

2017 National Conference on Alcohol and Opioid Use in Women and Girls: Advances in Prevention, Treatment and Recovery
October 26 - 27, 2017
Washington, DC

Executive Summary

On October 26 – 27, 2017 hundreds of researchers, health care providers, health policymakers, and addiction prevention and treatment professionals gathered in Washington, D. C. for the first National Conference on Harmful Alcohol and Opioid Use in Women and Girls. Sponsored by the National Institute on Alcohol Abuse and Alcoholism, the Office of AIDS Research/NIH, the National Institute on Drug Abuse, the Office of Research on Women’s Health/NIH, and the Substance Abuse and Mental Health Administration, the conference reviewed key findings from current research on the causes, consequences, prevention and treatment of harmful alcohol, opioid, and other substance use among women and girls, and best approaches to sustaining recovery. The overarching goal of the conference was to identify important directions for future research on harmful alcohol and opioid use among women and girls, and to provide a platform for the development of a coordinated public-private response to recent alarming trends in harmful substance use among women. Equally important was the opportunity to provide a setting where stakeholders from diverse professional backgrounds could be energized and motivated to start new collaborations and to strengthen existing ones.

The conference opened with a powerful and moving testimonial by a woman in recovery from co-occurring mental and substance use disorders, followed by 25 didactic presentations organized into ten general topic areas:

- Epidemiology of Harmful Alcohol and Opioid Use Among Women and Girls
- Health Impacts of Alcohol and Opioid Use Among Women and Girls
- Specialty Treatment for Women and Girls
- Model Programs for Mothers Living with Harmful Substance Use
- Screening, Brief Intervention, and Referral to Treatment and Beyond
- Prevention and Treatment for Special Populations
- Sustaining Recovery
- Co-Occurring Substance Use and Mental Health Disorders
- Reducing the Stigma of Addiction and Fetal Alcohol Spectrum Disorders
- Future Directions for Research on Harmful Substance Use Among Women and Girls

In addition, federal agency representatives reported on ongoing activities to address harmful substance use among women and girls within their respective organizations.

This report summarizes key information from the presentations and discussions related to each of the topic areas. It is intended to serve as a blueprint for future collaborative activities that will bring Federal, state, and community partners together to develop and implement a coordinated and effective response to one of the nation’s most daunting public health challenges: harmful substance use among women and girls. Several of the key themes that emerged over the course of these highly interactive and informative discussions are highlighted below.

Epidemiology of Gender Differences in Substance Use and Related Problems (References pp. 13 - 16)

There have been significant increases in alcohol and opioid use patterns in the last two decades, including both increases in the prevalence of alcohol use and binge drinking in women, as well as in rates of prescription opioid, heroin and fentanyl use among women.

Alcohol

In both adolescents and adults, descriptive data suggests that the historical gender gap in drinking, binge drinking and alcohol-related problems has narrowed to the point that in adolescents and for some adult indicators, the gap no longer exists at all, leaving the risk virtually the same in males and females. Among adolescents, there has been an overall decline in drinking over recent decades. However, the rate of decline has been greater among adolescent boys than among adolescent girls. Whether different factors now cause binge drinking in adolescent boys and girls, or if the risk factors have also become similar is unknown. In contrast, US adults are in a period of marked increases in drinking, binge drinking and alcohol-related harms, as shown by most surveys and many other health indicators. Due to the increases in women, the historical gender gap in drinking and alcohol problems is also narrowing in adults, as well as adolescents. What is not known is how risk factors for drinking are evolving for women. Exposure to new social environments through entering the workforce may have seemed a reasonable explanation in the 1970s, but is no longer tenable in the 21st century, when the large increases in drinking and drinking problems among adult women occurred. More information is needed about the causes of heavy drinking and AUD among women, and how these differ from men. In addition, most alcohol-related deaths occur among older adults when metabolism of alcohol is slower and medication contraindications predict more harm, so the increases seen in older women are especially concerning. An optimistic part of the current picture is the lack of increases in drinking and binge drinking in US pregnant women, who differ significantly from non-pregnant women of the same age. This important difference in trends suggests that appropriate, consistent public education and health messaging can have a substantial positive effect in reducing alcohol-related harms.

Recommended areas for future research include but are not limited to:

- Studies to determine whether male-female convergence in rates varies in important population groups (e.g., race, socioeconomic status, rural vs. urban), or by clinical characteristics (e.g., depression).
- Research examining whether risk or protective factors for drinking and binge drinking (e.g., face-to-face time with peers, perceived risk) are changing differentially over time for adolescent boys and girls.
- Research examining whether risk factors for adult heavy drinking and AUD are changing differentially in women and men, and if not, if the influence of these factors has changed due to newly emerging risk factors.
- Studies to determine if social policies, the media, or public education efforts influence women and men differently.
- Research examining whether women remain still less likely than men to receive treatment for AUD, and if stigma remains a more potent barrier to treatment for women than men.

Opioids

(References pp. xx)

The pathway to opioid use for women is more likely to be through medical treatment than for men. The main reason for prescribing opioids is to treat pain, and population-based studies suggest women are at increased risk for pain and more sensitive to the aversive aspects of most painful stimuli. When opioids were prescribed during US outpatient care visits between 1993 and 2014, women were more likely to be given prescriptions than men (54% vs 46%). Similarly, a large study of patients with chronic pain who were prescribed opioids showed that women were overrepresented (>63%), and this percentage increased with age (≥ 61 years) to 80%. Women are also more likely than men to be prescribed opioids for chronic conditions, such as headache, that do not have data showing treatment benefit. Furthermore, prescribing opioids with other medications that increase overdose risk is more common in women than men. For example, benzodiazepine co-prescribing, which increased each year from 2002 to 2014 in the USA, was more common for women than men (e.g., 11% vs 7.7% in 2014).

Although there are more prescription opioid-related deaths among men than among women in the USA, the rate of increase in deaths is higher in women than men. There are other concerns about opioid prescribing practices in women. Substance use treatment admissions in the USA between 1992 and 2012 show that the percentage of pregnant women admitted with OUD due to prescription opioids increased from 2% to 28%. This increase raises concerns for maternal and newborn health, including neonatal abstinence syndrome.

Recommended areas for future research include but are not limited to:

- Studies examining gender differences in pain and response to opioid and non-opioid analgesics
- Research on potential gender differences in response to emerging pharmacotherapies for OUD
- Studies to identify effective interventions for co-occurring OUD and mental health disorders

Health Impacts of Alcohol and Opioid Use

(References pp. 17 - 20)

There are significant sex differences in the harmful effects of alcohol and opioids which stem from sex differences in pharmacodynamics, the effects of these substances on pain, reward and stress circuits in the brain, and in the distribution of opioid receptors (μ , κ , δ) in the brain. Each of the neurochemical pathways affected by alcohol and opioids is highly sexually dimorphic, and both the acute and regular, binge and chronic effects of these drugs of use are highly sexually dimorphic. More specific to harmful effects, the well-known “telescoping” effects of opioids and alcohol indicate that women are more sensitive to the rewarding effects of drugs and may also develop tolerance more easily. As a result, rates of regular alcohol and other drug use, dependence, and related harmful health effects increase more rapidly among women than among men who use alcohol and other drugs at comparable levels. Gender differences in the medical consequences of binge and chronic alcohol use in women and girls include higher risk of E2 positive breast cancer (direct association to amount of alcohol intake) among women, as well as higher rates of heart disease, immune and infectious diseases and brain disorders (depression, PTSD, anxiety, dementias) than in men who drink at comparable levels. There are

also important gender differences in the development of alcohol use disorder and comorbidity, and in response to pharmacotherapy.

The harmful medical consequences of opioid abuse in women and girls include higher risk of HCV and HIV, opioid overdose, other immune and infectious diseases, and higher rates of sexual trauma, PTSD and mood disorders. As with regular alcohol use, there are gender differences in opioid use disorder development and comorbidity, and pharmacotherapy response differences. Women with OUD also experience higher rates of distress and craving than men with OUD.

Recommended areas for future research include but are not limited to:

- Preclinical and clinical research on the psychobiological effects of alcohol and opioids to address sex-specific risk of developing disease and addiction.
- Application of precision medicine models to medications development and improving treatment outcome in addiction. A number of pharmacologic targets may be overlooked by not considering the possibility of sex-specific biological pathways.
- Studies to improve screening and assessment of opioid and alcohol use and misuse in women and girls. The most effective approaches will include assessment of risk of harmful mental health and medical effects.
- Research to develop, validate, and disseminate women-specific interventions for harmful substance use, given women's higher vulnerability to the harmful effects of alcohol and opioids.

Specialty Treatment for Women and Girls with Harmful Substance Use

(References pp. 21 - 24)

Women with AUD experience more rapid development of health, mental health and behavioral consequences of alcohol consumption than men, but are less likely to access and engage in traditional alcohol treatment facilities. To improve access and address barriers to care, women's-only treatment programs have been designed to meet needs specific to or more commonly a concern for women. Although it is important to note that women and men appear to have comparable outcomes in mixed-gender alcohol treatment settings, research indicates that women's outcomes improve when they receive care in women-only treatment settings. Specifically, when we compare outcomes for women receiving treatment in women-only vs mixed-gender programs, it appears that women may do better in women-only residential and outpatient settings that offer enriched wrap-around services (e.g., childcare, parenting training, assertiveness training, family planning). Across studies, patients in women-only treatment averaged significantly more days in care, were more than twice as likely to complete treatment, and were more than two times less likely to report substance abuse at follow-up compared with women in mixed-gender treatment. Research suggests that women-only treatment programs are particularly more effective than mixed-gender programs for engaging subgroups of women with more complex characteristics and problems, including women who are pregnant, trauma-affected, or experiencing comorbid psychiatric disorders.

Recommended areas for future research emphasis include but are not limited to:

- Identifying the most effective strategies for improving treatment engagement for women with a substance use disorder. Should engagement strategies differ as a function of specific patient characteristics such as comorbid psychiatric symptoms, childcare responsibilities, trauma history, or sexual orientation?
- Determine how treatment services should be designed to address differing needs across the lifespan. What long-term supportive services for women and girls are needed to address quality of life and psychological distress during extended recovery?
- Examine whether we can improve treatment outcomes by providing targeted services for specific concerns with high prevalence among substance abusing women (e.g., intimate partner violence, comorbid psychiatric disorders).
- Current women-tailored services are having their primary impact on improved psychosocial well-being. Identify best approaches to achieving a greater impact directly on alcohol and other drug use.

Maternal Substance Use

(References pp. 25 - 32)

Prenatal exposure to alcohol and other substances is common. The estimated rate of prenatal alcohol use is about 15%, with past month use about 12.6%. Marijuana is the most commonly used illicit drug during pregnancy, with as many as 14.6% of pregnant adolescents in California reporting past month use. Opioid use among pregnant women has been described to be at epidemic proportions, accompanied by a four-fold increase in neonatal abstinence syndrome (NAS) between 2000 and 2014. The consequences of these exposures are potentially significant. For example, a recent multi-site study using active case ascertainment methods estimated the prevalence of fetal alcohol spectrum disorders among first graders ranged from 1.1 to 5.0%. This is concerning because these disorders are associated with life-long disabilities. While the adverse effects of prenatal marijuana use are unclear, estimates of its use are increasing as states legalize its recreational and medical use. With regards to prenatal opioid exposure, infants are typically born smaller and may have neonatal opioid withdrawal syndrome (NOWS). Furthermore, mothers of infants with long-term exposure to prenatal opioids but who did not develop NOWS have been found to be at similar, elevated risk for mental health conditions as mother of infants with NOWS.

There is a paucity of research on concurrent use of opioids and alcohol during pregnancy. Two recent studies reported a high prevalence of prenatal alcohol use among pregnant women with substance/opioid use disorder. These findings are underscored by NSDUH data from 2005 to 2014 showing that among women who were pregnant and reported non-medical opioid use, almost 50% reported alcohol use and almost 33% reported binge drinking in the past month. Since alcohol and other substance use are not typically disclosed spontaneously by patients, the American College of Obstetricians and Gynecologists [ACOG] recommends early universal screening of pregnant women for alcohol and other substance use. However, a recent multi-site study involving a head to head comparison of 5 self-report screening tools for prenatal substance use found that none of the screening instruments had satisfactory performance with regards to the identification of current alcohol and substance use, and of substance use disorders. Furthermore, there are few treatment resources to help women and their children affected by alcohol, opioid, and other substance use problems.

Recommended areas for future research emphasis include but are not limited to:

- Research to develop and implement effective screening instruments for polysubstance use among pregnant women
- Research to identify optimal approaches to the treatment of pregnant and/or parenting women, including critical wrap-around services.
- Determine best approaches to strengthening families affected by maternal substance use, including research on services to improve and maintain the health of families over the long-term.
- Elucidate the impact of stigma and punitive laws and policies on access to services for pregnant and/or parenting women. Identify best approaches to eliminating stigma and resulting discrimination.

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

(References pp. 36 - 40)

In recent years, girls' rates of AOD use have caught up with and in many cases surpassed those of boys, particularly with regard to alcohol, and drugs other than cannabis. Additionally, girls are more likely to report co-occurring mood symptoms, suicidal ideation, anxiety and other mental health problems than boys. Similarly, girls with AOD problems are more likely to have medical comorbidities such as gastrointestinal problems, migraine, and sexually transmitted infections, as well as, of course, unplanned pregnancies. While AOD use and other behavioral health problems are among the most common pediatric health conditions in the U.S., far fewer than half the children and adolescents in need of care ever receive services, particularly specialty substance abuse treatment, and certain population groups, including Latinos and African Americans, are especially unlikely to receive care. Many families never seek care, and many of those that do have difficulty obtaining it because of issues of system capacity and insurance coverage. Primary care visits thus provide critical opportunities for detection of and early intervention for AOD problems.

Primary care and other health care settings, such as OB/Gyn, may be particularly good contexts for engaging girls with AOD use problems, because they tend to use health care services more often than boys, especially as they move through adolescence and into young adulthood. Studies have found that PCPs, when well-trained, may be especially effective agents to provide screening, brief intervention, and referral to treatment. Adolescents and their parents have been found to be receptive to AOD screening and intervention by pediatricians, and to have positive perceptions of care when their pediatrician discusses "sensitive" topics, including substance use, with them. While the evidence base for SBIRT for adolescents lags behind the adult SBIRT literature, recent studies have produced promising findings. A number of pilot studies, quasi-experimental studies and randomized clinical trials have found positive effects of screening and brief interventions, including: reductions in alcohol and cannabis use initiation among non-users; drinking and cannabis use cessation among current users; reductions in binge drinking; reductions in drinking and driving; reductions in alcohol-related injuries; reductions in victimization and perpetration of violence; reductions in dating violence; and improvement in mood symptoms. There have also been several excellent systematic reviews and meta-analyses suggesting that brief interventions for adolescents can produce moderate but significant improvements in alcohol consumption and related problems across settings and populations, with effects that persist for a year or longer. Recent studies have also found that SBIRT can improve specialty behavioral health treatment initiation, while also reducing overall healthcare services utilization.

- Research focused explicitly on SBIRT outcomes among girls and young adult women. Very few published studies have focused primarily on SBIRT for adolescent girls, and in many studies, sample sizes have limited robust gender analyses. SBIRT does seem promising for outcomes which are especially salient to girls and young women, such as dating violence, sexual victimization, eating disorders, sexually transmitted infections and unplanned pregnancy.
- Research on screening approaches and interventions which encompass different but closely related problems of co-occurring AOD use, mood and anxiety disorders, and other emotional distress.
- Studies informed by an expanded conception of SBIRT beyond 1 or 2 sessions of M.I.-based brief advice or brief intervention. Studies examining “expanded” versions of SBIRT are needed because 1-2 sessions are frequently not enough, even for less severe AOD use among adolescents. Multi-session models and approaches using “booster” sessions over time, whether in-person or technology-enabled, should be examined.
- Research into primary care-based, family-inclusive interventions. Most children and adolescents live in the context of a family, and families are crucial to setting the trajectory of children’s and adolescents’ health and well-being.
- Research to develop and test interventions to concurrently address both AOD use and the frequently underlying causes, including adverse childhood experiences, trauma and toxic stress exposure, to which girls are particularly vulnerable.

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

(References pp. 46 - 50)

Expanding the role of general health care in addressing women’s alcohol problems can potentially improve prevention, screening and treatment. The literature to date is optimistic that primary care and other health care settings can accomplish this. Women with alcohol problems have high rates of medical and mental health problems (higher than for men). However, there are large differences among women associated with age, as well as with other social and medical characteristics. Family members of women with alcohol use disorders also have high rates of medical and mental health problems. The evidence suggests that the spectrum of alcohol problems can be successfully addressed in health care through screening and interventions in primary care or with referral to specialty treatment. Much is known about the life course and other demographic and clinical needs of women. Innovative interventions are being developed in primary care, but they have not been widely implemented. Innovative use of health information technology, including the electronic health record, can facilitate research based on large samples, and with the potential to reach many more women. This area of research calls for much more study.

Recommended areas for future research emphasis include but are not limited to:

- Women-focused SBIRT implementation research in primary care clinics. Women are less likely to be identified by physicians and are under-represented groups in most relevant studies to date.

- Efficacy and effectiveness research to develop and evaluate services that are more intensive than brief interventions for use in primary care and other health departments. Such research should be followed by implementation studies.
- Research on co-occurring medical and psychiatric problems among women with alcohol and opioid misuse/unhealthy use vs. more severe use and substance use disorders. This research is important for developing targeted interventions and prevention.
- Epidemiologic studies to elucidate differences in types of substance-related problems and problem trajectory by life course, by co-occurring medical and mental health conditions, and by other characteristics. Research is required that not only examines women as a group, but also the differences among them. Innovative ways of increasing sample sizes through other approaches are also required, such as using large EHR systems.
- Research is needed on how to address health disparities in health care among women with alcohol and opioid-related problems. Development of prevention and treatments specifically for women, and also for women by age and race/ethnicity/cultural backgrounds, is needed. Some race/ethnicity/cultural groups are particularly under-represented in research. Research on Health IT options for women (who may have more barriers to treatment access, such as those with young children) may facilitate addressing disparities.

