ALCOHOL AND WOMEN’S HEALTH: STUDIES REVEAL PROBLEMS

Increases in the prevalence of alcohol misuse and alcohol use disorder (AUD) among women point to a growing adverse effect of alcohol on the health of women in the United States, according to findings by NIAAA scientists. While alcohol misuse by anyone presents serious public health concerns, women have a higher risk of certain alcohol-related pathologies compared to men.

“The harms associated with alcohol misuse in women escalate more quickly, and at lower drinking levels, than in men, and the damage tends to be more severe,” says NIAAA Director George F. Koob, Ph.D.

Alcohol resides predominantly in body water, and pound for pound, women have less water in their bodies than men. This means that after a woman and a man of the same weight drink the same amount of alcohol, the woman’s blood alcohol concentration will tend to be higher, putting her at greater risk for harm. Other biological differences may contribute as well.

“The worrisome trends we’ve seen lately should make clinicians, researchers, and the public take note and spur action to improve diagnosis, prevention, and treatment of alcohol misuse among women,” Dr. Koob says.

A 2015 study led by Aaron White, Ph.D., NIAAA’s senior scientific advisor to the Director, indicates that longstanding differences between men and women in alcohol consumption and alcohol-related harms might be narrowing in the United States. The analysis of annual data from the National Survey on Drug Use and Health found that differences in measures such as current drinking, number of drinking days per month, reaching criteria for AUD, and driving under the influence of alcohol in the past year, all narrowed for females and males between 2002 and 2012. The findings suggest that, while males still consume more alcohol, the differences between men and women are diminishing.

In March, researchers led by Rosalind Breslow, Ph.D., M.P.H., R.D., of the NIAAA Division of Epidemiology and Prevention Research, reported upward trends in drinking among adults ages 60 and older in the United States, especially among women. (See News From the Field: Study Finds Older Americans Are Drinking More.) While the analysis of data from more than 65,000 participants ages 60 and older in the National Health Interview Survey found that men continue to drink more than women, the prevalence of current drinking increased over time more significantly among women than men, narrowing the gender gap by about

Continued on page 3
A new study led by NIAAA scientists demonstrates that aldosterone, a hormone produced in the adrenal glands, may contribute to alcohol use disorder (AUD). The novel research, conducted in collaboration with a team of investigators in the United States and Europe, appears in the May 2017 issue of the journal Molecular Psychiatry.

“This intriguing work—conducted in humans as well as two other species—provides a compelling example of how basic and preclinical research is translated into studies with direct relevance to humans,” says NIAAA Director George F. Koob, Ph.D., a co-author of the study. “Our overall hypothesis has been that aldosterone may play a role in AUD via its MR receptor and that this neuroendocrine pathway may be particularly important in anxiety, stress, and stress-induced alcohol drinking.”

The new report describes three separate studies, conducted with non-human primates, rats, and humans, that investigated the potential contribution of the aldosterone/MR pathway to AUD.

In a study conducted with non-human primates, the researchers found that animals that self-administered alcohol every day for 6 to 12 months had significantly higher blood aldosterone concentrations, compared with those measured prior to alcohol administration. Furthermore, the researchers found that in the amygdala, lower MR gene expression was associated with increased alcohol drinking in the animals.

In a study conducted in a rat model of AUD, lower levels of MR gene expression in the amygdala (but not in the prefrontal cortex) were associated with increased anxiety-like behavior and compulsive drinking, compared to rats not exposed to alcohol.

In a human study of about 40 individuals undergoing treatment for AUD, the researchers found that blood aldosterone concentrations were higher in individuals who continued drinking during the 12-week period, compared with those who were abstinent during the same time frame. The researchers also found that increasing blood aldosterone concentrations correlated with increasing levels of both alcohol craving and anxiety.

Taken together, the researchers conclude that the findings across three different species suggest that there is a relationship between alcohol misuse, AUD, and specific changes in the aldosterone/MR pathway marked by increased circulating aldosterone and decreased MR gene expression in the amygdala.

Reference:
5 percent between 2006 and 2014. The gender gap in binge drinking among adults ages 60 and older also narrowed.

“These trends among older adults are particularly concerning, since older adults who drink are at higher risk of unintentional alcohol-related injuries, health problems exacerbated by alcohol use, and alcohol-prescription medication interactions,” says Dr. Breslow.

Deidra Roach, M.D., a medical project officer in NIAAA’s Division of Treatment and Recovery Research, points to cultural changes as a leading explanation for the increase in alcohol misuse among women.

