

# NIAAA SPECTRUM

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

## FEATURE

### ADVANCES IN UNDERSTANDING AND ADDRESSING UNDERAGE DRINKING



Combating underage drinking is a major public health priority, as alcohol use by young people increases the likelihood of short- and long-term consequences, including altered brain development, academic problems, sexually transmitted infections, physical and sexual assault, traffic crashes, injuries, overdoses, and alcohol use disorder (AUD).

Epidemiological data from the 2018 Monitoring the Future (MTF) survey, funded by the National Institute on Drug Abuse, indicate that underage drinking among 8th, 10th, and 12th graders has declined by half, on average, over the past 2 decades (see the By the Numbers story “Underage Drinking in the United States, 1998–2018”). Although these declines are encouraging, alcohol remains the most widely used substance among U.S. youth. In 2018, about 8 percent of 8th graders, 19 percent of 10th graders, and 30 percent of 12th graders drank alcohol in the past month. According to the National Survey on Drug Use and Health, nearly 443,000 adolescents ages 12–17 had AUD in

2017. Underage binge drinking and high-intensity drinking in college settings are also a concern. (For more information, see the Noteworthy story “NIAAA Holds Working Group Meeting on High-Intensity Drinking.”)

So, what can be done to prevent or reduce underage drinking or catch problem drinking early on? And what have we learned about how alcohol use impacts the developing brain?

Advancing research on the development, evaluation, and implementation of underage drinking interventions and translating the findings into resources to prevent and reduce underage alcohol use have long been NIAAA priorities. A number of evidence-based interventions that target underage drinking are available but are underutilized. Such interventions can be delivered at the individual, family, school, community, and policy levels. For example, a recent NIAAA-supported study demonstrated that a combined individual- and community-level intervention effectively reduced underage drinking among Native American youth ages 13–20 living on rural California reservations. It is important to note that not all available underage drinking interventions are effective for all populations of youth or in all environmental contexts, emphasizing the need for a greater repertoire of developmentally and culturally appropriate preventive interventions. A current NIAAA-supported study is evaluating the

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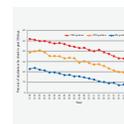
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## FEATURE

## ADVANCING ALCOHOLIC HEPATITIS RESEARCH



Breakthroughs in neuroscience have firmly established our understanding of alcohol use disorder (AUD) as a chronic brain disease. But when it comes to the adverse health effects of alcohol, the brain is not the only game in town.

Drinking too much—on a single occasion or over time—can take a serious toll on just about every organ

in the body. The liver is perhaps the most familiar of the nonbrain targets of alcohol-related harm. As the chief organ responsible for metabolizing alcohol, the liver is especially vulnerable to alcohol-related injury. In the United States, nearly half of liver disease deaths involve alcohol.

“Alcohol-associated liver disease [AALD] comprises a broad spectrum of illnesses varying in severity,” says Kathy Jung, Ph.D., Director of the NIAAA Division of Metabolism and Health Effects (DMHE). “Some of the more well-known forms of AALD are fatty liver, cirrhosis, and liver cancer. A particularly severe form of AALD is alcoholic hepatitis [AH].”

AH is a severe, sudden-onset form of AALD with high mortality—from 30 percent to 50 percent within 3 months of diagnosis. Treatment with

prednisolone, a steroid medication, has been the standard of care for AH for about 40 years. Prednisolone has limited efficacy and many side effects, but no other pharmacological treatment has consistently shown long-term survival benefit for people with AH.

To stimulate translational and clinical research into the causes of and cures for AH, NIAAA funded four AH research consortia in 2012. Research objectives of the consortia included:

- Investigating the underlying mechanisms of AH pathology
- Identifying genetic and environmental factors that influence AH risk and disease outcomes
- Conducting phase II clinical trials of potential AH pharmacotherapies
- Developing biomarkers as indicators of AH severity and response to treatment

“From 2012–2017, the AH research consortia collaborated to draft standard definitions for the condition, and to develop common data elements for clinical trials,” explains Svetlana Radaeva, Ph.D., the DMHE Program Director for Alcohol-Associated Liver Disease—Mechanism and Treatment, who provided programmatic oversight of the consortia. Common data elements in this context constitute a set of standardized approaches and vocabulary for use by hepatologists in the diagnosis of AH. Dr. Radaeva says that eliminating ambiguity about AH definitions and diagnostic criteria should speed up shared advances in the field.

