alcohol exposure.

Using the same sample, Colrain and colleagues examined K-complex incidence and amplitude during sleep.[6] K-complexes are high-voltage, delta frequency events that occur during NREM sleep when large numbers of healthy neurons fire together at the same time. They provide a sensitive measure of typical, healthy, brain aging. In this study, participants with AUD had both reduced K-complex incidence and amplitude. Men and women also showed the same pattern of AUD-related change in K-complex amplitude, despite women having less lifetime alcohol consumption.

In a sample that included 26 participants (ages 32 to 63, 10 were women) with alcohol dependence who were in subacute withdrawal from alcohol and 23 control participants (ages 24 to 61, 9 were women), overall, women spent a larger proportion of time awake during the sleep period, and they had shorter time to REM sleep.[7] The relationships between sleep parameters and group did not vary by sex; however, this analysis may have been underpowered because of the sample size. The investigators noted that the distribution of sex across groups was not equal.

A population-based study of sleep among 400 Swedish women (ages 20 to 70) found that women who self-reported alcohol dependence had longer sleep onset latency, reduced REM sleep, and more stage N2 sleep compared to women who did not report alcohol dependence.[30] In addition, alcohol dependence was related to decreased time spent in REM sleep and increased sleep onset latency, independent of age, body mass index, apnea-hypopnea index, smoking, and hypertension.

Summary

Sleep is a complex neurological function, and the extent that it may be affected after a single night of alcohol compared to chronic alcohol misuse can differ. Thus, sex differences in the acute effects of alcohol may not necessarily coincide with sex differences in the chronic effects of alcohol. The single experimental study that examined sex differences in the effect of acute alcohol consumption found sex differences in objectively measured sleep among healthy subjects (with equivalent BrAC levels before sleep), with women showing more disrupted sleep than men.[28]

Sex differences in alcohol pharmacokinetics may underlie these differences. Even at equivalent starting points, BrAC levels decline more rapidly for women than for men.[28] As alcohol metabolizes, alcohol metabolites disrupt sleep. Chronic alcohol misuse leads to changes in brain macrostructure and microstructure that can manifest as sleep disturbance.[25] Few studies have examined sleep in both men and women during recovery from AUD, and those studies have not had sample sizes large enough to statistically examine sex differences.

Further study is needed to examine potential sex differences in sleep among individuals with AUD who are abstinent. Dose effects, time in recovery, and the effects of interaction between age and sex should be considered. Sleep structure changes across age, and these changes vary by sex.[31] For example, women have a greater amount of slow wave activity than men, and although men tend to show a decrease in slow wave activity with age, women do not show the same pattern of decline.[12]

Sleep Physiology

Limited experimental work has examined whether the effects of alcohol on the functioning of physiological systems (e.g., respiratory or cardiovascular) during sleep differ according to sex.

Effects of acute alcohol use

In an investigation of the acute effects of alcohol, Block and colleagues monitored breathing and oxygenation during sleep for 78 participants (20 were men ages 20 to 40 years, 20 were men ages 40 years and older, 20 were women ages 20 to 40, and 18 were postmenopausal women ages 51 to 66) following consumption of 2 milliliters of alcohol per kilogram of body weight.[32] Men in both groups had more oxygen desaturation episodes across the night and greater severity of desaturation, but no effect of alcohol on breathing or oxygenation was found for either group of women. As expected, postmenopausal women had significantly more episodes of apnea and oxygen desaturation than premenopausal women, although this difference was unrelated to alcohol consumption.

A large, observational study of 1,420 men and women (mean age of 51, 645 were women) demonstrated similar findings.[33] Men showed increased likelihood of sleep-disordered breathing for each drink consumed per day (measured via a self-report questionnaire), whereas no association between minimal to moderate alcohol consumption and sleep-disordered breathing

was found for women. The investigators posited that circulating progesterone may protect young women in particular from the depressant effects of alcohol and consequent sleep apnea and oxygen desaturation,[32,34] and that hormonally mediated increased ventilatory drive and anatomical differences may also protect women from sleep-disordered breathing events.[33,35,36] Since alcohol had no effect on breathing for postmenopausal women, other nonhormonal factors may have played a role in the sex differences related to sleep-disordered breathing and alcohol consumption.

Effects of chronic alcohol use

A study of 24 patients with chronic AUD who were recently abstinent (10 were women ages 25 to 58) compared with 24 control participants (10 were women ages 25 to 58) showed that both males and females with AUD had a high number of observed apneic/hypopneic episodes, and this result did not differ by sex.[37] The researchers concluded that women with AUD were as likely as men with AUD to have a sleep-related breathing disorder.

In a study investigating autonomic nervous system functioning during sleep, de Zambotti and colleagues found that patients with AUD who were recently sober (n = 14, 7 were women ages 28 to 54) compared with healthy control participants (n = 16, 8 were women ages 30 to 62) had elevated heart rates, reduced total heart rate variability, and reduced high-frequency activity (a measure of vagal functioning) across the night.[4] Together, this pattern of findings indicates disrupted autonomic nervous system functioning during the night, providing compelling evidence of impaired cardiovascular functioning during sleep. Effects did not differ by sex, and women with AUD, despite having less lifetime alcohol consumption, were affected to the same extent as men with AUD. In a follow-up investigation across the first few months of abstinence, as the duration of abstinence increased, individuals with AUD showed substantial recovery in heart rate and vagal functioning during sleep, although examination of any modifying effect by sex was not possible in this small sample.[3]

Periodic limb movements can also contribute to disturbed sleep. Aldrich and Shipley found that periodic limb movements were more likely to occur at a clinically significant frequency among adults ages 19 to 81 who self-reported consuming 2 or more drinks per day (heavy users, n = 112, 24 were women) when compared with adults who consumed less than 2 drinks per day (abstainers and light to moderate users, n = 872, 317 were women).[38] In addition, women who were heavy users were more likely to report symptoms of periodic limb movements than women who were light users, whereas no difference was observed between the two groups of men.

Summary

For physiological measures, the evidence from one large, experimental study suggests that acute alcohol consumption does not affect women's breathing during sleep to the same extent it does for men, who demonstrate more oxygen desaturation events during the night. Also, among men, self-reported alcohol use is positively associated with greater likelihood of sleep-disordered breathing, although this relationship is not observed in women. However, women with AUD are just as likely as men to have sleep-disordered breathing.[37]

Women may be more susceptible to periodic limb movements, and alcohol use could be a potential trigger of these movements. Also, women who experience periodic limb movements may self-medicate with alcohol. One study with a small sample size suggested that chronic alcohol use may affect cardiovascular functioning in women more than it does in men, as women and men did not differ in these measures despite women having less lifetime alcohol consumption.

These results are consistent with other studies that have demonstrated that women are at greater risk of alcohol-induced cardiomyopathy and peripheral neuropathy despite fewer years of drinking and lower quantities of alcohol consumption.[39] Given that two of these studies examined men and women early during their recovery,[4,37] some of the effects found could reflect

residual withdrawal effects of alcohol. Further longitudinal studies across a period of recovery among men and women with AUD are needed to separate effects of alcohol withdrawal and chronic heavy alcohol use on sleep as well as on physiological measurements taken during sleep.

Self-Reported Sleep Behavior

Many individuals report using alcohol as a sleep aid,[40,41] even though the use of alcohol to help initiate sleep can further perpetuate sleep disturbance. In women older than age 60, using alcohol to sleep and shorter sleep onset latency each are associated with greater risk for alcohol misuse.[42] However, moderate alcohol use is associated with fewer insomnia symptoms in women, but not in men, older than age 65.[43]

In a study of healthy men and women, self-reported insomnia symptoms at baseline were associated with greater odds of heavy drinking at a 5-year follow-up.[44] Likewise, heavy drinking and binge drinking at baseline were associated with greater odds of insomnia symptoms at a 5-year follow-up. Although results specific to sex were not reported, the investigators noted that these associations were similar among men and women but reached statistical significance only for women.

Some epidemiological studies have considered associations between alcohol use and insomnia symptoms among women in midlife and after menopause, an age group in which sleep problems are common. Blümel and colleagues reported that troublesome drinking (assessed with the Brief Scale of Abnormal Drinking) in a group of women ages 40 to 59 was strongly associated with increased risk for insomnia symptoms more than other factors, including mood and vasomotor symptoms, education level, and use of hypnotics.[45] In contrast, frequency of alcohol use (i.e., not currently, occasionally, or regularly in the past week) was not associated with sleep disturbances in a group of postmenopausal women ($N = 322$, ages 60 to 70).[46] These findings show that relationships between alcohol use and insomnia for women may differ depending on whether frequency of alcohol use or troublesome drinking are examined.

A large, longitudinal study of 9,941 Norwegian adults (53.6% were women) found that men reporting high levels of alcohol consumption at baseline were at higher risk of reporting sleeplessness at a follow-up 13 years later.[47] Similarly, men who experienced sleeplessness at baseline also were at higher risk of reporting high levels of alcohol consumption at the follow-up, demonstrating the bidirectionality of associations between sleep problems and alcohol use. In contrast, no such relationships were found for women.

A population-based study of 3,450 French adults (52.4% were women ages 18 to 64) reported that drug use for insomnia (prescription or nonprescription) was associated with alcohol misuse among men but not among women.[48] The only study of insomnia prevalence among individuals in treatment for AUD found that women and men reported similar rates of insomnia symptoms, despite a larger prevalence of insomnia among women in the general population.[49] Also, insomnia symptoms at baseline were significantly associated with relapse to AUD for both men and women.

The extant data are mixed regarding whether women show differential risk for associations between self-reported sleep disturbance and alcohol use. However, these observational studies, which rely entirely on self-report methods to measure both alcohol use and sleep disturbance, use different questionnaires and, in some cases, use measures limited to a single item. More research is needed to characterize the relationship between sleep behavior and alcohol use among women, especially studies that help distinguish sleep problems as predictors of relapse and alcohol use as a predictor of insomnia. Further investigation should use more comprehensive, frequent measures of sleep behavior (e.g., sleep diaries) potentially combined with objective measures (e.g., actigraphy) and measures of alcohol consumption to better characterize sex differences in these relationships.

Sleep as a Predictor of Adolescent Alcohol Use

As early as childhood, self-reported sleep problems are related to onset of substance use in adolescence.[50] In the first prospective study of sex differences in this relationship, Wong and colleagues found that sleep problems in childhood were a significant predictor of onset of drinking in both boys and girls but at earlier ages for boys (8 to 14) than girls (15 to 17).[51] In a large, community-based sample of 7,507 children and adolescents in Hong Kong (48.5% were females ages 6 to 17), Zhang and colleagues found that boys with insomnia symptoms were more likely to report regular consumption of alcohol (sometimes or often), whereas no such relationship was found for girls.[52]

In a population-based study of 4,187 Finnish adolescents (51.8% were females ages 11 to 15), perceived tiredness was related to increased likelihood of drinking and smoking for boys, but for girls it was only related to an increased likelihood of smoking.[53] In contrast, in a large sample of 13,381 U.S. adolescents (48.8% were females ages 12 to 17), there was a stronger relationship between subjective sleep problems and substance use in general (i.e., use of cigarettes, alcohol, or illicit drugs) for girls than for boys.[54]

Unpublished data from Hasler and colleagues (2017) suggest that in a sample of 729 adolescents (368 were females ages 12 to 21) from the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) study, females with worse sleep quality were more likely to report binge alcohol use at baseline. However, males with worse sleep quality at baseline were at a greater risk of worsening binge alcohol use a year later.

Emerging data from longitudinal studies that track sleep patterns in adolescents before the onset of alcohol use suggest there may be sex differences in the relationships between sleep behaviors and alcohol use.[50] However, further data are required before definitive conclusions can be reached. Such work is needed to determine sex differences in the directionality of the relationships between substance use and sleep and circadian factors, as well as the underlying mechanisms of these relationships.

Sleep and Circadian Timing

Circadian rhythm disturbance can underlie sleep problems, and alcohol use alters many circadian functions (e.g., blood pressure, body temperature, hormone release).[55] Proper assessments of melatonin level, cortisol level, or body temperature, which are validated methods for measuring circadian rhythm, require rigorous laboratory protocols conducted over multiple hours to days and, thus, are not always feasible. Measurements of circadian preference (i.e., morningness-eveningness), chronotype, or sleep timing can serve as proxies for direct measures of circadian patterns of sleep–wake activity. To our knowledge, no studies have directly examined whether sex moderates the relationship between alcohol use and circadian rhythms in humans. One preclinical study that used mice with a knockout of adenosine equilibrative nucleotide transporter type 1 (ENT1), which is associated with both AUD and circadian/sleep disruptions, showed that circadian rhythm disruption increased alcohol consumption in male but not female mice,[56] suggesting that further investigation of sex differences in this area is warranted in humans.

Although more bona fide circadian research is needed, proxies for circadian rhythm, such as eveningness and late chronotype, consistently are associated with more alcohol use and problems with alcohol.[57] On average, women tend towards a relatively earlier sleep and activity pattern (i.e., morningness/early chronotype), which theoretically might lower the risk of alcohol use associated with circadian factors.

Hasler and colleagues investigated the effect of sleep timing on response to alcohol among 148 young adults (50 were women ages 21 to 35).[58] In males (White males only) but not in females, later sleep timing and greater eveningness preference were associated with a greater self-reported stimulating effect of alcohol immediately following alcohol consumption. In addition, greater variability in sleep duration was related to

greater sedation following alcohol consumption for both men and women. Further work is needed to examine links between circadian factors and heavy alcohol use, particularly among adolescents, to establish potential sex-specific predictors of alcohol use.

CLINICAL CONSIDERATIONS AND TREATMENT

Some sleep abnormalities may predate the effects of alcohol and also may differ between men and women. In addition, the prevalence of different sleep disorders must be taken into consideration. As already described, women are 40% more likely to develop insomnia than men.[20] Individuals may be vulnerable to the development of insomnia for a variety of reasons.[1] Predisposing factors such as genetics (e.g., *CLOCK* gene polymorphism or family history of AUD), childhood trauma, and childhood sleep problems increase an individual's risk of developing insomnia. Precipitating factors are stress-promoting events that trigger acute insomnia. Perpetuating factors are maladaptive compensatory behaviors, such as reading in bed or drinking alcohol, used to cope with sleep difficulty. Screening women for sleep problems may help providers intervene before problematic use of alcohol develops or may increase the likelihood of maintaining abstinence.

Pathways toward alcohol use vary developmentally, and sleep characteristics during childhood and adolescence predict risk for onset of alcohol use and misuse.[59] Childhood sleep problems are related to the onset of alcohol use in adolescence; therefore, treating sleep problems early in life may confer some benefit by delaying the onset of alcohol use. Furthermore, sleep disorders often manifest during reproductive transitions (e.g., puberty, pregnancy, menopause).

Females tend to develop insomnia after puberty, and the later sleep timing that occurs during puberty is positively associated with alcohol use.[16] Addressing the sleep disturbances of pregnant women is especially important. Alcohol consumption during pregnancy acutely affects fetal sleep behavior, and research suggests that prenatal alcohol exposure is related to persistent sleep disruption in affected children.[60] For many women, sleep disturbance and complaints of insomnia increase during and after the menopause transition.[12] The sleep changes related to aging, hormonal fluctuations, and psychological adjustment may contribute to women in this age group being particularly vulnerable to developing AUD.[61]

Improved understanding of the mechanisms by which these hormones modulate sleep may help guide development of novel therapies for treatment of problematic alcohol use. Such studies will help health care providers make informed decisions about medications (and dosages) and behavioral interventions that will be effective for treating sleep problems among women with AUD.

Cognitive behavioral therapy for insomnia is the first line of treatment for insomnia and is equally effective for men and women.[8,62] This nonpharmacological treatment method focuses on behaviors, cognitions, and associations that contribute to poor sleep.[63] The therapy uses a combination of sleep restriction (i.e., limiting time spent awake in bed), stimulus control, sleep hygiene (that is, healthy sleep habits such as consistent bed and wake times, comfortable bedroom environment, or avoiding caffeine and alcohol before bedtime), and cognitive therapy to address distorted beliefs about sleep. Up to 80% of patients benefit from this therapy, and treatment effects are maintained at follow-up a year later.[9] Pharmacotherapy is the next evidence-based approach for treatment of sleep disturbance, and it often is used in conjunction with cognitive behavioral therapy for insomnia, although it can be contraindicated for individuals with AUD.

Although women tend to have better long-term treatment outcomes than men, they are less likely to receive services specifically for alcohol-related issues, and they are more likely to seek treatment in settings that are not alcohol specific.[39] Educating health care providers in the primary

care setting to screen women for AUD and sleep problems may help reduce the stigma many women face when seeking appropriate treatment for AUD.

In addition, management of sleep problems is not typically a first line of treatment for individuals with AUD, despite the association between insomnia symptoms and increased risk of relapse. Sleep is a modifiable behavior that, if improved, may have downstream benefits for other health outcomes.[23] Medication trials (e.g., trazodone, gabapentin, quetiapine) have shown mixed efficacy and can be contraindicated in individuals with AUD, whereas behavioral treatments for insomnia consistently have been more effective in treating sleep problems, with moderate to large effect sizes.[1]

Treating sleep problems early may reduce risk for subsequent AUD. Considering that for women depressive symptoms predict alcohol consumption, cognitive behavioral therapy for both insomnia and depression may help prevent problematic alcohol use with two points of intervention. Although cognitive behavioral therapy for insomnia has not been shown to differentially improve alcohol outcomes,[64,65] more randomized controlled trials are warranted. This therapy has already shown promise as a treatment for insomnia among individuals with AUD, and men and women with no AUD respond to the therapy equally well.[66] It will be valuable for future studies to investigate the utility of cognitive behavioral therapy for insomnia and of other treatments that aim to improve sleep in individuals with AUD, as well as to examine whether these treatments are equally effective in men and women.

FUTURE DIRECTIONS AND CONCLUSION

Suggested areas for future research on sex differences related to alcohol and sleep include examination of:

- Alcohol's neurotoxic effects on circuits important for sleep generation
- Sleep during sustained abstinence from alcohol
- Cardiovascular functioning at night following alcohol use
- Alcohol use and its relationships with circadian misalignment and shiftwork
- Hormonal change and reproductive phase (e.g., puberty, the menstrual cycle, pregnancy, menopause) effects on alcohol use and sleep
- Other demographic factors (e.g., age, race, ethnicity, socioeconomic status) and how they affect alcohol use and sleep
- Longitudinal studies of sleep before initiation of alcohol use and across the course of recovery in individuals with AUD who are abstinent
- Cognitive behavioral therapy for insomnia and other treatment efficacy and effectiveness in improving sleep for individuals with AUD

Women historically have been underrepresented in research studies on alcohol use and sleep. Although AUD currently is more prevalent among men, the male/female differences in patterns of alcohol consumption are converging. Now, more than ever, sex differences need to be considered in all aspects of alcohol research. Only a small body of literature has investigated sex differences or interactions with sex in relation to sleep outcomes and alcohol use, making it challenging to draw definitive conclusions from the research thus far. Sleep and alcohol use vary by race and ethnicity,[67] and further research examining these characteristics in the context of sex differences is needed.

In addition to understanding sex differences in the relationship between alcohol and sleep, understanding the consistencies in the effects of alcohol on sleep among men and women is important. Alcohol has the same detrimental effects on many aspects of sleep and sleep physiology, regardless of sex. Given that sleep disturbance is so commonly reported by individuals with AUD, and the strong associations among sleep, daytime functioning, and mental and physical health, understanding how these relationships might differ in women compared to men is crucial to developing targeted and appropriate treatment recommendations.

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Alcohol and Liver Function in Women

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Alcohol-related liver disease generally has been ascribed to men because men reportedly consume alcohol at an increased rate and quantity as compared to women. Recent literature has reported, however, that rates of liver disease attributed to alcohol use by women have increased, largely due, in part, to the increased number of women who consume alcohol regularly. This increase is a paramount concern, as women are more susceptible than men to the effects of alcohol-related liver injury. Health care providers should make efforts to counsel women on the risks of excess alcohol consumption to prevent further increase in alcohol-related liver disease and its associated complications.

KEY WORDS: alcohol; estrogen; liver disease; women

EPIDEMIOLOGY

The prevalence of alcohol use disorder is increasing, and one of the most devastating complications is end-stage liver disease. Interestingly, the consequences of alcohol use do not affect all heavy-drinking individuals with the same frequency. Only 15% of people who drink heavily develop cirrhosis from heavy alcohol consumption.[1] Certain populations, including those with genetic predispositions (e.g., presence of the *PNPLA3* genotype) and women, are more susceptible to end-stage effects of alcohol-related liver injury.

Historically, alcohol-associated liver injury has been reported to be more prevalent in men, despite women's increased susceptibility to the detrimental effects of alcohol.[2] This difference in prevalence largely is due to the fact that men generally consume more alcohol than women. However, a recent study that examined the presence of alcohol-related liver disease from 2009 to 2015 demonstrated increased incidence (50%) of alcohol-related liver injury in women, as compared to a 30% increase among men during the same time period.[3] The increase in alcohol-related liver injury among women appears to parallel the increase in alcohol consumption observed in women.

A study examining alcohol use patterns in the United States from 2001 to 2002, as compared with 2012 to 2013, reported an 80% increase in

heavy alcohol consumption among women and a 30% increase among men.[4] Similar patterns have been seen globally, with a Japanese study noting a twofold to fourfold increase in alcohol consumption among women from 1968 to 1987.[5] In this study, the rates of alcohol consumption in men remained static. A meta-analysis examining the effects of alcohol use and cirrhosis reported that cirrhosis was more frequent in women versus men, despite similar amounts of alcohol consumption.[6]

MECHANISTIC FACTORS

Previous studies have shown that, when controlling for the amount of alcohol consumed and for body weight, women had increased levels of blood alcohol when compared with men.[7] This increase likely is due to decreased body water content in women, thus leading to a smaller volume of distribution. Moreover, women have reduced gastric alcohol dehydrogenase compared with men and therefore impaired first-pass metabolism, resulting in increased susceptibility to injury.[7] Additional studies also have shown gender differences in alcohol metabolism by hepatic enzymes such as cytochrome P450 2E1, with lower levels in women due to regulation of growth hormone.[8] The role of estrogen is also a culprit.

Kupffer cells reside within hepatic sinusoids and play a role in clearance of foreign compounds within the liver. Activation of Kupffer cells leads to cytokine release and subsequent hepatic inflammation.[9] Rat models have shown that estrogen exposure increases Kupffer cell susceptibility to endotoxin. When animals that received exogenous estrogen were studied, increased Kupffer cell sensitization to lipopolysaccharide was observed.[10] Additional animal models have demonstrated that increased endotoxin release related to Kupffer cell activation resulted in more severe hepatic injury and necrosis.[11] In fact, estrogen blockade in mouse models has been shown to attenuate alcohol-related injury in females.[12]

IMPLICATIONS

These factors likely account for studies showing that women, compared to men, are more susceptible to liver disease with less alcohol consumption, and that women have a faster progression to cirrhosis over a shorter time period. In a study conducted in Australia, the rate of progression to cirrhosis for women was 13.5 years, as compared to 20 years for men, when controlling for less alcohol consumption among the women.[13] More vexing is that although alcohol abstinence has been linked to fibrosis regression, reports show that among people who had cirrhosis and then abstained from alcohol, women had lower 5-year survival rates than men.[14]

Current recommendations from the "Dietary Guidelines for Americans 2015–2020" advise that women should not consume more than 14 grams of alcohol daily, and men should not consume more than 28 grams of alcohol daily.[15] The relative risk of alcohol-related liver disease increases in women who drink any more than one drink per day. Recently, the Million Women Study in the United Kingdom published prospective data and reported observed liver disease patterns among women from 1996 to 2001.[16]

An interesting observation from the Million Women Study is that people who reported drinking daily were more susceptible to liver injury than those who reported binge drinking.[16] Thus, recommendations from this study advise that women abstain from drinking daily. This study also noted that women who drank alcohol with meals were less susceptible to alcohol-related injury than those who drank without eating. A possible explanation for this finding is the increased metabolism of alcohol for those who drank with meals as compared to the metabolism of those who did not drink with meals.