“The culture around women’s drinking has changed dramatically over the past 50 years,” says Dr. Roach. “These days, women often go out for a night on the town with the intention of drinking heavily, and we see the evidence for this all over social media. Stress is another factor. Women experience higher rates of anxiety and depression than men do, and more often drink in response to negative mood states. But while alcohol may ‘take the edge off’ anxiety or elevate a depressed mood in the moment, over the long term, alcohol misuse only makes these problems worse.”

Just last month, NIAAA researchers provided still more evidence of this troubling trend. Reporting online in *JAMA Psychiatry*, researchers in the NIAAA Epidemiology and Biometry Branch and their colleagues compared data from the 2001–2002 and the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions. They found that the prevalence of alcohol use, high-risk drinking (defined as drinking, on any day, four or more drinks for women and five or more drinks for men), and AUD increased across almost all sociodemographic groups in the United States over the period between the surveys. With few exceptions, increases in all the outcomes were the greatest among women, older adults, racial/ethnic minorities, and those with lower educational levels and family income.

NIAAA is committed to better understanding the causes and consequences of alcohol misuse among women and to developing strategies for addressing it. The new *NIAAA Strategic Plan 2017–2021* identifies a number of research priorities spanning the Institute’s broad portfolio that are relevant to this issue. Raising awareness about the effects of alcohol on women’s health and safety is a key component of this effort. On June 22, Drs. Koob and Roach joined Carlo DiClemente, Ph.D. (University of Maryland, Baltimore County), Barbara McCrady, Ph.D. (University of New Mexico), and Martha Woodroof, former public radio journalist, at a congressional briefing sponsored by the Friends of NIAAA. Titled “The Changing Patterns of Women’s Drinking and Their Impact on Public Health,” the briefing discussed recent trends in alcohol misuse by women and alcohol’s effects on women’s health, as well as evidence-based practices for diagnosing, preventing, and treating alcohol-related conditions in women.

“The briefing was an important opportunity to present timely information to congressional staff, an interested and influential audience, on this growing problem,” says Dr. Koob.

For more information about women and alcohol use or general information about the health risks of alcohol misuse, visit https://www.niaaa.nih.gov.

References:

### What Are the Health Risks Related to Alcohol?

**Alcohol Use Disorder (AUD)**—AUD is a chronic relapsing brain disease characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. AUD can range from mild to severe, and recovery is possible regardless of severity.

**Liver Damage**—Women who regularly misuse alcohol are more likely to develop alcoholic hepatitis, a serious acute illness, than men who drink the same amount of alcohol. This pattern of drinking can also lead to cirrhosis of the liver. Alcoholic liver disease includes a broad range of diseases, from the less severe—steatosis (fatty liver)—to end-stage liver disease, or cirrhosis (liver cell death).

**Heart Disease**—Long-term alcohol misuse is a leading cause of heart disease. Women are more susceptible to alcohol-related heart disease than men, even though they may consume less alcohol over a lifetime than men.

**Brain Damage**—Research suggests that alcohol misuse produces brain damage more quickly in women than in men. In addition, because alcohol can disrupt the development of the brain during the adolescent years, teen girls who drink may be more vulnerable to brain damage than teen boys who drink. Women also may be more susceptible than men to alcohol-related blackouts, defined as periods of memory loss of events during intoxication without loss of consciousness.

**Breast Cancer**—There is an association between drinking alcohol and developing breast cancer. Women who consume about one drink per day have a 5–9 percent higher chance of developing breast cancer than women who do not drink at all. That risk increases for every additional drink they have per day.

**Pregnancy**—Any drinking during pregnancy can be harmful. A woman who drinks during pregnancy puts her fetus at risk for physical, cognitive, or behavioral problems. Drinking during pregnancy can also increase the risk for preterm labor.
LABORATORY OF CARDIOVASCULAR PHYSIOLOGY AND TISSUE INJURY

NIAAA’s Laboratory of Cardiovascular Physiology and Tissue Injury (LCPTI) investigates how alcohol affects the heart. Research from the lab shows that in animal models a single episode of binge drinking can dramatically impair the heart and its blood vessels. Pictured left to right, front row: Adam Mehal and Partha Mukhopadhyay, Ph.D., and back row: Pal Pacher, M.D., Ph.D., Chief of LCPTI; Janos Paloczi, Ph.D.; and Zoltan Varga, M.D., Ph.D.