Addressing Alcohol-related Health Disparities

Women At-risk and Living with HIV/AIDS

(References pp. 79 - 87)

Alcohol misuse is associated with decreased HIV testing and increased HIV transmission risk behaviors among women. It is also an important, but modifiable barrier to optimal engagement in the HIV Care Continuum. Alcohol misuse disrupts both antiretroviral adherence and retention in HIV care, both of which are associated with lower viral suppression, and thus increases HIV transmission risk and poorer health outcomes. Further compounding its impact on engagement in the HIV care continuum, alcohol misuse is frequently co-morbid with depression and other mental health disorders, including anxiety and trauma, all of which can increase the likelihood of HIV sex and drug risk behaviors and complicate the management of both HIV and alcohol misuse. It also further complicates barriers to prenatal care among pregnant women at-risk and living with HIV/AIDS. Given the adverse effects of alcohol misuse on HIV outcomes among women, it is critical to implement effective alcohol reduction interventions. Brief alcohol intervention can reduce alcohol use among women with HIV, but may be less effective among women with heavier alcohol use, polysubstance use, and or/other mental health comorbidity, including depression and trauma. There are effective evidence-based interventions available but the essential questions have not been answered.

Recommended areas for future research emphasis include but are not limited to:

- Research to determine which interventions work for which types of women living with HIV/AIDS across the life span. For example, which interventions will work best for women living with HIV and a particular substance use/mental health constellation. Under what conditions will these interventions be most effective? Examples:
 - How do comorbid alcohol and mental health disorders affect women's engagement in the HIV prevention and care continuum?

- How does the co-occurrence of IPV, alcohol and HIV (SAVA) impact 1) HIV care continuum outcomes among women with HIV and 2) prenatal care for pregnant women with HIV?
- Younger women, whether at risk or HIV infected, tend to drink in a binge pattern and would have more recently experienced childhood sexual trauma, both of which are associated with HIV sexual risk behaviors. This pattern differs from older women who drink in a more predictable daily pattern and potential posttraumatic stress disorder is often likely to have settled into a more chronic depressive disorder. Interventions for these two groups would likely vary as a function of disorder and lifespan, though this is not yet established.
- African American women continue to be disproportionately affected by HIV/AIDS, suggesting that our interventions may not be sufficiently tailored to address some of their particular stressors or barriers.
- Implementation research to identify the most suitable approaches, settings, and agents to screen, engage, and maintain women in prevention and intervention in real world settings.
- Studies examining whether and how alcohol use may affect women's use of and adherence to HIV Pre-Exposure Prophylaxis (PrEP).
- Research to determine the level of alcohol use that increases complications from non-communicable diseases (liver disease, cardiovascular disease, malignancy, frailty) among women living with HIV.

American Indian and Alaska Native Women

(References pp. 56 - 61)

There are limited data on the rates of opioid use among AIAN women, but available data suggest rates are higher among AIAN women than non-AIAN women. The National Indian Health Board reported that the opioid epidemic “poses one of the most significant public health threats in recent history and is particularly virulent in AIAN communities.” AI women in rural communities are experiencing a higher risk of death due to opioids and other drugs. Rates of maternal opioid use and neo-natal abstinence syndrome (NAS) are higher in AIAN communities than in non-AIAN communities and are increasing. For example, the incidence opioid abuse among pregnant Canadian first nations women increased from 8.4% in 2009 to 17.2% by 2010.

Rates of alcohol use and disorder are higher among some groups of AIAN women compared to the general population; at the same time, rates of abstinence are substantial among AIAN women. An epidemiological survey of 3 community-based reservation samples found significantly higher lifetime alcohol dependence rates among Northern Plains tribal women than among women in the U.S. (20.5% vs. 8.2%), but no difference in the rates between Southwest tribal women and women in the U.S. (8.7% vs. 8.2%). Although there is evidence that AI women are more likely than women in the general U.S. population to be lifetime abstainers from alcohol, when AIAN women drink they are more likely to engage in risky drinking, having a higher prevalence of weekly heavy drinking and a higher prevalence of binge drinking. In tribal communities, alcohol and drug use disproportionately contribute to and, in turn, are influenced

by racism, mental health problems, early trauma and childhood abuse, domestic violence, cultural displacement, unemployment, and poverty. It is not surprising, then, that alcohol use has played an important role in rising mortality rates among AIAN women over recent decades. Access to culturally-grounded treatment for alcohol and substance disorders is limited, but when available, such services are promising and may be preferred to non-culturally grounded services.

It is especially concerning that some AI women are at greater risk for alcohol-exposed pregnancy (AEP) than women in the general U.S. population because they more likely to drink prenatally and to drink at risky levels, while being less likely to use birth control. AEP risk may be especially pronounced among AI teen girls. For example, a recent study found that the AI teen birth rate for the Great Plains area was 123.2 per 1,000 live births, or 60.5 per 1,000 teens aged 15-17 and 235.1 per 1,000 teens aged 18-19. Among this same age group, binge drinking was also an important issue. Nearly 40% of AI youth aged 12-17 reported current alcohol use; 24% reported binge drinking; and 16% reported symptoms consistent with substance dependence or abuse. AI women who drink during pregnancy experience a multitude of other problems and stressors. For example, pregnant women from Northern Plains who drank were more likely than abstinent women to be single; have limited education; lack transportation; smoke cigarettes; use illicit drugs; and report relationship breakups and abuse. Rates of Fetal Alcohol Spectrum Disorder (FASD) are estimated to be higher among AIAN populations than the general population, but current data are scarce and older data are limited. In Alaska, rates of FASD are more than 10 times higher among ANs than non-ANs (3.0 v. 0.2 cases per 1,000 live births).

These serious disparities notwithstanding, there is a growing body of evidence that AEP risk can be reduced among AIAN women. For example, one recent study evaluated a case management system to prevent FASD in AI communities through motivational interviewing and social support for heavily drinking pregnant women, finding that 76% of the women involved had normal deliveries and did not appear to have a child affected by FASD. In addition, when the Centers for Disease Control and Prevention Project CHOICES curriculum was culturally adapted to be appropriate for Oglala Sioux women at-risk for an AEP, AEP risk was reduced at 3- and 6-month follow-ups.

Recommended areas for future research emphasis include but are not limited to:

- Current epidemiology of alcohol and opioid use, patterns of use, and rates of disorder in diverse AIAN communities, including urban and reservation-based.
- The development and testing of gender- and culturally-based models of prevention and intervention for alcohol and opioid use and disorders in diverse AIAN communities.

- The development and testing of culturally-based models of prevention and intervention for AIAN women at risk of or using alcohol or opioids during pregnancy.
- Ongoing research about risk factors for and problems co-occurring with comorbid alcohol and opioid use disorder and best culturally-based models to address them.

Future Directions for Research on Harmful Substance Use Among Women and Girls

There have been significant and alarming increases in alcohol and opioid use patterns among some groups of women in the past 2 decades, including increases in the prevalence of alcohol use and particularly binge drinking among women, as well as in rates of prescription opioid, heroin and fentanyl use and related morbidity and mortality among women. These are universal phenomena affecting women of all cultures and economic backgrounds. They are also transgenerational phenomena influenced by complex historical, cultural, and socioeconomic factors. Trauma (physical, emotional, psychological) and violence are a large part of the problem of substance misuse and substance-exposed pregnancies that cannot be ignored, and comorbid psychological distress must be addressed. Given the complexity of the environment in which women and girls engage in harmful alcohol, opiate use, and other substance use, preventing and reducing substance use disorders among women will require the commitment of a community of partners (e.g., parents, peers, health care providers, policymakers, media) willing to plan and implement multi-level solutions.

At the individual and program level, the evidence is clear that screening, assessment, and treatment work. At the community and societal level, the time is now for government and community partners to be willing to work together “over the long haul” to prevent and effectively treat alcohol, opiate, and other substance use disorders among women, and to prevent substance-exposed pregnancies. The problem of harmful substance use among women and substance-exposed pregnancies has a long and complicated history that involves every domain of community life, from law and social policy (e.g., enforcement of underage drinking laws; high density of alcohol and drug outlets in impoverished urban communities), to commerce and marketing (e.g., alcohol advertising targeting an increasingly young and female demographic; high volume packaging of alcohol products, such as 40 oz. bottles of beer), to health behaviors and services (e.g., interaction of environmental and intrapsychic factors in health decision-making; paucity of integrated primary care, mental health, and substance abuse treatment services). Solving the problem will require a long-term commitment from individuals and organizations in all of these sectors to conceptualize and implement a cohesive community framework within which they may collaborate to develop and implement sustainable, multi-level solutions.

Epidemiology of gender differences in alcohol problems: differing trends in teens and adults

Deborah Hasin, PhD

What we know

Adolescents. Studies show that rates of adolescent drinking and binge drinking have *decreased* considerably, since the mid-1970s, coinciding with the movement of states to a uniform minimum legal drinking age of 21. These rates decreased considerably more in boys than in girls, resulting in a historic near-convergence of male-female rates by 2016. These trends are mirrored in rates of alcohol-related emergency room visits, which also decreased more in adolescent boys than in girls. The differential time trends in boys and girls have resulted in virtually the same risk for drinking and binge drinking in girls as in boys.

Adults: survey results. In contrast to adolescents, several national surveys of adults show *increasing* rates of drinking and binge drinking since 2000, also found in a meta-analysis. The meta-analysis further suggested that rates of drinking and binge drinking increased significantly in adult women but not men. In studies of alcohol use disorders (AUD), one national survey showed no change over time, but two others showed that rates of AUD increased in both women and men; the larger of these found an increase in the prevalence of AUD in women that was more than twice that of men. A different study of older US adults also found increases over time in binge drinking and AUD that were greater in women than men. Finally, a series of national surveys on health and nutrition showed increases in alcoholic liver disease, again with greater increases found in women than men.

Adults: other national indicators. Other indicators of alcohol problems also show increasing US rates since 2000, with greater increases in women than men. This includes rates of alcohol-related diagnoses in emergency department visits and inpatient hospitalizations; and rates of age-adjusted alcohol-related liver cirrhosis mortality. These studies all show converging rates in men and women due to greater increases in women than in men. Another important area of alcohol-related harm is driving while intoxicated (DWI; BAC \geq 0.08), formerly much more common in men than in women. Since 1996, national roadside surveys of drivers show sharp decreases in rates of DWI, potentially reflecting successful public health messaging and legal enforcement efforts. However, men decreased at a much greater rate than women, so that by 2014-2015, male-female rates of DWI had converged to the point of being nearly equal.

Drinking during pregnancy. Considerable public health messaging has focused on reducing maternal drinking during pregnancy. In US mothers with live-born hospital deliveries, rates of alcohol-related diagnoses were stable across a period when opioid- and cannabis-related diagnoses were increasing. In addition, among pregnant women entering substance abuse treatment, rates of those with alcohol problems declined over time while rates of those with other drug problems increased during the same time period. In national survey data on adults ages 21-44, men, pregnant and non-pregnant women were analyzed separately. Across time since 2004, binge drinking increased significantly in non-pregnant women, was unchanged in men, and decreased significantly in pregnant women. This suggests the success of public health messaging about drinking during pregnancy. However, about 10% of the pregnant women surveyed

acknowledged drinking in the prior 30 days, and 5% acknowledged binge drinking, indicating that drinking during pregnancy remains a public health issue.

Gender differences in correlates of adult AUD. A national study shows that women with AUD are more likely than men to have experienced early parental loss and a family history of alcohol and depressive disorders. They are more likely than men to be unemployed, to have had a spouse with alcohol disorders, to have mood, anxiety and other substance disorders, and to use alcohol or drugs to relieve mood or anxiety symptoms. Treatment for AUD is generally underutilized, but even more so in women. Women are more likely than men to endorse stigma as a reason for not seeking help.

Summary

In both adolescents and adults, descriptive data suggests that the historical gender gap in drinking, binge drinking and alcohol-related problems has narrowed to the point that in adolescents and for some adult indicators, the gap no longer exists at all, leaving the risk virtually the same in males and females. Among adolescents, the overall declines in drinking are welcome from a public health perspective. However, whether different factors now cause binge drinking in adolescent boys and girls, or if the risk factors have also become similar is unknown. In contrast, US adults are in a period of marked increases in drinking, binge drinking and alcohol-related harms, as shown by most surveys and many other health indicators. Due to the increases in women, the historical gender gap in drinking and alcohol problems is also narrowing in adults as well as adolescents. What is not known is how risk factors for drinking are evolving for women. Exposure to new social environments through entering the workforce may have seemed a reasonable explanation in the 1970s, but is no longer tenable in the 21st century, when the large increases in drinking and drinking problems among adult women occurred. More information is needed about the causes of heavy drinking and AUD among women, and how these differ from men. In addition, most alcohol-related deaths occur among older adults when metabolization of alcohol is slower and medication contraindications predict more harm, so the increases seen in older women are especially concerning. An optimistic part of the current picture is the lack of increases in drinking and binge drinking in US pregnant women, who differ significantly from non-pregnant women of the same age. This important difference in trends suggests that appropriate, consistent public education and health messaging can have a substantial positive effect in reducing alcohol-related harms.

Future Areas of Research: What we do not know

- Studies are needed on whether male-female convergence in rates varies in important population groups (e.g., race, socioeconomic status, rural vs. urban), or by clinical characteristics (e.g., depression).
- As launching into adult social roles has become delayed in recent years, trends in underage adult drinkers age 18-20 are increasingly more like adolescents than other adults. However, studies of adults usually combine those age 18-20 with other adults, which can mask effects in this age group as well as in adults as a whole. Research is needed on gender differences in trends, protective factors and risk factors that differentiate those age 18-20 from other adults.
- Studies are needed to determine if gender convergence is occurring across birth cohorts, or if gender convergence has occurred mainly in specific birth cohorts. If the latter, then

studies are needed of factors that specifically influenced the women in these cohorts, and of their life course drinking trajectories.

- Research is needed to determine if risk or protective factors for drinking and binge drinking (e.g., face-to-face time with peers, perceived risk) are changing differentially over time for adolescent boys and girls.
- Research is needed to determine if risk factors for adult heavy drinking and AUD are changing differentially in women and men, and if not, if the influence of these factors has changed due to newly emerging risk factors.
- Studies are needed on how patterns of co-use of alcohol with other substances (e.g., opioids, cannabis) differ by gender in adolescents or adults, and whether such patterns are changing over time.
- Research is needed to determine if social policies, the media, or public education efforts influence women and men differently.
- Studies are needed to determine if women remain still less likely than men to receive treatment for AUD, and if stigma remains a more potent barrier to treatment for women than men.

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HARMFUL EFFECTS OF ALCOHOL AND OPIOIDS AMONG WOMEN AND GIRLS: THE NEXT STEPS

Rajita Sinha, PhD

What We Know

There are significant rises in alcohol and opioid use patterns in the last 2 decades, both with increases in prevalence of alcohol use and particularly binge drinking in women as well as in rates of prescription opioid, heroin and fentanyl use among women. There are also significant sex differences in the harmful effects of alcohol and opioids which stem from sex differences in opioid receptor (μ , κ , δ) distribution in the brain, differences in pharmacology and also their effects on pain, reward and stress circuits in the brain. Although there is no specific alcohol receptor, alcohol is highly lipophilic, entering all types of cells easily and has its effects via Gamma-Aminobutyric Acid (GABA), benzodiazepine receptor complex, opioids, neuroactive steroids and indirectly on dopamine but also acts directly on several stress neurochemicals including the corticotrophin releasing factor (CRF), glucocorticoids, norepinephrine and others. Opioids also have powerful effects on stress pathways in addition to direct effects on peripheral and central pain pathways. Each of these neurochemical pathways are highly sexually dimorphic and both acute and regular, binge and chronic effects of these drugs of use are highly sexually dimorphic. More specific to harmful effects, the well-known “telescoping” effects of opioids and alcohol indicate that women are more sensitive to the rewarding effects of drugs and may also develop tolerance more easily thereby resulting in increasing their drug use at more rapid rates than men, and developing dependence more quickly than men and also the harmful health effects more quickly than men.

THE HARMFUL EFFECTS of alcohol and opioids in women and differences from men may be summarized well by Agabio and colleagues (2016). There are greater medical consequences of binge and chronic alcohol use in women and girls, including higher risk of E2 positive breast cancer (direct association to amount of alcohol intake), heart disease, immune and infectious diseases and brain disorders (depression, PTSD, anxiety, dementias), alcohol use disorder development and comorbidity and pharmacotherapy response differences. Harmful, medical consequences of opioid abuse in women and girls include higher risk of HCV and HIV, opioid overdose, other immune and infectious diseases and higher rates of sexual trauma, PTSD and mood disorders; opioid use disorder development and comorbidity and pharmacotherapy response differences; higher rates of distress and opioids craving in women than men.

WHY ARE EFFECTS DIFFERENT IN MEN AND WOMEN? Why does substance use and abuse have telescoping and other harmful effects in women and girls. We do not have definitive answers to these questions but there are several clues that point towards the underlying differences in men and women. First, there are clear sex differences in brain anatomy, chemistry and function. Second, pharmacokinetics and pharmacodynamics of alcohol and opioids are each known to be different in men and women, which with greater reinforcing and harmful effects at lower doses of intake and with shorter intake histories for adverse medical consequences. Third, menstrual cycle effects and steroid hormone (sex steroids and stress steroids) directly affect and modulate limbic striatal circuits and prefrontal effects, facilitating adaptations in these circuits but also in autonomic physiology that modulates health effects.