Dr. Radaeva and the consortia investigators also worked with scientists from the U.S. Food and Drug Administration (FDA) to standardize AH terminology definitions, data collection, and clinical trial end points. This standardization ensures that clinical trial results will be adequate for regulatory evaluation of AH pharmacotherapies. In March 2018,

### AALD—A Spectrum of Liver Disease

It’s important to remember that alcoholic hepatitis is one form (albeit a particularly severe form) of alcohol-associated liver disease (AALD), which comprises a broad spectrum of liver diseases. The multiple forms of AALD occur in no predictable sequence and include:

**Alcoholic steatosis (fatty liver disease):** An asymptomatic condition that affects an estimated 90 percent of people with heavy alcohol use. Alcoholic steatosis can be reversed by abstaining from drinking.

**Alcoholic steatohepatitis:** Liver inflammation caused by continued drinking and characterized by fat accumulation in liver cells, infiltration of the liver by infection-fighting white blood cells, and damage to liver cells.

**Alcoholic hepatitis:** A severe and acute form of AALD characterized by rapid elevation in serum bilirubin levels, jaundice, and liver-related complications after prolonged, heavy alcohol use. Many alcoholic hepatitis patients also have underlying severe fibrosis or cirrhosis.

**Fibrosis:** An accumulation of fibrous connective tissue around liver cells, forming a chicken-wire pattern that distorts normal liver architecture and function.

**Cirrhosis:** The most severe form of fibrosis characterized by scarring of the liver. Cirrhosis increases risk of AALD complications such as abdominal fluid accumulation, bleeding in the gastrointestinal tract, loss of brain function, kidney failure, and bacterial infection.

**Hepatocellular carcinoma:** Malignant liver cancer that develops in about 10 percent of patients with alcoholic cirrhosis.

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efficacy of a “toolbox” of interventions, which are based on local cultural practices, in reducing AUD and related suicide among rural Yup’ik Alaska Native youth.

NIAAA also supports research to encourage the implementation and uptake of alcohol screening and brief intervention (SBI) among youth. A growing body of evidence shows that alcohol SBI in primary care can effectively identify youth who have or are at risk for alcohol problems, as has been demonstrated for adults.

In 2011, NIAAA created “Alcohol Screening and Brief Intervention for Youth: A Practitioner’s Guide,” a 2-item screening guide that helps clinicians quickly identify 9- to 18-year-olds who are at risk for alcohol use, are using alcohol, or have AUD—and to intervene as appropriate. Previous studies have shown that the NIAAA youth screening guide is an effective tool in a variety of settings, including in primary care and pediatric emergency departments, among youth who have a chronic health condition, and in schools. Most recently, a new study in primary care clinics serving racially and ethnically diverse patients validated the Guide’s utility in

appropriately identifying youth ages 12–17 who are at risk for AUD.

Through effective alcohol SBI, healthcare providers can detect and treat alcohol problems early. This is an important step, because heavy alcohol use during adolescence may result in long-lasting functional and structural changes in the brain. Recent findings from NIAAA’s National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), a longitudinal study of brain structure and function in approximately 800 youth, show that adolescents who initiated heavy alcohol use during the study experienced faster declines in brain gray matter volume and slower expansion of brain white matter relative to those who initiated no or low alcohol consumption during the same time. These changes may reflect irregularities in the developing brain’s normal processes of “pruning” infrequently used synapses and enhancing brain connectivity, respectively. NCANDA researchers also found that youth with a history of alcohol use exhibited weakened connections between brain networks involved in the regulation of emotional and cognitive functioning.