BY THE NUMBERS

EXTREME BINGE DRINKING

Binge Drinking and the Likelihood of Emergency Room (ER) Visits
Compared to non-binge drinkers, individuals who engaged in:

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Increased Risk of ER Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Level I binge drinking had a</td>
<td>13X</td>
</tr>
<tr>
<td></td>
<td>4–7 drinks on a single occasion for women &amp; 5–9 drinks on a single occasion for men.</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Level II binge drinking had a</td>
<td>70X</td>
</tr>
<tr>
<td></td>
<td>8–11 drinks on a single occasion for women &amp; 10–14 drinks on a single occasion for men.</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Level III binge drinking had a</td>
<td>93X</td>
</tr>
<tr>
<td></td>
<td>12+ drinks on a single occasion for women &amp; 15+ drinks on a single occasion for men.</td>
<td></td>
</tr>
</tbody>
</table>

Level I = 4–7 drinks on a single occasion for women & 5–9 drinks on a single occasion for men.
Level II = 8–11 drinks on a single occasion for women & 10–14 drinks on a single occasion for men.
Level III = 12 or more drinks on a single occasion for women & 15 or more drinks on a single occasion for men.

Drinking at Levels II and III is consistent with extreme binge drinking.

Nearly 32 million adults in the United States (13 percent of the U.S. population ages 18 and older) consumed more than twice the number of drinks considered binge drinking—defined as extreme binge drinking—on at least one occasion in the past year, according to the most recent National Epidemiologic Survey on Alcohol and Related Conditions.

Binge drinking, defined as having four or more drinks on an occasion for women, or five or more drinks on an occasion for men, can produce blood alcohol levels greater than 0.08 percent, which is the legal limit for driving in the United States. Reaching this level is well known to increase the risk of harms to the drinker and others.

However, evidence suggests that many people drink far beyond four or five drinks per occasion. The researchers identified three levels of past-year binge drinking. Level I is defined as four to seven drinks on a single occasion for women and five to nine drinks on a single occasion for men. Level II is defined as eight to 11 drinks on a single occasion for women and 10 to 14 drinks on a single occasion for men. Level III is defined as 12 or more drinks on a single occasion for women and 15 or more drinks on a single occasion for men. Drinking at Levels II and III in the study is consistent with extreme binge drinking.

Compared to non-binge-drinkers, Level I binge drinkers are 13 times more likely to have an alcohol-related emergency room visit. The likelihood is even higher for people who engage in extreme binge drinking: Level II binge drinkers are 70 times more likely, and Level III binge drinkers are 93 times more likely, than non-binge drinkers to have an alcohol-related emergency room visit.

Reference:
RESEARCHERS GET PRACTICAL LESSON IN TREATING AUD AT RSA—VIDEO NOW AVAILABLE

How is alcohol use disorder (AUD) treated in the real world? An ambitious symposium set out to answer this question for alcohol researchers at the 2017 annual meeting of the Research Society on Alcoholism (RSA). The symposium, “Everything You Ever Wanted to Know About Alcohol Treatment But Were Afraid to Ask: A Primer for Non-Clinicians,” covered screening and diagnosis, brief interventions, and referral to treatment, as well as the many treatment options and potential pathways through treatment. The symposium included discussions of approved and experimental medications and various behavioral therapies. This goal of this session was to describe the nuts and bolts of alcohol treatment for researchers who are not typically exposed to these topics.

The symposium was organized by NIAAA’s Anita Bechtholt, Ph.D., and Robert Huebner, Ph.D., and chaired by NIAAA Director George F. Koob, Ph.D. Speakers included Richard Saitz, M.D., Boston University Schools of Medicine and Public Health, who spoke about determining when someone needs treatment; Carrie Wilkens, Ph.D., the Center for Motivation and Change, who addressed the kinds of behavioral treatments delivered in treatment programs; Keith Humphries, Ph.D., Stanford School of Medicine, who

As people age, they tend to grow more sensitive to alcohol’s effects on balance, attention, reaction time, and driving skills. In addition, people 65 and older generally are prescribed more medications, and the potential for adverse health effects from alcohol-medication interactions can increase. Such issues are an emerging public health concern underscored by a recent report that found Americans over age 60 are drinking more than they were 20 years ago.

Dr. Rosalind Breslow, in the NIAAA Division of Epidemiology and Prevention Research, and colleagues examined data from more than 145,000 responses to the National Health Interview Survey between 1997 and 2014. In addition to observing an increase in the number of older adults who consumed alcohol, the researchers found that the largest increase in the percentage of current drinkers was among women.

Twenty years ago, 37.8 percent of women reported being current drinkers; in 2014, the rate jumped to 47.5 percent. The rate of male current drinkers also increased, from 54 percent to 59.9 percent over two decades.