Fourth, Alcohol and opioids each directly activate the hypothalamic-pituitary-adrenal-axis (HPA axis), and regular, binge and chronic use alters stress hormones of cortisol and adrenocorticotrophic hormone (ACTH) in a sex -specific manner with adaptations and plasticity that has an effect on drug motivation, downstream physiology and health effects in each case, which in turn may increase higher risk of harm in girls and women. For example, opioid misuse leads to greater neuroendocrine tolerance in girls and women, that in turn, decreases analgesic properties of opioids and increases pain sensitivity and chronic pain symptoms in women and girls. Another example is of alcohol related widespread alterations in estrogen receptor physiology and function with binge and heavy alcohol use that affects sensitivity and risk of estrogen positive breast cancer. However, there has not been adequate research in this area. Finally, there are also significant sex-specific effects of chronic opioid and alcohol effects on autonomic physiology, catecholamines and recent data on opioid and alcohol-related effects on immune function that are likely modulated by sex steroids, but there is not adequate basic and human research in this area. Furthermore, opioid and alcohol effects on the stress pathways (HPA axis and autonomic) may also have indirect immune effects affecting peripheral organ physiology differently in men and women, with sex specific inflammatory responses to drugs and to traumas, that are known to be highly sex specific. Again, research is severely lacking in these areas, especially with regard to both acute but chronic adaptations in these pathways as a function of chronic drug use and repeated adversity and trauma effects, both of which impact these peripheral and central physiology differently for men and women.

HOW ARE THESE DIFFERENTIAL EFFECTS RELEVANT: While other sections directly address sex-specific prevention and non-pharmacologic, behavioral treatment effects, it is important to note that there is some evidence of sex differences in efficacy of pharmacologic treatment responses in alcohol use disorder (AUD) as well as in opioid use disorder (OUD). For example, Naltrexone's efficacy in AUD is significantly better for men than women (O'Malley, Sinha et al., 2007; Garbutt et al., 2005). There is very little data of direct comparison of efficacy across men and women for OUD medications, but sex differences in blood levels of a number of commonly used opioids such as morphine, oxycodone and others have been reported . This suggests the need for careful research to assess agonist medication efficacy in men and women separately.

Future Areas of Research: What we do not know

While the neurobiology of alcohol and opioids suggests addiction pathophysiology in stress, reward and immune pathways is sex-specific, there are significant major gaps in basic and clinical research on sex differences in drug effects, chronic drug effects, binge-intoxication, withdrawal, tolerance effects of substances and harmful effects on end-organ systems. Such research is significant, because so far, medications and treatment development in alcohol and opioid use disorder has not been sex-specific, despite the fact that addiction relapse and treatment failure rates are high and there is great need to apply precision medicine models to medications development and improving treatment outcome in addiction. In particular, a number of pharmacologic targets may be overlooked by not considering the possibility of sex-specific biological pathways. Finally, screening and assessment of opioids and alcohol use and misuse in women and girls should include assessment of risk of harmful effects, and also the need for development and validation of specific interventions for only women, given their higher vulnerability for harmful effects of these two substances. Some behavioral treatments have received focus in this area, but research on psychobiological effects of alcohol and opioids to

address sex-specific risk of harmful effects on disease risk but also on addiction risk are largely lacking and need further attention.

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WOMEN'S ALCOHOL AND DRUG TREATMENT ENGAGEMENT & OUTCOMES: EVIDENCE AND IMPLICATIONS

Mary E McCaul, Ph.D.

What we know

Only a small percentage of persons with alcohol misuse or alcohol use disorder (AUD) ever receive treatment in a formal, specialized alcohol treatment facility (Cohen et al, 2007; Lipari et al, 2016). Gender-specific results from the 2015 National Survey on Drug Use and Health (NSDUH) suggested that among persons with AUD in the past year, only 7.4% of men and 5.4% of women received treatment (SAMHSA, 2015). Thus, women with alcohol disorders (singular?) appear to be under-represented in specialty alcohol and drug treatment facilities, despite having a shorter interval between drinking initiation and treatment entry (Alvanzo et al, 2014). In part, this may reflect that women are more likely to seek care in non-substance abuse settings, particularly primary care and mental health settings, where their drinking problems may not be recognized (Brienza and Stein, 2002). Further, compared with men, women report less social support for treatment engagement (Bendtsen et al. 2002; Grella and Joshi, 1999) and greater barriers to treatment access, including pregnancy, childcare responsibilities, threat to child custody, trauma (e.g., childhood and adult sexual and physical abuse), social stigma, and lack of economic resources (e.g., unemployment and lack of insurance)(Greenfield et al, 2010; SAMHSA, 2009).

To improve access and address barriers to care, women's-only treatment programs have been designed to meet needs specific to or more commonly a concern for women. Currently, 46% of addiction treatment facilities provide specialized services for women (SAMHSA, 2015). Specific program components that women identify as helpful include: women's only groups, childcare services, and individual counseling (Nelson-Zlupko et al, 1996). Research suggests that women-only treatment programs are more effective for engaging subgroups of women with more complex characteristics and problems than mixed-gender programs. Specialized women's services have shown to be particularly effective for women who are pregnant, trauma-affected or experiencing comorbid psychiatric disorders (SAMSHA, 2009).

Importantly, research indicates that women and men have comparable outcomes in mixed-gender addiction treatment programs. Gender is generally not a significant predictor of treatment retention, completion, or post-treatment outcomes. But when we compare outcomes for women receiving treatment in women-only vs mixed-gender programs, it appears that women may do better in women-only residential and outpatient settings that offer enriched wrap-around services (e.g., childcare, parenting training, assertiveness training, family planning). Across studies, patients in women-only treatment averaged significantly more days in care, were more than twice as likely to complete treatment, and were more than two times less likely to report substance abuse at follow-up compared with women in mixed-gender treatment (Greenfield et al, 2008; Grella, 2009, Prendergast et al, 2011). In a meta-analysis (Orwin et al, 2001), enhanced, wrap-around women's services were associated with an overall improvement in outcomes, with strongest effects seen for pregnancy outcomes, psychological well-being, and HIV risk reduction. Moderate improvements were observed in psychiatric

symptoms, and small effect sizes were reported for alcohol and drug use. Thus, it may be that the greatest benefits of women's-specific treatment occur in areas beyond substance use per se, including psychosocial well-being, psychiatric health, pregnancy outcomes, and health improvement. The importance of these enhanced long-term improvements associated with women's-specific services is highlighted by a recent paper by Kelly and colleagues (2018). Specifically, the National Recovery Survey suggests that during the first 5 years of recovery, women report lower quality of life and self-esteem and greater psychological distress compared with men. This is consistent with the earlier findings that women who misuse alcohol have poorer quality of life, particularly higher rates of depression and greater sleep disturbance, compared with men (Hasin et al, 2018; Peters et al, 2003), and suggests that women may face greater long-term challenges to recovery than men.

Summary

Women with AUD experience more rapid development of health, mental health and behavioral consequences of alcohol consumption than men, but are less likely to access and engage in traditional alcohol treatment facilities. Although women and men appear to have comparable outcomes in mixed-gender alcohol treatment settings, research indicates that women's outcomes improve when they receive care in women-only treatment settings. The greatest benefits of women-tailored services appear in long-term psychosocial and psychiatric well-being – key areas of improvement to enhance achievement of long-term recovery.

Future Areas of Research: What we do not know

- What are the most effective strategies for improving treatment engagement for women with a substance use disorder? Should engagement strategies differ as a function of specific patient characteristics such as comorbid psychiatric symptoms, childcare responsibilities, trauma history, or sexual orientation?
- How should treatment services be designed to address differing needs across the lifespan?
- Can we improve treatment outcomes by providing targeted services for specific concerns with high prevalence among substance abusing women (e.g., intimate partner violence, comorbid psychiatric disorders)?
- Is there a “dose-effect” for the quantity or types of women-specific services that are provided? For example, are there differential effects of integrating a women's only group into a mixed-gender program (currently the most common pattern of integrating women's services) versus providing all services in a women's only program?
- Current women-tailored services are having their primary impact on improved psychosocial well-being. How can we achieve a greater impact directly on alcohol and other drug use?
- What long-term supportive services for women are needed to address quality of life and psychological distress during extended recovery?

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Opioid and Alcohol Use among Women: A Focus on Pregnancy

Hendree Jones, PhD

What we know

The prevalence of opioid use disorder (OUD) and opioid-related overdose deaths have harmed women.¹⁻³ (e.g., 100,000 women have died from opioid overdoses from 2000 to 2015⁴) and brought prenatal opioid exposure into the forefront⁵. While the USA focuses on the opioid crisis, the quiet rise of women's alcohol use and increasing prevalence of alcohol use disorder,⁶ alcohol-induced deaths (a 75% increase in alcohol-induced deaths from 2000 to 2015) and alcohol exposed pregnancies (e.g., 2006 to 2010 1 in 13 pregnant women and in 2011 to 2013 rates were 1 in 10 pregnant women) has gone less noticed.⁷ Given that 40 years of prenatal alcohol exposure literature reports physical and behavioral alternations in children,⁸ alcohol use during pregnancy must be included in the focus within the opioid epidemic.

Among women who use opioids in their childbearing years, there is concern that prenatal opioid exposure will result in a baby showing signs and symptoms of opioid withdrawal shortly after birth (e.g., over 50% of in utero opioid-exposed newborns show signs/symptoms of withdrawal called Neonatal Opioid Withdrawal (NOWS) or neonatal abstinence syndrome (NAS)).⁵ Infants with NAS may show irritability, dysregulated sleep-awake patterns, and autonomic signs of stress can affect and influence maternal responses to the newborn's cues and early dyad bonding.⁹ Further, maternal mood disorders, extent of active substance use and adverse childhood experiences can also affect the mother's emotional and physical availability to help regulate and organize her newborn exhibiting NAS.⁹ To date, there has been a paucity of treatment access for women before, during or after pregnancy that can help her, her child and the dyad.¹⁰

In contrast to NAS, evidence is strong for lifelong consequences for some children with prenatal alcohol exposure such Fetal Alcohol Spectrum Disorder (FASD) on growth, behavior, cognition, language, and achievement.¹¹⁻¹² Like women who have opioid use disorders, there are few treatment resources to help women and their children affected by alcohol problems.¹³ Further, few publications focus on concurrent use of opioids and alcohol during pregnancy.¹⁴ In fact, only two publications focus on concurrent use and both reported a high prevalence of prenatal alcohol use among pregnant women with substance/opioid use disorder.¹⁵⁻¹⁶ These results are underscored by NSDUH data from 2005 to 2014 showing that among women who were pregnant and reported non-medical opioid use, almost 50% reported alcohol use and almost 33% reported binge drinking in the past month.¹⁷ Thus, there is a group of women and children who would benefit from a more specific focus on co-occurring opioid and alcohol treatment and recovery supports.

Summary

Given the risks of FASD, efforts are needed to advance greater access to screening, assessment, treatment and sustained recovery efforts for alcohol use, including women with OUD, whose children may also have NAS. There are effective treatments for opioid use disorder as well as alcohol use disorder during the perinatal period.¹⁸⁻¹⁹ However, efforts are needed by state and federal governments and the private sector to ensure there is a focus on supportive not punitive policies towards pregnant women.²⁰⁻²¹ Meaningful reduction in the incidence and prevalence of prenatal opioid and alcohol use, as well as tobacco and other

substances, will likely only occur with a private-public partnership to create and maintain a sustainable financial infrastructure to support nationwide efforts to provide appropriate evidence-informed treatment and a recovery oriented system of care for all individuals affected by substances, including pregnant and/or parenting women.

Future Areas of Research: What we do not know

Research needs to answer questions regarding the most optimal approaches to screening for opioid and alcohol use before, during, and after pregnancy. The fact that only about 33% of women are screened for alcohol use during pregnancy,²²⁻²³ suggests that there is much work to be done.

- Like screening, questions about how to best support women with opioid and/or alcohol use disorders in entering and completing treatment and maintaining recovery need answers. Which treatments provide the best outcomes for which types of patients before, during and after pregnancy and during parenting?
- While opioid and/or alcohol use disorders occur among all social classes, we need to know the role that social determinants of health play in exacerbating or mitigating the effects of NAS and FASD.
- What parenting, treatment and recovery supports are most beneficial to the maternal-child dyad? What family, maternal, child, and community variables need to be considered in yielding optimal outcomes?
- What are the most effective and cost-effective approaches to provide care for women with opioid and/or alcohol use issues that will lead to optimal maternal and child outcomes?

What are the best public policies and reimbursement structures for promoting engagement of and access, treatment, and optimal outcomes for women with opioid use and/or alcohol use disorders and their children?

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Screening for Prenatal Alcohol and Substance Use: Next Steps

Grace Chang, MD

What we know

Prenatal exposure to alcohol and other substances is common. The estimated rate of prenatal alcohol use is about 15%, with past month use about 12.6%.^{i,ii} Marijuana is the most commonly used illicit drug during pregnancy, with as many as 14.6% of pregnant adolescents in California reporting past month use.ⁱⁱⁱ Opioid use among pregnant women has been described to be at epidemic proportions, accompanied by a four-fold increase in neonatal abstinence syndrome (NAS) between 2000 and 2014.^{iv,v}

The consequences of these exposures are potentially significant. For example, a recent multi-site study using active case ascertainment methods estimated the prevalence of fetal alcohol spectrum disorders among first graders ranged from 1.1 to 5.0%. This is concerning because these disorders are associated with life-long disabilities.^{vi} While the adverse effects of prenatal marijuana use are unclear, estimates of its use increase, as states legalize its recreational and medical use.^{vii,viii,ix,x} With regards to prenatal opioid exposure, infants are typically born smaller and may have neonatal opioid withdrawal syndrome (NOWS). Furthermore, mothers of infants with long-term exposure to prenatal opioids but who did not develop NOWS, have been found to be at similar, elevated risk for mental health conditions as mother of infants with NOWS.^{xi, xii, xiii}

Early universal screening of pregnant women for alcohol and substance use has therefore been recommended by the American College of Obstetricians and Gynecologists [ACOG] since alcohol and substance use is not typically disclosed spontaneously by patients. Whereas routine laboratory screening is not required, ACOG has indicated that universal screening can take place either by the administration of validated questionnaires or conversations with patients.^{xiv,xv}

Future Areas of Research: What we do not know

Optimal approaches to screening for prenatal substance use have yet to be determined. The purpose of our study was to evaluate the ability of five self-report questionnaires, each with some evidence to support their use, to identify alcohol and substance use disorders as well as recent alcohol and substance use in a sample of 1220 pregnant women seeking prenatal care in New Haven, Boston, and Detroit. Substance use disorders are distinct from substance use, and represent a more significant and persistent pattern of consumption.^{xvi} The five questionnaires compared are the NIDA Quick Screen,^{xvii} CRAFFT,^{xviii} Substance Use Risk Profile – Pregnancy (SUR-P),^{xix} Wayne Indirect Drug Use Questionnaire (WIDUS),^{xx} and the 5 Ps.^{xxi,xxii} 1220 pregnant women, 18 years of age or older, able to understand written and spoken English, and who gave informed consent were recruited from study sites. There were two study phases; phase 1 which gave the study questionnaires in counterbalanced order, and phase 2 which included a diagnostic interview, timeline followback interview for the preceding 30 days, and urine toxicology screening.

Nearly 10 percent of participants satisfied diagnostic criteria for current alcohol or substance disorders and one third used alcohol or other substances while pregnant. The participants were socioeconomically diverse, with a mean age of 29 years and evenly distributed across all three pregnancy trimesters. Performance of all instruments varied significantly with race, site, and economic status. No screening instrument had satisfactory performance with regards to the identification of current alcohol and substance use, and the substance use disorders.

Conclusions: No screening instrument showed both high sensitivity and high specificity, and AUC was low for nearly all measure/outcome combinations. Better-performing options are urgently needed.

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Prenatal Substance Exposure: Prevention and Risk Communication through MotherToBaby.GA

Claire D. Coles, PhD

Presentation as part of Panel II: Model Programs for Mothers with Alcohol Use Disorder, other Substance Use Disorder, and Children with Prenatal Substance Exposure.

What we know

Alcohol and drug use during pregnancy and particularly use that conveys risk to the developing child is an on-going concern. Like other members of society, pregnant women consume alcohol, smoke cigarettes, take prescription drugs, and abuse a variety of illicit substances, most notably marijuana, opiates and stimulants. Many do so before recognition of pregnancy but others continue to use these substances throughout pregnancy. These include both women struggling with substance use disorders and those who are “social drinkers”. Surveillance studies suggest that the prevalence of such use remains high despite public health messaging^{1,2,3}. Ideally, prevention of these exposures is the most effective and least expensive approach to this problem. Many women, when they know the risk of exposure, can stop or reduce use^{4,5}. Others, when informed of the risk, will seek treatment. While such an approach will not eliminate all addiction-related substance abuse, it has the potential to reduce the impact of prenatal exposure on the child’s outcomes.

Based on the idea that information about risk can lead to prevention of negative outcomes, one model is to provide counseling to pregnant and breast feeding women, their families, and health care providers about the risk associated with use. MotherToBaby, an organization supported by the Organization of Teratology Information Services (OTIS)⁶, is a network of 12 organizations in North America that support pregnant women, breastfeeding mothers, their families and those who work with them regarding exposures of any kind. Similar is the European Network of Teratology Information Services (ENTIS), a global collaborative network of Teratology Information Services consisting of physicians, pharmacists, genetic counselors, and scientists working together to prevent birth defects and developmental disabilities arising from maternal or paternal exposures.

Summary

In 2014, with the support of the Georgia Division of Behavioral Health and Development Disabilities, MotherToBaby.GA (M2B.GA), a counseling service providing accurate, empirically based information accessible by phone, text or email, was initiated to serve Georgia and the Southeastern United States, where no such resources had existed before. The goal was to prevent prenatal alcohol and drug use by intervening with those most likely to respond to a message about the risk of substance use and abuse during pregnancy. Among possible targets for prevention activities, we selected the public at large for Universal prevention messages, and providers, gate-keepers and women using substances in pregnancy as Indicated targets most likely to be open to change. Our goal was to communicate directly with pregnant women and

provide them with the information that they wanted and needed in order to make informed decisions about their own medical care and personal habits. The service was provided free of charge to anyone who communicated with us through a “warm line” available 5 days a week. The contact can be anonymous and the person answering is a trained childbirth educator with experience in teratology. In talking with callers about their substance use, the counselor provides empirically-based information about the risk of the exposure for pregnancy loss, birth defects or neurobehavioral consequences. She explains that there is a “background risk” for these problems for all pregnancies and that she will talk with them about any increased risk associated with the drug/alcohol use. If there is no increased risk or if it is unknown, she explains that as well. MotherToBaby.GA does not make medical recommendations. We do make referrals for care and will refer women to their medical providers, as appropriate, to provide them with referrals for other services as required.