The effects of alcohol consumption outside of meals appear to coincide with the observation that women with eating disorders (e.g., bulimia, anorexia) are more susceptible to alcohol-related liver injury than women with no eating disorder.[17,18] These findings may be explained by the nutritional deficiencies associated with eating

disorders, which are hepatotoxic independent of the effects of alcohol. Other studies have shown that increases in alcohol-related liver disease coincide with obesity.[1] Thus, the presence of eating disorders is not the only risk factor that implicates accelerated progression of alcohol-related liver disease. In a study examining risk factors for liver disease in both men and women, an increased waist-to-hip ratio (a measure of fat distribution) portended a worse prognosis for development of severe liver disease.[1]

OBESITY AND ALCOHOL USE

A possible explanation for the paradoxical discrepancy between alcohol-related liver injury in people with eating disorders and the recent observed increase in those with obesity may be due to the overlap of non-alcoholic fatty liver disease co-existing with alcohol-related liver disease, thus explaining the latter.

In a non–gender focused study, researchers replaced alcoholic beverages with non-alcoholic beverages to examine the effects on hepatic triglyceride fat content.[19] Individuals who received a sugary beverage as a substitute for alcohol, as compared with those who received a non-sugary beverage, had increased hepatic triglyceride fat content. Even more intriguing was that the hepatic triglyceride levels for those who consumed the sugary beverage were comparable to the levels observed for those who consumed the alcoholic beverage. The effects of non-alcoholic beverages on the liver warrant further study, but these results may explain the increase of cirrhosis in patients with concomitant alcohol use and obesity.

MANAGEMENT

Abstinence for individuals with alcohol-related liver injury is paramount to preventing liver-related complications. Although liver disease progression may persist even with abstinence, prevention of further hepatic damage is crucial. After enrolling in alcohol treatment programs, women had higher rates of abstinence than men.[20] However, women are less likely to use face-to-face counseling and pharmacologic therapy to prevent relapse because of family/childcare barriers and a perceived stigma associated with attending programs.[21]

Moreover, if a woman experiences complications of liver disease and needs a transplant, she is often disadvantaged. A recent study that examined early liver transplantation across multiple centers within the United States reported that few women undergo early liver transplantation for alcoholic hepatitis.[22] In addition, few women with any type of alcohol-related liver disease receive transplants. In a retrospective study of individuals evaluated for transplantation for alcohol-related liver disease, men were more likely than women to be listed for transplantation.[23] Also, of all the participants listed, men were more likely than women to receive a transplant.

The lack of proper counseling for alcohol use disorder must be addressed, as studies have demonstrated increased risk of relapse of harmful drinking among women with alcohol-related liver disease who received transplants.[24] This increased relapse for women is problematic, as it has been associated with a higher incidence of recurrent disease for women than for men.

Determining why women are drinking more and exceeding the drinking observed among men is imperative. Several hypotheses include the paradigm shift of women assuming male gender roles, for example, more women are working outside the home and fewer women are having children.[25] Another hypothesis is that the increasing stress of family and work balance for women leads to the use of alcohol to manage stress.[26] In addition, alcohol advertisements targeted toward females have increased, beginning with advertisements for wine coolers in the early 2000s[27] to the advertisements for "female-friendly" drinks such as wine in the current decade, and have made alcohol use more socially acceptable. Increased alcohol use may inadvertently be used to manage stress.

Research shows that the association between problematic drinking and post-traumatic stress

disorder, anxiety, and depression is stronger for women than for men.[28] Moreover, women are more likely to use alcohol to regulate negative reinforcement, whereas for men, investigators have speculated that drinking results in positive reinforcement.

FUTURE AREAS OF RESEARCH

It is quite evident from currently available literature that women, compared to men, have an increased risk of end-stage liver disease from alcohol use. Although it has been established that women should consume less alcohol than men, observations vary as to whether binge drinking or moderate daily drinking (i.e., not exceeding 14 grams per day) is more likely to lead to end-stage liver disease. Future studies should be conducted to provide more detailed recommendations, although in the interim, health care practitioners should advise women to consume no more than one drink per day.

In addition, the Million Women Study's observation that women who did not eat meals while consuming alcohol had increased alcohol-related liver injury needs further corroborative evidence. Currently available literature also indicates that women with obesity should be advised to avoid drinking heavily and to avoid substituting alcohol with beverages that have high sugar content, as these beverages may lead to further hepatic fibrosis despite alcohol abstinence.

Moreover and more significantly, public awareness of current hazardous drinking is needed, as many women are unaware they are increasing their risk of liver disease. Public policies need to minimize alcohol advertising targeted toward women.

CONCLUSION

Although alcohol-related liver injury previously has not been linked to women, it is paramount to educate women about the dangers of consuming alcohol given that women are more susceptible than men to injury after consuming less alcohol. Globally, alcohol consumption has increased, particularly among women. Safe drinking habits, including not exceeding 14 grams of alcohol consumption in a day, not drinking without eating meals, and avoiding daily drinking, should be recommended. If alcohol use disorder is identified, adequate and appropriate counseling and pharmacologic therapy should be provided. Additionally, further study into the neurobiologic basis leading to alcohol use disorder should be made by clinicians and researchers.

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Maternal Substance Use: Consequences, Identification, and Interventions

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Alcohol, tobacco, and cannabis are the substances most frequently used during pregnancy, and opioid-exposed pregnancies have increased fourfold. The purpose of this review is to describe the prevalence and consequences of prenatal exposure to alcohol, tobacco, cannabis, and opioids. Currently available screening questionnaires for prenatal substance use are summarized and contrasted with the measures available for prenatal alcohol use. Because screening for prenatal alcohol and substance use is but the prelude to efforts to mitigate the potential adverse consequences, attempts for the modification of these consequences are briefly reviewed. In addition, areas of future research related to the criminalization of prenatal substance use, which may inhibit both inquiry and disclosure, are discussed. Indeed, the full potential of effective interventions has yet to be realized.

KEY WORDS: prenatal alcohol substance use; screening and intervention

INTRODUCTION

Prenatal exposure to alcohol and other substances has become increasingly common. The substances used most frequently during pregnancy are alcohol, tobacco, and cannabis. Moreover, between 1999 and 2014, the number of women with opioid use disorder during labor and delivery quadrupled.[1] The purpose of this review is to describe the prevalence and consequences of prenatal exposure to alcohol, tobacco, cannabis, and opioids. Currently available screening questionnaires for prenatal substance use are summarized and contrasted with the measures available for prenatal alcohol use. Because screening for prenatal alcohol and substance use is but the prelude to efforts to mitigate the potential adverse consequences, attempts for the modification of these consequences are also briefly reviewed.

It should be noted that this review article is not intended to be a systematic review of the world literature on either prenatal substance use or its prevention. Rather, it is a narrative literature review

that is meant to be illustrative and to stimulate areas of future research because the full potential of effective interventions has yet to be realized.

THE CONSEQUENCES OF PRENATAL SUBSTANCE USE

The consequences of prenatal substance use differ depending on the specific substances used. The most commonly used substances include alcohol, tobacco, cannabis, and opioids.

Prenatal Alcohol Use and Its Consequences

The estimated percentage of prenatal alcohol use is approximately 15%, with past month use being approximately 13%.[2,3] A Centers for Disease Control and Prevention survey conducted from 2015 to 2017 found that nearly 4% of pregnant women had engaged in binge drinking in the prior 30 days.[4] Alcohol use during pregnancy is a highly preventable cause of birth defects and developmental disabilities.[5] Despite the recognition of the teratogenic properties of alcohol, many women continue to disregard advisories on avoiding alcohol during pregnancy.[6]

There is no known safe level of alcohol use while pregnant because there is no exact dose-response relationship between the amount of alcohol consumed during the prenatal period and the extent of damage caused by alcohol in the fetus.[7] Thus, an infant born to a mother who drank alcohol while pregnant may be normal or may manifest alcohol-related birth defects (e.g., problems with the heart, kidneys, bones, or hearing), alcohol-related neurodevelopmental disorders (e.g., intellectual disabilities or problems with behavior and learning), or fetal alcohol spectrum disorders (FASD), which includes a wide range of effects, from mild to severe. An individual with FASD might have abnormal facial features; small head size; shorter than average height; low body weight; poor coordination; hyperactive behavior; difficulty with attention; poor memory; difficulties in school, especially with mathematics; learning disabilities; speech and language delays; intellectual disability or low IQ; poor reasoning and judgment skills; sleep and sucking problems as a baby; vision or hearing problems; and problems with the heart, kidneys, or bones.[8]

A recent multisite study using active case ascertainment methods estimated that the prevalence of FASD among first graders ranged from 1% to 5%.[9] This is concerning because these disorders are associated with life-long disabilities. However, early intervention treatment services can improve a child's development and function.[8]

There is continuing uncertainty about the effects of low and low-to-moderate levels of alcohol intake during pregnancy.[10] For example, a recent cohort study reported craniofacial changes with almost any level of prenatal alcohol intake, but the clinical significance of these changes is not known.[11] Factors that may influence the effects of prenatal alcohol use include patterns of maternal drinking, maternal and fetal genetics, as well as socioeconomic and ethnic factors. Because there is no proven "safe" level of alcohol exposure during pregnancy, the most prudent advice for pregnant women is to abstain from drinking.[12]

Prenatal Tobacco Use and Its Consequences

Cigarette smoking in the antepartum period is common. Past month use of tobacco products among pregnant women was approximately 15% according to the 2017 National Survey on Drug Use and Health report.[13] Tobacco products include the use of alternative forms of nicotine, such as e-cigarettes and vaping, which until recently, have been perceived to be less harmful. For example, in 2015, as many as 7% of women with a recent live birth in Oklahoma and Texas reported using an electronic vapor product shortly before, during, or after pregnancy.[14] Data specific to the effects of prenatal use of electronic vapor products are sparse. However, the Centers for Disease Control and Prevention has issued interim guidance that electronic cigarette products should never be used by pregnant women or adults who do not currently use tobacco products as it investigates

the more than 200 cases of severe pulmonary disease associated with their use.[15]

The use of any tobacco product during pregnancy is associated with adverse maternal, fetal, and neonatal outcomes. Examples of the adverse consequences of tobacco use may begin with subfertility and delay in conception among women who smoke and extend to pregnancy outcomes, which include increased risk of spontaneous pregnancy loss, placental abruption, preterm premature rupture of membranes, placenta previa, preterm labor and delivery, low birth weight, and ectopic pregnancy. Prenatal cigarette smoking may exert effects beyond pregnancy as well and is associated with increased risks of asthma, infantile colic, and childhood obesity.[16]

Prenatal Cannabis Use and Its Consequences

Past month cannabis use among pregnant women ages 18 to 44 increased between 2002 and 2017 from approximately 3% to 7%.[17] Among pregnant adolescents, past month use (15%) was even higher.[18] A recent cross-sectional study using data from 367,403 pregnancies among 276,991 women in Northern California found that self-reported daily, weekly, and monthly cannabis use before and during pregnancy increased between 2009 and 2017. The greatest increases were for daily use, reaching 25% among those who used in the year before pregnancy and 21% among those who used during pregnancy.[19] Explanations for the increases in prenatal use include increasing acceptance of cannabis use and decreasing perceptions of cannabis-related harms.[20]

The association between prenatal cannabis use and maternal, perinatal, and neonatal outcomes is unclear.[21] A 2016 systematic review and meta-analysis concluded that maternal marijuana use during pregnancy was not an independent risk factor for adverse neonatal outcomes, such as low birth weight or preterm delivery, after adjusting for confounding factors like tobacco use.[22] However, limitations to the generalizability of this meta-analysis include the relatively few women in the risk-adjusted group, indicating that the meta-analysis was underpowered to stratify for all secondary outcomes of interest. Another systematic review and meta-analysis from the same time frame found that pregnant women who used marijuana had increased odds of being anemic and that infants exposed to cannabis in utero had decreased birth weight and were more likely to require neonatal intensive care.[23] The researchers from this review acknowledged that because many cannabis users often use tobacco and alcohol as well, discerning a cannabis-only effect was not possible. A population-based cohort study of 661,617 women in Ontario, Canada, showed that the percentage of preterm births among self-reported cannabis users was 12% compared to 6% among nonusers, with this increase persisting even after adjusting for confounding factors.[24] Until there is definitive evidence demonstrating the safety of prenatal marijuana use, concerns that marijuana may interfere with neurodevelopment as well as have other effects have resulted in the American College of Obstetricians and Gynecologists (ACOG) advising women who are pregnant or thinking about pregnancy to avoid using marijuana and other cannabinoids.[25]

Prenatal Opioid Use and Its Consequences

Opioid use among pregnant women increased fourfold between 1999 and 2014 and is present in approximately 3% of pregnancies.[26] Women who use opioids during pregnancy are a diverse group because opioid use may occur in the context of medical care, opioid misuse, or untreated opioid use disorder.[27]

Prenatal opioid use can have a far-reaching clinical impact on infant outcomes. Infants with prenatal opioid exposure are typically born smaller and may have neonatal opioid withdrawal syndrome (NOWS). Infants with NOWS experience withdrawal from opioids and require additional medical care.[28] Characteristics of NOWS, also known as neonatal abstinence syndrome (NAS), include disturbances in gastrointestinal, autonomic, and central nervous systems, leading to irritability,

high-pitched crying, poor sleep, and uncoordinated sucking reflexes that lead to poor feeding. In 2014, a baby was born with NOWS in the United States every 15 minutes.[29,30]

The full impact of opioid exposure during pregnancy on fetal, infant, and childhood outcomes, however, is still unknown. Explanations include the possibility of exposure to other substances as well as concomitant maternal, medical, psychological, and socioeconomic issues. There is a growing body of evidence about the association of opioids with specific birth defects, such as congenital heart defects, neural tube defects, and clubfoot.[31]

For pregnant women with opioid use disorder, substitution treatment with opioid agonists, such as methadone and buprenorphine, imparts important benefits particularly when compared to continued illicit drug use. Advantages include more stable maternal drug levels, reduced withdrawal and drug-seeking behavior, and improved self-care, which should lead to a better pregnancy outcome because of reduced risk for fetal distress, miscarriage, growth restriction, and preterm birth.[32]

Compared to data on buprenorphine-maintained pregnancies, more longitudinal data on methadone-exposed pregnancies are available. In a prospective longitudinal study, 68 methadone-exposed children and 88 nonmethadone-exposed children were evaluated at 2.0 and 4.5 years for executive functioning and later emotional behavioral and emotional adjustment.[33] The methadone-exposed children had worse inhibitory control than the nonexposed children, when taking maternal education and prenatal benzodiazepine use into account. Another study used a school readiness framework to assess the health and neurodevelopmental outcomes of a regional cohort of 100 methadone-exposed children and 110 randomly identified nonmethadone-exposed children who were studied from birth to 4.5 years. Children born to opioid-dependent mothers had higher rates of delay and impairment across all outcome domains, with multiple domain problems being common. Impaired school readiness was associated with greater maternal substance use, higher social risk, male sex, and lower quality caregiving environments.[34]

A systematic review and meta-analysis synthesized data from 41 studies on the neurodevelopment of prenatal methadone-exposed children. The analysis included 1,441 children whose mothers were prescribed methadone during pregnancy and 842 children whose mothers did not receive methadone.[25] Methadone-exposed children appeared to be at increased risk for neurodevelopmental impairment, with lower scores on the Mental Development Index and Psychomotor Development Index, as well as atypical visual evoked potentials, strabismus, and nystagmus. However, these findings about impairment may be biased, with the studies not accounting for factors other than methadone. Indeed, results from this meta-analysis confirm the need for more research and the many factors that can impact pregnancy outcome.

SCREENING FOR PRENATAL SUBSTANCE USE

Early universal screening of pregnant women for alcohol use, substance use, or both is recommended by ACOG because alcohol and substance use is not typically disclosed spontaneously by patients. ACOG recommends clinicians use validated questionnaires or have a conversation with patients but does not endorse using routine urine toxicology tests.[35,36] Moreover, a positive screening questionnaire does not result in a diagnosis. Rather, such a result is an opportunity for a patient and her clinician to review health practices and make changes, if appropriate.[37]

Screening for Prenatal Alcohol Use

There is no known safe level of alcohol consumption during pregnancy.[38] Alcohol is a teratogen; in other words, it is capable of interfering with fetal development, resulting in birth defects. Although the consequences of light alcohol use among women, defined as consuming up to 32 g of alcohol per week, on pregnancy outcomes remain unsettled in the absence of

sufficient evidence, the potential for harm cannot be ruled out.[12] Hence, ACOG has recommended that all women seeking obstetric–gynecologic care be screened for alcohol use annually and within the first trimester of pregnancy.

Screening questionnaires for prenatal alcohol use have been well studied. For example, a systematic review of brief screening questionnaires to identify problem drinking during pregnancy evaluated seven instruments given to 6,724 participants.[39] The measures included the TWEAK (Tolerance, Worried, Eye-Opener, Amnesia, K/Cut Down); the T-ACE (Tolerance [number of drinks], Annoyance, Cut Down, Eye-Opener); CAGE (Cut Down, Annoyed, Guilty, Eye-Opener), NET (Normal Drinker, Eye-Opener, Tolerance); AUDIT (Alcohol Use Disorder Identification Test); AUDIT-C (AUDIT Alcohol Consumption Questions), and SMAST (Short Michigan Alcoholism Screening Test). The screening questionnaires were compared with a structured interview to ascertain drinking status as a reference standard. The T-ACE, AUDIT-C, and TWEAK were the three questionnaires identified to be the most promising screening tools for identifying risk drinking in pregnant women. However, the sensitivity and specificity of these three questionnaires outside the United States is unknown.

Screening for Prenatal Substance Use

Screening instruments for prenatal alcohol use have been well studied, whereas screening instruments for substances other than alcohol have been less well developed.[26,40] The World Health Organization (WHO) guidelines for the identification and management of substance use and substance use disorder during pregnancy list the Substance Use Risk Profile-Pregnancy (SURP-P) scale,[41] the proprietary 4P's Plus©,[42] and the National Institute on Drug Abuse (NIDA) Quick Screen–Modified Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)[43] as potential screening measures for pregnant women, even though not all of these instruments had been evaluated among that population at the time of its recommendation.[44]

Several recent studies have evaluated the accuracy of various screening tools for prenatal substance use. In one prospective cross-sectional study conducted in Baltimore, MD, with 500 pregnant women, stratified by trimester and use of prenatal care, researchers administered three index tests and compared them to reference tests.[45] The three index tests were the proprietary 4P's Plus©, NIDA Quick Screen–ASSIST), and the SURP-P. The reference tests were urine and hair testing, which captured substance use up to the past 90 days. Alcohol use was not evaluated. The researchers found that there were differences in validity indices (i.e., sensitivity, specificity, positive predictive value, and negative predictive value) by age and race, but not by trimester, for all screening tools. The SURP-P and 4P's Plus© were highly sensitive across all trimesters, races, and age groups.

Another prospective cross-sectional screening accuracy study compared five screening instruments on their ability to identify illicit drug, opioid, and alcohol use under privacy expectations consistent with current practice. The participants included 1,220 pregnant women who were receiving care in Boston, MA; Detroit, MI; or New Haven, CT. The women were socioeconomically diverse and had a mean age of 29 years. The study used a reference standard of substance use in three classes (i.e., illicit drugs, opioids, and alcohol); results were considered positive if use was evident via a 30-day calendar recall or urine toxicology analysis.[46] The illicit drug use reference standard included marijuana, cocaine, heroin, amphetamines, barbiturates, and hallucinogens. The five screening instruments for substance use in pregnancy were the SURP-P; CRAFFT, a five-item screener with items related to car, relax, alone, forget, friends, and trouble; 5Ps, with items on parents, peers, partner, pregnancy, past (i.e., an adaptation of the 4P's Plus©); Wayne Indirect Drug Use Screener (WIDUS); and NIDA Quick Screen–ASSIST. None of the five measures showed both high sensitivity and high specificity, and the area under the curve was low for nearly all measures,

indicating that none could be recommended for applied practice with pregnant women.

A companion study compared the same five measures in the identification of substance use disorder, including alcohol, cannabis, opioids, and stimulants, among the 1,220 pregnant women.[47] Participants completed the Mini International Neuropsychiatric Interview 7.0.2, a short, structured diagnostic interview to identify substance use disorder, including alcohol; cannabis; stimulants, such as cocaine or amphetamines; and opioids, such as heroin and the nonmedical use of prescription drugs.[48] Substance use disorder is distinct from substance use and represents a more significant and persistent pattern of consumption that may increase the risk of adverse infant outcomes as well as indicate that the pregnant woman may need evaluation and referral for specialty treatment.[49] Of the 1,220 women in this study, more than 15% satisfied diagnostic criteria for substance use disorder and more than 30% reported having used alcohol or other substances in the past month. There was little overlap between the women who had substance use disorder and the women who had used alcohol or other substances within the past month. Nearly 10% of the women satisfied criteria for alcohol use disorder, as defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, and 9.0% satisfied criteria for substance use disorder. Specifically, cannabis use disorder was the most common substance disorder diagnosed (8%). Approximately 3% satisfied criteria for more than one disorder.

There were considerable variations by site. For example, alcohol use disorder was the most common in Boston (15%) but infrequent in New Haven (5%). In contrast, substance use disorder was the most common in Detroit (17%) but less frequent in Boston (3%). Measures of merit (i.e., sensitivity, specificity, accuracy, and area under the receiver operating curve [AUROC]) were calculated with 95% confidence intervals [CI] for the NIDA Quick Screen, CRAFFT, SURP-P, WIDUS, and 5Ps, using substance use disorder as the criterion standard. The CRAFFT (AUROC=0.75, 95% CI [0.72, 0.79]) and SURP-P (AUROC=0.74, 95% CI [0.71, 0.78]) had the highest AUROCs for identifying substance use disorder, including alcohol. In contrast, the NIDA Quick Screen had the lowest AUROC (AUROC=0.62, 95% CI [0.59, 0.65]) for identifying substance use disorder, including alcohol. Overall, the tested measures were more accurate in identifying alcohol use disorder than substance use disorder (e.g., for identifying alcohol use disorder, the AUROCs for the CRAFFT and SURP-P were 0.78 and 0.77, respectively).

Barriers to Early Identification by Screening

Pregnant women with substance use disorder are at increased risk for adverse health and social outcomes, making early identification crucial.[50] Because substance use is substantially underreported, even among women who participate regularly in urine drug screens, use of validated questionnaires to identify prenatal alcohol and substance use has been recommended.[26,51]

There are, however, at least two barriers to these recommendations. First, as discussed in the preceding section, current screening questionnaires have been found to be inadequate measures. According to a 2010 survey of obstetrician-gynecologists, 58% did not use a validated screening tool to assess alcohol risk despite there being several validated tools available.[52] It is likely that even fewer will use a screening tool for prenatal substance use, particularly as such tools are less well developed. A second barrier includes the punitive consequences stemming from state laws regarding prenatal substance use, which can result in patients not wanting to disclose and physicians not wanting to learn about their patients' behaviors.[53-55] Hence, in addition to patients' previous fears about stigmatization because of use, disclosure could now pose a legal risk.[56] An example of a punitive policy includes treating substance use during pregnancy as child abuse or neglect. This policy may arise from a desire to discourage women from using substances while pregnant, to encourage

women to seek treatment, and to ensure the safety of the neonate.[57]

The association between states with punitive or reporting policies related to substance use in pregnancy and rates of NAS was recently evaluated in a study of 4,567,963 births from 8 U.S. states in varying years between 2003 and 2014.[57] States without punitive or reporting policies were compared with states that had such policies, before and after policy enactment. The main outcome measure was the rate of NAS. States that criminalized substance use during pregnancy (e.g., grounds for civil commitment, child abuse, or neglect) had significantly higher rates of NAS in the 1st full year after enactment and more than 1 full year after enactment. In contrast, there was no association with neonatal abstinence rates in states with policies requiring reporting of suspected prenatal substance use. A possible explanation for this difference includes the extent to which pregnant women disengage from health care services when punitive measures are enforced, whereas reporting policies may not dissuade pregnant women from engaging with health care services, resulting in greater conversations between physicians and their patients. However, neither the punitive nor the reporting approach resulted in reduced rates of NAS, which was the presumed, desired outcome of these policies.

AFTER SCREENING: INTERVENTION

Because screening for prenatal alcohol and substance use is but the prelude to efforts to mitigate the potential adverse consequences, brief intervention and referral to treatment, if indicated, have also been recommended.[56] Brief interventions and psychosocial interventions have been examined by investigators and organizations such as the WHO, which sought to develop evidence-based global guidelines for identifying and managing substance use and substance use disorder in pregnancy.[42] Global guidelines were desired because although several high-income countries had developed national guidelines, low- and middle-income countries had not. However, the WHO noted that much of the evidence underlying the effectiveness of screening and brief interventions during pregnancy originated from a time when reporting standards and measures of bias were not in consistent use. Nonetheless, the evidence indicated that asking women about alcohol and other substance use in a detailed and comprehensive way may increase their awareness of the risks associated with these practices and prompt them to modify their behavior.