From 1997 to 2014, rates of binge drinking—defined for the purposes of this study as consuming five or more drinks in a single day—among older drinkers changed slightly, but not enough to be considered statistically significant. However, among older female drinkers, the prevalence of binge drinking increased from 4.9 percent to 7.5 percent, a significant increase. Among older male drinkers, the increase was not significant.

The findings spotlight the growing number of women in this age group who reported binge drinking, matching trends seen in separate studies among younger populations. (See feature story Alcohol and Women’s Health: Studies Reveal Problems). The authors concluded that these upward trends in drinking among adults ages 60 and over, particularly among women, suggest the importance of public health planning to meet future needs for alcohol-related programs for older adults who drink.

Reference:

Continued on page 8
OXYTOCIN SHOWS PROMISE AS TREATMENT FOR AUD

Administration of oxytocin, a naturally occurring hormone and neurotransmitter in the brain, reduced alcohol consumption in a variety of mouse models, reports a new NIAAA-funded study. These results provide evidence that the oxytocin system may play a role in the motivational effects that contribute to alcohol use disorder (AUD) and, as such, may be a promising target for diagnosis, prevention, and treatment of AUD.

Well-known for its role in childbirth and maternal bonding, oxytocin also influences social interactions and emotions. Accumulating evidence suggests that oxytocin plays a role in neuropsychiatric disorders that affect social behaviors, including AUD. In animal models, oxytocin has been shown to decrease alcohol consumption and alter alcohol’s motivational effects.

To gain a better understanding of the effectiveness and specificity of oxytocin’s effects on alcohol consumption and motivation, Howard C. Becker, Ph.D., Director of the Charleston Alcohol Research Center at the Medical University of South Carolina, and colleagues examined alcohol consumption in mice using three different models. The first approach involved a binge-like drinking model, where mice are given the opportunity to drink alcohol for a relatively short period of time. The second method was a two-bottle choice model in which mice are presented two bottles—one with alcohol and the other with tap water—to examine preference for alcohol. In the third model, mice must press a lever to access alcohol or sucrose (sugar); this approach allows investigators to evaluate the animals’ motivation to obtain alcohol compared to a natural reward. The researchers systemically administered a range of doses of oxytocin to the mice in each of these experimental conditions.

The researchers found that oxytocin reduced alcohol consumption in a dose-related manner in all three animal models. In the binge-drinking model, the higher doses of oxytocin reduced the mice’s alcohol intake by as much as 45 percent. In both the binge-drinking and two-bottle choice models, the

INTESTINAL FUNGI MAY WORSEN ALCOHOLIC LIVER DISEASE

Alcoholic liver disease (ALD) includes a broad range of diseases, from the less severe—steatosis (fatty liver)—to end-stage liver disease, or cirrhosis (liver cell death). Liver cirrhosis is a leading cause of mortality worldwide, with about half of those deaths due to alcohol misuse.

Alcohol misuse has been linked to bacterial overgrowth in the intestines, as well as a shift in the types of bacteria found there. Now, a new NIAAA-funded study is among the first to suggest that intestinal fungi may contribute to the development of ALD.

A team of researchers led by Bernd Schnabl, M.D., at the University of California San Diego, and Derrick Fouts, Ph.D., at the J. Craig Venter Institute in Rockville, Maryland, has shown that oral antifungal treatment protects mice from alcohol-related liver disease progression. In separate components of the study conducted in humans, the researchers linked intestinal fungi to ALD and to increased risk of death for people with ALD.

In animal studies, the researchers found that fungi flourished in the intestines of mice with chronic alcohol exposure. In turn, researchers noted that fungal overgrowth worsened the alcohol-induced liver disease. However, mice treated with the antifungal agent amphotericin B had lower levels of liver injury and fat accumulation.

The researchers also examined intestinal fungi in people with alcohol use disorder (AUD) and various stages of liver disease. The researchers observed less variety in the types of fungi in the intestines of individuals with AUD and
You wear two hats in your work at NIAAA. You manage a grant portfolio focused on aging and chronic disease, and you also publish in peer-reviewed journals. Tell us about some of your original research.

My aim is to shed light on research areas that are new, promising, and understudied. I generally collaborate with statisticians and other experts, and we almost always use data available to the public; for example, the National Health Interview Survey (NHIS) or the National Health and Nutrition Examination Survey (NHANES).

Our most recent papers focused on trends in alcohol consumption among older adults and on use of prescription medications by drinkers. We were drawn to these areas because there wasn’t much previous information on either that was national in scope, and they were clearly important areas. In the trends paper, we found an increase in the percentage of older drinkers in the U.S. population between 1997 and 2014, with a bigger increase among women than men. In the prescription medications paper, we found that 42 percent of all adult current drinkers used at least one alcohol-interactive medication and that the percentage almost doubled, to 78 percent, among older drinkers. In earlier papers, we found that people’s diet quality worsened as drinking increased.