Making the community aware of this service required extensive dissemination of information about the new service using a variety of methods. We appeared on broadcast media (television and radio, including Spanish language media), created a web page, and are active through Facebook and Twitter. To communicate with professionals we presented grand rounds at a number of medical schools and hospitals, exhibited at conventions and conferences, worked with community organizations like Healthy Start, and distributed materials to all 159 Health Departments in Georgia, as well as many counties in Alabama, Mississippi and Tennessee. We believe that when the public hears a message through multiple, trusted sources, the information becomes more acceptable and women are more likely to access MotherToBaby. It is also important to communicate through a variety of sources, since young women are more likely to rely on social media than on traditional media.

We started small but grew. In 2015 we had 35 contacts. In 2016, there were 1112, and in 2017 there were 1691. The majority were through texts (754), but many, were through public meetings and interactions (682) as well as other means including calls, on-line communication, emails, or in person (Total: 255). It took some “spade work” for people to know about us. In FY 2017 we distributed 7375 brochures, flyers and other written information, and reached 40,498 women between 18 and 45 on Facebook.

The majority of those seeking us out were pregnant women (58%), with breastfeeding women (28%) next. Five percent of women called to ask about the risk if they were to become pregnant. Two percent were adoptive or potential adoptive parents, usually inquiring about the risk of alcohol and drugs for prospective adoptees. Referrals came from the Centers for Disease Control and Prevention, family and friends, health care providers, social media/Facebook, the internet, and adoption agencies. Most callers were white, followed by Hispanic and Black. Among substances of abuse women asked about, we found opiates were the most common, followed by alcohol and marijuana.

The experience of MotherToBaby.GA suggests that women are anxious to learn more about how to have a healthy pregnancy and that a service of this kind is readily accepted by both public and professional groups. While a counseling service of this type will not address all of the issues associated with substance abuse in pregnancy, it can be an effective model for prevention of some of the negative effects of exposure.

To learn more:

<https://mothertobaby.org/>

<https://mothertobaby.org/benefits-otis/>

<https://www.entis-org.eu/>

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Health care settings and prevention, identification and intervention for alcohol problems for adolescent girls.

Stacy Sterling, DrPH, MSW

What we know

Alcohol and other drug (AOD) problems can be devastating to the health, mental health and life trajectories of adolescents.(1) Although rates of substance use have generally declined over the past forty years among youth in the United States (U.S.), the most recent Monitoring the Future national survey of 8th, 10th and 12th graders found upticks in alcohol use in many cases, and the continued high rates of binge drinking, even among young adolescents, are worrisome: 8% of 8th graders, 20% of 10th graders and 33% of 12th graders reported past 30-day alcohol use; and 4% of 8th graders, 10% of 10th graders and 17% of 12th graders reported having engaged in binge drinking in the past 2 weeks. (2) AOD use is closely associated with the three leading causes of mortality and morbidity in this age group – accidents, homicide and suicide (3) – as well as with medical (4,5) and mental health comorbidities (6,7), and early detection and intervention can make a critical difference in adolescents' health and wellbeing. (8-10). Recent research has demonstrated the significant and potentially irreversible damage which the use of alcohol and other drugs, when left untreated, can cause to developing adolescent brains.(11-27)

In recent years, girls' rates of AOD use have caught up with and in many cases surpassed those of boys, particularly in regard to alcohol, and drugs other than cannabis. Additionally, girls are more likely to report co-occurring mood symptoms, suicidal ideation, anxiety and other mental health problems than boys. Similarly, girls with AOD problems are more likely to have medical comorbidities such as gastrointestinal problems, migraine, and sexually transmitted infections, as well as, of course, unplanned pregnancies.

While AOD use and other behavioral health problems are among the most common pediatric health conditions in the U.S., (28) far fewer than half the children and adolescents in need of care ever receive services, particularly specialty substance abuse treatment,(29,30) and certain population groups, including Latinos and African Americans, are especially unlikely to receive care.(29-32) Many families never seek care, and many of those that do have difficulty obtaining it because of issues of system capacity and insurance coverage. (33) Primary care visits thus provide critical opportunities for detection of and early intervention for AOD problems. (34,35) Studies have found that PCPs, when well-trained, may be especially effective agents to provide this, and adolescents and their parents have been found to be receptive to AOD screening and intervention by pediatricians, (36) and to have positive perceptions of care when their pediatrician discusses "sensitive" topics, including substance use, with them. (37) Moreover, there is precedent for behavioral health service provision in pediatric primary care; more children in the U.S. with mental health conditions receive care for these from their primary care provider than from any other type of provider. (38) Primary care and other health care settings, such as OB/Gyn, may be particularly good contexts for engaging girls with AOD use problems, because they tend to use health care services more often than boys, especially as they move through adolescence and into young adulthood.

Screening, brief intervention and referral to treatment (SBIRT) offers one approach to primary care-based identification and intervention for adolescents. While the evidence base for SBIRT for adolescents lags behind the adult SBIRT literature, recent studies have produced promising findings. A number of pilot studies, quasi-experimental studies and randomized clinical trials have found positive effects of screening and brief interventions, including: reductions in alcohol and cannabis use initiation among non-users; drinking and cannabis use cessation among current users; reductions in binge drinking; reductions in drinking and driving; reductions in alcohol-related injuries; reductions in victimization and perpetration of violence; reductions in dating violence; and improvement in mood symptoms. Recent studies have also found that SBIRT can improve specialty behavioral health treatment initiation, while also reducing overall healthcare services utilization. There have also been several excellent systematic reviews and meta-analyses suggesting that brief interventions for adolescents can produce moderate but significant improvements in alcohol consumption and related problems across settings and populations, with effects that persist for a year or longer.

Future Areas of Research: What we do not know

Far more research is needed in a number of areas pertaining to addressing alcohol use in health care settings, among adolescents generally, and among girls specifically, as there is a dearth of research specifically focused on identifying and treating girls with alcohol and other drug problems in pediatric primary care.

- Most studies have not found significant differences between girls and boys in SBIRT outcomes. However, very few published studies have focused primarily on adolescent girls, and in many studies sample sizes limited robust gender analyses. SBIRT does seem promising for outcomes which are especially salient to girls and young women, such as dating violence, sexual victimization, eating disorders, sexually transmitted infections and unplanned pregnancy. Future research should explicitly focus attention on outcomes among girls and young adult women.
- As discussed above, girls seem to be particularly vulnerable to co-occurring AOD use, mood and anxiety disorders, and other emotional distress. Research is needed on screening approaches and interventions which encompass these different but closely related problems.
- We need to expand our conception of SBIRT beyond 1 or 2 sessions of M.I.-based brief advice or brief intervention. Studies examining “expanded” versions of SBIRT are needed because 1-2 sessions are frequently not enough, even for less severe AOD use among adolescents. Multi-session models and approaches using “booster” sessions over time, whether in-person or technology-enabled, should be examined.
- In primary care settings, the field needs to look beyond pediatricians to evaluate the role and effectiveness of various members of primary care teams, including paraprofessionals, and should assess workforce development needs in the area of adolescent substance use screening and treatment .
- Research into primary care-based, family-inclusive interventions is needed. Most children and adolescents live in the context of a family, and families are crucial to setting the trajectory of children’s and adolescents’ health and well-being.
- Research to develop and test interventions to concurrently address both AOD use and the frequently underlying causes, including adverse childhood experiences and trauma and toxic stress exposure, to which girls are particularly vulnerable.

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- Research should take advantage of the technological capacity many health care systems have to offer their patients, whether through tele-care, video encounters, or EHR-based patient portals, by studying technology-enhanced alcohol interventions.
 - More evidence is needed on programs and interventions which could remove barriers to engagement for vulnerable groups and those who have been found to be especially affected by stigma and shame around behavioral health problems, potentially reducing health disparities. More research is needed on the efficacy and effectiveness of linguistically- and culturally-tailored prevention and early intervention programs for adolescents in health care settings.
 - Finally, studies should include a broader range of relevant, developmentally-appropriate outcomes, and approaches to program development and evaluation, such as: 1) alcohol and other drug use initiation prevention or delay; 2) cutting back and harm reduction; 3) initiation of regular use vs. non-progression of use; 4) risky behaviors common to adolescents; e.g., driving, biking, skateboarding, sex; 5) RT → treatment initiation and engagement; 6) comorbidity; e.g., depression, anxiety, suicide; 7) academic outcomes; 8) family functioning; 9) medical outcomes; 10) health services utilization and costs.

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Does who you are matter? Gender, race, ethnicity, and youth alcohol intervention outcomes

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What we know

Adolescence is a critical phase in the initiation and development of alcohol use and dependence.¹⁻⁴ Risk and protective factors in the context of alcohol use can diverge across gender due to gender role socialization and differ in importance across racial/ethnic groups.⁵⁻⁷ Although the gap between alcohol use for boys and girls has been narrowing over the past few decades, boys tend to engage in higher rates of risky alcohol use, particularly binge drinking, a pattern of alcohol use associated with more negative developmental consequences.⁸ Girls more frequently report patterns of consistent heavy drinking over time while boys more frequently report patterns of sudden increases in consumption.⁹ When examining race and ethnicity in isolation, White and Hispanic adolescents report the highest drinking rates by 12th grade, followed by Black/African American youth and Asian/Asian American teens.⁸ Hispanic and Black/African-American teens are more likely to drink alcohol for the first time before age 13 than their White counterparts,¹⁰ which is concerning as drinking initiation before age 15 is associated with a higher likelihood of developing alcohol dependence later in life.¹¹ Ethnic minority adolescent drinkers report more negative alcohol-related consequences than their White counterparts, despite lower or comparable levels of consumption.¹²⁻¹³ These findings suggest important differences in alcohol use and consequences based on youth demographics.

Differences in drinking behaviors associated with gender, race, and ethnicity and their intersections indicate that these factors should be considered in the design and implementation of intervention programs¹⁴; some efforts have been made to consider ethnic diversity in this process.¹⁵⁻¹⁶ Based on identified racial/ethnic differences as mediators of adolescent substance use, interventions targeting individual-level factors, such as negative expectancies and refusal self-efficacy, may be of particular utility among some Hispanic youth, while interventions highlighting perceived peer use and positive familial communication could be successful in reducing substance use among some Asian-American youth.¹⁷ Very little research has examined the impact of gender composition on group processes for youth in alcohol interventions; Garcia and colleagues¹⁸ found both boys and girls reported higher satisfaction with intervention services when there were proportionally more girls in the group. Further, the levels of engagement and responsiveness to group facilitators were higher with a greater proportion of girls in the group. In a study examining the differential effectiveness of

prevention programs focusing on refusal skills and affect management across gender and race in seventh graders, these programs were more effective than a psychoeducational control for girls, but not for boys, and for Asian-American and Hispanic students, but not Black or White students.¹⁹

Although interventions targeting specific groups based on common demographics are one avenue to address the needs of diverse youth,¹⁶ this approach can be time and resource intensive. A complementary approach is to design intervention programming that is flexible to adapt to the needs of each specific school context. Motivationally-enhanced (ME) approaches might be an optimal and alternative avenue to pursue, as its principles allow interventionists to adjust to the needs of participants. In fact, some studies have found ME interventions to be particularly effective for ethnic minority individuals.^{12, 20-21} Schools represent one setting that offers broad access to ethnically and socioeconomically diverse adolescent populations, and considerable resources have been dedicated to developing and improving school-based interventions. Recent reviews and meta-analyses suggest that school-based alcohol prevention programs are associated with small but significant reductions in alcohol use.²²⁻²⁴ For developmental considerations and to maximize use of limited resources, these programs are often provided in group formats.²¹

In conjunction with Drs. Brown, Myers, Wagner, and Winters, we recently completed a multisite, hybrid effectiveness-efficacy trial of Project Options (PO) in three geographic locations across the United States (Pacific Northwest, Midwest, Southeast) and examined issues related to gender, race, ethnicity, and their interactions on alcohol intervention outcomes. PO is a voluntary, brief, school-based alcohol intervention program adopting an ME-based group approach with the goal of preventing higher risk substance use engagement in high school students. The intervention demonstrated effectiveness in earlier trials at facilitating attempts to reduce or abstain from alcohol use in high frequency drinkers.²⁵⁻²⁶ Findings from the multi-site trial showed that intervention youth matched the diversity of the general school population and were highly likely to return after their first session regardless of their individual ethnic background.²⁷ When examining the impacts of gender, race, ethnicity, intervention condition, and their interactions on use cognitions (desire and intentions to cut down or stop drinking, intentions to use) and behaviors (cut down/quit attempts, current use), we found that Whites were more likely to have engaged in recent alcohol use behavior, express intentions to drink in the next month, and were less likely to express a desire or attempt to modulate their alcohol use. Boys who identified as White and Hispanic in the ME condition were less likely to intend to drink in the future when compared to Non-Hispanic girls of color in the didactic condition.²⁸

Future Areas of Research: What we do not know

1. A high proportion of studies on intervention services do not account for the influence of gender, race, and ethnicity, and the interaction of these factors on process and outcome.²⁹ Intersectionality, or the consideration of multiple categories of group,³⁰ must be studied in the evaluation of alcohol interventions for youth.
2. The existing literature is sparse in terms of how gender identity, particularly for individuals with trans identities or those who do not identify using gender binary distinctions, impacts

alcohol use in youth.³¹ Future research should consider using dimensional scales of gender identification to better capture the identities held by individuals served in alcohol interventions.

3. Relying on a single definition of ethnicity (i.e., Hispanic/Latino) does not capture the many other ethnic identities that need to be considered in the future. Given the diversity in the US population, research must consider the needs of Hispanic/Latino youth as well as other ethnic minority groups.

4. Future research should provide more comprehensive assessments of identity, in contrast to traditional gross definitions of demographics, in determining sociocultural influences on alcohol consumption and intervention outcomes for youth.

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The role of health care in addressing alcohol problems among women

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What we know

Primary care is an especially important venue for screening and addressing alcohol problems for women. While only about 10% of women with alcohol use disorders access specialty treatment, they do often access primary care, Ob-Gyn, and other health departments. One study of a California county found that of the women who accessed services of any kind, 73% accessed them in primary care, whereas only 7% accessed specialty alcohol treatment. Primary care is the most likely place to identify unhealthy alcohol use and alcohol use disorders, and to provide brief or more intensive interventions, appropriate medications, and referrals to specialty care. Women usually visit primary care for reasons other than to get help with their drinking, so screening is crucial. Importantly, primary care offers the opportunity to help women with any of the full range of alcohol problems (risky or unhealthy use to severe addiction and alcohol use disorders (AUD)).

Studies show that screening and brief interventions for women in primary care are successful. However, the screening must be systematic, because women are often missed. When screening is conducted systematically with a standardized screener and a protocol that screens all women (rather than leaving the decision to clinician judgement), there is no longer a difference in screening rates between men and women.

Brief interventions show improved drinking and health outcomes for many, but those with severe problems need more care. Many women in addiction treatment have other health and mental health problems as well. These are often not addressed and they are a major predictor of relapse.

Family members (children and spouses) of women with alcohol use disorders have higher rates of many medical and mental health conditions. They use more emergency (ER) and inpatient services than other families without alcohol disorders. This is also the case when compared to family members of adults with other chronic diseases, such as asthma and diabetes. However, when women are successfully treated, their families' costs (ER and inpatient – proxies for outcomes) are no longer higher than for matched families without alcohol or drug problems.

Following specialty alcohol treatment, continuing services in primary care for women is extremely important. Their co-occurring medical problems need ongoing attention for their own sake, but these problems can also lead to relapse. When they receive annual primary care and addiction and psychiatric care as needed, women are much more likely to be remitted over nine years, and their costs (due to reduced ER and inpatient care) are significantly reduced.

Summary

Expanding the role of general health care in addressing women's alcohol problems can potentially improve prevention, screening and treatment. The literature to date is optimistic that

primary care and other health care settings can accomplish this. Women with alcohol problems have high rates of medical and mental health problems (higher than for men). However, there are large differences among women associated with age, as well as with other social and medical characteristics. Family members of women with alcohol use disorders also have high rates of medical and mental health problems. The evidence suggests that the spectrum of alcohol problems can be successfully addressed in health care through screening and interventions in primary care or with referral to specialty treatment. Much is known about the life course and other demographic and clinical needs of women. Innovative interventions are being developed in primary care, but they have not been widely implemented. Innovative use of health information technology, including the electronic health record, can facilitate research based on large samples, and with the potential to reach many more women. This area of research calls for much more study.

Future Areas of Research: What we do not know

Research in several key areas can greatly advance clinical practice within health care for women with alcohol problems. These research areas include: implementation and sustainability of SBIRT interventions; women-related interventions that provide more intensity than SBIRT does; interventions in health care that address medical and psychiatric problems of women whose drinking is unhealthy and are at risk for future alcohol use disorders; interventions that address health disparities; pragmatic trials and comparative effectiveness studies using EHRs to study large samples of women in order to develop targeted interventions for the needs of diverse groups of women; and continuing care interventions (following specialty addiction treatment) in primary care. Because of EHRs in health care systems, the traditional research problems related to small sample sizes of women can be addressed. These are briefly discussed below.