Psychosocial Interventions for Prenatal Alcohol Use

In late 2018, the U.S. Preventive Services Task Force (USPSTF) renewed its recommendation for screening adults ages 18 year or older, including pregnant women, for unhealthy alcohol use and providing persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce unhealthy alcohol use (i.e., a grade B recommendation meaning that there is high certainty that the net benefit is moderate, or moderate certainty that the net benefit is moderate to substantial).[56] The USPSTF bounds the harms of screening and brief behavioral counseling interventions for unhealthy alcohol use in adults as small to none, based on the likely minimal risks of completing screening questionnaires, the noninvasive nature of the interventions, and the absence of reported harms in the evidence of the behavioral interventions.

The USPSTF makes three special comments with regards to pregnant women. First, any alcohol use by pregnant women is unhealthy. Second, validated alcohol screening tools for pregnant women are available, including the T-ACE and TWEAK. Third, brief counseling interventions among pregnant women have increased the likelihood that women remain abstinent from alcohol use during pregnancy.

Most interventions for FASD have been reported in North America, which has lower FASD prevalence compared to Europe and other sites around the world.[57] Context-related differences may impact on the effectiveness of

the interventions. For example, in a systematic review of prevention interventions to reduce prenatal alcohol exposure and FASD in indigenous communities, reviewers evaluated studies conducted from 1989 to 2017. A total of 10 studies from an initial sample of 712 articles were included if inclusion criteria were met. Comparisons of study effects were made difficult by heterogenous study designs, target populations, and interventions. The reviewers concluded that there was minimal evidence to support the belief that interventions intended to reduce the risk of prenatal alcohol exposure or FASD in indigenous populations have been effective.[58]

Psychosocial Interventions for Prenatal Cigarette Smoking

Psychosocial interventions for supporting women to stop smoking during pregnancy were assessed by the Cochrane Pregnancy and Childbirth Group.[59] This review included 102 randomized controlled trials, with 120 intervention arms. Data from 88 randomized controlled trials, involving more than 28,000 women, were analyzed. Intervention strategies included counseling, health education, feedback, incentives, social support, and exercise. Nearly all studies were conducted in high-income countries. Results from the review yielded moderate- to high-quality evidence that psychosocial interventions increased the proportion of pregnant women who had stopped smoking by late pregnancy (35%), with a 17% reduction in infants born with low birth weight, and a 22% reduction in neonatal intensive care admissions. There did not appear to be any adverse psychological effects from the interventions.

Psychosocial Interventions to Reduce Other Prenatal Substance Use

Screening, brief intervention, and referral to treatment in the perinatal period have been recommended for prenatal substance use.[60] Subsequent to this recommendation, at least two systematic reviews of the evidence for psychosocial interventions have been completed.

The first systematic review included four articles published between 2002 and 2013. It began with 3,792 unique potential publications, but the vast majority did not meet a priori quality criteria. Limited, but promising, evidence of brief interventions reducing illicit drug use among postpartum women was found.[61]

The second systematic review was completed by researchers from the Cochrane Collaboration. They sought to evaluate the evidence on the effect of psychosocial interventions, such as contingency management (CM) and motivational interviewing-based (MIB) techniques compared to that of usual care for pregnant women in outpatient illicit drug treatment programs.[62] This group reviewed 14 studies, with 1,298 pregnant women who received either CM or MIB techniques in addition to other comprehensive care. The women in the control group received usual care that included pharmacological management, counseling, prenatal care, transportation, and/or childcare. There were no differences in retention or abstinence behavior between CM/MIB techniques and usual comprehensive care. The quality of evidence from these studies was assessed to be low to moderate.

SUMMARY

Prenatal exposure to alcohol, tobacco, and marijuana has become increasingly common. In addition, there has been a fourfold increase in the number of opioid-exposed pregnancies. Prenatal exposure to alcohol and other substances may have an adverse impact on a developing fetus. Since pregnant women may be reluctant to disclose their use or may not appreciate the potential for harm, early identification is desirable. However, identification is currently limited by the lack of adequate screening tools and the fear of legal and other sanctions, which may limit both inquiry and disclosure. Although effective interventions for prenatal alcohol, cigarette, and other substances are available, these interventions rely on identification and behavioral counseling. It is likely that the full potential of effective interventions cannot yet be realized in the current setting.

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Alcohol's Effects on Breast Cancer in Women

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Globally, more than 2 million new cases of breast cancer are reported annually. The United States alone has more than 496,000 new cases every year. The worldwide prevalence is approximately 6.8 million cases. Although many risk factors for breast cancer are not modifiable, understanding the role of the factors that can be altered is critical. Alcohol consumption is a modifiable factor. Studies of alcohol in relation to breast cancer incidence have included hundreds of thousands of women. Evidence is consistent that intake, even intake of less than 10-15 grams per day, is associated with increased risk of this disease. In addition, evidence, although less extensive, shows that possible early indicators of risk, such as benign breast disease and increased breast density, are associated with alcohol consumption. Evidence is less strong for differences based on geographic region, beverage type, drinking pattern, or breast cancer subtype. Some studies have examined the association between alcohol and recurrence or survival after a breast cancer diagnosis. These findings are less consistent. Public awareness of alcohol as a risk factor for breast cancer is low, and public health measures to increase that awareness are warranted.

KEY WORDS: alcohol drinking; breast cancer incidence; breast cancer survival; drinking pattern; women

INTRODUCTION

In 1987, the *New England Journal of Medicine* published two reports about alcohol consumption and breast cancer risk.[1,2] In the two reports, both prospective cohorts, alcohol consumption, even at modest levels of intake, was associated with risk of breast cancer. An accompanying editorial indicated that based on the existing epidemiologic studies, approximately 17 at the time, one could conclude "despite variations in study design, population, culture and language of the country of origin, and methods of determining the amount of alcohol ingested, most investigations have found at least a small increase in risk with increases in intake, particularly among premenopausal women."[3] Since those landmark papers were published, studies have been conducted among hundreds of thousands of women. Findings of an association between

alcohol consumption and an increase in breast cancer risk for women have persisted.

SCOPE OF THE PROBLEM

Breast cancer affects more than 2 million women each year around the world.[4] The age-adjusted rate is 46.3 new cases of this disease per year for every 100,000 women. In the United States, more than 496,000 new cases are diagnosed every year, and the age-adjusted incidence is 84.8 per 100,000 women. Globally, 626,679 deaths from breast cancer occur annually, and in the United States, close to 89,000 deaths were reported. The age-adjusted breast cancer mortality rates are 13.0 deaths per 100,000 women globally, and 12.6 deaths per 100,000 women in the United States. It is estimated that the prevalence of breast cancer around the world is 6.8 million cases.

ALCOHOL AND BREAST CANCER INCIDENCE

A large body of research provides evidence that alcohol is a risk factor for incidence of breast cancer. The World Cancer Research Fund and the American Institute for Cancer Research (WCRF-AICR) collaborated to organize a continuous systematic review of dietary factors in relation to cancer.[5] The WCRF-AICR reports include examinations of alcohol and breast cancer. In a 2018 update, they concluded that, based on the existing literature (16 prospective studies of premenopausal breast cancer and 34 of postmenopausal disease), alcohol consumption is a "probable cause" and a "convincing cause" for premenopausal and postmenopausal breast cancer, respectively. The meta-analysis showed that for a 10-gram increase in alcohol consumed per day on average, risk increased 5% among premenopausal women and 9% among postmenopausal women. A standard drink contains approximately 14 grams of alcohol.[6]

As noted in the 1987 editorial in the *New England Journal of Medicine*, an association between alcohol and breast cancer was found across geographic locations for a range of beverage types consumed and for a variety of drinking patterns.[3] Most of the studies on alcohol and breast cancer have been conducted in North America and Europe, but there are some from other locations.

The WCRF-AICR meta-analysis reported some differences by location.[5] For premenopausal breast cancer, the summary meta-analysis was significant only for North America. Results were similar in magnitude but not statistically significant for analyses of findings from Europe and Asia. For postmenopausal cancer, in the meta-analysis of dose-response, the association was statistically significant only for studies of Europe and North America.

In a study that pooled data from 20 cohorts in the United States, Canada, Europe, Australia, and Japan, no significant heterogeneity was found among studies, although the association between alcohol and breast cancer was stronger for the North American cohorts than for the others.[7] Even within regions, there can be considerable differences in quantities of alcohol consumption, types of beverages consumed, and intensities of drinking (e.g., frequency of binge drinking, drinking with meals or not). For example, within Europe, drinking patterns vary considerably. In a study of 335,000 women in Europe, of whom 11,600 had invasive breast cancer, a significant, 4% increase in risk was shown for each additional 10 grams of alcohol consumed per day.[8]

Studies of individual European countries, including Italy,[9] France (among postmenopausal but not premenopausal women),[10] and the United Kingdom,[11] but not Greece,[12] also reported evidence of increased risk. In a case-control study of more than 2,000 cases and 2,000 controls from 3 countries in sub-Saharan Africa, an association between alcohol consumption and risk was reported, despite considerable differences in the prevalence of alcohol consumption in those countries.[13] In South America, studies in Brazil reported some evidence of an association.[14,15] For studies in Asia, where women's alcohol consumption generally is lower, results have been inconsistent.[16-20]

Few studies have examined the association between alcohol and breast cancer by race/ethnicity. The African American Breast Cancer Epidemiology and Risk (AMBER) Consortium, a pooled analysis of studies of African American women, found a J-shaped association between alcohol consumption and breast cancer risk.[21] The magnitude of the association for higher intakes of alcohol was similar to results reported in other studies of women of European descent.

Overall, there is strong evidence that alcohol increases breast cancer risk. Evidence is strongest for North America and Europe, where more studies have been conducted, but other regions also show some evidence of a similar association. Much additional research has been done regarding the details of the alcohol consumption (e.g., beverage type, drinking pattern, the participant's age at the time of consumption) and the details of the breast cancer (e.g., tumor subtype). These findings are less consistent.

Variability in findings may be a function of the small sample size of some studies, for instance, in those studies that examined associations between alcohol consumption for breast cancer by subtype (e.g., estrogen receptor–positive or –negative). In addition, alcohol consumption can be difficult to assess for a variety of reasons, including difficulty recalling usual intake, change in consumption over the lifetime, and response bias. In this context, the consistency of the findings regarding overall risk of breast cancer associated with alcohol consumption is noteworthy.

Beverage Type

Several studies of alcohol and risk examined whether there are differences depending on the beverage consumed: wine, beer, or spirits. The pooled analysis of 20 cohorts reported no difference in risk based on the beverage type.[7] The Million Women Study in the United Kingdom reported similar associations for those who drank wine only and for those who consumed other drinks.[11] In the WCRF-AICR meta-analysis, only beer was associated with a statistically significant increase in risk among premenopausal women, and only wine was associated with risk among postmenopausal women.[5] However, in all of the studies, there was an indication of increased risk with each of the beverages, even if not statistically significant. In addition, the evidence was that there was not a statistical difference of the association with each of the three types of beverage for both premenopausal and postmenopausal analyses. Some studies provided evidence of a stronger effect for a particular beverage, but most of the evidence pointed to effects from any alcoholic beverage.

Drinking Pattern

When examining the effects of alcohol consumption on health and disease, how participants consumed the alcohol must be considered. Not only the absolute quantity consumed, but also the intensity of consumption may have biological effects. For example, the effects of an average consumption of seven drinks per week may differ for consumption of one drink daily and for seven drinks on one day once per week.

Just a few studies have examined drinking intensity. In the Nurses' Health Study I (NHS), binge drinking (defined as six or more drinks in one day) was associated with increased risk, even after adjusting for total consumption.[22] The frequency of alcohol consumption was not associated with risk in that cohort after adjusting for total consumption. In the Sister Study, a cohort of women with a family history of breast cancer, self-report of ever binge drinking (defined as four or more drinks in one sitting) or ever having blacked out while drinking were associated with increased breast cancer risk.[23] These associations were not adjusted for overall alcohol intake.

Even among people who drink lightly, evidence of increased risk has been reported. In a systematic review of light drinking, which used the World Health Organization definition of less than 21 grams of alcohol consumed per day, Shield and colleagues found consistent evidence of increased risk.[24] In a meta-analysis, Choi and colleagues found statistically significant increases in risk of 4%, 9%, and 13% for individuals who drank less than 0.5 drinks per day, less than or

equal to 1 drink per day, and 1 to 2 drinks per day, respectively; in this analysis, one drink was defined as 12.5 grams of alcohol.[25] There is no evidence of a lower threshold for an effect of alcohol consumption on risk of breast cancer. Collectively, results from these studies on intake indicate that drinking pattern may affect risk, as drinks per drinking day are associated with increased risk even after adjusting for total intake.

Breast Cancer Subtype

Breast cancer can be classified into subtypes by tumor markers. The subtypes may have different risk factors, and they are different in terms of aggressiveness, treatment, and prognosis. A number of studies have examined the association between alcohol consumption and invasive breast cancer by subtype.

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which examined a cohort of more than 360,000 women from 23 centers in 10 countries in Europe, the association between alcohol consumption and risk was stronger for women with estrogen receptor–positive tumors than for those with estrogen receptor–negative tumors.[26] In a report on postmenopausal breast cancer from the Million Women Study in the United Kingdom, no heterogeneity by estrogen receptor status was found for the association between alcohol consumption and risk.[27] A pooled analysis of 20 cohort studies, which comprised more than 1 million women, reported no difference in the associations of alcohol and estrogen receptor–positive tumors or of alcohol and estrogen receptor–negative tumors.[7] Finally, in the systematic review by the WCRF-AICR, the findings for postmenopausal cancer indicated an increase in risk for estrogen receptor–positive tumors but not for estrogen receptor–negative tumors.[5]

In one study, alcohol consumption and risk of human epidermal growth factor receptor 2 (HER2)–positive and triple-negative breast cancers were compared to risk of estrogen receptor–positive tumors.[28] Alcohol consumption was associated with a lower risk of HER2-positive tumors and no difference in the risk of triple-negative tumors, as compared to its association with risk for estrogen receptor–positive tumors. In an analysis of data from the AMBER Consortium of African American women, the association between alcohol consumption and risk was stronger for estrogen receptor–negative, progesterone receptor–negative, and HER2-negative tumors than for tumors with positive receptor status.[21] Overall, findings from studies of associations between alcohol consumption and breast cancer subtypes have been inconsistent.

Period of Exposure

Alcohol consumption patterns generally vary during the life span, and effects of exposures may differ depending on the stage of breast development when the drinking occurred. A number of studies have examined risk associated with alcohol consumption at particular time periods, especially during adolescence and early adulthood.

The NHS II, a prospective study of women ages 24 to 44 at baseline, reported an 11% increase in breast cancer risk associated with consumption of 10 grams of alcohol per day between menarche and first pregnancy, adjusting for subsequent intake.[29] A similar increase in risk was observed for consumption of alcohol after the first pregnancy, adjusting for intake before that time. In NHS I, a cohort of women ages 30 to 55 at baseline, there was an 8% increase in risk associated with 10 grams of alcohol consumed per day between ages 18 and 40, even after adjusting for consumption after age 40.[22] For consumption after age 40, there was a 7% increase in risk, after adjusting for earlier intake.

Benign breast disease is associated with increased breast cancer risk and may be an early indicator of risk. In the NHS II, evidence indicated a 15% increase in risk of benign breast disease for each additional 10 grams per day of alcohol consumed during adolescence.[30] Another study of young women reported a 50% increase in risk of benign breast disease for each additional drink per day during the period of ages 9 to 15.[31] In one study, associations for alcohol with risk

were similar for pre-cancerous conditions as for invasive breast cancer.[32]

The EPIC cohort study examined the association between risk and alcohol consumption for parous women before their first, full-term pregnancy compared with women who did not begin drinking until after their first pregnancy.[8] Point estimates were similar but there was a significant association only for those who started drinking before their first pregnancy. In addition to intake during adolescence and young adulthood, even exposure to alcohol *in utero* may predispose to increased risk. Evidence from animal models indicates that ethanol exposure *in utero* can lead to increased breast tumorigenesis in the adult offspring when exposed to carcinogens.[33]

These studies indicate that the association of lifetime alcohol consumption with breast cancer risk may be different depending on when the alcohol was consumed. Evidence shows, with some inconsistency among studies, that consumption in adolescence and before a first pregnancy may particularly affect risk.

Breast Density

Breast density is a measure of breast tissue from radiography. It is associated with subsequent breast cancer and is one of the strongest breast cancer risk factors.[34,35] Understanding factors related to increased density may provide insight into early stages of carcinogenesis. A number of cross-sectional analyses have shown that alcohol consumption is associated with increased breast density. In a study in Germany, consumption of more than 10 grams of alcohol per day was associated with increased risk of high mammographic density.[36] Similarly, increases in risk of increased breast density were associated with alcohol drinking in Japan,[37] Sweden,[38] and the United States in Hawaii[39] and New York City.[40] There was a nonsignificant association in a study in China.[41]

In some studies, the association between alcohol consumption and risk varied depending on other breast cancer risk factors. In the Swedish study, the association was strongest for the group that also had other factors that predicted increased risk of breast cancer.[38] In a multicultural population in New York City, the association was strongest among individuals who had lower body mass index.[40] In a study of Mexican women, alcohol use was associated with increased breast density.[42] In a study of NHS II participants, no association was found between breast density and alcohol consumption.[43] A meta-analysis of studies reported an association between increased breast density and higher levels of alcohol consumption.[35] Although these reported findings are not consistent, effects of alcohol consumption on breast density may be one mechanism for the associations with risk for breast cancer.

Diet

A number of studies have examined alcohol consumption in concert with other known breast cancer risk factors. In particular, there has been study of interactions of alcohol with other dietary factors such as folate and other B vitamins, which play a role in alcohol metabolism. Alcohol negatively affects folate status, impacting folate absorption and metabolism and increasing folate excretion.[44] A systematic review reported evidence of interaction between alcohol and folate in relation to breast cancer risk.[45] Breast cancer risk decreased with increased folate consumption among individuals who drank heavily but not lighter drinkers.

Several recent studies examined plasma folate as a measure of vitamin status. In the NHS II, there was an interaction between alcohol and plasma vitamin concentrations, with a trend toward plasma folate being protective for breast cancer risk among individuals who consumed greater amounts, but not among those consuming lesser amounts of alcohol.[46] However, in the NHS I, plasma folate was not associated with breast cancer risk and did not vary by alcohol consumption.[47]

Further, in the EPIC cohort study in Europe, no interaction was found for alcohol and plasma folate consumption in relation to breast cancer risk.[48] This study found some evidence of an interaction of alcohol and plasma vitamin B_{12} consumption in

relation to breast cancer risk; vitamin B_{12} also is a cofactor in one-carbon metabolism. A study that examined the Women's Health Study cohort found no interaction between plasma concentrations of B vitamins and alcohol consumption in relation to risk.[49] A systematic review found evidence for an association between higher levels of folate consumption and decreased risk of breast cancer among participants with moderate or high alcohol intake.[50] Collectively, these results show that diet, particularly vitamins related to one-carbon metabolism, may modify the association between alcohol and the risk for breast cancer.

Genetic Factors

Several studies have examined genetic variation in the association between alcohol consumption and breast cancer risk. There have been several studies of the genes that code for the alcohol dehydrogenases (ADH), which are critical enzymes for alcohol metabolism. In a cohort in the Netherlands, variants in the genes for ADH were not associated with breast cancer risk nor did they modify the risk associated with alcohol consumption.[51] The NHS I reported similar findings; the association between alcohol consumption and risk for breast cancer was not modified by genetic variation in ADH.[52] There was, however, evidence that an association between alcohol and steroid hormone levels differed depending on ADH genotype.

A Danish cohort study examined variation in the *CYP19A1* gene, which codes for aromatase, an enzyme important to estrogen metabolism.[53] Although these researchers found an interaction of genetic variation with blood steroid hormones with acute alcohol consumption, they found no evidence of an association of the genetic variant with breast cancer risk. Among women who have the *BRCA1* or *BRCA2* genes, mutations that confer a particularly elevated risk of breast cancer, alcohol was not associated with breast cancer risk.[54] Overall, the evidence for genetic factors modifying the association between alcohol consumption and the risk for breast cancer is not strong.

Other Potential Modifying Factors

Understanding of whether other factors modify the observed association between alcohol consumption and breast cancer is another area of active research. In a pooled analysis, alcohol was positively associated with risk among both nulliparous and parous women.[55] Point estimates of risk were similar and not significantly different for the two groups. There is some evidence of a stronger association between alcohol and breast cancer risk among women receiving hormone therapy as compared to those not receiving hormone therapy, particularly the risk for estrogen receptor–positive breast cancer.[56] Further examination of modifying factors such as other dietary factors, body mass index, level of physical activity, and smoking is warranted.

ALCOHOL AND SURVIVAL AFTER DIAGNOSIS

Although most of the research regarding the association between consuming alcohol and the risk for breast cancer has focused on incidence, some studies have examined the effects of alcohol on survival after a breast cancer diagnosis. Studies used different time frames (before or after diagnosis) for the alcohol consumption and different outcome measures, such as breast cancer recurrence, breast cancer–specific survival, and all-cause mortality. Most studies did not distinguish by breast cancer subtype, which can affect prognosis.

A meta-analysis of 11 studies found evidence of improved survival after breast cancer diagnosis among individuals who reported any prediagnostic alcohol consumption, when compared with those who reported none.[57] The association differed somewhat by the estrogen receptor status of the tumor, with some evidence of reduced all-cause mortality for women with estrogen receptor–negative disease and no association with mortality in those with estrogen receptor–positive disease. Studies of lifetime alcohol intake found no association with all-cause mortality or

death from breast cancer (breast cancer–specific mortality).[58,59]

In the National Institutes of Health (NIH)-AARP Diet and Health Study cohort, alcohol consumption at the study baseline was not statistically significantly associated with breast cancer–specific survival.[60] In the Women's Health Initiative, there was no association between prediagnostic alcohol consumption and breast cancer–specific or all-cause mortality.[61] There was some evidence of decreased breast cancer–specific mortality for estrogen receptor–negative tumors. Among breast cancer patients from the Moffitt Cancer Center, self-reported alcohol consumption one year before diagnosis was associated with improved breast cancer–free survival.[62] Another study of women in the United States reported that prediagnostic alcohol intake was associated with an increased risk of breast cancer–specific mortality.[63]

Alcohol consumption pattern may affect mortality as well as incidence. In a study in western New York among women who had postmenopausal breast cancer, drinking intensity before diagnosis was associated with prognosis.[59] Participants who drank four or more drinks per drinking occasion had increased mortality from breast cancer and from all causes, and participants who drank fewer drinks per drinking occasion had decreased mortality from both breast cancer and all causes.

Few studies have examined alcohol consumption following a breast cancer diagnosis. One study reported an increased risk of breast cancer recurrence with alcohol consumption after diagnosis among premenopausal but not postmenopausal women.[64] In another study, investigators found no association between postdiagnostic intake and breast cancer–specific mortality.[63] There was better overall survival for those with greater postdiagnostic alcohol consumption. Findings regarding alcohol consumption and prognosis after a breast cancer diagnosis are not consistent. More research is needed to examine alcohol consumption, including patterns of consumption, following diagnosis.

More analyses regarding breast cancer subtype and treatment are required to better understand a possible role of alcohol consumption following diagnosis. Recent studies examining alcohol consumption and the efficacy of breast cancer treatments have not found any effect of alcohol consumption on radiotherapy[65] or on adjuvant hormone therapy.[62] More data regarding in-depth analysis of alcohol consumption both before and after diagnosis are needed, along with more research examining the total amount of alcohol consumed, drinking patterns in relation to outcomes, and the effects of drinking alcohol during treatment.

MECHANISMS FOR ALCOHOL EFFECTS

The role of alcohol consumption in breast carcinogenesis is a complex process likely acting through a number of mechanisms. Although alcoholic beverages contain a variety of compounds, for breast carcinogenesis, alcohol itself appears to be the more important carcinogen,[66] consistent with the finding that overall, risk does not differ based on the type of beverage consumed. However, much is not understood regarding the underlying mechanisms for alcohol and breast carcinogenesis. Potential mechanisms include oxidative stress, cell proliferation, effects on hormones, particularly steroid hormones, and effects on one-carbon metabolism.