Learning more about the health effects of underage drinking and understanding how to effectively deter adolescents from alcohol use, as well as how to treat those who have already developed alcohol-related problems, continue to be key NIAAA research priorities. For more information about underage drinking, please access the following NIAAA resources:

- Alcohol Screening and Brief Intervention for Youth: A Practitioner’s Guide: <https://www.niaaa.nih.gov/publications/clinical-guides-and-manuals/alcohol-screening-and-brief-intervention-youth>
- Factsheet: Underage Drinking: <https://pubs.niaaa.nih.gov/publications/UnderageDrinking/UnderageFact.htm>
- College Drinking website: <https://www.collegedrinkingprevention.gov>

*Note: NIAAA defines binge drinking as a pattern of drinking that increases a person’s blood alcohol concentration (BAC) to .08 g/dL (the legal driving limit for adults) or higher. This typically occurs after 4 drinks for women or 5 drinks for men in about 2 hours. Research suggests that youth reach this BAC with fewer drinks than adults.*

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## NEWS FROM THE FIELD

## MOTHER'S IMMUNE PROFILE MAY INFLUENCE PRENATAL ALCOHOL EXPOSURE OUTCOME



A new study has found that alcohol use during pregnancy can affect a woman's immune system in ways that may predict her child's neurodevelopmental outcome. Specific changes in a mother's immune system can also serve as an indicator of prenatal alcohol use. Prenatal alcohol use can cause an array of health effects in offspring, collectively called fetal alcohol spectrum disorders (FASD). The most profound effects of prenatal alcohol exposure are brain damage and the resulting impairments in behavioral and cognitive functioning. These deficits can contribute to learning disabilities, problems holding a job, and poor social skills throughout a person's life.

Cytokines are immune system messengers that help to control immune responses and play an important role in brain development. Alterations in the maternal immune system during pregnancy can result in changes in the cytokine balance of the fetus, thus affecting typical brain development. For example, alterations in maternal immune system molecules have been linked to childhood neurodevelopmental disorders such as autism and schizophrenia.

The NIAAA-supported Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) recently found that alcohol consumption disrupted the levels of eight maternal cytokines that may influence the risk for FASD. The

Fall 2018 issue of *NIAAA Spectrum* reported on the results of that study in "Maternal Cytokine Balance May Play Role in FASD Risk." The present study extended this work. Cytokines do not act individually but, rather, are part of functional networks involving many other kinds of molecules. A CIFASD research team led by Joanne Weinberg, Ph.D., at the University of British Columbia evaluated a panel of 40 cytokines and related factors. They analyzed individual cytokines as well as networks of interacting cytokines. The goal was to identify maternal immune profiles predictive of alcohol intake and child neurodevelopmental outcomes.

In collaboration with Christina Chambers, Ph.D., at the University of California San Diego, researchers enrolled pregnant women who reported "moderate to heavy" alcohol consumption or "low to no" alcohol consumption during pregnancy. Blood samples were collected from these women during the second and third trimesters of pregnancy, and their children were evaluated at ages 6 months and 12 months for physical and neurodevelopmental features typically associated with FASD.

Researchers identified distinct networks of activated and inhibited cytokines that were associated with whether women consumed alcohol during pregnancy and whether the children showed neurodevelopmental delay. Certain cytokines and growth factors were elevated in mothers who engaged in moderate to heavy alcohol consumption and had children with neurodevelopmental delay. Importantly, mothers who engaged in moderate to heavy alcohol consumption but whose children were without neurodevelopmental delay had a different cytokine profile, and the networks in both groups differed from the networks of the group of women who had low to no alcohol consumption.

These findings suggest that the maternal immune profile during pregnancy may be predictive of child risk for, and resilience to, the adverse effects of alcohol on neurodevelopment, potentially serving as a biomarker to facilitate early identification of children at risk for neurodevelopmental delay.

For more information about CIFASD, please visit <https://cifasd.org>.

*Note: In this study, moderate to heavy alcohol consumption was defined as at least weekly binge drinking episodes (5 or more drinks), at least 5 occurrences of 3–4 standard drinks, or at least 10 occurrences of 1–2 standard drinks, either in the month of conception or in the most recent month of pregnancy. Low to no alcohol consumption was defined as no binge episodes, minimal or no alcohol in the month around conception, and no drinking in the most recent month of pregnancy.*

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## NEWS FROM THE FIELD

### PRENATAL CHOLINE MAY AMELIORATE EFFECTS OF PRENATAL ALCOHOL EXPOSURE



Prenatal supplements with the nutrient choline may help protect against alcohol-related deficits in children born to women who drink alcohol during pregnancy, according to a small clinical trial supported by NIAAA. The new findings were reported in the July 2018 issue of *Alcoholism: Clinical and Experimental Research*.