- Research shows SBIRT is effective, but it seldom occurs in busy primary care clinics. Thus implementation research is crucial, particularly for interventions for women. Women are less likely to be identified by physicians and are under-represented groups in most relevant studies to date.
- Since women rely on health care extensively throughout their life course, services more intensive than brief interventions in primary care and other health departments are needed. Research on this needs to be followed by implementation studies.
- Research is lacking on the medical and psychiatric problems among women with alcohol misuse/unhealthy use rather than more severe alcohol use disorders. This research is important for developing targeted interventions and prevention.
- Epidemiologic studies show that women's alcohol problems differ by life course, by co-occurring medical and mental health conditions, and by other characteristics. Research is required that not only examines women as a group, but also the differences among them. Innovative ways of increasing sample sizes through other approaches are also required, such as large EHR systems.
- Research is needed on how to address health disparities in health care among women with alcohol problems. Development of prevention and treatments specifically for women, and also for women by age and race/ethnicity/cultural backgrounds, are needed. Some race/ethnicity/cultural groups are particularly under-represented. Research on Health IT options for women (who may have more barriers in accessing treatment, such as those with young children) may facilitate addressing disparities.

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- Research is needed on effective prevention strategies to persuade women (and their partners) to not drink when they may be getting pregnant. These interventions could be placed within health care – in primary care and emergency departments, as well as Ob-Gyn.
 - As alcohol use disorders are a chronic health problem, research is needed on interventions to motivate women to access continuing health care, where the need for services to facilitate recovery or referral back to treatment can be identified and is essential.

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Alcohol and the Female Brain

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Alcohol is a growing women's health issue. In the 85 years since the end of Prohibition in the United States, previously large gaps in alcohol use and related consequences between men and women have narrowed considerably. For those born near 1900, males outnumbered females roughly 3:1 for measures of alcohol consumption (e.g., prevalence and frequency of drinking), problematic drinking (e.g., binge drinking and early onset drinking) and alcohol-related harms (e.g., having an alcohol use disorder and drunk driving). Many of these ratios are closer to 1:1 for today's adults (Slade et al., 2016) and alcohol use continues to increase for women. An analysis of six different national surveys between 2002-2013 suggests that the number of women who drink increased 6.2% but decreased 0.2% for men, and the number of women who binge drink increased 14.0% but only 0.5% for men (Gruca et al., 2018).

As alcohol use by women increased over the last few decades, so did our knowledge about the potential health consequences faced by female drinkers. Between 2006-2014, there was an increase in the rate of alcohol-related emergency department visits that was larger for women (55.5%) than men (43.4%) (White et al., 2018). Research suggests that women are at greater risk for liver inflammation, memory blackouts, progression of alcohol use disorder, cardiovascular diseases, and certain cancers (Nolen-Hoeksema, 2004; CDC, 2013). Compared with their male counterparts, women with alcoholic liver disease have a more rapid progression to fibrosis that persists even after abstinence from alcohol (Guy and Peters, 2013). 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 was associated with a 12% increase in the risk of breast cancer (Allen et al., 2009). Because of physiological differences, women reach higher blood alcohol levels than men after each drink, which means their organs are exposed to more alcohol and they could potentially experience more severe impairments in brain function and behavior.

Despite advances in our knowledge of the health risks women face if they drink, relatively little is known about the potential contribution of sex differences in brain development to alcohol use, alcohol use disorders, or to treatment and recovery. In a recent review of 230 neuroimaging studies on substance abuse, the authors noted that 79% included both sexes but only 26% of those studies evaluated sex effects (Lind et al., 2017). The available evidence suggests that chronic alcohol use might impact the female brain harder than the male brain in some ways. Female alcoholics perform more poorly than male alcoholics on a variety of cognitive tasks even with fewer years of alcoholism (Nixon et al., 2014). Animal studies suggest that females are more vulnerable than males to the neurotoxic and neuroinflammatory effects of alcohol (Alfonso-Loeches et al., 2013). And research indicates that alcohol use disorders and related brain atrophy progress more quickly in women than men (Hommer, 2003; Diehl et al., 2007). But how differences in female and male brains contribute to the initial motivation to drink, the reinforcement provided by drinking, the development of drinking patterns, the progression to alcohol use disorder, or optimal treatment strategies remain unclear. Recent brain research has begun to shed light on these questions. As we will see, there is no such thing as a patently

female or male brain, but the often subtle differences in wiring could contribute to alcohol use and related outcomes.

When males and females enter puberty, brain organization and function are quite similar (Kaczurkin et al., 2019). By the end of the second decade of life, a combination of genes, hormones and experiences lead male and female brains to differentiate in potentially important ways. For instance, females exhibit more extensive communication between the two cerebral hemispheres across the corpus callosum, while men create more extensive networks within the individual hemispheres (Ingathalikar et al., 2014). The female brain requires more energy to fuel these elaborate circuits at rest and receives more cerebral blood flow (Kaczurkin et al., 2019). According to Tomasi and Volkow (2012) "Men's lower brain connectivity might reflect optimization of functions that require specialized processing, such as spatial orienting, whereas the women's higher brain connectivity may optimize functions that require integration and synchronization across large cortical networks such as those supporting language." While men develop brains that are larger overall by about 9-12%, the ratio of gray to white matter is bigger for females and both the thickness and density of cortical gray matter is greater in females (Kaczurkin et al., 2019).

Reasons for these developmental differences and their implications remain unclear. Herting and Sowell (2017) make a compelling case that, in order to understand sex-related differences in behavior that emerge during adolescence, it is necessary to take into account the broad panoply of changes that occur during this stage of life. They suggest, "pubertal-related timing of region specific brain changes may contribute to sex-specific differences in the rapid and disproportionate increases in rates of psychopathology seen between girls and boys... Additional evidence for this idea stems from functional MRI studies linking pubertal development and sex steroids to emotional and social processing, emotional-cognitive interactions, and risk and reward processing." In short, differentiation of male and female brains alone is unlikely to adequately explain differences in behavioral tendencies during adolescence. In fact, Kaczurkin et al (2019) argue against using the term "dimorphic" to characterize male and female brains given that they are far more similar than different. They suggest that the brain is not "'sexually dimorphic,' which implies that male and female brains are distinct. Rather, the high degree of overlap between distributions of males and females argues against a dimorphic view of the human brain... As noted in previous work, the human brain consists of a 'mosaic' of features, with the relative proportion of male, female, and unisex attributes varying substantially between individuals."

Differences in male and female adolescent experiences, including brain changes and socialization, could give rise to slight differences in reasons for using alcohol. Substance use during the teenage years has long been associated with exploration and risk taking. However, research suggests that males exhibit significantly bigger increases in sensation seeking and have lower levels of impulse control than females (Shulman et al., 2015). It appears that positive reinforcement (an increase the likelihood of a response by adding a positive state) might be more important for males than females, at least initially. For young males, alcohol increases dopamine release in the reward system and the amount of increase is associated with the amount of intoxication they report (Urban et al., 2010). This relationship does not occur in females, suggesting female reward circuitry might be less responsive to alcohol. In contrast, some studies suggest that adolescent females are more likely to report drinking for the purpose of negative reinforcement (an increase in the likelihood of a response by removing a negative

state). As Kuntsche et al. (2015) concluded, “The results from the largest drinking motive study conducted to date suggest that gender-specific prevention should take differences in the motivational pathways toward (heavy) drinking into account, that is, positive reinforcement seems to be more important for boys and negative reinforcement for girls.” Alcohol produces negative reinforcement in part by calming activity in a brain area known as the amygdala. The job of the amygdala is to attach emotions, like fear and anxiety, to stimuli. The amygdala helps keep us vigilant and alive. However, it also can generate uncomfortable emotions. Quieting the amygdala with alcohol can make it easier to socialize and cope with life, at least temporarily. Repeated drinking leads to tolerance and rebound increases in anxiety when the alcohol wears off. A four year daily diary study of college students found that drinking to cope with problems predicts worsening problems with anxiety and depression (Armeli et al., 2015).

The number of stressors and the strength of the stress response increases for both males and females across adolescence (Tottenham and Galvan, 2016). Interestingly, while females are roughly twice as likely to develop anxiety disorders or depression and might be more likely to drink for negative reinforcement, males actually exhibit a more robust stress response. Laboratory studies in which male and female subjects are placed under mild duress and stress-related hormones (e.g., ACTH, cortisol) and brain areas (e.g., amygdala) are monitored find a larger stress response in males (Stephens et al., 2016). However, as alcohol misuse progresses, heavy drinking females exhibit larger increases than males in anxiety and alcohol craving in response to a stressor. Eventually, both males and females who continue drinking heavily experience rebound anxiety and craving during periods of abstinence, which motivates a return to use (Koob and Volkow, 2016). This cycle of drinking to cope, feeling emotional and physical discomfort during periods of abstinence, and being preoccupied with drinking again is known as the “Dark Side” of addiction (Koob and Volkow, 2016).

Positive and negative reinforcement facilitate learning, and the adolescent brain is built to learn. It is well known that the earlier a person starts to drink alcohol the more likely they are to drink excessively and develop an alcohol use disorder. It seems that the intense learning that occurs naturally during adolescence makes it easier to acquire both healthy and unhealthy habits, including alcohol misuse. For this reason, preventing or delaying the onset of alcohol and other drug use for as long as possible is recommended to allow the brain to learn healthy habits and coping skills and to minimize the risk of developing a potential lifelong drinking problem. It is important that we learn more about how relationships with alcohol take shape for females and males, and how best to intervene in appropriate ways at each stage life. While it is inaccurate to suggest there are distinctly “male brains” and “female brains”, it is clear that the myriad sex- and experience-related changes in the brain during adolescence can influence drinking patterns and related harms.

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Harmful Alcohol and Opioid Use among American Indian (AI) and Alaska Native (AN) Women and Girls

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What Is Known about Alcohol Use among AIAN Women

Rates of alcohol use and disorder are higher among some groups of AIAN women compared to the general population. At the same time, rates of abstinence are substantial among AIAN women. In an epidemiological study of 3 community-based reservation samples, Northern Plains AI women had a significantly higher lifetime alcohol dependence (20.5%) than women in the U.S. (8.2%) but the prevalence was similar among Southwest AI women (8.7%).¹ Another study reported that the prevalence of lifetime alcohol use among AI girls in grades 7-12 was ~71%, which was significantly higher than the percentages reported by White girls (56%) and AI boys (58%).² A lower prevalence was reported in a study of 1,436 AIs age 16 and older selected at random from the tribal rolls of 4 different reservations: ~40% of AI females reported abstinence from alcohol in the last 12 months.³ Other reports document that AI women are more likely to be lifetime abstainers from alcohol than U.S. women.⁴ Yet despite the high prevalence of abstinence, when AIAN women drink, they are more likely to engage in risky drinking. Compared to other racial groups, AIAN women have a higher prevalence of weekly heavy drinking.⁵ More specifically, compared to non-AI women in the U.S., AI women who drink are more likely to drink 5 or more drinks in one day (66% to 87% vs. 47%) and are more likely to have been intoxicated at least once in the last year (68.7%-69.2% vs. 46.1%).⁴

Alcohol use (and substance use more broadly) is complicated in tribal communities by mental health, trauma, and poverty. AIs are especially at risk for alcohol- and drug-related consequences when compared to the U.S. population in general.⁶ Within AI communities,

alcohol and drug use disproportionately contributes to and is, in turn, influenced by mental health problems, early trauma and childhood abuse, cultural displacement, unemployment, and poverty.⁷ Historical trauma significantly increases the odds of developing substance use disorders among AIs,⁸ as does the trauma associated with domestic violence, loss, and racism.⁷ Alcohol use among AIAN women also contributes to increased mortality rates. In this regard, the number of deaths due to chronic liver disease and cirrhosis increased among all age groups of women (25-39, 40-49, and 50-64), ranging from 12.1 to 35.6 deaths per 100,000 between 1999-2014.⁹ The highest increase was among women ages 40-49. The high mortality may be, in part, linked to limited access to culturally grounded treatment for alcohol and substance disorders. Such services appear promising¹⁰ and may be preferred to non-culturally grounded services.¹

What Is Known about Risk for Alcohol-Exposed Pregnancies among AIAN Women

AIAN women are at greater risk for an alcohol-exposed pregnancy (AEP) because they are more likely to drink prenatally, drink at risky levels, and less likely to use birth control. AI women are also more likely to drink during pregnancy than U.S. women. In this regard, ~16% of AI women seen at an Indian Health Service prenatal clinic reported drinking alcohol during pregnancy;¹¹ in contrast, a national study found that ~10% of pregnant women drank.¹² In a study of 125 AIAN women from urban and remote rural areas surrounding Anchorage, 35% of respondents reported using alcohol during the first trimester, a highly vulnerable period for the fetus, and 8% reported consuming alcohol beyond the first trimester.¹³ Similarly, a study with 3 Northern Plains tribes found that nearly 30% of women who reported binge drinking were not using birth control.¹⁴ The South Dakota Tribal Pregnancy Risk Assessment Monitoring System reported that 43% of AI women from Aberdeen Area tribes were binge drinking in the 3 months prior to pregnancy.¹⁵ Among this same sample, 65% were sexually active, were not trying to get pregnant, and yet were not using any birth control.¹⁵ Furthermore, the AI teen birth rate for the Great Plains area was 123.2 per 1,000 live births, or 60.5 per 1,000 teens ages 15-17 and 235.1 per 1,000 teens ages 18-19.¹⁶ In this age group, binge drinking is also a large issue; 22.9% of AI youth aged 12-20 report current alcohol use in the past month, 18.4% report binge drinking, and 16% of AI ages 12 and older reported substance dependence or abuse.¹⁷

AI women who drink during pregnancy experience a multitude of other problems and stressors. For example, pregnant women from Northern Plains who drank were more likely than abstinent women to be single; have limited education, lack transportation, smoke cigarettes, use illicit drugs, and report relationship breakups and abuse.¹⁸ Likewise, Inuit women in Alaska were more likely to binge drink in pregnancy if they had drinking problems before pregnancy, depressive symptoms, and histories of domestic violence.¹⁹

Rates of Fetal Alcohol Spectrum Disorder have historically been thought to be higher among AIAN populations than the general population, but current data are scarce and older data are very limited. Fetal Alcohol Spectrum Disorder among Northern Plains AIs occurs as often as 8.5 per 1,000 births²⁰ However, a recent rigorously conducted investigation in a general population of first graders in the Upper Midwest that used active case ascertainment estimated Fetal Alcohol Spectrum prevalence to be 6 to 9 per 1,000 children.²¹ In Alaska, Fetal Alcohol Spectrum Disorder is 10 times more common among ANs than non-ANs (3.0 v. 0.2 cases per 1,000 live births).²²

AEP risk can be reduced among AIAN women. Using a case management system to prevent Fetal Alcohol Spectrum Disorder in AI communities through motivational interviewing and social support with heavily drinking pregnant women, one study found that 76% of the women involved had normal deliveries and did not appear to have an affected child.²³ The Centers for Disease Control and Prevention Project CHOICES curriculum was culturally adapted for AIAN women to create Oglala Sioux Tribe CHOICES^{24,25} and implemented with 3 communities around the Pine Ridge Reservation. Among a sample of 193 non-pregnant AI women at-risk for an AEP, Oglala Sioux Tribe CHOICES reduced the risk for AEP at the 3- and 6-month follow-ups.²⁶ Of importance, AEP risk reduction among AIAN teens should be a priority. In this regard, a qualitative study in a Midwest tribal community found that both unplanned pregnancies and alcohol and other substance use among AI teens made AEP risk reduction a priority for this age group.²⁷

What Is Known about Opioid Use among AIAN Women

In the midst of a national opioid crisis, opioid use is also taking a heavy toll on AIAN communities. In fact, the National Indian Health Board reported that the opioid epidemic “poses one of the most significant public health threats in recent history and is particularly virulent in AIAN communities.”²⁸ In a qualitative study that used talking circles to discuss OxyContin misuse, participants in one AI community reported an increase in OxyContin use, negative effects on individuals, families, and the tribe, a lack of treatment options, and growing problems on other reservations.²⁹ Data on initiation and prevalence of opioid use among AIAN women are extremely limited, but AIAN women appear to experience a higher risk of death due to opioids and other drugs. In Washington State, for example, the number and age-adjusted rates (per 100,000 population) of total drug overdose deaths for AIANs was substantially higher than their non-Hispanic White counterparts between 2013–2015³⁰ (30.1 vs. 12.5). Furthermore, among AIAN women, rates were highest in the 40-54 age group (89.7), followed by the 25-39 age group (57.0), and higher among urban than rural women (43.4 vs. 30.5).