Alcohol likely contributes to carcinogenesis partly through oxidation from alcohol metabolism and through oxidative stress from production of the alpha-hydroxyethyl radical, a reactive oxygen species.[67] Alcohol is metabolized to acetaldehyde, classified as a carcinogen by the International Agency for Research on Cancer (IARC), part of the World Health Organization, in 2010.[67] Although production of acetaldehyde from alcohol primarily occurs in the liver, it also occurs in breast tissues.

There is in vivo evidence that acetaldehyde can concentrate in mammary cells following a single exposure. In an animal model, acetaldehyde accumulated and persisted in higher concentrations

in breast tissue than in blood.[68] Adverse effects of acetaldehyde include DNA adduct formation, oxidation, and altered DNA methylation.[67] Further, in vitro, at low concentrations, alcohol can increase cell proliferation, including proliferation of breast cells.[69] Higher concentrations of alcohol and red wine exposure may reduce cell proliferation.

In addition to the carcinogenic effects of alcohol consumption and acetaldehyde on breast tissue, alcohol consumption's effects on hormones also may contribute to cancer in the breast. There are both acute and chronic effects of alcohol on steroid hormone level. At doses of even 15 to 30 grams of alcohol per day, serum estrogens increase.[24] In one study of premenopausal women, alcohol consumption was associated with plasma estrogens, but not androgens, when measured during the luteal phase. Neither hormone was associated with alcohol during the follicular phase.[70] In that same cohort, urinary estradiol measured at the mid-luteal phase was more than 20% higher in women who drank more than 15 grams per day, when compared with those who did not drink.[71] Further, a mediation analysis provided evidence that changes in hormones associated with alcohol consumption may explain part of the relationship between alcohol and breast cancer.[72]

Altered DNA methylation also contributes to carcinogenesis. Alcohol significantly affects one-carbon metabolism, including DNA methylation, in part by effects on folate status, as discussed previously. Studies that examined DNA methylation in breast tumors made comparisons based on drinking history and found differences by the amount of alcohol consumption.[73,74] Another study found some evidence of these differences in normal, noncancerous breast tissues.[75] Alcohol's effects on estrogen also may play a role in altered DNA methylation. There is evidence that higher concentrations of the steroid hormone affect DNA methylation.[24]

Other possible mechanisms for an effect of alcohol on carcinogenesis in general and breast cancer in particular are still emerging. For example, the microbiome in the mouth and gut may affect breast cancer risk,[76,77] and alcohol can affect the microbiome.[78,79] Alcohol likely has other effects on breast carcinogenesis, including effects on metastasis, angiogenesis, and cancer stem cells, affecting both cancer initiation and tumor aggressiveness.[80]

Alcohol's effects on oxidative stress, cell proliferation, steroid hormones, and one-carbon metabolism may explain, in part, the observed associations with breast cancer risk. Additional research is needed regarding these and other mechanisms, including research on those specific to tumor subtypes and mechanisms for exposures following a breast cancer diagnosis.

PUBLIC AWARENESS OF RISK

A limited number of studies have examined public understanding of alcohol and breast cancer. In a study of women attending a breast screening clinic in the United Kingdom, only 19% were aware that alcohol consumption is a breast cancer risk factor.[81] Among university students in a survey conducted in 23 countries around the world, overall, 3.3% were aware of alcohol consumption as a breast cancer risk factor.[82] Although awareness was highest in the United States, only 10% of students correctly identified alcohol consumption as a risk factor.

Awareness tends to be greater among women who have been diagnosed with breast cancer, with resulting lower alcohol intake in that group. In a systematic review, 62% to 97% of participants adhered to recommendations to limit alcohol consumption in a study of women completing initial treatment for breast cancer.[83] These studies were conducted primarily in the United States; a small number of participants were in Europe. In spite of the strength of the overall evidence connecting alcohol consumption to breast cancer,[5,67] there is little public awareness of alcohol consumption as a breast cancer risk factor.

RECOMMENDATIONS

Reduction of alcohol consumption could measurably affect the burden of disease related to breast cancer. Based on global data of the prevalence of alcohol consumption and of the incidence rate of breast cancer, an estimated 144,000 new cases of breast cancer and 38,000 breast cancer deaths annually are accounted for by alcohol consumption, which is 8.6% of all incidence and 7.3% of mortality.[24] The magnitude of effect of a decrease in consumption in a particular region depends on the prevalence of alcohol consumption in that region. For example, in Australia, it has been estimated that any regular consumption of alcohol accounts for 12.6% and 6.6% of premenopausal and postmenopausal breast cancer, respectively.[84] Alcohol consumption accounts for 12% of breast cancer in the United Kingdom.[11] In the United Kingdom, regular consumption of each additional drink per day accounts for 11 additional breast cancers per 1,000 women in their lifetime, up to age 75.[11] As further indication of the effect, one estimate is that the increase in cancer risk for drinking one bottle of wine per week is approximately equivalent to smoking 10 cigarettes per week, with breast cancer accounting for most of that increase.[85]

Although the evidence is strong for an increase in breast cancer with alcohol consumption, some areas of research still require further attention. A better understanding of the roles of drinking pattern, or drinking intensity, in relation to total consumption is needed. More studies of alcohol consumption and breast cancer subtypes would help increase insight into the relationship. A clearer understanding of the effects of exposures in early life, including *in utero* exposure, is warranted. Examination of how other breast cancer risk factors (e.g., physical activity, body mass index, smoking, reproductive history) interact with alcohol consumption in relation to both breast cancer risk and prognosis is needed. More studies of the association by race/ethnicity, by age at diagnosis, and conducted in regions outside of Europe and North America would contribute to our understanding. Additional research linking epidemiological information with biological information regarding the role of alcohol in carcinogenesis could enhance the ability to leverage this important relationship toward prevention efforts.[44] Further, additional study is needed of the effects of alcohol consumption, both before and after diagnosis, on breast cancer recurrence, breast cancer–specific mortality, and overall mortality.

Given the strength of the evidence linking alcohol to breast cancer, increasing awareness of risk is critical. It is time for a clear public health message identifying the role of alcohol in breast carcinogenesis and indicating that that there is no apparent lower threshold of effect. Consumption levels of less than one drink per day are associated with increased risk. Further, drinking alcohol affects risk at all phases of life, including early and late life. The science is consistent and clear, but awareness is low. It is time for a focus on developing public understanding of alcohol, which is a very common exposure, and its connection with increased risk of breast cancer.

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Gender Differences in Binge Drinking

Prevalence, Predictors, and Consequences

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Just as binge drinking rates differ for men and women, the predictors and consequences of binge drinking vary by gender as well. This article examines these differences and how binge drinking definitions and research samples and methods may influence findings. It also describes the relationship between age and binge drinking among men and women, and how drinking culture and environment affect this relationship. It examines gender-specific trends in binge drinking, predictors of binge drinking for men and women, and binge drinking in the context of smoking. The article reviews current findings on gender differences in the health consequences of binge drinking, including morbidity and mortality, suicidality, cancer, cardiovascular disorders, liver disorders, and brain and neurocognitive implications. It also discusses gender differences in the behavioral and social consequences of binge drinking, including alcohol-impaired driving, sexual assault, and intimate partner violence, and includes implications for treatment and prevention.

Key words: Alcohol and other drugs (AODs); AOD associated consequences; binge AOD use; gender differences; physical health; predictive factors

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Introduction

A large research literature shows that women consistently consume less alcohol than men, and they experience fewer social problems resulting from drinking than men, but these gender differences vary culturally, demographically, and historically.[1-3] This literature often has not given close attention to gender differences in binge drinking and its consequences. This lack of attention is unfortunate, because binge drinking is recognized as a major contributor to the social and health burdens of alcohol consumption.[4] Binge drinking has been linked specifically to a wide variety of adverse consequences, acute (e.g., accidents and injuries) and chronic (e.g., liver disease), that harm not only the drinker but also communities and societies as a whole (e.g., productivity losses, crime, and public disorder).[5,6] In this article we review recent research findings on gender differences in the prevalence, predictors, and consequences of binge drinking, and we note how interpretation of these findings has been limited by differences in concepts, measurements, and research methods.

Measurement Issues

There is considerable variation in the research literature as to how binge drinking is measured (4+, 5+, 6+ drinks) and labeled (binge drinking, heavy episodic drinking, or risky single-occasion drinking).[7-10] Furthermore, many studies use gender-specific measures of binge drinking (e.g., 5+ drinks for men and 4+ drinks for women),[11] but many other studies use the same measure for men and

women (e.g., the Alcohol Use Disorders Identification Test uses 6+ drinks).[12-16] Other studies define binge drinking by estimated blood alcohol concentration (BAC) level (e.g., a BAC of at least .08%), which may be a less sensitive criterion for men than for women.[17]

Finally, different studies measure different frequencies of binge drinking over different time periods (e.g., in the past 2 weeks or past 30 days). Measuring the frequency of binge drinking in a given time period (e.g., once in the past 30 days) may produce greater apparent gender differences than measuring binge drinking as any or none. Moreover, using longer time periods for measurement (e.g., a year versus a month) may reduce gender differences when binge drinking is measured as any or none but may magnify gender differences when binge drinking frequency is measured. Because of the inconsistent measurement methods used across the research, we cannot focus our discussion on any one criterion of quantity, frequency, or time period. However, for examination of the consequences of acute and chronic binge drinking, the importance of measurement variation remains uncertain.

Prevalence

There has been widespread alarm in the mass media about the extent of women's binge drinking. A frequent theme is that, traditionally, men have been binge drinkers more than women, but this gender difference is declining rapidly because of a growing epidemic of binge drinking among women.[18,19] However, research evidence indicates that these media stories oversimplify men's and women's patterns of binge drinking.

Recent survey data consistently illustrate that men in the United States and throughout the world binge drink more than women (see Table 1).[20-33] Although studies measure binge drinking in various ways and over various periods of time, the gender difference persists, whether or not studies use gender-specific criteria for defining binges. Another analysis of data from 15 countries reached a similar conclusion.[34] However, binge drinking rates and gender differences vary greatly across populations. One explanation of the difference is that recent changes in binge drinking have not yet erased the sizable gender gap present in many societies. A second explanation is that gender differences in binge drinking cannot be attributed only to biological or cultural differences but may result from a combination of these influences.[3]

Age

One response to these explanations has been concern that gender differences in binge drinking may be disappearing specifically among younger drinkers. In the United States, binge drinking is most prevalent in late adolescence or early adulthood, with rates declining as drinkers grow older.[35] However, a focus on binge drinking in any one age group may be an oversimplification, for several reasons:

- Women's binge drinking has not caught up with men's in any age group in the United States or any other country, judging from large, general-population surveys.
- As drinkers get older, binge drinking (versus none) declines consistently in Europe, North America, Australia, and New Zealand, but these declines do not occur consistently in other areas of the world.[3]
- Frequency of binge drinking by men and women often shows complicated nonlinear relationships with age.[28,36,37]
- Gender-specific associations of age with binge drinking may vary among regions within countries.[38]

Taken together, these findings suggest that how age modifies effects of gender on binge drinking depends on the specific drinking culture and environment where the binge drinking occurs.

Gender-Specific Trends

Complex age effects are one reason why it is difficult to evaluate trends in women's and men's binge drinking. Much of the research and discussion of those trends focuses on two questions:

1. Is binge drinking changing (in recent years) in ways that differ by gender?
2. Are gender-differentiated changes leading to a convergence of men's and women's rates of binge drinking?

In the mass media, the common answers to these questions are that women's binge drinking is increasing faster than men's, and, as a result, men's and women's binge drinking rates are converging.

Research to answer these questions is hard to interpret for many reasons besides age effects. In addition to the variation in how binge drinking is measured, some analyses of binge drinking rates include abstainers, whereas others do not. Some studies analyze changes in binge drinking frequency, whereas others analyze changes in rates of ever/never binge drinking. Furthermore, many studies that measure trends over extended periods do not separate period effects (historical trends in whole populations) from age effects (changes that occur more in one age group than others) and cohort effects (changes that are greater in groups born in one historical period than others).

Nevertheless, a small set of large longitudinal studies has provided consistent answers to the two questions about trends. From 2000 to 2010, large U.S. studies found that any binge drinking (measured as ever or never) in the preceding month increased in prevalence more among women than among men.[35,39,40] This trend was consistent with findings from binge drinking studies that used different

Table 1 Prevalence of Binge Drinking

Source	Population	Binge Drinking Measure	Men	Women
2014 National Survey on Drug Use and Health[20]	United States, ages 18 and older	5+ drinks, 1 occasion, past 30 days	33%	17%
China Chronic Disease and Risk Factor Surveillance, 2007[21]	China, ages 15 to 60	50+ grams (men), 40+ grams (women), ethanol, 1 day, past 12 months	32%	4%
Health Survey for England, 2007[22]	England, ages 16 and older	>2 times recommended daily maximum (>8 units for men, >6 units for women), past week, among drinkers	35%	27%
Kangwha Cohort Study, Korea, 1988[23]	Kangwha County, Korea, ages 55 and older	6+ drinks, 1 occasion, past year	21%	<1%
Moscow Health Survey 2004[24]	Moscow, Russia, ages 18 and older	80+ grams (men), 60+ grams (women), ethanol, 1+ occasion per month	30%	6%
National Health Survey 2004, Singapore[25]	Singapore, ages 18 to 69	5+ drinks, 1 occasion, past month	9%	5%
National survey, Denmark, 2003[26]	Denmark, ages 15 to 99	6+ drinks, 1 occasion, once a month or more	38%	18%
National survey, Mozambique, 2005[27]	Mozambique, ages 25 to 64	5+ drinks (men), 4+ drinks (women), or equivalent drink container, 1 day, past week	25%	11%
National survey, Spain, 2008 to 2010[28]	Spain, ages 18 to 64	80+ grams (men), 60+ grams (women), ethanol, 1 occasion, past month	10%	4%
Nationwide survey on alcohol consumption patterns, Brazil, 2005 to 2006[29]	Brazil, ages 18 and older	5+ drinks (men), 4+ drinks (women), 1 occasion, past year	40%	18%
South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2008[30]	South Africa, ages 15 and older	5+ drinks (men), 4+ drinks (women), 1 occasion, past month	17%	4%
Survey, Hong Kong, 2006[31]	Hong Kong, ages 18 to 70	5+ drinks, 1 occasion, past 30 days	15%	4%
Survey of Lifestyle, Attitudes and Nutrition in Ireland, 2007[32]	Ireland, ages 18 to 29	6+ drinks, 1 occasion, past year	92%	79%
Third National Health Examination Survey, Thailand, 2004[33]	Thailand, ages 15 and older	Multiple beverage-specific measures	40%	7%

time periods (a week and a year) and with findings from other countries (England, Finland, Russia, and Singapore).[25,36,41-43] The greater increase in prevalence among women resulted in partial convergence of men's and women's *likelihood* of binge drinking.

In contrast, in the United States, convergence of women's and men's *frequency* of binge drinking more likely occurred because of greater *declines* in frequency among men than among women.[40,44] Furthermore, evidence of men's and women's convergence in the United States often has been stronger in young adults (20s and 30s) than in other age groups.[40,45] Trends in men's and women's binge drinking may be modified by drinking pattern changes in different birth cohorts. In the United States and Finland, evidence has shown that both men and women in more recent birth cohorts have been increasingly likely to become binge drinkers, at least until the 1980s birth cohort.[35,36,44] These patterns indicate that further convergence of women's and men's binge drinking patterns may be hard to predict and cannot be attributed entirely to women's increased binge drinking.[46]

Predictors of Adult Binge Drinking

Childhood Experiences

Childhood experiences are possible early predictors of binge drinking. However, evaluations of gender differences in childhood influences on binge drinking are scarce, particularly in the United States. Most studies lack data on binge drinking, do not analyze effects of childhood experiences on men and women separately, or provide data for only one gender.

Child maltreatment. Child maltreatment (including childhood sexual abuse, childhood physical abuse, and neglect) has consistently been found to be a robust predictor of many adverse mental health outcomes, including high-risk drinking and alcohol use disorder (AUD).[47-51] Typically, research has found that women more often report childhood sexual abuse than men,[52-54] and men more often report childhood physical abuse than women,[55,56] but not always.[57] Gender differences in experienced neglect are uncertain.[58-60]

Given these gender differences in types of child maltreatment, one might infer that childhood sexual abuse is more of a risk factor for women's binge drinking, and childhood physical abuse is more of a risk factor for men's binge drinking. Unfortunately, research has infrequently compared how forms of child maltreatment affect women's versus men's binge drinking. The few relevant studies show inconsistent patterns, suggesting that gender differences in maltreatment effects likely depend on the groups of men and women studied and the measures of binge drinking used.

Widom and colleagues studied men and women with childhood histories of abuse or neglect that resulted in court cases and compared them 30 years later with approximately matched controls (from a Midwest U.S. metropolitan area).[51] The researchers found no significant differences in frequency of past-month binge drinking (defined as 8+ drinks) between men with and without histories of child maltreatment. However, women who had been neglected (with or without other abuse) were more frequent binge drinkers in the past month than same-sex controls. In South Africa, on the other hand, a history of childhood physical punishment nearly doubled the prevalence of binge drinking as the usual behavior on a drinking day, although this effect did not differ significantly between men and women.[61]

Concerning childhood sexual abuse, a Pennsylvania study of adults ages 31 to 41 found a direct effect on binge drinking in women but not in men,[62] whereas a much larger study of U.S. naval recruits found that binge drinking was more prevalent among those men and women who had experienced childhood sexual abuse (and was also more prevalent among those men, but not women, who had experienced childhood physical abuse).[63] The variation in the findings does not allow simple conclusions about how gender may modify connections between childhood maltreatment and adult binge drinking.

Parental problem drinking. Another childhood experience linked to adult alcohol problems is exposure to problematic parental drinking.[64-67] Gender-specific analyses by Merline and colleagues[64] and White and colleagues[67] found that heavy drinking by parents adversely affected the drinking behavior of their male and female adult children. Unfortunately, reports on parental drinking generally have not provided data on gender-specific effects or on binge drinking, and often they have focused only on adolescent drinkers or parents with diagnosed alcohol disorders (e.g., studies of adult children of alcoholics). However, a community study in Finland found that heavy parental drinking was significantly associated with binge drinking at age 42 for men but not for women, when controlling for individual drinking history.[68] In data from the Young in Norway Longitudinal Study, parental binge drinking (not gender specific) was related to adult children's intoxication, or 5+ drink binges at age 28, but there were no significant gender differences for this parental influence.[69] The lack of other recent data means the question of how gender modifies parental drinking effects on binge drinking by adult children remains unresolved.

Early onset of alcohol use. In the United States, early onset of alcohol use is linked to adult alcohol problems,[70,71] although the strength of this relationship has been challenged.[72] Boys in the United States begin drinking earlier than girls, which could increase male risk of later binge drinking, but recent gender differences in age of onset are not large and are not entirely consistent with data from outside the United States.[73-75] The few studies of gender-specific associations between early onset of alcohol use and later binge drinking suggest that gender effects may be culturally dependent. Caetano and colleagues, who studied Hispanic national groups in the United States, found that drinking onset at age 14 or younger versus 21 or older increased the prevalence of binge drinking among women more than among men for Mexican Americans, Puerto Ricans, and South/Central Americans but not for Cuban-Americans.[76] In Korea, both men and women who began drinking at age 17 or younger were more likely to binge on drinking days, and later onset of drinking reduced binge drinking (as typical drinking behavior) among women more than among men.[77] In a Finnish community sample of middle-aged men and women, binge drinking was more frequent among those who began drinking at age 16 or younger, but this effect did not have a clear gender difference.[78]

Psychological Characteristics

The alcohol studies field has a long history of research on associations between personality traits and alcohol use in clinical and nonclinical samples.[79-81] For this article, we selected two clusters of personality characteristics that have known gender differences in prevalence and that may affect men's and women's binge drinking differently: disinhibiting traits (i.e., impulsivity, sensation-seeking, and risk-taking) and affective characteristics (i.e., anxiety and depression).

Disinhibiting traits. Research has shown that heavy or binge drinking in young adulthood is associated with a set of related disinhibiting personality traits, including impulsivity, sensation-seeking, and risk-taking.[82-84] These behavior traits are more prevalent in

men than in women,[85-87] although the size of the gender difference varies across age groups and traits. From these two findings, one could infer that these disinhibiting traits contribute to the excess of binge drinking among men compared with women. However, it is not so clear that disinhibiting traits are associated with men's binge drinking more strongly than with women's. Some studies found stronger associations between disinhibiting traits and frequency of binge drinking or intoxication among men than among women.[88,89] Other studies concluded that disinhibiting traits were more clearly associated with women's heavy drinking.[90,91] The most common finding, however, was that disinhibiting traits were associated with binge drinking, intoxication, or problem drinking among both women and men, with more similar than dissimilar gender-specific effects.[92-95] It is important to be cautious about interpreting such associations causally, because the extent to which a history of heavy or binge drinking facilitates men's and women's impulsivity, sensation-seeking, and risk-taking is unknown.

Anxiety and depression. Anxiety and depression are more prevalent among women than men,[96-99] and some patterns of anxiety and depression, such as patterns defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), are associated with some patterns of alcohol consumption, such as AUD.[100-102] However, it is not clear that depression and/or anxiety are associated with binge drinking, specifically. Many studies with gender-specific data have failed to find connections among anxiety, depression, and binge drinking for women or men.[68,103-107] There are some exceptions. A 2006 U.S. Behavioral Risk Factor Surveillance System (BRFSS) survey found that men with current depression were more likely to be binge drinkers than nondepressed men.[108] In a U.S. survey of men and women older than age 56, heavy-drinking or binge drinking men scored higher than other men on a measure of depressive symptoms.[103] The 2006 BRFSS survey also reported that women with lifetime diagnoses of anxiety or depressive disorders or with current depression were more likely to binge drink than women without anxiety or depression, and the severity of depression increased women's (but not men's) odds of binge drinking.[108]

In a national Canadian survey, for both men and women, depression was associated with drinking larger quantities per drinking occasion, but the association was stronger for women.[109] In the large U.S. National Epidemiologic Survey on Alcohol and Related Conditions (NESARC),[105] women's binge drinking was associated only with post-traumatic stress disorder and panic disorder (without agoraphobia). A survey at a large public university found that students with general anxiety disorder were more likely than other students to engage in frequent binge drinking, and students with major depression were less likely than other students to engage in frequent binge drinking.[110] Both of these associations were stronger among men than women. These mixed findings suggest that depression and anxiety do not have simple or gender-determined associations with binge drinking. Studying how drinkers' ages and drinking opportunities differently affect links between binge drinking and anxiety or depression among men versus women may be worthwhile.

Adult Binge Drinking and Smoking

Typically, studies that have examined adult binge drinking and other substance use have focused on tobacco smoking, particularly cigarettes. In the United States, among the whole young adult population,[111] college students,[112] adults ages 18 to 25,[113] and adults older than age 50,[114] binge drinkers consistently have higher odds than non–binge drinkers of being smokers. In the United States and worldwide, smoking is more common among men than among women.[115-117] To the extent that smoking may be part of a lifestyle that encourages or leads to binge drinking, the general patterns described here might contribute to the gender gap in which men binge drink more than women. However, prolongation of smoking may have unknown effects on women's binge drinking, and evidence indicates that women find it more difficult than men to stop smoking.[118-120]

Multiple gender-specific studies worldwide have shown that smoking is strongly related to both men's and women's binge drinking, typically showing stronger connections for women than for men. U.S. surveys have reported that men and women who smoke have three times higher odds than nonsmokers of being binge drinkers,[121] and smokers have a higher probability than nonsmokers of heavy drinking behavior at ages 35 and older.[122] In China in 2007, the majority of men and women smokers were also binge drinkers, an association that was much stronger in women.[21] A separate 2006 study in Hong Kong found that smoking multiplied the odds of binge drinking by 3.7 for men and 12.3 for women.[31] In Brazil, the São Paulo Epidemiologic Catchment Area Study found that men and women who were binge drinkers were more than twice as likely as non–heavy drinkers to be current smokers, and the relationship was stronger for women.[123] In a national Canadian survey, the odds of binge drinking were significantly greater than 1.0 for all women smokers, but only for men who smoked more than six cigarettes a day.[124] The 2004 Moscow Health Survey found that women who were binge drinkers had higher odds of daily smoking than other women, but men who were binge drinkers did not have higher odds of daily smoking than other men.[125] Most of these studies were cross-sectional and could not distinguish the degree that smoking influenced binge drinking or vice versa. These studies also did not

explore the possibility that both smoking and binge drinking were part of a syndrome with shared antecedents. It would be worth examining the extent to which women who both smoke and binge drink are attempting to show independence from older feminine stereotypes that discouraged both behaviors.