2 Nutrition has figured prominently in your work. Tell us about your background.

My Ph.D. was in nutrition from the University of Maryland. Subsequently I did a post-doc at the National Cancer Institute, during which I obtained an M.P.H. in epidemiology from Johns Hopkins University. Through that training, I developed an interest in associations between diet, including alcohol, and cancer and other chronic diseases.

3 How does your background in nutrition influence your work on alcohol?

Alcohol can be thought of both as a food and a drug. As a nutritional epidemiologist, I view alcohol as a food, a dietary component that’s consumed, generally in moderation, by the majority of the U.S. population. It can affect the intake of other dietary components and interact with them or with other factors to affect health outcomes.

4 Alcohol, nutrition, and chronic disease—How do these areas fit together?

I think aging is a key process that ties them together. The U.S. population of older adults is rapidly expanding, primarily due to the baby boom generation that began turning age 65 in 2011. By 2056, the population ages 56 and older will be larger than the population ages 18 and younger. As people age, they are more likely to develop chronic diseases. Diet, including alcohol intake, can influence the initiation and progression of these diseases. In addition, having more chronic diseases is related to taking more prescription medications. Older drinkers can’t tolerate alcohol as well as their younger counterparts. Among drinkers, even low-level drinkers, alcohol-medication interactions can increase the risk of harmful outcomes. I think it’s important to learn more about alcohol and aging to prepare to meet the challenges of an increasingly large population of older adults in the future.

5 If you weren’t a scientist at NIAAA, what would you be doing?

Great question! For sure, I’d be a musician. As an undergraduate, I studied piano and voice at the Oberlin Conservatory and worked in New York City for several years as a professional actress, singer, and pianist. I still play piano and sometimes sing for the occasional Afternoon Tea at the Strathmore Mansion.
SPOTLIGHT: Researchers Get Practical Lesson . . . Continued from page 5

spoke about the role of mutual support groups like Alcoholics Anonymous; Barbara Mason, Ph.D., Scripps Research Institute, who presented on the medications available for AUD; and Kimberly Johnson, Ph.D., Substance Abuse and Mental Health Services Administration, who gave a broad overview of the treatment system, including treatment settings, provider credentials, and payment mechanisms.

The session was videorecorded and can be viewed here: https://niaaa.nih.gov/video-everything-you-ever-wanted-know-about-aud-treatment.

NEWS FROM THE FIELD: Oxytocin Shows Promise . . . Continued from page 6

researchers observed that mice given oxytocin delayed consumption from the bottles containing alcohol. In the lever-pushing model, low doses of oxytocin reduced alcohol seeking and intake in the mice without altering their self-administration of a natural reward—sucrose. These findings suggest that oxytocin reduces the motivational effects of alcohol.

To investigate how oxytocin exerts its alcohol-related effects in the binge-like drinking model, the research team pretreated a separate group of mice with a molecule that interferes with oxytocin’s receptor before they administered the hormone. They found that the ability of oxytocin to reduce alcohol consumption was blocked in these animals compared to animals that were not pretreated. This finding suggests that the oxytocin receptor may play a role in reducing alcohol consumption.

Taken together, these findings, along with other recent reports, provide support for the potential role of oxytocin in the motivational effects that drive alcohol misuse. However, additional studies are needed to determine the mechanisms by which oxytocin reduces alcohol consumption.

Reference:

NEWS FROM THE FIELD: Intestinal Fungi May Worsen . . . Continued from page 6

ALD compared to healthy volunteers, and an overgrowth of species of the fungus *Candida*. They also found that the more prevalent the exposure to fungi in the bloodstream in people with ALD, the higher the likelihood of mortality.

Taken together, this research suggests that fungi may play a greater role than previously understood in controlling the diverse array of microbes that live on and inside the human body. If fungi are confirmed to play a role in worsening ALD, antifungal agents might be useful as therapy.

Reference:

ABOUT US
*NIAAA Spectrum* is NIAAA’s triannual webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field for a wide range of audiences.

Each issue includes feature-length stories, new research findings from the field, image and data analyses, and an interview with an NIAAA staff member or alcohol researcher.

CONTACT US
National Institute on Alcohol Abuse and Alcoholism (NIAAA)
5635 Fishers Lane, MSC 9304
Bethesda, MD 20892–9304
Communications/Public Info: 301–443–3860
https://www.spectrum.niaaa.nih.gov