What Is Known about Risk for Opioid-Exposed Pregnancies among AIAN Women

Despite limited data on opioid exposed pregnancies, evidence suggests that rates of maternal opioid use and neo-natal abstinence syndrome are both higher in AIAN communities than in non-AIAN communities and are increasing. A 2016 study in Wisconsin found 27.2 opioid users per 1,000 delivery hospitalizations among AIAN women – a rate twice that of White (11.7) and Black (13.9) women. This same study found a neonatal abstinence rate of 18.9 per 1,000 delivery hospitalizations among AIAN women, which was over 3 times that of deliveries among White (6.2) and Black (4.8) women.³¹ The incidence of opioid abuse among pregnant Canadian First Nations women increased from 8.4% in 2009 to 17.2% in 2010.³²

Future Areas of Research: What we do not know

Research in several fundamental areas is needed to improve our knowledge about alcohol and other substance use and abuse among AIAN women, particularly during pregnancy. Better quality data, better study designs, and longitudinal investigations hold promise to elucidate the prevalence, manifestations, and consequences of alcohol and substance use and abuse among

AIAN women. Because health systems and providers that serve AIAN women are often overburdened and underfunded, large pragmatic trials are needed to identify feasible, cost-effective, and relatively easily administered interventions that can be disseminated and are culturally acceptable. Broad topics for future work include:

- Epidemiology of alcohol and opioid use, patterns of use, and rates of disorder in diverse AIAN communities, including urban and reservation-based settings
- Development and testing of culturally based models of prevention and intervention for alcohol and opioid use and disorders and their risk factors
- Development and testing of culturally based models of prevention and intervention for women both at risk of, or actively using, alcohol or opioids during pregnancy
- More research on risk factors for, and co-occurring disorders and problems with, alcohol and opioid use, misuse, and actual disorders
- Prevention strategies for initiation, especially for teens
- Strategies to leverage the resilience and strengths within Native communities to reduce alcohol and substance abuse problems and rates of AEP

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Alcohol and Opioid Use in African American Women and Girls

Anika Alvanzo, MD

Sex and Race Differences in Alcohol and Opioid Use in Adults

Misuse of alcohol and alcohol use disorder (AUD) are a major public health problem internationally, accounting for approximately 4% of deaths and about 5% of disability adjusted life years globally.¹ In the United States, it is estimated that almost 1/3 (29%) of adults will meet criteria for an AUD in their lifetime.² Important sex and race/ethnicity differences in alcohol consumption, alcohol use disorder, and other alcohol-related consequences have been identified. Multiple studies have demonstrated that compared to men, women are more likely to report abstinence, initiate alcohol at a later age and report lower rates of AUD.³⁻⁵ Similarly, multiple studies have demonstrated that, compared to Whites, Blacks in general and Black women in particular are more likely to report abstinence, initiate alcohol at an older age, report lower rates of alcohol use disorder (AUD) and have a slower transition from first drink to development of AUD.⁶⁻⁹

Despite lower overall rates of drinking and AUD when compared to men and Whites, for those women and Blacks, respectively, who do drink the medical and psychosocial consequences are more severe. Women are more likely to experience alcohol-related medical consequences such as alcohol-associated cardiovascular disease and liver cirrhosis.¹⁰⁻¹³ Compared to other racial and ethnic groups, Blacks report lower rates of alcohol-related problems in adolescence and in their mid-twenties; however, by their mid-thirties this relationship has reversed, with Blacks reporting higher rates of alcohol-related consequences.^{14,15} When compared to White drinkers, Black drinkers endorse greater alcohol-associated injuries and social consequences.^{16,17} Among current drinkers, Blacks are at greater risk for development of alcohol use disorder¹⁶ and data suggest that once an AUD develops, Blacks have higher rates than Whites of recurrent and persistent AUD.¹⁸ Further, Blacks are disproportionately affected by alcohol-related medical consequences (e.g. cirrhosis, alcohol-associated malignancies) and alcohol-related mortality.¹⁹⁻²¹

Finally, differences in service use and treatment for alcohol problems and AUD are another factor contributing to the sex and race-related drinking disparities. While studies suggest that those women who receive services related to their alcohol use enter treatment faster than men,^{22,23} overall women are less likely than men to report receipt of alcohol-related services in their lifetime.²²⁻²⁵ Data on racial differences in service utilization are varied, with some studies reporting that Blacks are more likely,^{26,27} equally likely^{24,28} or less likely^{29,30} than Whites to receive alcohol-related services. Sample differences may explain these findings. For example, compared to Whites,

Blacks are over-represented in public sector and criminal justice systems.^{31,32}

While there have been fewer studies looking at gender and race/ethnicity differences and trajectories of opioid use, available data shows that again women and Blacks have lower lifetime and current rates of opioid use with respect to their male and White counterparts, respectively. Additionally, as with alcohol, women are less likely to access services for their drug use. However, for those women who do access services, they get there faster or have a shorter trajectory of use and problems, compared to men, before presenting to treatment.²³ Data suggests that Blacks are more likely than Whites to report receipt of services for substance use, but are less likely to report use of professional services.³³

Alcohol and Opioid Use in Youth

While the above noted sex and race differences exist in adults, there are some notable differences in adolescents. Several studies have demonstrated that in younger cohorts the gender gap in drinking is narrowing^{10,34-36}, with rates of problem drinking and alcohol-related problems of women beginning to converge with those of men. For youth ages 12-17 year old, there are no significant differences in lifetime or past month alcohol use or past month binge drinking between boys and girls.³⁷ (NSDUH 2015). While Black youth have lower rates of alcohol and other opioid use compared to their White counterparts, the typical gender differences are also disappearing, with Black girls having comparable rates of drinking.

The data with respect to opioid use and adolescents are more alarming, particularly for Black girls. While White girls and boys, 12-17 years old have comparable rates of past month prescription opioid misuse, Black girls have the highest rates of past year and past month prescription opioid misuse, higher than those not only for Black boys but also White girls and boys. Reasons for this are unclear but warrant further investigation.³⁷

Etiology of Sex and Race Differences

The etiology of these sex and race disparities in alcohol consumption and alcohol-related consequences is likely multifactorial, inclusive of baseline genetic differences, gender and cultural norms, variations in environmental and social stressors with potential differential epigenetic responses, and differential access to and utilization of service. Biological differences in total body water and pharmacokinetics of alcohol are one contributor to this sex difference in alcohol consumption and alcohol-related problems but do not account for all of the difference.¹⁰ Differences in gender roles and cultural norms, including differences in perceived social sanctions associated with drinking and intoxication, also contribute substantially, adding to the biological differences.^{5,10,38} There are disparities in risk factors between men and women, such as affective disorders, particularly depression, that are associated with alcohol misuse and AUD.^{2,39,40} Women are disproportionately affected by depression and co-occurring depression and AUD, and are more likely to reporting drinking in response to depressive symptoms.

With respect to racial differences, socioeconomic status has been identified as one factor that may contribute to the aforementioned disparities. Neighborhood disadvantage and neighborhood poverty, markers of socioeconomic status, have been associated with increased frequency of binge drinking, increased consumption of high alcohol content beverages and increased negative alcohol-related consequences.^{41,42} Stressors specific to racial and ethnic minority populations may also contribute to the disproportionate impact of alcohol on Blacks.

Multiple studies have demonstrated a relationship between discrimination and alcohol misuse and alcohol use disorder, though some differences exist by nativity and country of origin.⁴³⁻⁴⁵

Areas for Future Research: What we do not know

Further research in several areas can advance the field and improve clinical care, health and quality of life for women and girls, including Black women and girls.

- Additional investigation on factors contributing to the disparities, with comparable focus on protective or resiliency factors as opposed to just risk factors.
- Elucidation of etiological factors of increased morbidity at comparable rates of use.
- Better understanding of the impact of trauma and early childhood adverse experiences, including the epigenetic effects of such experiences.
- Further exploration of the impact of sex and race discrimination on women and girls' substance use
- Development, testing and dissemination of effective, culturally-tailored treatment and prevention interventions
- Research to advance understanding of where and how to identify, assess and intervene with women and girls who are not engaged in clinical and educational settings

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Reducing Alcohol-Related HIV Risk and Alcohol Use among Young African American Women

A Tale of Two Studies

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Context. Alcohol consumption adversely affects sexual health practices. There is also a dearth of effective HIV risk-reduction interventions for African American women who report drinking alcohol. The higher HIV prevalence in the African American community combined with the adverse effects of alcohol on HIV preventive behavior have created a “perfect storm” in which the risk associated with any single high risk act is greatly amplified.

Study 1. *Efficacy of a Telephone-Delivered Sexually Transmitted Infection/Human Immunodeficiency Virus Prevention Maintenance Intervention for Adolescents: A Randomized Clinical Trial (JAMA Pediatrics, 2014).*

IMPORTANCE. Behavioral change interventions have demonstrated short-term efficacy in reducing sexually transmitted infection (STI)/human immunodeficiency virus (HIV) risk behaviors; however, few have demonstrated long-term efficacy.

OBJECTIVE. To evaluate the efficacy of a telephone counseling prevention maintenance intervention (PMI) to sustain STI/HIV-preventive behaviors and reduce incident STIs during a 36-month follow-up.

DESIGN, SETTING, AND PARTICIPANTS. In a 2-arm randomized supplemental treatment trial at 3 clinics serving predominantly minority adolescents in Atlanta, Georgia, 701 African American adolescent girls aged 14 to 20 years received a primary treatment and subsequently received a different (supplemental) treatment (PMI) to enhance effects of the primary treatment.

INTERVENTIONS. Participants in the experimental condition (n = 342) received an adapted evidence-based STI/HIV intervention (HORIZONS) and a PMI consisting of brief telephone contacts every 8 weeks over 36 months to reinforce and complement prevention messages. Comparison-condition participants (n = 359) received HORIZONS and a time- and dose-consistent PMI focused on general health.

MAIN OUTCOMES AND MEASURES. The primary outcomes were percentage of participants with a laboratory-confirmed incident chlamydial infection and percentage of participants with a laboratory-confirmed gonococcal infection during the 36-month follow-up. Behavioral outcomes included the following: (1) proportion of condom-protected sexual acts in the 6 months and 90 days prior to assessments; (2) number of sexual episodes during the past 90 days in which participants engaged in sexual intercourse while high on drugs and/or alcohol; and (3) number of vaginal sex partners in the 6 months prior to assessments.

RESULTS. Table 2 below displays the effects of the intervention on laboratory-confirmed new STDs. During the 36-month follow-up, the longest follow-up of any adolescent study that includes biomarkers, fewer participants in the experimental condition than in the comparison condition had incident chlamydial infections (94 vs 104 participants, respectively; risk ratio = 0.50; 95% CI, 0.28 to 0.88; P = .02) and gonococcal infections (48 vs 54 participants, respectively; risk ratio = 0.40; 95% CI, 0.15 to 1.02; P = .06).

Table 2. Effects of the Experimental Intervention on Sexually Transmitted Infection Incidence During the Entire 36-Month Follow-up

Incident Infection From Baseline to 36 mo ^a	Participants, No.	Participants, %		GEE Model	
		Unadjusted	Adjusted	ARR (95% CI) ^b	P Value
Chlamydial					
Experimental	94	9.33	8.52	0.50 (0.28-0.88)	.02
Comparison	104	10.52	10.36		
Gonococcal					
Experimental	48	3.91	3.33	0.40 (0.15-1.02)	.06
Comparison	54	4.50	5.02		

Abbreviations: ARR, adjusted risk ratio; GEE, generalized estimating equation.

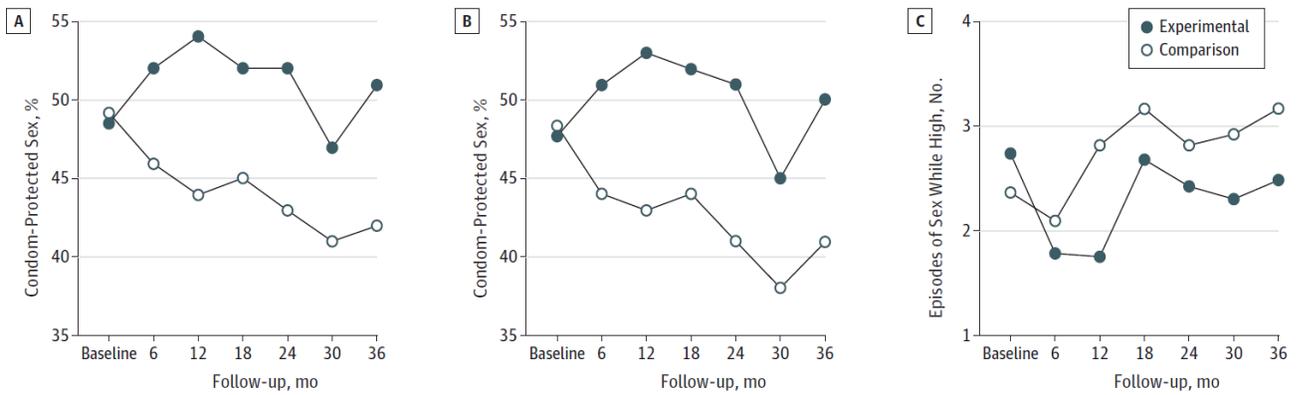
^a Number of participants detected with an incident chlamydial or gonococcal infection at the 6-, 12-, 18-, 24-, 30-, or 36-month assessment (therefore, total comparison participants with ≥ 1 follow-up included in analyses, n = 318; total experimental participants with ≥ 1 follow-up included in analyses, n = 309).

^b Biological outcome adjusted by baseline variables: clinic, family aid index (receipt of government assistance), years in school, partner communication frequency, unprotected vaginal sex in the past 90 days, history of emotional and physical abuse, depression, perceived partner concurrency, corresponding baseline result, and dose of telephone contacts.

Dose-response association between completed telephone contacts and lower incidence of Chlamydial infections. While there are few dose-response effects observed in behavioral trials, we did observe that participants completing more telephone contacts had a lower risk of chlamydial infection (risk ratio = 0.95; 95% CI, 0.90 to 1.00; P = .05).

Behavioral Effects of the Intervention. Figure 2 and Table 3 show behavioral effects of the intervention. Participants in the experimental condition reported a higher proportion of condom-protected sexual acts in the 90 days (mean difference = 0.08; 95% CI, 0.06 to 0.11; P = .02) and 6 months (mean difference = 0.08; 95% CI, 0.06 to 0.10; P = .04) prior to assessments and **fewer episodes of sexual acts while high on drugs and/or alcohol (mean difference = -0.61; 95% CI, -0.98 to -0.24; P < .001).**

Figure 2. Overall Effects on the Primary Behavioral Outcomes During the 36-Month Follow-up Period



All figures represent adjusted numbers. A, Proportion of condom-protected sex in the 6 months prior to follow-up assessments. B, Proportion of condom-protected sex in the 90 days prior to follow-up assessments. C, Episodes of sex while high on drugs and/or alcohol in the 90 days prior to follow-up assessments.

Table 3. Effects of the Experimental Intervention on Behavioral Outcomes at the 36-Month Follow-up Assessment

36-mo Behavioral Outcome	Mean (SE)				Mean Difference (95% CI) ^b	Relative Change, % (95% CI) ^b	P Value
	Experimental		Comparison				
	Crude	Adjusted ^a	Crude	Adjusted ^a			
Proportion of condom use							
Prior 90 d	0.52 (0.04)	0.50 (0.02)	0.37 (0.04)	0.41 (0.02)	0.17 (0.05 to 0.29)	0.23 (0.06 to 0.40)	.008
Prior 6 mo	0.52 (0.04)	0.51 (0.02)	0.39 (0.04)	0.42 (0.02)	0.14 (0.02 to 0.25)	0.18 (0.03 to 0.33)	.02
Episodes of sex while high on drugs and/or alcohol in prior 90 d, No.	4.87 (1.39)	2.49 (0.37)	2.83 (0.81)	3.18 (0.24)	2.04 (0.45 to 3.63)	0.42 (0.09 to 0.75)	.01
Vaginal sex partners in prior 6 mo, No.	1.49 (0.12)	1.42 (0.03)	1.60 (0.12)	1.69 (0.03)	-0.11 (-0.22 to -0.00)	-0.07 (-0.15 to -0.00)	.046

^a Behavioral outcome adjusted by baseline variables: clinic, family aid index (receipt of government assistance), years in school, partner communication frequency, unprotected vaginal sex in the past 90 days, history of emotional and physical abuse, depression, perceived partner concurrency,

corresponding baseline level of the outcome variable, and dose of telephone contacts.

^b Mean difference and relative change of adjusted means.

CONCLUSIONS AND RELEVANCE. Sustaining the long-term impact of an STD/HIV intervention for young African American women is achievable with brief, tailored telephone counseling.

Co-occurring alcohol use disorder and post-traumatic stress disorder (PTSD)

Sudie Back, PhD and Julianne Flanagan, PhD

What we know

Many women with alcohol problems have a history of trauma. More than half of all women experience at least one traumatic event in their life, with the most common types of events being child sexual abuse, sexual assault during adulthood, and intimate partner violence (IPV). In fact, approximately 1 in 3 women experience IPV and 1 in 10 teenage girls experiences dating violence.

Post-traumatic stress disorder (PTSD) is a debilitating and chronic condition that can develop after exposure to traumatic life events. In comparison to men, the prevalence rate of PTSD is more than twice as high among women (approximately 10% of women vs. 4% of men have a lifetime diagnosis of PTSD). Similarly, one study that surveyed over 10,000 adolescents aged 13–18 years old (49% female) in the U.S. found that 7% of females and 2% of males met criteria for lifetime PTSD. The reasons for the higher rates of PTSD among women are multifactorial, but may be due in part to the types of traumas that women are exposed to (e.g., repeated sexual abuse by someone the victims knows or a relative), which are associated with a particularly high probability of developing PTSD.

PTSD and alcohol problems often co-occur. Among individuals with PTSD, approximately 42% meet diagnostic criteria for an alcohol use disorder at some point in their lifetime, compared to only 29% of individuals in the general population. Research shows that trauma and PTSD typically precede the development of alcohol use disorder, suggesting an etiological role of PTSD in the development and maintenance of alcohol-related problems. Several recent studies of treatment-seeking adults in the U.S., Australia and Sweden found that the average age of the first trauma is often very young. For example, one study of 103 individuals (62% women) with alcohol/drug use disorders and PTSD found that 75% had experienced childhood trauma (before the age of 15) and the average age of first trauma was 8 years old. A more recent study of 22 women with alcohol use disorder and PTSD found that 91% had experienced childhood trauma, with an average age of 9 years old. In addition to exposure to early life traumas, exposure to multiple traumatic events is highly common. On average, studies find that participants with PTSD and substance use disorders are exposed to an average of 6 or more different types of traumatic events during their lifetime (e.g., physical assault, natural disaster, combat or warzone, serious injury or accident).

Many patients with PTSD and substance use problems report using alcohol/drugs in an attempt to “self-medicate” or “numb” the distressing symptoms of PTSD, such as nightmares, flashbacks and intrusive memories of the trauma, negative moods and cognitions (e.g., shame, self-blame, anger and irritability), hypervigilance and feeling “on edge,” as well as impaired sleep. In research using focus groups, nearly all participants (e.g., 96%) indicate that their PTSD symptoms and substance use are related, and that an increase or worsening of their PTSD symptoms is typically (86%) associated with an increase in their substance use. There is also shared neurobiology

between alcohol use disorder and PTSD (e.g., dysregulation in prefrontal cortex and limbic systems, as well as disruptions in the hypothalamic-pituitary-adrenal axis), that may help explain the common co-occurrence of alcohol use disorder and PTSD. Over time, each disorder can worsen the other (e.g., chronic alcohol use further impairs the body's natural stress response system, and increases in PTSD symptoms can lead to an increase in alcohol consumption).