Differences in Health Consequences

Research on how gender affects the health consequences of adult binge drinking is scarce, for several possible reasons. Studies of chronic alcohol-related health problems may neglect binge drinking episodes because researchers may assume binge drinking has acute, not chronic, effects. Gender-specific analyses may be neglected because including enough women who binge drink (e.g., in Asian countries) for reliable statistical analysis is often difficult. Research may focus on adolescent rather than adult binge drinking because of greater concern about acute and long-term health consequences for young drinkers. And, investigators may have difficulty distinguishing between effects of binge drinking and effects of chronic heavy drinking, because the two drinking patterns are correlated. Nevertheless, research does suggest where binge drinking has gender-related health effects, and where it does not.

Morbidity and Mortality

Several recent studies have found that binge drinking adversely affects mortality and morbidity for both men and women. In a sample of U.S. moderate drinkers ages 55 to 65, the odds of dying in the next 20 years were twice as great for moderate drinkers who initially reported binge drinking in the preceding month than for moderate drinkers who did not report such binge drinking. No significant difference between genders was found.[126] National U.S. surveys (2008 to 2010) found that among binge drinkers, women reported more days of physical and mental ill health than men, and men and women who had recent heavy binge drinking episodes (7+ drinks for women and 8+ drinks for men) were more likely to report poor health–related quality of life than binge drinkers who drank less.[127]

In contrast, a study that analyzed National Health Interview Survey (NHIS) data from 1997 to 2004 found that episodic heavy drinking (5+ drinks in 1 day) added only modestly to the mortality risk of light and moderate drinkers.[128] And, a population-based study of nearly 27,000 men and women who participated in the Danish National Cohort Study from 1994 to 2005 reported that binge drinking (6+ drinks on an occasion) among male and female moderate drinkers was not associated with increased all-cause mortality when they were compared with moderate drinkers who did not binge drink.[129] The authors suggested that Danish customs around binge drinking (which usually occurs during a long evening of eating and drinking) may account for the results.

A Russian survey asked respondents about the health of close relatives after age 30 and found that men who had engaged in any binge drinking were more likely to have died than other male drinkers, but for women, increased mortality occurred only among those who binge drank at least once a month.[130] In Norway, women and men who binge drank on 10 or more occasions in the past year were more likely to report alcohol-related sickness that caused absence from work than those who binge drank no more than 5 times, and the pattern of more frequent binge drinking was associated with sickness-related absence more strongly for women than for men.[131]

Suicidality

A special case of mortality risk among binge drinkers is the potential effect of binge drinking on suicidal behavior (including thoughts of suicide and suicide attempts). Research has found that suicidal behavior often is associated with chronic heavy drinking,[132,133] which may be a symptom of psychological problems or a way of coping with such problems. For both men and women, completed suicide has been associated with acute alcohol intoxication,[134] which may precipitate or enable the behavior.

How episodic binge drinking as a behavior pattern is related to men's or women's suicidality has been studied much less often. Available research suggests that binge drinking has stronger associations with women's suicidality than with men's. According to U.S. National Violent Death Reporting System suicide data from 2003 to 2011, the likelihood of high postmortem blood alcohol concentrations (BACs) of more than .08 g/dL was much greater than the likelihood of high BACs in general population survey data.[134] Women's postmortem BACs generally were higher than men's, but they were not statistically significantly higher. Data from the 2008 to 2012 U.S. National Survey on Drug Use and Health showed that among women and men who had not experienced major depressive episodes, women's binge drinking was associated with planned and attempted suicide, but men's binge drinking was associated only with suicidal thoughts.[135] These data showed no association between suicidality and binge drinking in men and women who had past major depressive episodes. In a nationally representative sample in France, binge drinking at least monthly predicted suicidal ideation and suicide attempts better for women than for men.[136] And, in a survey of U.S. college undergraduates, reported past suicide attempts were significantly associated with reported past binge drinking among young women but not among young men.[137] However, the time order of binge drinking

and suicidality remains unclear, except as shown in the postmortem data reported by Kaplan and colleagues.[134]

Cancer

A possible life-endangering effect of binge drinking is an increase in women's and men's risks of various forms of cancer. Evidence clearly shows that heavy alcohol consumption is a risk factor for cancers in the oral cavity, pharynx, esophagus, liver, colon and rectum,[138,139] and pancreas.[140-142] In general, research on these cancers has not provided information about binge drinking and its gender-specific effects. One exception is a San Francisco Bay Area population-based case-control study, which found that the risk of pancreatic cancer was higher specifically among men who had a history of binge drinking, particularly if the binge drinking persisted over years and involved large numbers of drinks.[143] Another recent exception is a Korean longitudinal study of differentiated thyroid cancer, which found that acute, heavy alcohol consumption (more than 151 grams of ethanol on one or more lifetime occasions), when compared with no alcohol consumption, doubled men's cancer risk and tripled women's cancer risk.[144]

In studies of gender-specific (or nearly so) cancers, gender-specific effects of alcohol get closer attention. Research on gynecological cancers (i.e., cervical, ovarian, and endometrial/uterine) has consistently found no association between women's drinking and the risks of these cancers.[145-148] In contrast, a large set of evidence has consistently shown that women's risk of breast cancer increases with increased alcohol consumption, even at moderate levels, resulting in more than 100,000 alcohol-related cases of breast cancer worldwide each year.[149,150] (Alcohol is apparently less relevant in the rarer male breast cancer.[151]) Hypothetically, alcohol may increase women's breast cancer risk through multiple processes, including increasing tumor-promoting estrogen levels (now debated) and acting as a cumulative carcinogen (through increased exposure to acetaldehyde and byproducts of the CYP2E1 enzyme, likely activated by binge drinking).[152,153]

Research on associations between binge drinking and breast cancer has been scarce. In the Danish Nurse Cohort Study, data from 1993 to 2001 showed that women who binge drank on weekends (Friday through Sunday) or on the latest weekday had greater risk of breast cancer than women who were light drinkers, even after adjusting for total volume of alcohol consumed.[154] In the U.S. Nurses' Health Study, data from 1980 to 2008 showed that monthly binge drinking was associated with a 33% increase in risk of breast cancer, but controlling for cumulative alcohol consumption weakened the association.[155] A New Zealand case-control study found that weekly binge drinking was associated with a 55% increase in risk of breast cancer among Maori women.[156] A case-control study in North Carolina found a positive association between binge drinking and risk of breast cancer among women who drank an average of 91 grams or more of ethanol per week, but the association was not significant after controlling for other variables, possibly because the sample size was small.[157]

Evaluating the effects of alcohol consumption and binge drinking on male-specific cancers has been difficult. The effects of drinking on testicular cancer are unknown, because no recent or major research on testicular cancer has evaluated the drinking patterns of the men studied. Also, although research on prostate cancer has examined alcohol consumption, the findings conflict. Some studies found that heavier drinking was associated with a greater risk of prostate cancer.[158,159] Some research reported that drinking raised risk only for advanced cancer[160] or only for non-advanced cancer.[161] In other studies, heavier drinking raised prostate cancer risk for men only if they had consumed low amounts of dietary fiber,[162] were African American,[163] or had been lifetime, rather than current, heavy drinkers.[164] And, some large or meta-analytic studies found that drinking had little or no association with prostate cancer.[165-167]

The picture is just as confused for the limited research on associations between binge drinking and prostate cancer risk. In the 1986 to 1998 Health Professionals Follow-Up Study of men ages 40 to 75, men who were binge drinkers (compared with abstainers) had the greatest increase in prostate cancer risk.[168] In this study, binge drinking was defined as drinking 105 grams or more of ethanol on 1 to 2 occasions per week. The older part of the Finnish Twin Cohort study, which surveyed twins (mean age of 40) from 1981 to 2012, found that binge drinkers had a greater risk of prostate cancer than non–binge drinkers.[158] In contrast to these cohort-based studies, case-control data from the 2000 NHIS survey,[169] the U.K. Prostate Testing for Cancer and Treatment (ProtecT) study,[170] and the U.S. Prostate Cancer Prevention Trial[171] showed no connection between binge drinking and prostate cancer. Our conclusion from the conflicting research is that binge drinking does not have simple or unconditional effects on prostate cancer.

Cardiovascular Disorders

Heavy drinking (variously defined) by both men and women consistently has been associated with higher risks of hypertension,[172,173] atrial fibrillation,[174] and stroke.[175,176] Relationships between chronic heavy drinking and coronary heart disease (CHD) have been less consistent. Some studies found that such drinking was a risk factor for both women and men,[177] whereas other studies failed to find such connections.[178-180]

Generally, binge drinking has been associated with a higher risk of

cardiovascular disorders, but reports of such associations often are not gender specific.[181-183] Available gender-specific data have shown that men's risks from binge drinking usually are greater than women's risks. For example, men's risk was greater than women's for CHD and hypertension,[184] death from cardiovascular disease,[185] and death from ischemic stroke.[186] However, findings for women were often limited by small sample size, and some studies found that women and men binge drinkers had similar risks for hypertension[187] and for death after myocardial infarction.[188]

Liver Disorders

Research has shown conclusively that heavy drinking increases risk of a variety of liver diseases and damage.[189-191] From our review of this research, we draw three general conclusions about gender and the effects of binge drinking on the liver:

1. Research on the effects of binge drinking on the liver is scarce and reveals little about gender differences.[192,193]
2. Research on liver damage specifically from binge drinking may be scarce because research has repeatedly found that harm to the liver results from continuous (frequent) drinking rather than episodic drinking (such as binges).[194-196] Binges may merely increase the cumulative toxic exposure to alcohol.
3. The risk of liver damage from chronic drinking is greater for women than for men,[190,197] possibly because of differences in how the body distributes and metabolizes alcohol.[189,198] A European study reported an exception to this gender difference, however. The study found that for men, binge drinking created a higher risk of alcohol-related hepatic steatosis (fatty liver) than it did for women.[199]

In general, not enough research has been conducted to draw any firm conclusions about how gender modifies the adverse effects of binge drinking on the liver.

Brain and Neurocognitive Consequences

Damage that some patterns of alcohol consumption can do to the brain is both well-known and well-studied, particularly in adolescents and individuals with AUD.[200-202] Furthermore, many studies have specifically examined the harmful effects of binge drinking on the brain and neurocognition. However, it is difficult to draw general and reliable conclusions from these studies about gender differences in binge drinking effects on the brain,[203] in part because many of these studies (e.g., those that used functional magnetic resonance imaging) examined small, nonrepresentative samples, which does not allow reliable, within-gender evaluations (i.e., comparing binge drinkers with same-sex controls). Nevertheless, certain patterns have emerged that may guide future gender-specific research and interventions.

One pattern is that binge drinking may alter the anatomy of the young brain in ways that could have persistent adverse effects. In adolescents and college students who have binge drinking histories, studies have shown evidence of poorer integrity (as indicated by lower fractional anisotropy) of white matter in multiple areas of the brain,[204,205] an effect that at least one study found mainly in males and in areas of the brain related to cognitive function and attentional processes.[206] Studies also have shown that adolescent binge drinkers had reductions in white and gray matter in the cerebellum (for both genders)[207] and changes in frontal cortices (thicker for females, thinner for males).[208] In the latter study, the increased cortical thickness was associated with worse performance on visuospatial, inhibition, and attention assessments, possibly reflecting impairment of the normal neuronal pruning process in binge drinking females.[209]

A larger set of studies of cognitive functioning has identified at least three general areas in which binge drinking adolescent and young adult males and females may be impaired.

1. In tasks involving working memory, binge drinking females showed less activation of spatial working memory than same-sex controls, and binge drinking males showed greater activation than controls.[210] In other working memory tasks, the brains of binge drinkers apparently had to work harder to perform at the same level as non–binge drinkers, but no gender differences were reported for those tasks, possibly because of small sample sizes in these studies.[211,212]
2. In studies of response inhibition and monitoring of one's own behavior, binge drinking generally impaired females more than males,[90,213,214] but at least one study found an increase in performance self-monitoring among females, who were possibly compensating for alcohol effects.[215] No such increase was found among male binge drinkers.
3. In evaluations of executive functioning and decision-making, one study found the worst performance in male binge drinkers,[216] another study found males and females were similarly impaired,[217] and a laboratory test of acute impairment reported that males and females performed similarly, although the females had higher BAC levels.[218]

All these performance tests are more descriptive than explanatory, saying little about why gender differences sometimes occur and sometimes do not, or about the extent to which these levels of impairment are reversible or might affect adult life.

Differences in Behavioral and Social Consequences

Research has repeatedly documented and decried multiple adverse behavioral and social consequences of binge drinking.[219-222] This research, however, has not reported much about gender differences for many of these consequences. The research has revealed even less about possible gender-specific links between binge drinking and behavioral or social harm. Our focus here, therefore, is on three major behavioral and social problems for which gender-specific effects of alcohol consumption have been recognized and studied: alcohol-impaired driving (AID), sexual assault, and intimate partner violence (IPV).

Alcohol-Impaired Driving

In recent U.S. research on AID, two gender patterns are clear. Men engage in AID more than women, but the prevalence of both men's and women's AID has been declining since the 1990s, judging from self-reports[40] and the National Roadside Survey.[223] However, from 1982 to 2004, women's arrests for driving under the influence increased (while men's decreased),[224] possibly reflecting changes in laws and law enforcement (including lower limits for BACs) and increases in women's driving.[225,226]

U.S. surveys indicate that more than 80% of AID episodes were self-reported by binge drinkers.[227,228] It is unclear, however, whether binge drinking immediately preceded the episodes of drunk driving, and U.S. reports have not indicated how many binge drinking drivers were men and how many were women. Cultural differences may affect AID gender patterns. In Sweden, men and women arrested for driving under the influence drank a similar amount beforehand (typically more than five drinks).[229] Among Australian drivers killed in single-vehicle crashes, 50% of the males, compared with 29% of the females, had BACs of more than .07 g/dL.[230]

Although AID episodes are very likely to involve binge drinkers, a majority of binge drinkers do not report driving after drinking. In 2003 to 2004 U.S. survey data from self-reported binge drinkers, 13.2% of the men and 8.1% of the women reported driving after drinking.[231] However, tendencies to binge drink and to drive while intoxicated often occur together. The odds of AID are more than 5 times greater for binge drinkers than for other drinkers, and the odds are more than 10 times greater for those who binge drink frequently or who generally drink heavily, and these odds increases may be greater for men than for women.[227,232,233] A study of daily diaries kept by college students estimated that each 0.1% increase in estimated daily blood alcohol level was associated with a 4% increase in men driving after drinking, and a 1% increase for women.[234]

Sexual Assault

Knowledge about how binge drinking is related to sexual assault has three important limitations:

1. Because the great majority of reported sexual assaults involve men assaulting women, research has focused on how alcohol is related to these assaults.[235,236] Little is known about the circumstances in which men are sexually assaulted.[237,238]
2. Most research has focused on assaults among college students and young adults, groups most likely to be both heavy drinkers and sexually active.
3. Research may reveal associations between binge drinking and sexual assaults, but understanding the extent that binge drinking causes or results from the assaults is difficult because of uncertainties about the order of events and time lags between drinking and the assaults.[239,240]

Nevertheless, research findings show several clear patterns in how binge drinking and sexual assaults are likely to be connected.

Perpetration. One repeated finding is that binge drinking among male college students can make them more likely to engage in sexual aggression. In terms of immediate consequences, a study found that men were more likely to engage in sexual aggression if they had BACs of more than .15 g/dL, particularly if they were otherwise light drinkers.[241] Another study determined that the number of drinks men drank in the 4 hours before a sexual encounter affected their odds of aggressive sex with new partners.[242] And, among men who reported perpetrating past sexual violence, having consumed a larger number of drinks at the time led to greater aggression (up to the point where severe intoxication was disabling).[243] One college study found 1-year lagged effects of men's binge drinking on sexual aggression,[244] suggesting that binge drinking as a continuing pattern among men might reinforce recurrent sexual aggression, at least in the college years.

Victimization. There is much evidence that women's drinking, in general, is associated with subsequent sexual assault.[245] A lingering question is whether women's binge drinking increases this apparent risk. Incapacitated rape, which can occur when women have drunk too much to be able to resist an attack, is a major adverse effect of binge drinking. Among college women, a majority of rapes occur when women have drunk enough to be incapacitated.[236,240] Apart from incapacitation and rape, women who binge drink are also at greater general risk of sexual victimization[246-248] for many possible reasons: men's misinterpretation of women's drinking as a sign of sexual availability, miscommunication of women's refusals, and women's underestimation of hazards from male companions.[245] One study of college women found evidence that binge drinkers may overestimate their ability to resist rape attempts.[249]

It is not clear whether experiences of sexual victimization lead women to binge drink, possibly to help cope with the emotional aftereffects of assault. In some studies of women in college[250] and in the general U.S. population,[235] experiences of sexual assault did not predict subsequent binge drinking. Other studies, however, did find that experiences of incapacitated rape[251] or repeated victimization[252] were associated with subsequent binge drinking. These apparent contradictions suggest two more complex patterns:

1. Women's experiences of sexual victimization may perpetuate (not just initiate) binge drinking (and controlling for effects of prior drinking might obscure effects of victimization on subsequent drinking).[247,250]
2. In the short term, such as during college or the young-adult years, women's binge drinking and sexual victimization might become a vicious circle, each making the other more likely, increasing risk of revictimization.[245]

These more complex patterns should be further evaluated.

Intimate Partner Violence

Research on IPV has focused largely on male violence against female partners and the aftereffects for female partners.[253,254] Consistent with this focus, 2005 U.S. survey data have shown that women were roughly twice as likely as men to report being victims of IPV over their lifetimes and in the past year.[255] However, this focus neglects women's violence against male partners, which may be more prevalent at times in some groups, particularly outside the United States.[256-259] It also neglects the degree that IPV is an interactive process in which violence can be reactive and defensive as well as proactive, with both partners as victims and attackers.[260,261] To understand how binge drinking may be related to IPV, therefore, it is important to study binge drinking among both men and women as perpetrators and as victims of IPV.

A large body of research links alcohol use in general to IPV perpetration and victimization.[258,262] One might expect binge drinking, in particular, to increase the likelihood of IPV perpetration through disinhibition and increased aggression.[263] Indeed, in bivariate analyses of survey data, binge drinking was associated with IPV perpetration among men and women in Canada and Costa Rica and among women in Brazil.[258] In bivariate analyses of U.S. survey data, rates of IPV perpetration were doubled for male binge drinkers and nearly tripled for female binge drinkers.[264,265] However, in multivariate analyses of U.S. data, the associations between binge drinking and IPV either disappeared[264,265] or became too small to be meaningful.[266]

Binge drinking might also increase women's vulnerability to IPV victimization. In surveys in Brazil, Canada, Mexico, and Peru, binge drinking women were more likely to report being victims of IPV.[258] A meta-analysis of three longitudinal U.S. studies found that women's binge drinking significantly increased the odds of their subsequent IPV victimization,[267] but other U.S. studies either could not confirm such a relationship[265,268,269] or found only very weak relationships.[266] These mixed findings about perpetration and victimization, particularly from multivariate analyses, suggest that binge drinking (as distinct from other drinking patterns) may not be a direct cause of IPV, but it may be an indicator of other personality and behavior patterns that may lead to IPV (e.g., antisocial traits).[270,271]

Research shows, somewhat more consistently, that a history of IPV victimization increases the likelihood that women will engage in binge drinking after varying time lags.[267,272,273] However, this relationship is not always evident or strong,[268,269] possibly because many women who are victimized cope with the distress in other ways. Indeed, male victims of IPV might be more likely to use binge drinking as a stereotypically male method of coping, but few studies have looked for or found evidence of men's binge drinking behavior after IPV victimization.[274,275] If binge drinking is becoming more prevalent among women (as noted earlier), there may be a greater need for interventions to reduce the use of alcohol as a coping mechanism.

Alcohol's Harm to Others

To date, alcohol research has focused mostly on how drinking harms the drinker.[276] Limited previous research on harm to people other than the drinker has focused mainly on AID,[277,278] fetal development,[279,280] and IPV,[281,282] largely neglecting broader harm to others' mental health, quality of life, living conditions, and resources. An Australian study has suggested that costs of such harm to others may be double those experienced by drinkers themselves.[283]

Some studies of alcohol's harm to others (AHTO) have examined gender differences in the types of harm caused and harm received. A common finding has been that women are considerably more likely than men to experience marital and family harm, and men are significantly more likely than women to experience physical assault from strangers and other crime victimization.[284-286] However, with a few exceptions,[287,288] AHTO research has focused on harmful effects of others' drinking or heavy drinking without exploring possible associations between specific drinking patterns (e.g., heavy episodic or binge drinking) and specific types of harm. Such associations might include relationships between binge drinking and AID, crashes, and fatalities, or relationships between binge drinking and increased risk of fetal alcohol effects. The harm to others paradigm is a relatively new development in alcohol epidemiology.[289] As this perspective matures, we hope

that greater attention will be given to associations between specific drinking patterns, such as binge drinking, and specific types of harm, as well as possible gender differences in those associations.

Possible Implications

Treatment

Our research literature search on gender differences in alcohol treatment outcomes found very little information specifically relevant to binge drinking. Nonetheless, research on gender-specific alcohol treatment is helpful when considering strategies to reduce binge drinking. Before the early 1990s, most alcohol and drug treatment programs were developed for and served primarily men.[290] However, more recent research on gender-sensitive treatment has focused on treatment strategies that may be particularly appropriate and effective for women. Much of this evolution of gender-sensitive treatment has been informed by empirical evidence of gender differences in treatment needs. This evidence includes research demonstrating higher prevalence among women of (1) comorbidity of substance use disorders and other psychiatric disorders (e.g., mood, anxiety, and eating disorders), (2) trauma exposure and associated physical and mental health needs, and (3) the central role of relationships (with children, intimate partners, and others) in women's addiction and recovery.[291-293] A number of studies have reported a general tendency for women to respond somewhat better to a variety of psychosocial interventions[294-296] and to show a less consistent or harder-to-detect response to some pharmacological treatments.[297,298] There is general agreement on the need for more well-controlled randomized clinical trials that examine the effects of gender-specific treatment.

Integrated Interventions for Binge Drinking and Smoking

Given the strong associations between binge drinking and smoking described in this article, there may be promise in combined interventions that target both smoking cessation and binge drinking. Indeed, preliminary data presented by Ames and colleagues suggest the potential value of integrated smoking cessation and binge drinking interventions, particularly for young adults.[299] Environmental interventions that disengage alcohol use and tobacco use (e.g., smoking bans in bars) may also help to reduce hazardous drinking behavior. Evidence from several countries indicates that female smokers find it more difficult than male smokers to stop smoking,[118-120] so combined interventions to reduce both smoking and binge drinking could prove especially helpful to women who both smoke and binge drink.

Prevention

In our search for prevention programs that specifically target binge drinking, we found an article that described gender-specific prevention strategies focused specifically on binge drinking college women.[300] Aimed primarily at nurse practitioners, this article argued that for women college students, several common consequences of binge drinking (e.g., sexually transmitted infections, sexual assault, and other physical injury) bring them into contact with health care providers, offering opportunities for intervention. The author suggested several intervention strategies that may be particularly effective for female binge drinkers, including brief motivational interventions.[294,301] She speculated that Web-based interventions may be particularly effective for women, perhaps due to women's greater involvement with electronic programs[302] and the greater feeling of anonymity online programs may provide for women who feel stigmatized by their alcohol use or misuse.[303]

Considerable anecdotal evidence,[304-306] supported by qualitative studies in several countries,[307-310] suggests that one motivation for binge drinking among women—younger women in particular—may be that "drinking like a man" produces feelings of power, status, and gender equality. To date, in all countries studied, men drank more alcohol than women, and men engaged in extreme forms of drinking, such as high-volume drinking and heavy episodic or binge drinking, more than women. In many traditional societies, heavy alcohol consumption symbolizes and enhances men's greater power relative to women, serving as an emblem of male superiority and a privilege that men have often denied to women.[311] Indeed, in contemporary higher-income countries, numerous studies of young men have reported associations among endorsement of traditional masculine norms, heavy and binge drinking, and adverse drinking consequences.[312,313] With changing gender roles in many societies, and increasing opportunities for women, increased access to and consumption of alcohol understandably may seem like an expression of liberation and empowerment for many young women.

To our knowledge, prevention scientists have not tried to reduce binge drinking in young women by changing the significance of heavy alcohol consumption as a symbol of gender equality. A critical question is how best to persuade women that alcohol is a poor way to demonstrate gender equality—clearly not through simple educational approaches[314] or by trying to frighten or shame them, such as with warning labels.[315] One modest policy step might be to restrict advertising that links drinking to liberation from traditional feminine roles and stereotypes.[316] It is possible, also, that mass media and marketing methods could be used to sell the positive advantages of abstention or

low-risk alcohol consumption. A powerful message might be that women do not gain status or express liberation by emphasizing their sameness with men or by trying to outdrink them, but by setting their own standards—in their drinking decisions and in other areas of their lives.[305,317] Such messaging may be most effective if it provides gender-specific information about drinking norms[318] and is reinforced by multiple community sources.[319]

Parallel prevention strategies could be targeted to men, especially younger men, to weaken associations among traditional constructions of masculinity, heavy episodic drinking, and other risk-taking behavior. Specific strategies might include media literacy training to recognize and resist media images that link masculinity and excessive alcohol use, and interventions designed to change expectancies about alcohol's effects on sexuality, aggression, and other dimensions of traditional masculinity.[313]

Future Research Needs

When attempting to review gender differences in the prevalence, predictors, and consequences of binge drinking—and gender-sensitive strategies to reduce binge drinking—we became aware of many gaps that future research could fill. Some of the major gaps and challenges in this area are listed and discussed briefly in this section.

First, the use of different *definitions and measures* of binge drinking poses a serious challenge to research on many aspects of binge drinking. For researchers interested in gender similarities and differences, the use of more consistent definitions and measures would permit much firmer conclusions about gender-related patterns in binge drinking prevalence (across types of populations sampled and in various cultural contexts), as well as about gender-linked predictors of binge drinking and the consequences of binge drinking for men's and women's behavior and health.

Second, although a majority of prevalence studies have disaggregated binge drinking rates by gender, many studies of predictors and consequences of binge drinking have not. In some cases, studies have focused only on men or only on women, whereas other studies sampled both males and females but did not conduct or report gender-specific analyses. In the United States in the 1990s, actions by the National Institutes of Health led to increases in female research participants in both human[320] and animal studies.[321] Despite these increases, many researchers, from diverse scientific fields, fail to consider the role of (biological) sex and (culturally defined) gender when designing, analyzing, and reporting research. In addition to continued pressure on funding agencies to require sampling of both genders when appropriate for the research question being studied, editors and reviewers for scientific journals can play an important role in requiring adequate analyses and reporting of sex and gender differences in research publications.[322] A greater understanding of gender-differentiated aspects of binge drinking is one of many benefits that could result from development of new, and greater enforcement of existing, guidelines for attention to sex and gender in scientific research.

Third, the majority of studies reviewed in this article were cross-sectional, limiting inferences that can be drawn about time order and causality. Some of the many questions that well-designed longitudinal research could begin to answer are:

- The persistence or nonpersistence into adulthood of effects of adolescent and young-adult binge drinking on brain structure and function
- The extent that psychological characteristics such as impulsivity, anxiety, and depression precede and predict binge drinking versus being consequences of binge drinking or outcomes of some third factor that also predicts binge drinking
- Temporal and causal linkages (including possible bidirectional relationships) between smoking and binge drinking, binge drinking and suicide attempts, binge drinking and sexual assault, and binge drinking and intimate partner violence

Fourth, we were unable to find recent binge drinking literature, other than studies addressing age differences, that examined interactions of gender with other major demographic variables, such as race/ethnicity, sexual orientation, or socioeconomic status. Future research should give increased attention to such variables' associations with binge drinking prevalence, predictors, and consequences.

Finally, very little research has tested strategies specifically designed to reduce or prevent binge drinking. There are major conceptual and methodological challenges to designing and evaluating intervention strategies that specifically address binge drinking, as compared with more general interventions to reduce or prevent chronic heavy drinking or AUDs. Nonetheless, our review suggests that there may be promise (and possibly gender differences in effectiveness) in intervention strategies that specifically target the combination of binge drinking and smoking, as well as in strategies that attempt to weaken perceptions, expectancies, and norms that link men's binge drinking with ideals of traditional masculinity or women's binge drinking with feelings of status, power, and gender equality. In addition, the emerging perspective of AHTO may eventually suggest approaches for preventing or reducing binge drinking linked to gender-related harm, such as IPV and adverse fetal alcohol effects.

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The Influence of Gender and Sexual Orientation on Alcohol Use and Alcohol-Related Problems

Toward a Global Perspective

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Although there are wide differences in alcohol use patterns among countries, men are consistently more likely than women to be drinkers and to drink heavily. Studies of alcohol use among sexual minorities (SMs), however, reflect a more complex picture. Such research has found higher rates of alcohol use and alcohol-related problems among SM persons than among heterosexuals and greater differences between SM and heterosexual women than between SM and heterosexual men. A variety of factors may contribute to differences in alcohol use and alcohol-related problems between men and women and between SM and heterosexual people. An improved understanding of these factors is important to guide prevention and treatment efforts. Although there is a dearth of literature on use of alcohol by SMs in many parts of the world, especially lower- and middle-income countries, we attempt to review and integrate the sparse data that are available from these lower-resourced countries. The global perspective presented in this article is the first attempt to go beyond a general review of literature in the Western world to document the gender paradox in alcohol use among heterosexuals and SMs in diverse countries worldwide.

Key words: Alcohol consumption; alcohol use patterns; heavy drinking; alcohol-related problems; gender; sexual orientation; sexual minority; heterosexual; men; women; global perspective; literature review

The prevalence of alcohol use and the contrast between the drinking patterns of men and women vary widely across the globe. For instance, rates of current drinking ranged from 3 percent and 37 percent for women and men, respectively, in the Indian state of Karnataka to 94 percent and 97 percent for women and men in Denmark (Wilsnack et al. 2009). Overall, however, men have higher rates of alcohol use than women, both in the United States (Substance Abuse and Mental Health Services Administration [SAMHSA] 2013) and globally. In a multinational study of 35 countries (Gender, Alcohol, and Culture: An International Study [GENACIS]), Wilsnack and colleagues (2009) found that men were consistently more likely than women to be current drinkers and to engage in high-volume drinking, high-frequency drinking (5 or more days per week), and heavy episodic drinking. Women were more likely to be lifetime nondrinkers and to be former drinkers.

These patterns are quite different among sexual-minority women (SMW) and sexual-minority men (SMM). Although many large-scale surveys of alcohol and other drug (AOD) use have not included questions about sexual orientation, those that do show smaller gender differences in alcohol use and related problems among SMs than among heterosexuals. Notably, sexual-orientation–related disparities in AOD use are larger for women than for men. That is, SMW differ more in their rates of AOD use and related problems from heterosexual women than SMM differ from heterosexual men (Drabble et al. 2005; McCabe et al. 2009; Talley et al. 2014). This article examines the relationships that

gender and sexual orientation have to alcohol use and alcohol-related problems, using available literature in the United States and globally, and reviews some of the factors that seem to influence these relationships.

Sex versus Gender Differences in Alcohol Use and Related Problems

Sex differences refer to biological characteristics such as anatomy and physiology that distinguish female and male bodies. For example, differences in body composition partly explain why women consistently drink less than men. Because women's bodies generally contain less water than men's bodies, alcohol becomes less diluted, and women therefore reach higher blood alcohol levels than men even if both drink the same amount (Holmila and Raitasalo 2005).

Gender influences refer to the socially constructed roles, responsibilities, attitudes, behavioral norms, and relative power that a society differentially attributes to women and men. Research shows that countries or cultures with the largest differences in gender roles also have the largest differences between men's and women's drinking (Wilsnack et al. 2000). Therefore, social and cultural factors must be considered when attempting to understand gender differences in alcohol use across countries.

Gender Roles and Alcohol Use

Differences in men's and women's alcohol use often reflect gender roles and cultural expectations. Men may use drinking to demonstrate masculinity, facilitate aggression, exert power, and take risks. For these reasons, men may have greater motivation to drink than women. For example, research shows that risk taking is associated with heavy drinking among men but that women are more likely than men to use risk-reduction strategies when drinking (Iwamoto et al. 2011; Nguyen et al. 2011). In addition, a culture's acceptance of public drinking and intoxication for men but not women can serve to reinforce male superiority over women in status and authority in that culture. Whereas men have used drinking as a way to excuse themselves from responsibilities at work or home, women's drinking has traditionally been limited by their roles as mothers and caretakers and by the belief that drinking may have a more detrimental effect on their social behavior and their ability to fulfill responsibilities and to control their sexuality (Kuntsche et al. 2009, 2011). Women also are often expected to rein in the drinking of their male partners (Holmila and Raitasalo 2005).

Women who drink are more likely than men to stop drinking. This may be related to their generally lower levels of drinking, their social roles, and the fact that some women do not resume drinking (or return to pre-pregnancy levels) after pregnancy. However, a review of research examining birth cohorts and alcohol use across countries found high rates of heavy episodic drinking among women in younger cohorts in North America and Europe, suggesting a narrowing of the gender gap and a potential shift in social attitudes regarding gender and alcohol use (Keyes et al. 2011). In Finland, an examination of survey data collected over a period of 40 years suggests a cultural shift toward greater alcohol use, especially by women. Weekly drinking, frequency of moderate drinking, quantity of alcohol consumed per occasion, and intoxication increased among both genders over time but proportionately more among women. Drinking at home increased more than drinking in bars, and home drinking increasingly occurred only in the company of partners (Mäkelä et al. 2012). An analysis of survey data from Hispanics living in major U.S. cities found that high acculturation was associated with a higher volume of drinking and greater likelihood of binge drinking among women but not men (Vaeth et al. 2012), perhaps reflecting the greater tolerance of women's drinking in the United States.

Employment and other social roles are believed to be protective against drinking problems among heterosexual men and women. Jobs and social responsibilities tend to promote enhanced self-esteem and offer greater social support, and they entail responsibilities and more intensive social monitoring that may discourage excessive drinking. However, in part because of societal stigma and discrimination, fewer lesbian women and gay men engage in traditional roles such as marriage, childbearing, and childrearing or have responsibilities associated with social roles believed to limit alcohol use (especially among women) in the general population (Hughes 2005). Even SM couples in long-term relationships find less support for their relationships than do unmarried heterosexual cohabiting couples. For SM couples who do have children, the stressors associated with parenting may be exacerbated. For example, many lesbian and gay parents must deal with the realistic fear of custody battles over competency to raise children, homophobic remarks made to their children, and disclosing their sexual orientation to the children and others.

Efforts to reduce alcohol misuse and related problems among women and men (both heterosexual and sexual minority) should take into account cultural expectations regarding gender roles and alcohol use, as well as contemporary social and cultural changes that may be responsible for a narrowing gap between men's and women's drinking in some cultures.

Gender Differences in Alcohol Use Among Sexual Minorities

McCabe and colleagues (2009) analyzed data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a nationally representative survey of U.S. adults. They reported that, among those who identified themselves as SM based on sexual identity, behavior, or attraction,

lesbian women had more than 3 times greater odds of lifetime alcohol use disorders and of any lifetime substance use disorder than did heterosexual women. In contrast, the odds of lifetime alcohol use disorders for men with histories of only male sex partners were significantly lower than those for men who reported only female sex partners. Similarly, in a study based on data from the 2000 National Alcohol Survey, Drabble and colleagues (2005) reported that, among current drinkers, lesbians were approximately 7 times more likely and bisexual women nearly 6.5 times more likely than heterosexual women to meet *Diagnostic and Statistical Manual, 4th Edition* (American Psychiatric Association 1994) criteria for alcohol dependence. Lesbians were approximately 11 times more likely and bisexual women 8 times more likely to report 2 or more negative social consequences related to drinking compared with heterosexual women. Seeking treatment or other types of help for an alcohol problem was 8 times more likely among lesbians and 4 times more likely among bisexual women than among heterosexual women. There were no significant differences between SM and heterosexual men on any of these outcomes.

This gender-related pattern is similar among youth. In an analysis of data from the Youth Risk Behavior Surveillance System (YRBSS) survey, Talley and colleagues (2014) found that, among 13- to 18-year-olds surveyed, differences in alcohol use outcomes were greater between SM and heterosexual girls than between SM and heterosexual boys. Notably, SM girls reported higher rates of lifetime alcohol use and past-month heavy episodic drinking than did SM boys, heterosexual girls, or heterosexual boys. For instance, 30 percent of SM girls reported past-month heavy episodic drinking compared with 25.4 percent of SM boys, 16.4 percent of heterosexual girls, and 19.3 percent of heterosexual boys.

Studies of alcohol use among SMs outside the United States generally show smaller differences between SM and heterosexual populations, especially for men. For example, in a study examining sexual orientation differences in health risk behaviors among 1,725 15- to 21-year-old vocational school students in northern Thailand, van Griensven and colleagues (2004) found that AOD use patterns among SM females were similar to those of heterosexual males, whereas patterns of SM males were similar to those of heterosexual females. The authors speculate that one explanation for this pattern may be that SM males tend to socialize with heterosexual females who are less likely to use AODs and therefore are less likely to use substances themselves.

Using data from the GENACIS project, Bloomfield and colleagues (2011) analyzed alcohol use information from general-population surveys from 14 countries in Europe, Latin America, and North America. The researchers examined high-volume drinking (average daily consumption greater than 20 g of ethanol [pure alcohol] for women and greater than 30 g for men) and heavy single-occasion drinking (at least monthly consumption of large quantities of alcohol [in most countries, 60 g or more of ethanol in a day]) among heterosexual and SM respondents (defined on the basis of gender of romantic or cohabiting partner). In North America, SMW were significantly more likely than heterosexual women to report high-volume drinking and heavy single-occasion drinking, but no differences were found among men on these outcomes.[1] In the European countries, high-volume drinking was similar for SM and heterosexual women, and both drinking outcomes were similar for SM and heterosexual men.[2] Findings from the other regions examined either showed no significant differences between SM and heterosexual respondents or too few cases of high-volume or heavy single-occasion drinking to make comparisons.

In a meta-analysis of 25 studies from 8 countries in Europe, North America, Australia, and New Zealand, King and colleagues (2008) concluded that the risk of past-year AOD dependence was 50 percent higher among gay men, lesbian women, and bisexual men and women than among heterosexual men and women, with lesbian and bisexual women at especially high risk.

Nonadherence to traditional gender roles for women may influence drinking among SMW—especially in lower- and middle-income countries where the value placed on traditional gender roles remains strong. Using data from the 2005 National Youth Survey, a nationally representative sample of 12- to 29-year-olds in Mexico, Ortiz-Hernandez and colleagues (2009) found higher prevalence of alcohol use among lesbian and bisexual females, but not among gay and bisexual males, than among their heterosexual counterparts. The authors concluded that results support findings from previous studies of greater differences in the relationship between sexual orientation and alcohol use among women than among men. They further suggest that higher frequency and volume of drinking among SMW may be related to increased socialization in bars and more widespread adoption of masculine traits compared with heterosexual women. These findings are consistent with those from a study conducted in Taiwan, where the authors (Kuang et al. 2004) found adoption of nontraditional gender roles and higher rates of drinking among SMW than among heterosexual women.

Age Differences in Drinking

Rates of drinking generally decline with age for both men and women (World Health Organization 2014), although research with older adults suggests that men reduce their drinking later than women do (Brennan et al. 2011). In 2012, the

[1] The U.S. sample did not include men.

[2] There were too few cases of heavy single-occasion alcohol use among lesbians for comparison.

proportion of people in the United States reporting at least 1 drink in the previous 30 days (i.e., current drinkers) decreased from 69.2 percent among 21- to 25-year-olds to 60.1 percent among 40- to 44-year-olds and 53.1 percent among 60- to 64-year-olds (SAMHSA 2013). The same survey also found that 61.2 percent of men ages 26 and older were current drinkers, compared with 50.4 percent of women in the same age range. International surveys, however, show a somewhat different pattern. Based on GENACIS data, Wilsnack and colleagues (2009) reported that the prevalence of current drinking declined consistently with age in only a minority of the surveys for which 3 age groups were available. The prevalence of high-volume drinking declined with age among men in only 3 of the 34 surveys, and among women in only 11 of the 34 surveys. Most age-related declines in high-volume drinking occurred in high-income countries: Europe, the United States, Australia, and New Zealand.

Alcohol use among SM groups also decreases with age, but the declines tend to be smaller and to occur at later ages relative to heterosexuals. For example, in a community-based study of 447 women who identified as lesbian or bisexual, Hughes and colleagues (2006) found that, in contrast with the tendency for drinking among women in the general population to decline with age, there was relatively little variation in drinking rates among SMW across 4 age groups (≤30 years, 31–40 years, 41–50 years, >50 years). Using data from the 2003–2010 Washington State Behavioral Risk Factor Surveillance surveys, Fredriksen-Goldsen and colleagues (2013) found that lesbian and bisexual women ages 50 or older were significantly more likely than their age-matched heterosexual counterparts (adjusted odds ratio [AOR] = 1.43) to drink excessively, as were older (50 years or older) gay and bisexual men compared with older heterosexual men (AOR = 1.47). In an earlier study, McKirnan and Peterson (1989*a*) found similar rates of alcohol problems among 18- to 25-year-old gay men (26 percent) and heterosexual men (29 percent), but higher rates among gay men (19 percent) than heterosexual men (7 percent) who were ages 41–60. In the same study, lesbian women in the oldest age group (age 41–60) were 3 times as likely to report alcohol-related problems as were heterosexual women in that age group (15 percent vs. 4.5 percent).

Race/Ethnicity Differences in Drinking

Research examining alcohol-related problems across racial/ethnic groups in the United States suggests that gender and sexual orientation are important factors in this relationship. A recent analysis using pooled data from the 2005 and 2010 U.S. National Alcohol Surveys examined heavy drinking and alcohol-related consequences for White, Black, and Hispanic men and women (Witbrodt et al. 2014). The study found that, across all levels of heavy drinking, Black women drinkers had greater odds of alcohol dependence relative to White women drinkers, but no other significant differences were noted among the 3 groups of women.[3] Women showed low rates of alcohol dependence and alcohol-related consequences across ethnicities, except that Hispanic women were marginally more likely than White women to experience arguments and fights resulting from their drinking. Racial/ethnic differences were greater among men. Black men with no/low levels of heavy drinking had significantly greater odds than White men of having 3 or more alcohol-dependence symptoms and of having 2 or more negative drinking consequences. Compared with White men, Hispanic men who reported low or moderate heavy drinking also had significantly elevated odds of alcohol dependence. The authors suggest that the gender disparity may be partly explained by social norms that limit women's drinking across racial/ethnic boundaries.

Among SMs, there seem to be different associations among race/ethnicity, gender, and drinking. SMW who belong to racial/ethnic minorities seem to be at greater risk for AOD problems than heterosexual non-White women, whereas SM non-White men seem to be at comparable or less risk than heterosexual non-White men (Cochran et al. 2007*b*; Kim and Fredriksen-Goldsen 2012). In a race- and ethnicity-diverse community sample of SMW, Hughes and colleagues (2006) found that Black respondents were nearly four times more likely than White respondents to report heavy drinking. Mereish and Bradford (2014) found that Black and Hispanic SMW were more likely than Black and Hispanic heterosexual women and White SMW to report having had an alcohol- or other drug-use problem. Black and Hispanic SMM, however, did not differ in their risk compared with Black and Hispanic heterosexual men, and they had lower risk than White SMM.

Both White and non-White SM youth are at risk for alcohol problems. Talley and colleagues (2014) reported that, among 13- to 18-year-olds, White SMs were more likely than White heterosexuals to report ever drinking (79.9 percent vs. 69.1 percent), and Asian SMs were more likely than their heterosexual counterparts to report drinking (54.8 percent vs. 46.2 percent). Although bisexual White and racial/ethnic minorities initiated drinking at similar ages, heterosexual racial/ethnic minorities were significantly younger than their White counterparts when they had their first drink. For young women, there were fewer racial/ethnic differences in drinking among SMs than among heterosexual women.

Socioeconomic Status and Drinking

In the general population, higher levels of socioeconomic status (SES) are associated with more frequent

[3] Heavy drinking was defined by a gender-specific composite heavy-drinking variable based on five variables that are consistent determinants of alcohol-related health and social problems.

alcohol use, whereas lower SES often is associated with heavier drinking (Huckle et al. 2010), although these patterns vary somewhat across cultures (Bloomfield and Mäkelä 2010; Bloomfield et al. 2006). With regard to gender, analyses of survey data from the Netherlands showed that abstinence was inversely associated with educational level for both men and women. Among male drinkers, excessive drinking and very excessive drinking were more prevalent in the group with the lowest educational level. There was no significant relationship between educational level and prevalence of excessive drinking among women (van Oers et al. 1999).

Studies of adolescent alcohol use and SES in England (Melotti et al. 2013) and Brazil (Locatelli et al. 2012) suggest greater risk for higher-SES young people. In England, higher household income was associated with greater risk of alcohol use and problem use, especially among girls (Melotti et al. 2013). A study that compared alcohol use among Slovak adolescents in 1998 and 2006 found no socioeconomic differences among boys and greater likelihood for girls of high SES to be drinkers in 1998, but not in 2006 (Pitel et al. 2013).

Although scant research has examined the relationship between SES and alcohol use among SMs, studies of education and income are relevant. Some research has found that same-sex couples who live together earn less than heterosexual married couples, possibly because of workforce discrimination (Badgett and Lee 2001), whereas other studies find that cohabiting same-sex couples have more advantages in terms of education and income than opposite-sex cohabiting couples (Gates 2012, 2013; Kastanis and Wilson 2014; Krivickas 2010). In contrast, bisexual adults often show greater disadvantage in earnings than gay, lesbian, and heterosexual adults (Gates 2012). In terms of general health, same-sex cohabitors report poorer health than their heterosexual married counterparts at the same SES levels (Liu et al. 2013). In the only study we located that examined the relationship between educational level and substance use disorders (and other mental health problems) among SMs, Barnes and colleagues (2014) found that sexual-orientation disparities in substance use disorder rates were smaller among respondents with bachelor's degrees than among those with less education. These data were from the NESARC.

In addition to education and income, marital and parental status are likely associated with risk of heavy or problematic drinking. For example, in a nationally representative study of Australian women ages 25–30, Hughes and colleagues (2010*b*) found that, compared with married women, those in relationship categories more common among SMW (e.g., de facto, never married) reported significantly higher odds of AOD use. In addition, lower levels of education and not having children were each associated with significantly higher odds of at-risk drinking.

Using data from the U.S. National Health Interview Study, Denney and colleagues (2013) also found that same-sex cohabiting couples had both higher household incomes and higher educational levels than opposite-sex married couples and cohabiting couples. However, after adjusting for socioeconomic differences, same-sex cohabiting couples had worse health than opposite-sex married couples and similar health as opposite-sex cohabiting couples. These researchers also found a significant protective effect of having children in the household on partnered men's and women's self-assessed health (heterosexual and SMs alike), but the effect was significantly greater for heterosexual married women.

Factors Associated With Alcohol Use Among Sexual Minorities

Minority Stress

A variety of potential risk factors have been suggested to explain the higher prevalence of alcohol use and alcohol-related problems among SMs. The predominant theoretical explanation is minority stress (Meyer 2003). Underlying this perspective are the assumptions that minority stressors are unique (not experienced by nonstigmatized populations), chronic (related to social and cultural structures), and socially based (stemming from social processes, institutions, and structures). The minority stress perspective describes stress processes that include experiences of prejudice, expectations of such prejudice and of rejection (stigma consciousness), hiding, concealing, internalized homophobia, and ameliorative coping processes. Expectations of prejudice and discrimination and the vigilance that such expectations require vary based on individual and environmental contexts, but all SM persons are assumed to internalize society's negative attitudes toward homosexuality to some degree (internalized homophobia) (Meyer 2003).

In a large study using quantitative and qualitative methods to examine mental health and well-being among SMs in Ireland, more than 40 percent of 1,100 survey respondents reported that their drinking made them "feel bad or guilty," and almost 60 percent indicated feeling that they should reduce their alcohol consumption. Qualitative findings strongly suggested that self-medication to cope with minority stress was a primary motive for regular or heavy alcohol consumption (Mayock et al. 2008).