Given the high co-occurrence of alcohol use disorder and PTSD, and the detrimental effects of this comorbidity, it is important that regular screenings occur across various clinical settings in order to identify individuals who need further evaluation and possible referral to treatment. Primary care is an important place to screen women for alcohol use, trauma exposure, and symptoms of PTSD. Several brief (5-10 items) screenings for trauma/PTSD are available, such as the Primary Care PTSD Screen, the Short Form of the PTSD Checklist, the Short Post-traumatic Stress Disorder Rating Interview (SPRINT), and the Trauma Screening Questionnaire. These and other relevant assessments can be found online through the National Center for PTSD (<https://www.ptsd.va.gov>) and the National Child Trauma Stress Network (<https://www.nctsnet.org>). The Alcohol Use Disorder Identification Test (AUDIT) is a widely used screening tool to assess alcohol use and alcohol-related problems.

Women with co-occurring alcohol use disorder and PTSD present to treatment with a more severe clinical profile (e.g., polysubstance use, poor physical health and social functioning, early age of onset of substance use disorder, increased depression and suicide attempts). Among adolescents, this comorbidity is associated with higher rates of delinquent behaviors. Individuals with co-occurring alcohol use disorder and PTSD often have poorer response to treatment and growing attention has been focused on the development of effective, evidence-based integrated interventions that address both conditions concurrently. These studies show that integrated treatments are feasible and lead to significant reductions in alcohol use, PTSD symptoms and associated problems (e.g., depression).

Summary

Exposure to trauma and violence is common among women and girls. Women are at significantly greater risk of developing PTSD after exposure to trauma than men. Alcohol use disorders are common among individuals with PTSD, with almost half meeting criteria for an alcohol use disorder at some point in their lifetime. Co-occurring alcohol use disorder and PTSD are associated with a complicated clinical presentation and impairment across multiple domains of functioning. Research on effective treatments (both psychotherapy and pharmacotherapy) for co-occurring alcohol use disorder and PTSD is underway. The literature to date on integrated treatments is promising and shows that women who receive treatment for their alcohol use disorder and PTSD can experience substantial improvement in both. Screening for alcohol, trauma and PTSD symptoms is important to include across various healthcare settings, such as primary care, in order to identify women who are at risk and need further evaluation and care.

Future areas of research: What we do not know

Greater research is needed to help advance the comorbidity science in this area and improve treatment outcomes for women. For example, more research is needed to better understand the role of trauma in women's initiation of alcohol use and the progression to alcohol use disorder.

Given that many women experience early life traumas, research on ways to prevent escalation from early life trauma exposure to the development of chronic PTSD and substance use disorders is needed. Interventions targeting adolescent girls and young adult females is needed to intervene earlier in the developmental process. Information on the potential benefits of gender-specific treatments is also lacking and more information is needed about which behavioral interventions and pharmacotherapies, or combinations thereof, are most effective for women. Furthermore, greater research is needed to enhance understanding of how gonadal hormones and fluctuations over the menstrual cycle may influence women's vulnerability to cravings and alcohol use. Study retention is a significant issue for this population, and more research is needed on how we can better engage and retain women with alcohol use disorder and PTSD in treatment. This may include more consideration of family and childcare responsibilities and needs, as well as ways to reduce stigma for women. More research on racial/ethnic differences is needed to help identify factors related to the development of alcohol use disorder and PTSD among women of various cultural backgrounds, and to inform the development of effective interventions. Given the high rates of interpersonal violence, more attention to ways to involve partners/couples in treatment would be beneficial. Finally, many women with alcohol use disorder and PTSD engage in other substance use (e.g., nicotine, opioids, marijuana). Research is needed to explore the rates, motives and impact of other types of substance use on both addiction and PTSD-related treatment outcomes.

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Pharmacologic Interventions for Substance Use Disorders with Comorbidity-focus on Alcohol Use Disorders and PTSD: Special Considerations for Women and Girls

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What we know

There are several medications that are approved to treat alcohol use disorders (AUD), but no approved medications to treat comorbid psychiatric conditions such as posttraumatic stress disorder (PTSD). Yet in clinical populations these conditions commonly co-occur and there are high rates of PTSD among those with AUD and high rates of AUD among those with PTSD (McCarthy and Petrakis 2010). Comorbidity is associated with worse outcomes, both in terms of AUD and PTSD symptoms (McCarthy and Petrakis 2010). Recent data suggests that rates of AUD among women have increased greatly over the past decade, and at rates that exceed the increase among men (Grant, Chou et al. 2017). There is also evidence that men and women may respond differently to traumatic events, with women being more likely to develop PTSD.

Medications are used to treat both disorders, and, while there are psychosocial interventions also available, there are clinical indications when pharmacotherapy is initiated. Medications used to treat AUD (not including for detoxification, which is often conducted in medically supervised setting and is beyond the scope of this review) are used to help individuals initiate abstinence or to prevent relapse. Pharmacotherapy is indicated when there is severe AUD, prominent symptoms of craving, heavy use, and a desire on the part of the patient to use medication. Similarly, use of medications to treat PTSD usually occurs in the context of active symptoms and a patient choice to use medications.

Although most of the research studies establishing efficacy of the medications approved by the Food and Drug Administration (FDA) to treat each of these conditions have been conducted primarily in non-comorbid conditions, there is a small literature evaluating the use of medications to treat AUD and PTSD when they co-occur (reviewed in (Petrakis and Simpson 2017)). Studies that have been conducted in comorbidity have been designed to answer the following questions: Are medications to treat one disorder safe and effective when used in the context of comorbidity? Are there medications that can treat both disorders? Because there is little research that focuses on women and girls, there is a very small literature.

Summary

The results of recent research suggest that medications to treat AUD (specifically, the FDA-approved medications naltrexone and disulfiram) can be used safely and are somewhat effective in treating AUD when complicated by comorbidity. Some medications (e.g., acamprosate) have not been formally tested in comorbid conditions. Medications to treat PTSD (the FDA-approved serotonin reuptake inhibitor antidepressants) similarly have some efficacy for their intended indication (i.e., to treat PTSD), but are not particularly effective in reducing alcohol consumption. Prazosin, a noradrenergic agent used to treat nightmares associated with PTSD (although not FDA -approved) (Raskind, Peterson et al. 2013) and for which there is

some data suggesting it may improve alcohol outcomes (Simpson, Meredith et al. 2007), was also tested in comorbidity (Simpson, Malte et al. 2015, Petrakis, Desai et al. 2016). In these studies, there was no effect of prazosin on PTSD symptoms or nightmares, but one study found an effect on reducing alcohol consumption. The most promising medication to treat comorbidity to date is the (non-FDA approved for either AUD or PTSD) mood stabilizer topiramate (Batki, Pennington et al. 2014), which in a small pilot study showed active treatment improvements for both PTSD and AUD symptoms.

Studies in patients with comorbid conditions are often limited by the inherent difficulties in conducting studies with highly vulnerable populations. These difficulties include the need to screen large number of patients to yield adequate sample sizes. Because of the difficulties inherent in recruiting and retaining subjects with co-occurring disorders, most of the studies published to date have had very small sample sizes. Many of these studies have been conducted with veterans, since PTSD is of great importance to the Veterans Administration (VA). This means that many studies have *been conducted primarily with men*. Given the recent increases in the rates of drinking among women and that women maybe more vulnerable to develop PTSD, further research is imperative.

Future Areas of Research: What we do not know

Formal evaluation of effective treatments for comorbidity has previously been mostly overlooked, but there is increasing awareness that interventions need to be tested empirically in “real world” clinical populations, with emphasis on identifying and addressing gender differences in response to treatment. Since results of studies to date suggest that current treatments are only marginally effective, new pharmacologic agents should (and are) being tested. Given that there are also psychosocial interventions which can be effective in these disorders (reviewed in (Simpson, Lehavot et al. 2017)), one interesting question is whether combining interventions may also be effective. Behavioral therapies and medications are often combined in clinical settings; thus, there is an urgent need for more research on integrative therapies. Including enough women to answer questions regarding gender differences is of great importance when designing clinical trials. Some areas requiring increased research focus include:

- Research to elucidate gender differences in risk for developing comorbid AUD/PTSD following exposure to traumatic events.
- Studies to identify new pharmacologic treatments for co-occurring AUD/PTSD, with emphasis on identifying gender differences in response to treatment.
- Research on combined pharmacologic and psychosocial interventions, with focus on gender differences in response to treatment.
- Studies targeting general civilian populations in diverse clinical settings. To date, studies on AUD/PTSD comorbidity have been conducted primarily in male veterans. This body of research needs to be more generalizable.

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Alcohol use among women with and at risk for HIV

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What we know

Alcohol misuse among women with HIV (WWH) is a modifiable barrier to optimal engagement in the HIV Care Continuum. It disrupts both antiretroviral adherence and retention in HIV care, both of which are associated with lower viral suppression and thus increase HIV transmission risk and poorer health outcomes. In a study at the Johns Hopkins HIV clinic, among women who were 1) non-adherent or not virologically suppressed and 2) with infrequent binge alcohol use or non-heavy drinking at baseline, increasing drinking was significantly associated with lower odds of subsequently improving adherence or viral suppression. Addressing alcohol misuse among WWH, is essential to optimize their engagement in the HIV care continuum.

Alcohol misuse is common among WWH and exceeds alcohol misuse among the general population of women. Lifetime prevalence of alcohol use with or without dependence in the general population is 7.5% compared with 19.6% among a large, multisite cohort of WWH (n=1027). Among at risk women, alcohol misuse is associated with increased HIV transmission behaviors, including condom-less vaginal and anal sex, multiple sex partners, sex with partners of unknown HIV status and drug use. Binge drinking is associated with a gonorrhea diagnosis, decreased HIV testing and with delayed pregnancy care. Among WWH, alcohol misuse continues to be associated HIV transmission behaviors, although awareness of HIV status does decrease likelihood of engaging in transmission behaviors. The causal relationship between alcohol and risk behaviors is difficult to directly establish; however, WWH who exceed weekly drinking limits are more likely than nondrinkers to subsequently engage in unsafe sex (condom-less vaginal sex with partner of unknown serostatus) six months later. (Unlike men with HIV, for whom binge drinking increases likelihood of unsafe sex.)

Alcohol misuse is highly comorbid with mental health disorders, including major depressive disorder (MDD) and posttraumatic stress disorder (PTSD), both of which are prevalent among at risk women and WWH. The lifetime prevalence of depression is 2-3 times higher among WWH and PTSD is 3-5 times greater among WWH compared with the general population of women. Prevalence is even higher among African American (AA) WWH. In the Johns Hopkins HIV Clinic, 16.5% of AA WWH (N=315) are diagnosed with current PTSD as ascertained with a standardized psychiatric interview. This prevalence is 11-fold higher than the general population of African American women. Both MDD and PTSD increase the likelihood of suboptimal ART adherence, worse HIV treatment outcomes, and increased HIV acquisition and transmission. Although less common, bipolar affective disorder (BPAD) is twice as likely among WWH and contributes to sex and drug risk behaviors. BPAD however is missed on screening measures which typically assess depressive symptoms only. This can adversely affect allocation of mental

health treatment resources and pharmacological interventions (e.g., antidepressants can precipitate a manic episode).

Psychiatric disorders can exacerbate alcohol misuse and impede alcohol reduction strategies. However, the full spectrum and comorbid occurrence of these disorders are often missed because of reliance on single target screening methods and single target treatments. Finally, among individuals receiving alcohol treatment, the presence of depression and PTSD predict poorer alcohol treatment outcomes. Thus, in implementing alcohol reduction strategies among at risk and WWH, it is important to identify and treat comorbid mental health disorders.

Summary

Given the adverse effects of alcohol misuse on HIV outcomes among women, it is critical to implement effective alcohol reduction interventions. Brief alcohol intervention can reduce alcohol use among women with HIV; however, this intervention may be less effective among women with heavier alcohol use, polysubstance use, and/or other mental health comorbidity, including depression and trauma. There are effective evidence-based interventions available, but the essential questions have not been answered:

Future Areas of Research: What we do not know

There is a critical need for research to determine which interventions work for specific subpopulations of women across the life span (e.g., for women with a particular type of substance use/mental health constellation) and under what conditions these interventions will be most effective. Examples:

- Younger women, whether at risk or HIV infected, tend to drink in a binge pattern and would have more recently experienced childhood sexual trauma, both of which are associated with HIV sexual risk behaviors. This pattern differs from older women who drink in a more predictable daily pattern, and potential posttraumatic stress disorder is often likely to have settled into a more chronic depressive disorder. Interventions for these two groups would likely vary as a function of disorder and lifespan, though this is not yet established.
- HIV continues to disproportionately affect African American women, suggesting that our interventions may not be sufficiently tailored to address some of their particular stressors or barriers.
- What are the most suitable approaches, settings, and agents to screen, engage, and maintain women in prevention and intervention in real world settings?
- Given the high degree of comorbidity of alcohol use and psychiatric disorders, should alcohol interventions be single target or combined with mental health interventions? There is a very limited evidence base for treatment options for WWH (and men) with comorbid alcohol misuse and mood disorders, anxiety disorder and/or PTSD.
- Bipolar Affective Disorder (BPAD) is often missed in the context of substance use and single target screening contributes significantly to poor health outcomes in HIV.

Other gaps in the literature among women with and at risk for HIV:

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- It is unknown whether and how alcohol use may affect women's use of and adherence to HIV Pre-Exposure Prophylaxis.
 - It is unknown how comorbid alcohol and mental health disorders affect women's engagement in the HIV prevention and care continuum.
 - It is not known how alcohol use affects ART adherence and maternal-fetal HIV transmission among women who are pregnant and have HIV.
 - It is unknown how alcohol use affects HIV-associated neurocognitive disorders and whether this varies by sex in aging cohorts.
 - How does the co-occurrence of IPV, alcohol and HIV (SAVA) impact 1) HIV care continuum outcomes among women with HIV; and 2) a pregnant woman's engagement with HIV/prenatal care?
 - What is the level of alcohol use that increases complications from non-communicable diseases (liver disease, cardiovascular disease, malignancy, frailty) among women with HIV?

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Treatment and Prevention in Special Populations: HIV

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What We Know

Women represent more than 50% of all those living with HIV, and HIV-related illness is the leading cause of death among women of reproductive age. In many countries, young women are twice as likely to acquire HIV compared to males of the same age; and in some countries, such as Haiti, the rate is five times higher among young women compared to men. Some of the factors that account for these disparities are intimate partner violence, laws that restrict women's freedom and choice, and traditional practices and norms that harm and disempower women. In too many low resource countries, women must have spousal permission to access health services. As a result of these factors that burden women disproportionately, it is critical that power disparities are considered when trying to address the syndemic of HIV among women and girls.

The interaction of substance abuse, violence, and HIV/AIDS is so intertwined and detrimental that it has become known as SAVA.¹ The additive effect is driven by contextual factors, including poverty, intersecting stigma and bias related to gender and race, lack of legal protections or enforcement of rule of law for crimes and abuse against women, and disempowering cultural roles that prevent women from taking care of their health. Gender-related economic and social inequality is frequently associated with age-disparate sexual relationships among adolescent girls and transactional sex. Violence or threat is often accompanied by trauma and mental health issues. Consequently, researchers have begun to include contextual markers of trauma and abuse.² Based on this work, SAVA may need to be revised to TSAVA: Trauma, substance abuse, violence and HIV/AIDS.

We know that gender-based and intimate partner violence are associated with delay in seeking reproductive preventive services and HIV testing and reduce adherence to antiretroviral regimens.

In addition to these special structural vulnerabilities, women and girls also face particular biological vulnerabilities such as the ability of HIV to pass through the vaginal lining, the expansive surface area of the vaginal lining, and the relatively higher levels of genital inflammation in adolescent girls. Cervical and vaginal tissue also may affect the concentration levels of oral pre-exposure prophylaxis, requiring higher adherence levels compared to MSM.³ Although only partly attributable to sex differences in alcohol pharmacokinetics, women also seem more vulnerable to the deleterious health effects of alcohol and the progression to developing an alcohol use disorder, while also being less likely to seek help or treatment.⁴

We know from our own work in Miami that substance-abusing pregnant and post-partum women delay entry into prenatal care and also substance abuse treatment because of fear of mandated legal reporting requirements.⁵ Severity of comorbid mental illness greatly increases HIV transmission risk and interferes with the acquisition and use of skills that could reduce risk.⁶ In addition, our work among HIV-positive women in Haiti has shown that depression and PTSD symptoms are predictive of lower adherence and higher alcohol use and that a history of childhood sexual abuse is predictive of adulthood IPV and higher alcohol use.^{7,8} These intersections of risk

have been found by other researchers such as Wechsberg⁹, Koblin¹⁰, Wagman¹¹, and Kiene¹², and more recently by Washio et al.¹³

In May 2018, our team completed Aim 1 of U34AA026219-01, *Optimizing PrEP Utilization among Alcohol and Other Drug (AOD) Using Women of Color*. This aim involved the implementation of a summit, which engaged HIV- and HIV+ women of color, health care providers and community stakeholders, to disseminate the latest information about HIV epidemiology in their local communities, biomedical strategies of prevention including PrEP and U=U, and to gather formative data about barriers and potential strategies in three break-out sessions of African American, Haitian, and Latina women. With free registration and no continuing education credits, 208 attended of the 273 registered, and the majority stayed to the end of the daylong event. This was the first such gathering devoted to HIV and biomedical prevention for women of color in S. Florida, and also the first to include transgender women in the planning and programming.