Analyses of the National Survey on Midlife Development in the United States found that compared with heterosexuals, SM women and men more frequently reported both discrete discrimination events (e.g., being fired from a job) and day-to-day discrimination (e.g., being called names or insulted) (Mays and Cochran 2001). Perceived discrimination was associated with reduced quality of life and with indicators of psychiatric morbidity in both SM and heterosexual respondents. Other studies have shown that harassment and discrimination based on sexual orientation are associated

with psychological distress (Herek et al. 1997; Lewis et al. 2001, 2003; Meyer 1995), loneliness (Szymanski and Chung 2001), and lower self-esteem (Szymanski et al. 2001). Relatively few studies have examined the impact of such stressors on the drinking behaviors of SMs (Hatzenbuehler et al. 2008, 2010; McCabe et al. 2010). In an early study of lesbian women and gay men, McKirnan and Peterson (1989*b*) found that stress was associated with alcohol- or drug-related problems in high-vulnerability gay men (those with greater orientation to gay bars and positive expectancies about the tension-reducing effects of alcohol). However, such associations were not statistically significant for lesbians or for low-vulnerability gay men.

Drinking Norms

Drinking behavior is governed to a large extent by social structures (rules, role expectations, norms, and values) of the individual's cultural group and by the drinking behavior of peers. Because of their history of being excluded and discriminated against in mainstream settings, many SM people have traditionally found bars to be an important venue for social interaction. Findings from the 2000 National Alcohol Survey conducted in the United States (Trocki et al. 2005) indicated that SMW spend more time in bars and party settings and consume more alcohol in these settings than do heterosexual women. Although gay men spent more time in bars than did bisexual or heterosexual men, rates of heavy drinking among men did not vary by sexual orientation across settings.

According to Cochran and colleagues (2012), the adoption of a minority sexual identity and affiliation with gay-identified communities increase exposure to more tolerant social norms regarding AOD use. These researchers found that SMs report more tolerant norms about AOD use and greater availability of these substances. These two factors also mediated a substantial portion of the relationship between minority sexual orientation and substance use.

Experiences of Victimization

Abuse, violence, and victimization are considered major life stressors and are consistently linked with long-term adverse consequences, including hazardous drinking and alcohol use disorder (Briere 1988; Dube et al. 2002; Kendler et al. 2000; Nelson et al. 2002; Wilsnack et al. 2004). For example, a review of research linking childhood abuse to alcohol use and related problems in adulthood has estimated that globally, a history of child sexual abuse accounts for 4 percent to 5 percent of alcohol misuse/dependence in men and 7 percent to 8 percent in women (Andrews et al. 2004).

SMs are at increased risk for childhood abuse compared with heterosexuals (Alvy et al. 2013; Austin et al. 2008; Drabble et al. 2013; Hughes et al. 2010*a*, 2014; Tjaden et al. 1999), thereby further increasing their risk of developing alcohol-related problems. Using a pooled sample from two large studies of U.S. women, Wilsnack and colleagues (2008) found that those who identified as lesbian, bisexual, or mostly heterosexual reported significantly higher rates of childhood sexual abuse (CSA) compared with women who identified as exclusively heterosexual. In addition, SMW reported significantly higher rates of heavy drinking, heavy episodic drinking, and symptoms of potential alcohol dependence than exclusively heterosexual women.

In addition to high rates of CSA, accumulating evidence suggests that many other forms of lifetime sexual and physical abuse, violence, and victimization also are more common among SMs (Balsam et al. 2005; Drabble et al. 2013; Hughes et al. 2010*a*). Using the pooled sample described above, Hughes and colleagues (2014) found that SMW were significantly more likely than exclusively heterosexual women to report each of six types of lifetime victimization: CSA, childhood physical abuse, childhood neglect, adult sexual assault, adult physical assault, and intimate-partner violence. The number of types of victimization experiences was positively associated with hazardous drinking among both SM and heterosexual women but contributed to higher levels of hazardous drinking among SMW.

Hughes and colleagues (2010*a*) analyzed data from the NESARC. Results supported findings from previous studies suggesting that SM women and men are at higher risk for victimization than their heterosexual counterparts. Lesbian and bisexual women were more than twice as likely as heterosexual women to report any lifetime victimization. Lesbians, gay men, and bisexual women also reported a greater number of victimization experiences. The largest difference between lesbian and heterosexual women was in reports of CSA: 3 times as many lesbians (34.7 percent) as heterosexual women (10.3 percent) reported this experience (see figure). Bisexual women also were more likely than heterosexual women to report CSA, as well as three other lifetime victimization experiences. Women who reported two or more victimization experiences had two to four times the odds of alcohol dependence and drug use disorders as women who reported no victimization. Lesbians who reported childhood neglect had more than 30 times the odds of alcohol dependence as heterosexual women who reported neglect. In contrast, although gay men were significantly more likely than heterosexual men to report four of seven victimization experiences, these differences did not increase gay men's risk of substance use disorders (SUDs). Bisexual men were similar to heterosexual men in prevalence of victimization experiences, but associations between victimization and SUDs were stronger in bisexual men.

In addition to SMW's higher rates of childhood victimization, the severity of victimization experiences also may vary by sexual orientation. Two recent studies have found that women who

self-identify as lesbian report significantly greater severity of CSA (Wilsnack et al. 2012) and of childhood physical abuse (Alvy et al. 2013) than do women who identify as heterosexual.

Higher rates of victimization among SMs, especially SM youth, may be related to gender-atypical appearance and behavior. For example, in a recent review of findings from 12 countries (Australia, Austria, Belgium, Canada, Israel, Japan, the Netherlands, New Zealand, Norway, South Africa, the United Kingdom, and the United States), Collier and colleagues (2013) found that sexual orientation and gender expression were associated with peer victimization, which in turn was related to AOD abuse. Similarly, gender-atypical behavior was associated with more negative parental relationships (D'Augelli et al. 2008; Ryan et al. 2009), a factor that can lead youth to run away from home and/or to be more likely to participate in situations that put them at risk for victimization.

Societal Attitudes and Policies Regarding SMs

SMs and their families now are experiencing increasing public support and access to legal rights, such as marriage, in some parts of the world. According to the Pew Research Center, as of June 26, 2015, 22 countries worldwide permitted lesbian women and gay men to marry their same-sex partners, and same-sex marriage is legal in some parts of Mexico (Pew Research Center 2015). Although attitudes toward SMs also are changing in some other parts of the world, most people (and thus the majority of SM people) live in countries with strong anti-gay policies. In 2014, it was estimated that 2.79 billion people live in countries where being openly gay or lesbian is punishable by imprisonment or death—a number 7 times greater than those who live in countries with laws that recognize same-sex marriage (Ball 2014).

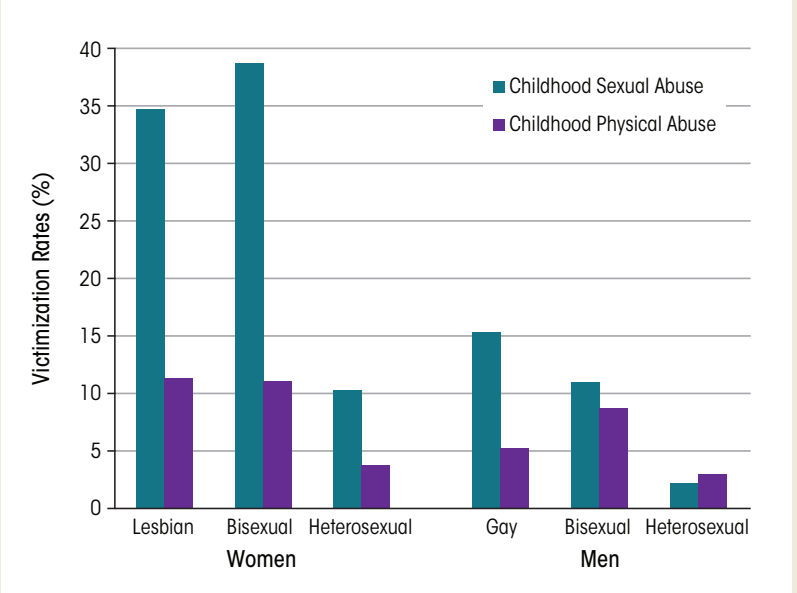

Figure Victimization rates among lesbian/gay, bisexual, and heterosexual women and men, based on findings from the National Epidemiologic Survey on Alcohol and Related Conditions, a nationally representative survey of U.S. adults.

SOURCE: Hughes et al. 2010*a*.

Increasing evidence throughout many parts of the world documents the negative effects of stigma, discrimination, and criminalization on SM people's health, including minority stress, depression, and fear of seeking help (Kates 2014). Whether and how the World Health Organization (WHO) should address SM health has been debated over the past few years. Although opposition from a number of African and Middle Eastern countries has prevented this topic from being included on the WHO agenda (Daulaire 2014), the Pan-American Health Organization (PAHO), the WHO regional arm representing the Americas, unanimously passed a resolution addressing SM health, including discrimination in the health sector. This marks the first time any United Nations body has adopted a resolution specifically addressing these issues (PAHO 2012, 2013).

Research suggests that societal norms and policies that discriminate against SMs increase the risk of alcohol use disorder for SMs. For example, one U.S. study that examined the relationship between State-level policies and psychiatric morbidity found that lesbians, gays, and bisexuals who lived in States without protective policies toward SMs (e.g., laws against hate crimes and employment discrimination) had higher odds of alcohol use disorder than those who lived in States with protective policies (Hatzenbuehler et al. 2009). The authors also examined psychiatric morbidity among SMs before (2001–2002) and after (2004–2005) States had enacted same-sex marriage bans (Hatzenbuehler et al. 2010). Mood disorder (36.6 percent), generalized anxiety disorder (248.2 percent), and alcohol use disorder (41.9 percent) all increased significantly among SM residents in these States between the 2 data collection points. Psychiatric disorders did not significantly differ over time among SMs living in States without marriage bans. In addition, the researchers found statistically significant increases in generalized anxiety, panic, and

alcohol use disorder among heterosexuals living in States with the bans, but these increases were not of the same magnitude as those experienced by SMs.

Conclusions/Recommendations/Future Directions

What Explains the "Gender Paradox"?

This review has documented clear differences in gender-related patterns of alcohol use between heterosexual and SM persons. Specifically, most studies that ask about sexual orientation find that SMW substantially exceed heterosexual women in high-risk drinking and adverse drinking consequences, whereas SMM may exceed heterosexual men but by a much smaller margin, if at all. This creates a "gender paradox": heterosexual men typically drink much more than heterosexual women, but the reverse is true among SM men and women.

An intriguing question is why these sexual orientation differences exist, and what they can tell us about gender and alcohol use more generally. In our opinion, one important factor contributing to the gender paradox is the differential adoption of traditional gender roles by SMs compared with heterosexuals. There is ample evidence that culturally defined gender roles in most societies link alcohol use (and especially heavier use) more closely with traditional masculine roles than with traditional feminine ones. As discussed earlier, men in many cultures use alcohol to demonstrate masculine gender superiority and power, whereas women's drinking is limited by cultural beliefs that drinking could threaten their performance of traditional feminine roles as mothers, caretakers, and controllers of men's drinking (Holmila and Raitasalo 2005; Wilsnack et al. 2005). To the extent that SM persons of both genders reject these traditional gender roles and expectations (Lippa 2000), SMW would be expected to drink more than heterosexual women and SMM would feel less pressure to engage in traditionally masculine heavy drinking. Thus, whereas minority stress may contribute to greater risk of drinking in both SM women and men (Hatzenbuehler 2009; Meyer 2003), relative freedom from traditional gender roles would predict larger increases in drinking by SM women than SM men, reversing the heterosexual pattern of men's drinking exceeding women's.

Additional influences may contribute to the gender paradox. For example, gay men may drink less due to weight and body image concerns (Kimmel and Mahalik 2005) or to greater socialization with heterosexual women, who evoke less pressure toward heavy drinking (van Griensven et al. 2004), and SMW's greater dependence on gay bars as venues for socialization may increase their risks of frequent and/or heavy drinking (Kuang et al. 2004; Trocki et al. 2005). However, the important links between traditional gender roles and heavier versus lighter drinking seem of central importance in understanding both the heavier drinking by heterosexual men than heterosexual women *and* the reversal of this pattern among SM women and SM men. This interpretation of the gender paradox also suggests that social change (and intentional intervention efforts) that produce less gender-role differentiation and greater gender-role flexibility could help to reduce gender-role–related alcohol use and alcohol problems among both heterosexual and SM women and men.

Research

Sexual Minority Research

Until the advent of HIV/AIDS in the 1980s, there was almost no funding for SM health research. Since then, apart from HIV/AIDS, there has been relatively little funding for research with SMs—even in the United States, where most of this research has been done. Recently, Coulter and colleagues (2014) conducted a review of grants funded by the National Institutes of Health (NIH). Between 1989 and 2011, apart from studies of HIV/AIDS, only 0.1 percent of all NIH-funded studies focused on SMs. Of these, most have focused on SMM, with only 13.5 percent focusing on SMW and only 13 percent of funded SM studies focusing on alcohol use. The dearth of funding is a major contributor to gaps in knowledge, especially in non-Western countries. In addition, researchers throughout the world who study SM health must move beyond the focus on disease and deviance, to also study strengths and resilience factors among SMs. And just as women (or men) should not be considered a single homogeneous group, SM people are extremely diverse in terms of their health behaviors and health outcomes (Boehmer 2002). Future research must take into account the nuances of gender and gender identity, sexual orientation, and culture as well as economic and social resources.

Gender and Alcohol Research

To some extent, research on sexual orientation disparities in alcohol use and related problems is following a trajectory similar to that of research on women and alcohol. Until the 1970s, research on alcohol use and misuse gave little attention to drinking by women; when women were even considered, it was assumed that their drinking and its consequences would be similar to those of men. In 1970, only 28 English-language alcohol research articles could be found that included women as research participants (Sandmaier 1980). Research on women's drinking, and on how gender is related to alcohol use and its consequences, has increased dramatically since the 1970s, to the point where more than 1,000 new articles related to gender and alcohol are published each year (Wilsnack and Wilsnack 2013). Reasons for the increased attention paid to women and gender

include effects of the U.S. women's movement of the 1960s and 1970s, growing awareness of fetal alcohol syndrome and other adverse outcomes of alcohol use in pregnancy, and a gradual recognition in medical and behavioral science that many diseases and disorders could not be understood and adequately prevented or treated without taking into account the multiple ways they are affected by gender.

Like research on SMs, research on women's drinking initially focused on comparisons between women (as a homogeneous group) and men (as an equally homogeneous group). Only gradually did investigators begin to explore variations *within* gender groups—by age, race/ethnicity, and socioeconomic status, and eventually by sexual orientation. We hope that this trend toward greater attention to within-group variations will also continue in research on SMs, and that the sections on demographic differences in this article (e.g., by age, race/ethnicity, and SES) will help to accelerate this trend.

Prevention, Intervention, and Treatment

Research on treatment for AOD use disorders among women and men in the general population comprises a large and growing body of literature whose review is beyond the scope of this article. However, it may be helpful to highlight a few investigations that have focused on treatment issues specifically relevant to SM persons and to consider factors that may influence SM women and men's access to and benefit from AOD interventions.

Interventions to promote the health of SMs need to address the intersections of multiple minority statuses (e.g., minority sexual orientation, minority race/ethnicity, female gender) and issues such as power, stigma, and victimization (Hatzenbuehler et al. 2013). Positive strategies such as strengthening resilience and promoting family, community, and workplace acceptance have the potential to contribute to long-term health promotion for SM women and men.

Both gender and SM status may affect a person's ability to find substance abuse treatment that is accessible, affordable, and socially and culturally appropriate. A 2007 review concluded that, although women-only treatment is not necessarily more effective than mixed-gender treatment, treatment approaches that address problems facing substance-abusing women, or that are designed for specific subgroups of women, are more effective (Greenfield et al. 2007).

Along the same lines, SM men and women may benefit from specialized treatment programs especially designed to address the unique issues of SMs, such as coming out; internalized homophobia; violence and discrimination; socialization, dating, and intimacy; family support; and spirituality and religion (Hicks 2000). It may be difficult to find such programs, however, and the lack of available programs may affect choice of and satisfaction with treatment. A telephone survey of substance abuse programs (Cochran et al. 2007*a*) found that 71 percent of agencies with listings indicating sexual minority-specific services did not in fact offer such services. Only 7.4 percent had any kind of specifically tailored treatment.

Using NESARC data to evaluate use of substance abuse treatment among SM adults, McCabe and colleagues (2013) found that, despite having a higher rate of substance use disorders, women who self-identified as lesbian or who reported only same-sex attraction or behavior did not enter substance abuse treatment more often than heterosexual women. The researchers did not find any significant differences in health insurance coverage between lesbian and heterosexual respondents. Likewise, research has found that SM men and women have lower levels of satisfaction with substance abuse treatment compared with heterosexuals (Drabble et al. 2005; Senreich 2009).

In conclusion, although research and clinical interventions are important, broader social and political action is needed to address social determinants of health and to remove barriers to opportunity and equality, whether these barriers are based on gender, minority sexual orientation, age, minority race/ethnicity, low SES, or other marginalized statuses. Such social action may be the ultimate prevention strategy, not only for negative alcohol-related outcomes but also for a wide variety of other health and social problems that affect both SMs and heterosexual persons throughout the world.

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Focus On: Women and the Costs of Alcohol Use

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Although light-to-moderate drinking among women is associated with reduced risks of some cardiovascular problems, strokes, and weakening of bones, such levels of drinking also are associated with increased risks of breast cancer and liver problems, and heavy drinking increases risks of hypertension and bone fractures and injuries. Women's heavy-drinking patterns and alcohol use disorders are associated with increased likelihood of many psychiatric problems, including depression, posttraumatic stress disorder, eating disorders, and suicidality, as well as increased risks of intimate partner violence and sexual assault, although causality in the associations of drinking with psychiatric disorders and with violence remains unclear. It is important for women to be aware of the risks associated with alcohol use, especially because gaps between U.S. men's and women's drinking may have narrowed. However, analyses of health risks and benefits need improvement to avoid giving women oversimplified advice about drinking. **KEY WORDS: Alcohol consumption; alcohol use, abuse, and dependence; alcohol use disorder; alcohol burden; drinking patterns; prevalence; alcohol burden; alcohol-related problems; alcohol-related injuries; women; pregnancy; cardiovascular disease; stroke; bone mass density; breast cancer; liver disease; psychiatric disorders; posttraumatic stress disorder (PTSD); depression; eating disorders; suicidal behavior; intimate partner violence; sexual assault**

Even though the prevalence of alcohol use in the United States generally is lower among women compared with men (Substance Abuse and Mental Health Services Administration [SAMHSA] 2011), this gap has narrowed (Grucza et al. 2008). Furthermore, although women consume alcohol at lower levels than men, their body composition puts them at higher risk than men of developing some alcohol-related problems, both acutely (because of higher blood alcohol levels from a given amount of alcohol[1]) and chronically (from alcohol-related organ damage). This article examines alcohol-use patterns (with particular attention to midlife) and how they differ for men and women and summarizes recent evidence on associations between women's alcohol consumption and their physical and mental health.

Drinking Practices and Patterns Among Women in Midlife

Rates of drinking decline with age for both men and women in the United States, and drinking remains less prevalent among women compared with men. In 2010, the proportion of people reporting at least one drink in the previous 30 days (i.e., current drinkers) decreased from 70 percent among 21- to 25-year-olds to 61.1 percent among 40- to 44-year-olds and 51.6 percent among 60- to 64-year-olds (SAMHSA 2011). The same survey also found that approximately 57.4 percent of males aged 12 or older were current drinkers, compared with 46.5 percent of females of the same age range (SAMHSA 2011).

Rates of binge drinking also are higher among men than women (Centers for Disease Control and Prevention [CDC] 2012). One survey (National Institute on Alcohol Abuse and Alcoholism [NIAAA] 2012) reported that 28.8 percent of women and 43.1 percent of men reported binge drinking (i.e., consuming within 2 hours four or more drinks for women and five or more drinks for men) in the previous year. In a multinational study of 35 countries, Wilsnack and colleagues (2009) reported that, as expected, men consistently drank more than women and were more likely to engage in high-volume drinking and high-frequency drinking. Women were more likely to be lifetime nondrinkers and to be former drinkers.[2] The authors suggest that women may find it easier than men to quit drinking because (1) women generally are lighter drinkers than men; (2) drinking is not as important to women's social roles as it is to men's; and/or (3) women who stop drinking during pregnancy and early childrearing may not resume drinking later on.

Despite these findings, Grucza and colleagues (2008) reported significant increases between 1990–1991 and 2000–2001 in the lifetime prevalence of drinking for women aged 38–47 in the United States. There also was an increase in lifetime prevalence of alcohol dependence among women drinkers aged 38-47. Similar increases were not found for male drinkers, suggesting that the gender gap in alcohol use and dependence is narrowing, at least in these age groups.

[1] Because women's bodies generally have less water than men's bodies, alcohol becomes less diluted, and women therefore reach higher blood alcohol levels than men even if both are drinking the same amount.

[2] Former drinkers reported drinking in the past but not in the last 12 months.

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Drinking During Pregnancy: Patterns and Predictors

Women who become pregnant in their thirties and forties may be more likely to drink during pregnancy than younger women. From 2001 to 2005, 17.7 percent of 35- to 44-year-old women reported drinking during pregnancy, compared with 8.6 percent of pregnant women aged 18–24 (Denny et al. 2009). Among women in eight States who gave birth between 1997 and 2002, 30.3 percent reported drinking during pregnancy, and 8.3 percent reported binge drinking (four or more drinks on one occasion). Whereas 22.5 percent of the women reported drinking during the first month of pregnancy, drinking declined during pregnancy; only 7.9 percent of women reported drinking during the third trimester, and only 2.7 percent reported drinking during all trimesters. Drinking during pregnancy was more prevalent among women over 30 (more than 30 percent drank) than among younger women (Ethen at al. 2009).

Understanding the predictors of drinking during pregnancy may help target prevention efforts. The eight-State study by Ethen and colleagues (2009) found that both drinking and binge drinking during pregnancy were predicted by prepregnancy binge drinking. Drinking and binge drinking during pregnancy also were more prevalent among women who were non-Hispanic whites, who smoked during pregnancy, and whose pregnancy was unintended. A recent review of 14 studies of drinking during pregnancy in nine countries (Skagerström et al. 2011) found that drinking during pregnancy was associated with heavier drinking prior to pregnancy in all seven studies that measured this; smaller numbers of studies consistently found that drinking during pregnancy was associated with higher income/social class and with histories of abuse or exposure to violence and histories of drinking problems.

Physical Health Effects of Women's Drinking

Light to moderate alcohol use has been found to generally be beneficial for many health outcomes and is associated with decreased mortality. Heavier use, however, is associated with poorer health and increased mortality. One meta-analysis of 34 studies in 13 countries found that, compared with abstaining, drinking less than two drinks per day among women and drinking less than four drinks per day among men was associated with significantly reduced total mortality, but higher levels of alcohol use were associated with increased mortality (Di Castelnuovo et al. 2006). These findings should not encourage people to start drinking alcohol for its health benefits, because of the significant health problems associated with heavier use, as described below.

Another study used data from a large survey of middle-aged (median age 58) female nurses in the United States and assessed the health of participants who lived to age 70 and older. The study found that light to moderate alcohol consumption at midlife was associated with modestly increased odds of good health at age 70 or older (no chronic illnesses, physical impairment, or mental problems). That is, women who averaged between one-third and one drink per day had about 20 percent higher odds than nondrinkers of good health at age 70 and older. Also, the women who drank frequently during the week (5 to 7 days) had better odds of good health at age 70 and older than the women who drank only once or twice a week (Sun et al. 2011). However, these findings should be interpreted with caution because the measures of alcohol consumption were quite limited.

Effects of Women's Drinking on Cardiovascular Health

Many studies have found that light to moderate alcohol use is associated with lower risks of cardiovascular disease and mortality, but these studies often have not reported specifically on women's drinking. However, studies of coronary heart disease risk in Denmark (Tolstrup et al. 2006) and England (Ward et al. 2011) found that the risks were lower in women who consumed more alcohol. In the United States, pooled data from nine National Health Interview Surveys (1987–2000) showed that women drinking up to seven drinks per week had lower risks of cardiovascular mortality than lifetime abstainers (Mukamal et al. 2010).

Light-to-moderate drinking also may be associated with lower risks of sudden cardiac death (SCD). The study of nurses in the United States, which examined heart problems in 4-year periods after reported drinking or abstaining, found the lowest risk of SCD among women who averaged approximately one-half to one drink per day. Women who drank more heavily (more than 30 g or two drinks per day) had SCD risks similar to risks of abstainers, but the number of SCD cases among women who consumed more than 30 g per day was limited (Chiuve et al. 2010). As noted earlier, however, these findings are based on limited measures of drinking.

In contrast to studies finding beneficial effects, a meta-analysis of six studies (Samokhvalov et al. 2010) found that women's risks of atrial fibrillation (AF) increased steadily with increasing alcohol consumption. Whereas women who averaged up to two drinks a day did not have significantly higher risks than abstainers, women who consumed more than two to three drinks daily had a 17 percent increased risk of AF, and women who consumed more than four drinks daily had twice the risk of AF.

Women's risk of hypertension also may increase steadily as alcohol consumption increases. A meta-analysis of eight studies indicated that the risk was reduced somewhat among women drinking lightly (averaging less than a drink a day), but the risk then rose steadily with higher levels of consumption. Compared with abstainers, women who averaged roughly four drinks a day had nearly twice the risk of hypertension, and women averaging roughly eight drinks a day had nearly three times the risk (Taylor et al. 2009).

Effects of Women's Drinking on Stroke Risk

The risk of stroke is lower among women who are light-to-moderate drinkers. The U.S. nurses' study found lower risk of

strokes among women who were recent light drinkers, averaging approximately one drink a day (Jimenez et al. 2012). Among 45,449 Swedish women aged 30 to 50 who were followed up approximately 11 years later, risks of ischemic stroke were significantly lower among women averaging less than one drink a day (compared with abstainers). The numbers of women with hemorrhagic strokes and/or strokes after drinking more heavily were too small for reliable evaluation (Lu et al. 2008). Meta-analyses of five to nine other studies found that women's light-to-moderate drinking was protective against both ischemic and hemorrhagic strokes (with lowest risks in women averaging about one drink a day), but risks of morbidity and mortality from both types of strokes increased rapidly as women's consumption rose above three to four drinks a day (Patra et al. 2010).

Effects of Women's Drinking on Liver Disease

Women apparently are more vulnerable than men to liver cirrhosis and other liver injury from alcohol use, possibly because of estrogens, although the mechanisms are as yet unclear (Eagon 2010). A meta-analysis of 12 studies found that women's risks of morbidity and mortality from liver cirrhosis increased steadily with higher levels of alcohol consumption, with no protective effect of light to moderate drinking, and the risks increased more rapidly for women than for men (Rehm et al. 2010). These risks may be increased by other personal characteristics and by drinking patterns. In a very large sample of women in the United Kingdom, followed up for an average of 6.2 years, risks of cirrhosis among women averaging two or more drinks a day increased greatly if their body mass indexes were greater than 28 kg/m^2 (Liu et al. 2010). In a large study of women in New York State, levels of γ-glutamyl-transferase (GGT), a liver enzyme that increases in all forms of liver disease (Niemelä and Alatalo 2010), were highest not only in women who averaged more than a drink a day but also in women who did their drinking only on weekends and without food (Stranges et al. 2004).

Effects of Women's Drinking on Breast Cancer Risk

Even moderate alcohol consumption increases breast cancer risk, and the risk rises as drinking increases. A multinational meta-analysis of 98 studies found that the risk of breast cancer increased an average of 10 percent for every increase of 10 grams per day in alcohol consumption (Key et al. 2006). A 10-year follow-up study of more than 38,000 U.S. women aged 45 and older found a significant trend of increased risk of invasive breast cancer associated with increased alcohol consumption at baseline, with the greatest risk among women averaging at least 30 grams of alcohol per day (Zhang et al. 2007). The risks from alcohol consumption were clearest for estrogen- and progesterone-receptor-positive tumors and for women currently taking postmenopausal hormones, consistent with the hypothesis that part of alcohol's effect on breast cancer is to increase estrogen exposure (Garcia-Closas et al. 2002; Onland-Moret et al. 2005). Another U.S. study, based on data from 184,418 postmenopausal women aged 50 to 71, reported similar findings (Lew et al. 2009). After 7 years of follow-up, the researchers found that risks of breast cancer increased steadily the more women drank. Risks were highest for estrogen- and progesterone-receptor-positive tumors, with risks of these tumors 46 percent higher for women drinking more than 35 grams of alcohol (more than two drinks) a day. However, when Suzuki and colleagues (2010) followed up 50,757 Japanese women (aged 40 to 69) over 13 years, they found that breast cancer risk increased 6 percent with every additional 10 grams per day of alcohol consumption, but the observed association was not modified by menopausal status or use of exogenous estrogens. These findings suggest that breast cancer risks associated with alcohol consumption involve more than just estrogen levels.

Effects of Women's Drinking on Bone Health

Higher bone-mineral density (BMD) is associated with resistance to fracture. A recent review of research relevant to 40- to 60-year-old women concluded that there was fair evidence that moderate drinking did no harm to BMD (Waugh et al. 2009). In fact, a number of studies have found that light to moderate drinking is associated with increased BMD, at least among postmenopausal women (Maurel et al. 2012). For example, Tucker and colleagues (2009) found that, in women from the Framingham Offspring cohort, hip and spine BMD were 5.0 to 8.3 percent greater in postmenopausal women who consumed more than two drinks per day than in nondrinkers. A study of 2,043 postmenopausal women in the United States found that BMD was 3.8 percent higher in women who had more than 29 drinking occasions per month than those who abstained, although this finding only was marginally significant (because of small numbers of daily drinkers) (Wosje and Kalkwarf 2007). Finally, a study in Scotland of 3,218 women aged 50 to 62 found significant increases in BMD in the femoral neck and lumbar spine in women who averaged more than one drink a day, compared with lifetime abstainers (McLernon et al. 2012). However, in general these studies were unable to evaluate effects of heavy drinking, and the processes by which alcohol affects BMD remain uncertain but may involve effects of increased levels of estrogen and calcitonin (Maurel et al. 2012).

In contrast, the prevailing wisdom is that heavy drinking (averaging multiple drinks per day) increases women's risks of fractures, such as from falls (Epstein et al. 2007). In a combined study of 11,032 women in Canada, Australia, and the Netherlands, the risks of hip fractures and osteoporotic fractures were higher in women averaging two or more drinks a day than in women averaging up to one drink a day (Kanis et al. 2005). In Sweden, a study of 10,902 middle-aged women showed that low-energy fractures were more likely in women who had higher levels of GGT, which is associated with chronic heavy drinking (Holmberg et al. 2006).

Women's Drinking and Psychiatric Disorders

Alcohol Use Disorders

In addition to physical health risks associated with alcohol use, women's risks of mental health problems also are related to their drinking. It is clear that women's heavy and binge drinking is associated with alcohol use disorders (AUDs). For example, U.S. data show that among women aged 50 or older, those who engage in binge drinking (four or more drinks on a drinking occasion) have more than three times greater risks of alcohol abuse, and more than five times greater risks of alcohol dependence, than women who drink but do not engage in binge drinking (Chou et al. 2011).

However, there has otherwise been limited attention to gender-specific ways in which women's drinking may be related to AUDs. One exception is that women, like men, are at greater risk of AUDs if they begin drinking at early ages. A large study in Missouri has found elevated risks of AUDs in women who began drinking before age 18 (Jenkins et al. 2011), confirming findings from U.S. national surveys (Dawson et al. 2008). A second exception is that it has long been thought that development of AUDs is "telescoped" in women compared with men, occurring in a shorter period of time after women begin to drink (Greenfield 2002). However, this pattern was identified in women in treatment for AUDs, and U.S. survey data now indicate that telescoping does not occur in women drinkers in the general population (Keyes et al. 2010) but may be related to the experiences that bring women to treatment.

Psychiatric Disorders Other Than AUDs

General-population studies often have found links between women's drinking and psychiatric disorders, but the time order and causes of these linkages are often unclear. For example, a German survey found that women with alcohol abuse or dependence, or women who drank an average of at least 20 to 30 grams of alcohol per day, were more likely than other women to have a variety of psychiatric disorders (affective, anxiety, or somatoform), and the connections between drinking and disorders were stronger for women than for men (Bott et al. 2005). A Danish survey found that any psychiatric disorders were more likely in women averaging more than three drinks a day, and anxiety disorders were specifically more likely among women averaging more than two drinks a day, compared with nondrinkers (Flensborg-Madsen et al. 2011). In addition, U.S. data on women aged 50 and older showed higher risks of both panic disorder and posttraumatic stress disorder (PTSD) in women who engaged in any binge drinking, compared with non–binge drinkers (Chou et al. 2011). Unlike the preceding studies, which linked drinking patterns to increased risks of general psychiatric comorbidity, most studies of women's alcohol use and psychiatric disorders have focused on comorbidity of specific disorders with AUDs and risky drinking patterns. These more specific linkages are discussed in the sections that follow.

Depression. Research clearly has established that depressive disorders and symptoms are more likely among people with AUDs (e.g., Grant et al. 2004), but studies have not always examined this connection specifically among women. However, a large U.S. twin study found that diagnoses of major depression and alcohol dependence were correlated among women (Prescott et al. 2000), and data from the large National Epidemiologic Study on Alcohol and Related Conditions (NESARC) showed that women with major depressive disorder were more likely to report multiple criteria for alcohol abuse and dependence (Lynskey and Agrawal 2008). Research also has repeatedly found associations of women's depression with binge drinking. For example, in a major Canadian survey, women's binge drinking (five or more, or eight or more, drinks per day) was associated with measures of recent and longer-term depression (Graham et al. 2007), and data from the large U.S. Behavioral Risk Factor Surveillance System surveys showed that lifetime depression was significantly more likely in women who engaged in binge drinking (four or more drinks in a day) (Strine et al. 2008).

PTSD. AUDs often have been associated with symptoms or diagnoses of PTSD. For example, in young adults followed up from the U.S. National Survey of Adolescents, women with PTSD in the past 6 months were more than twice as likely as other women to meet criteria for a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* diagnosis of alcohol abuse (Danielson et al. 2009). Among women from the large Missouri Adolescent Female Twin Study, PTSD was associated with a greater likelihood of AUDs (Sartor et al. 2010). In surveys of three Mexican cities, lifetime PTSD was more prevalent in women who misused alcohol (with at least one indicator of alcohol abuse or dependence) (Slone et al. 2006). In addition, in the large California Women's Health Survey, having symptoms of PTSD doubled the odds that women engaged in binge drinking (Timko et al. 2008). However, most of these studies have not found any effects of PTSD beyond the effects of the traumatic experiences that led to PTSD, a pattern also reported in other recent studies of women who have experienced sexual assaults (Najdowski and Ullman 2009; Testa et al. 2007). Therefore, PTSD may be an indicator of experiences distressful enough to lead women to drink to excess, but PTSD itself may not necessarily be a cause of such drinking.

Alcohol and Eating Disorders. Research often has found that eating disorders in women are associated with problem drinking. The strongest recent evidence is in a meta-analysis of 41 studies, mainly in the U.S. and Canada, in which women's eating disorders consistently were associated with AUDs (Gadalla and Piran 2007). The meta-analysis included a very large Canadian general-population survey in which risks of eating disorders also were associated with heavier weekly drinking among women ages 15 to 44 (Piran and

Gadalla 2007). Hypotheses to explain observed links between women's eating disorders and drinking typically have focused on possible common antecedents (distress, personality characteristics, and genetic factors) rather than on ways that eating disorders might cause or be caused by drinking (Conason and Sher 2006).

The meta-analysis by Gadalla and Piran (2007) showed that problem drinking was associated more specifically with bulimic behavior than with anorexia nervosa. The associations also were stronger among women in community or student samples but were weaker or absent when women in treatment for eating disorders were compared with women in the general population. A multisite European study comparing individuals (mostly women) in treatment versus healthy individuals in the general population also failed to find that those in eating disorders treatment drank more heavily (Krug et al. 2008). It is possible that such negative findings could result because many women receiving treatment or seeking treatment for eating disorders curtail their drinking.

Alcohol and Suicidal Behavior. Although research often has reported on factors affecting rates of suicide among women, only rarely have studies been able to show how individual women's drinking patterns are related to suicidal behavior. An exception was a 20-year follow-up of a large sample of Swedish women hospitalized because of suicidal behavior; those women diagnosed also with alcohol abuse or dependence had a higher risk of later committing suicide (Tidemalm et al. 2008). Most general-population surveys of individual women have shown that suicidal ideation (thinking about committing suicide) was associated with heavier, more frequent, or more hazardous drinking. In the United States, for example, women's suicidal ideation was associated with hazardous drinking patterns in a longitudinal study of women aged 26 to 54 (Wilsnack et al. 2004) and was associated with alcohol dependence in the large National Longitudinal Alcohol Epidemiologic Survey (Grant and Hasin 1999). A large study of active-duty U.S. Air Force personnel also found that women's suicidal ideation was associated with higher levels of alcohol problems, but only among women who were not mothers (Langhinrichsen-Rohling et al. 2011). In Seoul, Korea, women aged 18 to 64 showed a strong association of suicidal ideation with drinking nearly daily (Park et al. 2010). Finally, a French survey of women aged 18 to 30 found that suicidal ideation was more common in heavier drinkers, although the relationship no longer was statistically significant after controlling for effects of depression and other adverse experiences (Legleye et al. 2010).

Alcohol-Related Injuries

Similar to research on women's suicidality, research on women's alcohol-related injuries has given more attention to gender differences in injury rates and how women's injury rates are related to population drinking patterns and less attention to how drinking is related to the risks of injury in individual women. However, studies have reported two consistent findings about how individual drinking patterns are linked to injuries.

First, risks of injury increase among women who have consumed alcohol in the 6 hours before being injured; women's injury risks associated with drinking occur relatively rapidly. This conclusion has been confirmed by a combined analysis of 28 hospital emergency-department studies in 16 countries (Borges et al. 2006). Additional confirmation has come from a large emergency-department survey in Sydney, Australia, where the risk was greatest in women who had consumed more than 90 grams of alcohol in the 6 hours before being injured (Williams et al. 2011).

The other consistent finding is that risks of injury are greatest among women whose drinking patterns are particularly heavy or hazardous. A study of women outpatients at a Veterans Administration hospital found that the likelihood of multiple recent injuries was nearly doubled in the heaviest versus the lightest drinkers (Chavez et al. 2012). A study of women with high-risk drinking patterns at five U.S. colleges found that their risks of recent injury were directly related to their number of days of drinking five or more drinks (Mundt et al. 2009). In addition, large surveys of women aged 45 to 69 in three Eastern European countries found that the percentage of women with injuries was higher in women with high scores on the CAGE[3] screening instrument for problem drinking (Vikhireva et al. 2010).

Intimate Partner Violence

Associations between alcohol use and intimate partner violence (IPV) have been well documented in research in North America. Male-to-female IPV perpetration consistently has been linked to heavy and problem drinking by men (Caetano et al. 2000; Thompson and Kingree 2006). The large-scale NESARC survey found that past-year IPV victimization was more likely in women who have symptoms of alcohol abuse or dependence (La Flair et al. 2012), and meta-analysis of six surveys of adolescents and young adults showed that women's frequency and/or quantity of drinking was positively related to their perpetration of IPV (Rothman et al. 2012). Furthermore, a comparative study of alcohol consumption and IPV in Canada, the United States, and eight countries in Latin America found that in all 10 countries, rates of physical partner aggression were higher among drinkers than nondrinkers (men and women); and among drinkers, rates were higher among persons who reported drinking larger amounts per occasion. Women reported being victims of more severe aggression than men, and men were more likely than women to be drinking at the time of an incident of physical aggres-

[3] The CAGE is a screening instrument (Ewing 1984) consisting of the following four questions: Have you ever felt you should cut down on your drinking? Have people annoyed you by criticizing your drinking? Have you ever felt bad or guilty about your drinking? Eye opener: Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover? Two positive responses are considered a positive test and indicate further assessment is warranted.

sion (Graham et al. 2008). Other multinational studies have shown that odds of IPV were greater where one or both partners had alcohol problems (Abramsky et al. 2011) and that aggression severity was significantly higher if one or both partners had been drinking when the aggression occurred (Graham et al. 2011). However, in all this research, it is unclear to what extent drinking is a cause or an effect of IPV, or both.

Alcohol and Sexual Assault

It has been known for some time that women's drinking is positively associated with their risks of sexual assault, but how and why this association occurs remains unsettled (Abbey et al. 2004). Part of the association results because women often drink with men who drink, and the men's intoxication makes them more likely to be sexually aggressive toward women (Abbey 2011). Other links between women's drinking and sexual assaults are harder to interpret because investigators often lack time-ordered data, they differ in the types of sexual activity they evaluate (ranging from rape to much broader categories of unwanted sexual advances), and most of their studies are limited to college women (as a high-risk group).

Nevertheless, certain patterns have become clear in recent years. First, risks of sexual assault are most clearly higher in women who have established patterns of binge drinking or problem drinking. For example, in a large national survey of college women in 1999, women with alcohol problems were more likely to report experiencing unwanted sexual advances (Pino and Johnson-Johns 2009). At a large New York State university, women who increased their drinking during their first year in college (and who averaged more than four drinks per drinking occasion, with frequent such occasions) had higher odds of sexual victimization (Parks et al. 2008).

Second, women are more likely to experience rape or other severe sexual assault if they become intoxicated, at the time of the assault or as a typical drinking pattern. A large U.S. survey of college women found that the percentage who had been raped was high in women with any recent experience of binge drinking (four or more drinks per occasion) and that more than two-thirds of the women who had been raped reported being intoxicated at the time (Mohler-Kuo et al. 2004). A study of more than 300 young women who had been sexually assaulted since age 14 found that the odds of sexual penetration were greater only among women reporting high levels of intoxication (Testa et al. 2004). An earlier national survey of college women who had experienced sexual victimization found that the severity of the assault was predicted in part by the women's frequency of intoxication (Ullman et al. 1999).

Findings like these have led some investigators to conclude that one reason why drinking may increase women's risks of

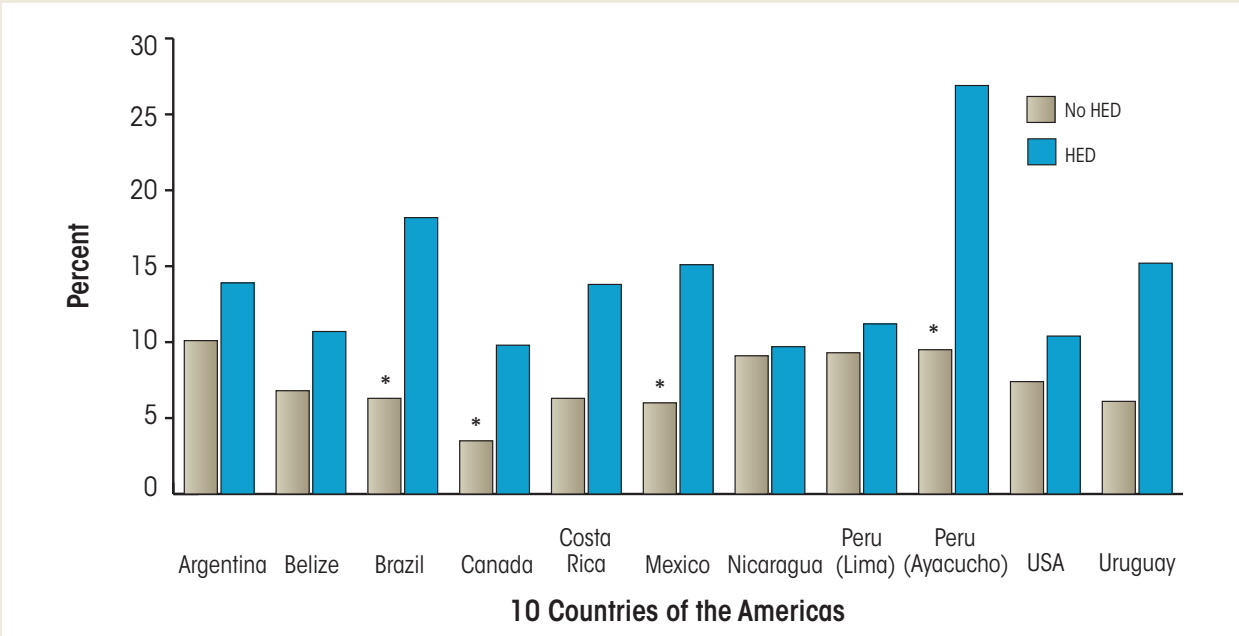

Figure Female intimate-partner violence victimization by women's past-12-month heavy episodic drinking (HED) (10 countries of the Americas).

NOTE: * $p < .05$ for logistic regression, controlling for age.
SOURCE: Graham, K.; Bernards, S.; Munné, M.; and Wilsnack, S.C.; Eds. *Unhappy Hours: Alcohol and Partner Aggression in the Americas.* Washington, DC: Pan American Health Organization, 2008.

sexual assault is that highly intoxicated women may be incapacitated, unable to resist unwanted sexual advances. A national survey of college women found that a past-year history of binge drinking (five or more drinks at a sitting) was specifically associated with experiencing incapacitated rape (McCauley et al. 2009). A study of first-year college students found that reported maximum consumption per occasion during the fall semester was strongly associated with experiencing incapacitated rape (Testa and Hoffman 2012). A number of related studies reviewed by Testa and Livingston (2009) led to the conclusions that in many rapes, especially of college students, women are incapacitated by some form of substance use, and that many rapes associated with alcohol use involve incapacitation.

Conclusions

Because alcohol consumption has become a more normal activity for women, it is important for women to have science-based information to help them decide whether and when to drink, and in what amounts, based on potential risks or benefits of drinking. Such past and current information has had some important limitations. Some of these limitations have been addressed in recent decades. In most recent studies (e.g., Mukamal et al. 2010; Patra et al. 2010), apparent health benefits of moderate drinking now are based on comparisons with lifetime abstainers, excluding potentially sicker ex-drinkers who were part of some earlier comparisons. Also, long-term studies of alcohol consumption in women now are likely to include more detailed measures of baseline drinking (Moore et al. 2005; Wilsnack et al. 2006) than earlier studies used (Stampfer et al. 1988). However, some research findings are still presented in terms of rates of health outcomes in whole *groups* of women (such as for injuries and suicidality; Landberg 2010; Ramstedt 2005), which can be misleading if these results are used to draw conclusions about the effects of drinking on *individuals*. Finally, research on long-term health effects of women's drinking can measure only some of the lifestyle characteristics (such as eating patterns and exercise) that may be associated with how women drink and that may account for some of the apparent effects of drinking (Mukamal et al. 2010; Rimm & Moats 2007).

A major current limitation of information about alcohol effects is that such effects often are reported, in scientific papers but particularly in the news media, as simple associations (this drinking pattern is associated with that health outcome). Less is said about how large the effects are (not very large for some cardiovascular benefits of moderate drinking), and adverse effects often are implied to increase in a linear way with each unit increase in drinking. There is too little attention paid to how the effects of drinking may not be linear (with the exception of research on cardiovascular benefits versus hazards at different levels of drinking). There also is too little attention paid to how drinking may be both a cause and an effect of some adverse health and behavioral outcomes (such as psychiatric disorders and intimate partner violence). Finally, research findings often are presented as if they applied similarly to all women drinkers, without discussing how other conditions and contexts (such as a drinker's other health conditions) might modify how alcohol affects health. (One exception, for example, is the research by Liu et al. [2010] showing that risks of cirrhosis from relatively heavy drinking are greater in women with high body mass indices.) Therefore, what we should strive for is information about health effects of women's drinking that shows not only the effect sizes, but also when and where and among which women the effects are greatest.

Keeping those limitations in mind, the findings summarized here may offer some guidelines for women making personal decisions about drinking in midlife. Light-to-moderate drinking is associated to some extent with reduced risks of some cardiovascular problems, strokes, and weakening of bones. On the other hand, even low levels of alcohol consumption may cause women some increase in risks of breast cancer and liver problems, and heavy drinking also increases risks of hypertension and bone fractures and injuries. Women's heavy drinking patterns and AUDs are associated with increased likelihood of many psychiatric problems, including depression, PTSD, eating disorders, and suicidality. Women's heavy drinking and AUDs also are associated with increased risks of intimate partner violence and sexual assault, although causality in the associations of drinking with psychiatric disorders and with violence remains unclear. On balance, the evidence summarized here suggests that, for those women who choose to drink, moderation in consumption is the safest or least costly strategy to adopt toward alcohol. ■

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