What we know so far from this U34 study is that 1) minority women do not know that antiretroviral therapy can prevent acquisition of HIV and can eliminate the practical risk of transmitting HIV; 2) there is tremendous grass-roots expertise on how to reach women at risk and get things done or GTD; 3) most of this expertise remains untapped by academic or government sponsored intervention programs; 4) community-based participatory research (CBPR) with full engagement in decisions makes a difference in not only mobilizing minority women and supportive community men but also in the content of what is delivered and the quality of what is learned from community participants; 5) medical mistrust is high and minority women at risk must be equipped to make health care contacts client-centered when they are not, even as future efforts seek to transform the continuum of care; and 6) health care providers may need debriefing interventions to process their own cognitions and emotions evoked by women who are trying to constructively cope with high-risk situations asking for PrEP. Thus far, our experience in the study is indicative that biomedical innovation increases rather than relieves the need for adapted, localized socio-behavioral interventions, and that community uptake is a function of whether and to what extent interventions are developed and implemented in cooperation with the target communities. As the study has proceeded, we have come to describe our CBPR approach as a *co-authored* model.

Future Areas of Research: What we do not know

Foremost in what we do not yet know that this U34 will be addressing is how to integrate interventions for harmful alcohol use with PrEP-focused HIV prevention for minority women at risk, among whom risk begins with unprotected sex, not knowing the HIV status of a sexual partner, and living in a high prevalence area. Many of these women are leading the average American life. Critical to what we mean by integration is how to introduce the issue to this population and formulate messaging and content that will be embraced by women and not spurned because of connotations of stigma/labeling or lack of perceptions of risk. Also, we do not know the barrier posed by the need for repeat HIV and other biomedical testing required to take PrEP. In addition, several other areas which are rarely discussed in the literature need further investigation, including but not limited to:

- What is the role of secondary AOD (similar to second-hand smoke) and how does it fit into uptake of HIV preventions by minority women? Many women become more vulnerable if partners use alcohol and substances because the partners are more likely to engage in violent behaviors, including forced sex, and to engage in risky behaviors and transmit

infections. AOD-using partners may also encourage substance use among female partners. Most of the studies on harms to intimate partners due to AOD use have been conducted by Australian researchers.¹⁴⁻¹⁷

- What are the cultural differences in how violence and abuse are perceived and manifested, and how might these relate to perceptions of HIV risk and thus uptake of PrEP?
- In breaking through misconceptions about risk among minority women, to what extent can a history of childhood maltreatment be used as a contextual marker for either screening or personalized risk assessments? Can prevention of child maltreatment be linked with HIV prevention for women?
- How can legal assistance be effectively linked with PrEP-focused HIV prevention? Highly vulnerable minority women often have need of legal assistance or advice. Fears about legal ramifications can inhibit seeking care.
- What is the role of sexual pleasure and conceptualizing sexual goals in promoting uptake of PrEP among minority women? This issue has been found to be important among MSM, but has not been fully explored among women.¹⁸

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Interventions to Improve Harmful Alcohol and Opioid Use Among Women and Girls Involved in the Criminal Justice System

Sandra A. Springer, MD

What we know

The United States incarcerates more people than any other country. While African American women comprise only 13% of the female population in the U.S., they make up more than 50% of the incarcerated population.¹ (GLAZE 2014) Approximately 1 million women are currently under some form of criminal justice supervision in the U.S.¹ The number of women in U.S. prisons has increased at double the rate of men since 1985 (40% compared to 20% in men). (The Sentencing Project and prisonpolicy.org) Currently there are approximately 219,000 women incarcerated in prisons.² Women in state prisons are typically more likely to be incarcerated for drug or alcohol offenses than men.³ Further, women who are incarcerated tend to be predominantly comprised of racial and ethnic minorities (44% black, 15% Hispanic; 36% who self-identify as white) and over 86% of women in jails reported some form of sexual violence.⁴ Further, HIV is three times more prevalent in the U.S. prison system^{5,6}, and in 2010 the HIV prevalence for imprisoned women was estimated to be 1.9%, which is greater than that of men (1.4%)⁵.

Incarcerated persons living with HIV (PLH) receive effective antiretroviral therapy (ART) and can achieve high levels of HIV viral suppression (VS) prior to release. However, despite high levels of VS achieved during incarceration,⁷ upon release to the community released PLH face low linkage to HIV care,⁸ high rates of relapse to substance use,⁹ homelessness,¹⁰ and overdose.¹¹ Together, these factors undermine adherence to ART after release and result in loss of VS.^{8,12-14} Higher viral loads in PLH impose higher morbidity and mortality for the individual, as well as increased risk of transmission of HIV to the uninfected.¹⁵⁻¹⁷

Alcohol use disorders (AUDs) and Opioid Use Disorders are 8-times more prevalent in criminal justice populations than in the community, with alcohol and opioid relapse being especially common and problematic post-release.^{18,19} Relapse to opioid use is very common after release and is the opioid overdose is number one cause of death in people released from jail and prison. (Binswanger NEJM etc) . In PLH, AUDs and OUDs exacerbate ART non-adherence, resulting in suboptimal HIV VS.²⁰ The majority of prisoners in the U.S. do not receive medication to treat AUDs or OUDs or prevent relapse to alcohol or opioid use at time of release.^{18,21} Extended-release naltrexone (XR-NTX) is an evidence-based and FDA-approved treatment for AUDs and OUD that delays and reduces alcohol and opioid consumption,²² (also add Krupitsky 2011; Lee NEJM 2016; Lee Lancet 2018 and Tanum JAMA Psychiatry 2018) including for incarcerated PLH with AUDs and OUDs who are released to the community.²³

Prior work by *Springer and colleagues* has identified that the use of certain types of medications approved to treat opioid use disorders (OUD) among PLH being released from prison and jail has led to HIV viral suppression.²⁴ A prospective trial of Buprenorphine among released HIV+ opioid dependent prisoners resulted in reduced opioid relapse and improved HIV viral suppression 6 months post-release as compared to those who chose not to start buprenorphine or those who used methadone.^{24,25} Further, this team recently published results of a multi-site randomized double-blinded placebo-controlled trial of XR-NTX among opioid dependent

prisoners and jail detainees in CT and MA who were transitioning to the community, showing that those who received XR-NTX had higher HIV VS (at < 50 copies/mL) compared to those who received placebo. (.insert Springer et al. JAIDS 2018) Notably, those who received 3 or more injections of XR-NTX also achieved longer periods of opioid abstinence compared to those who received any number of placebo injections.²⁶ There were no serious adverse events in the intervention group. The results of these studies have shown that medication treatment of OUD with buprenorphine and XR-NTX along with ART for HIV increases the likelihood of achieving and maintaining VS, the gold standard for measurement of success of treatment of HIV that is associated with reduction in morbidity and mortality from HIV as well as non-HIV complications and reduces transmission to the uninfected.

Encouraged by these results, *Springer S et al.* set out to determine whether XR-NTX, also FDA approved for AUDs, could also improve HIV VS among PLH with AUDs released from prison and jail. She and colleagues at the Yale School of Medicine conducted an NIAAA-funded randomized double-blinded placebo controlled trial of XR-NTX among prisoners in CT with hazardous drinking or alcohol abuse or dependence,²⁷ and found the same results generated by the opioid use disorder study: that XR-NTX improved HIV viral suppression and reduced alcohol relapse outcomes, and there were no serious adverse events when compared to placebo.^{23,28} In this trial, eligible participants who were being released from prison who had HIV disease and hazardous drinking or DSM IV alcohol abuse or dependence (N=100) were randomized 2:1 to receive 6 monthly injections of XR-NTX (n=67) or placebo (n=33) starting at release and continuing for 6 months. The primary and secondary outcomes were the proportion that maintained or improved HIV Viral Suppression (VS) at <200 copies/mL and <50 copies/ml from baseline to 6 months respectively using an intention to treat analysis. Participants assigned to XR-NTX improved VS from baseline to six months for <200 copies/mL (48.0% to 64.2%, p=0.024) and for <50 copies/mL (31.0% to 56.7%, p=0.001), while the placebo group did not (<200 copies/mL: 64% to 42.4%, p=0.070; <50 copies/mL: 42.0% to 30.3%, p=0.292). XR-NTX participants were more likely to achieve VS than placebo at six-months (<200 copies/mL: 64.2% vs. 42.4%; p=0.041; <50 copies/mL: 56.7% vs. 30.3%; p=0.015). XR-NTX independently predicted VS (<200 copies/mL: aOR=2.68, 95%CI=1.01-7.09, p=0.047; <50 copies/mL: aOR=4.54; 95% CI=1.43-14.43, p=0.009), as did receipt of ≥3 injections (<200 c/mL: aOR=3.26; 95% CI=1.26-8.47, p=0.010; <50 c/mL: aOR=6.34; 95%CI=2.08-19.29, p=0.001). Reductions in alcohol consumption (aOR=1.43; 95% CI=1.03-1.98, p=0.033) and white race (aOR=5.37; 95% CI=1.08-27.72, p=0.040) also predicted VS at <50 copies/mL. This study also found a reduction in alcohol consumption and a longer time to heavy drinking days for younger participants.²³ As expected based on prior research involving XR-NTX, there were no differences based on sex. Overall this was the very first study that has shown that a form of medication to treat AUD can also improve HIV viral suppression in persons living with HIV.

Summary:

There is an urgent need to identify medications and other interventions for women with HIV with AUD and/or OUD involved in criminal justice settings. Studies completed to date show high acceptability of medications to prevent relapse and also show both reductions in relapse to alcohol and opioid use and improvements in HIV viral suppression. Despite this work, there is little uptake of pharmacologic approaches to preventing and treating AUD or OUD among women in criminal justice settings prior to release to the community. Given the potential of AUD

and OUD medications to reduce individual morbidity and mortality from HIV, as well as to significantly improve public health by reducing the transmission of HIV, further investment in this area of research is warranted.

Future Areas of Research: What we do not know

1. Studies on the cost-effectiveness of XR-NTX therapy for PLH and AUD and OUD. One of the major impediments to adoption and implementation of any evidence-based treatment, particularly for criminal justice-involved persons, is cost. Findings from the previously discussed study by *Springer and colleagues* involving the treatment of released prisoners with HIV and AUD and OUD with XR-NTX²⁹ (2 references: Springer JAIDS 2018 for AUD; Springer JAIDS 2018 for OUD study) provide the highest level of support for treating AUDs and OUDs in transitioning incarcerated individuals with HIV. However, cost-effectiveness analyses are necessary prior to widespread adoption of this approach as part of the U.S. response to controlling the HIV pandemic.
2. Implementation research to assess the generalizability of this intervention to other communities, such as resource-limited countries where prevalence of HIV and AUDs are highest (e.g., Sub-Saharan Africa).
3. Studies involving newer, longer-acting naltrexone preparations. Formulations such as implantable naltrexone that lasts for 3 to 6 months could overcome challenges with returning for monthly injections.
4. Research to determine the effectiveness of pairing long-acting medications like XR-NTX and now long-acting injectable buprenorphine with long-acting injectable ART (Cabotegravir and Rilpivirine) as one approach to pre-exposure prophylaxis (PrEP) for HIV prevention among those with AUD/ OUD. The use of long-acting injectables for AUD and OUD and HIV should also be investigated in women living with HIV as means to improve VS in other settings beyond incarceration.
5. Studies to identify best approaches to screening women and girls involved in the CJS for AUDs and OUDs. To date, very few pharmacotherapy studies have included women. Thus, more focus should be on recruitment of women and girls into medication trials to reduce relapse to alcohol and opioid use, reduce HIV infection in concert with other ongoing HIV prevention efforts, and to increase the likelihood of suppressing HIV viral load and reducing morbidity and mortality among women living with co-occurring HIV and AUDs and OUDs.
6. Improving research related to finding more women and girls to recruit for medication studies related to OUD and AUD . At present women only represent at the most 30% of all medication studies involving OUD and AUD medications.

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Reducing the Stigma of Addiction and Fetal Alcohol Spectrum Disorders (FASD):

Creating a Circle of Hope

Kathleen Tavenner Mitchell, LCADC, MHS

“The real story should be very short “I was a dirt bag and did harm to my child--don’t be a dirt bag.”

Comment from Washington Post Reader

What we know

Stigma focuses negatively on differences amongst people. Stigma has been described as a powerful, complex social and cognitive process that leads to the discrediting, devaluing or excluding of a person or group of people based on a real or perceived difference (Corrigan, 2017). Stigma is “acted out” through labeling, social exclusion, prejudice, and discrimination against the stigmatized individual or group (Corrigan et al., 2017). Disorders that appear to be self-inflicted or due to poor or immoral behaviors are commonly the most stigmatized. Both alcohol use disorders (AUDs) and substance use disorders (SUDs) are among the most stigmatized of medical conditions (Kulesza, 2013).

No woman intentionally harms her own child. Women who have used alcohol or other substances while pregnant or have children with an FASD experience tremendous shame and guilt coupled with a long process of grief. Mothers typically exhibit shame-based thinking that can become permanent and pervasive without support. This shame can lead to extreme denial, defensiveness, blame, hopelessness and remorse. There are many reasons why women drink during pregnancy (Mitchell, 2017). According to a 2012 National Organization on Fetal Alcohol Syndrome (NOFAS) Circle of Hope survey of 93 birth mothers of children with an FASD, women were either misinformed about the facts on alcohol use while pregnant, unaware that they were pregnant, suffered with a substance use disorder (SUD) or alcoholism and were unable to stop on their own, too ashamed to talk to their physician, or afraid of losing custody of their children (Mitchell, 2014; NOFAS-COH, 2012).

Public Stigma: Negative public attitudes and social beliefs towards women who drink during pregnancy foster a cycle of fear, blame and shame that have far-reaching impact on FASD prevention, diagnosis, and treatment across the lifespan (Mitchell, 2016). A 2017 study (Corrigan, 2018) compared public perceptions of difference, disdain, and blame about four groups; women with mental health issues (MI), women with SUD, women that had jail experience, and women that had a child diagnosed with an FASD. The study was one of the first to systematically examine the public stigma of FASD. The survey showed the public viewed mothers of children with FASD with greater disdain, more different and more responsible than women with mental illness, SUD or women that had been in jail (Corrigan et al., 2018). Another study that included a one-year media analysis showed two themes reflecting FASD stigma:

sympathy for the child and disdain for the biological mother (Eguiagaray, Scholz, & Giorgi, 2016).

One of the ways that public stigma is acted out is on social media sites and print and media comment sections. The anonymity of social media brings much of the hidden stigma out in the open. One powerful example of public stigma towards a birth mother occurred in January, 2016 when the Washington Post featured an article about my life experiences ([This Mother Drank While Pregnant](#)). The Post reported that by day three, nearly 8 million readers had viewed it. The article soon went viral, trended on Face Book and was featured on websites, newspapers, magazines, radio and television around the world. Along with the global media attention came thousands of emotion-based comments from readers that were judgmental, blaming, and hateful (Mitchell, 2018). These comments serve as a true reflection of public stigma towards women with SUD and birth mothers of children with FASD.

Stigma leads to discrimination: Discrimination has been measured in the research literature in terms of policy decisions (Skitka and Tetlock, 1992). Legislators who endorse stigma of a group are less likely to support policies that provide or encourage resources for that group. Past research has shown that significantly fewer dollars are allocated for stigmatized conditions such as SUD and mental illness (MI) than for programs like *healthy kids* (Corrigan et al., 2014). Discrimination leads to policies that seek to control a stigmatized group. Taking children from their birth mothers without offering adequate treatment and support is an example of discrimination in action (Mitchell, 2017).

Stigma Reduces Support for Women and Increases Fetal Exposures: Stigma and stereotyping of women often prevent providers from asking women about their alcohol or other substance use while pregnant. The name of the condition, FASD, implies to some that the mother willingly or purposely caused harm to her own child. Corrigan et al., 2018, found that physicians and healthcare providers have hidden stigma and negative attitudes towards mothers who have children with an FASD. The research reported stereotypical beliefs about birth mothers of children with FASD that included: *They are ignorant. They are unstable. They are selfish. They are uneducated. They are child abusers. They are unable to change.*

Summary

Unless more effort is devoted to reducing the stigma towards women and mothers that experience SUD, the number of pregnancies that are substance-exposed will continue to rise. Historically, the most widely used FASD public health messages stated that FASD was caused by the mother's drinking. These messages had the unintended result of blaming the mother. As a first step to reduce public stigma around FASD, NOFAS revised the FASD public health language to be less stigmatizing and blaming of mothers. An example is, rather than say *FASD is an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy*, say instead, *FASD is an umbrella term describing the range of effects that can occur in an individual who was exposed to alcohol before birth* (NOFAS-SOS, 2016). NOFAS strives to have all government agencies, researchers, authors, healthcare professionals, and advocates from around the world agree to reframe the public health messages and work together to stop laying the blame for FASD onto birth mothers. It's up to all of us to do our part to reduce the stigma.

Future Areas of Research: What we do not know

NIAAA has decades of research on the causes, prevention and treatment of both alcoholism and FASD. We now have research on both public and provider stigma towards birth mothers of children with FASD. Any new research should focus on reducing the stigma by helping the public and providers understand more clearly the neurobiology of addiction, the effectiveness of treatment, and the very real potential for long-term recovery when women of childbearing age receive the wrap-around supportive services they need. By increasing the knowledge of who becomes addicted and why, we will ultimately reduce stigma and the number of substance-exposed pregnancies.

- Prioritize resources and efforts to educate medical and allied health students and professionals about women and addiction, FASD, and other conditions related to prenatal substance exposure.
- Research to determine whether education on the etiology of addiction and professional contact with recovering birth mothers of children with an FASD reduces stigma among medical and allied health students and professionals.
- Research examining the impact of appropriate addiction treatment on rates of FASD and substance-exposed pregnancies.
- Studies to measure the effects of physician screening, brief intervention and referral to treatment on the likelihood of long-term recovery in women (more than one year).
- Research on the long-term maternal-child health benefits of using 12-step recovery in specific high-risk populations of childbearing-age women.

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