Choline is found in large quantities in meat, dairy products, eggs, and some vegetables. It readily crosses the placenta and accumulates in the fetal brain, where it plays an important role in cell membrane integrity,

transmembrane signaling, and lipid and cholesterol transport and metabolism. It is also an important precursor to acetylcholine, as well as a methyl-group donor for DNA methylation, and thus influences downstream alterations in gene expression.

Previous studies conducted in animals have found that choline supplementation during pregnancy appears to protect animals' offspring from both physical and brain effects of prenatal alcohol exposure. Prenatal choline supplementation in animals has also been shown to protect against other forms of neurotoxicity and injury-induced brain impairments in the offspring.

In the new study, researchers led by Sandra W. Jacobson, Ph.D., and Joseph L. Jacobson, Ph.D., NIAAA grantees at Wayne State University School of Medicine in Detroit, worked with scientists from the University of Cape Town in South Africa to investigate the effectiveness of choline supplementation among a group of pregnant women in Cape Town.

Pregnant women who drank heavily were recruited into the study.

The 69 women in the study were recruited in midpregnancy, having started prenatal care by the 23rd week of gestation. They were randomly assigned to receive a daily oral dose of either 2 grams of choline or placebo from the time of their enrollment in the study until they gave birth. Each dose consisted of a powder that, when mixed with water, produced a sweet-tasting, grape-flavored drink.

Children born to the women in the study were tested at ages 6 months and 12 months on a variety of measures, including physical growth, as well as cognitive, learning, and memory performance. The researchers reported that, although infants in both groups were small at birth, choline-exposed infants showed considerable catchup growth in weight and head circumference at 6 months and at 12 months, when compared with infants in the placebo group. Also, at 12 months, the infants in the choline

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## NOTEWORTHY

### NIAAA HOLDS WORKING GROUP MEETING ON HIGH-INTENSITY DRINKING



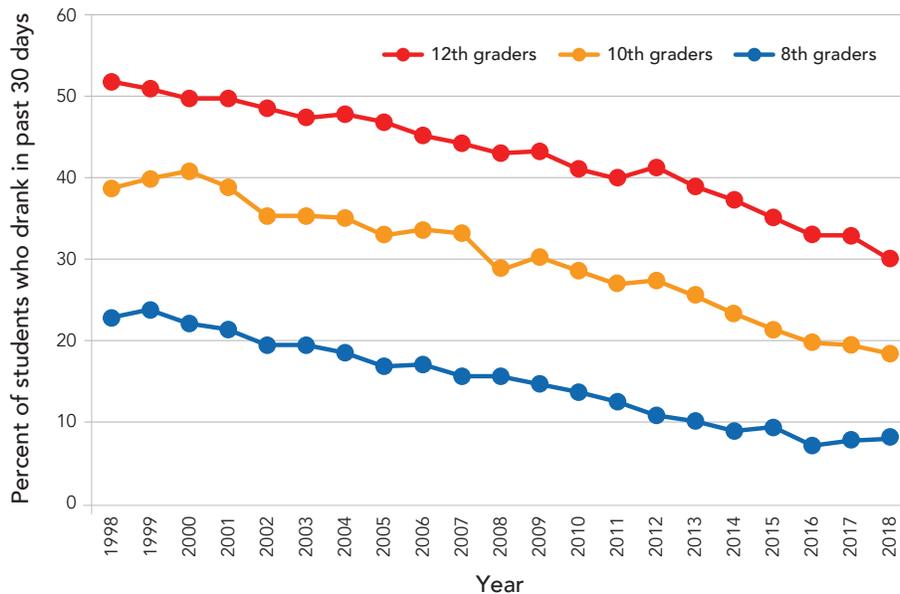
To help better understand and address a dangerous pattern of drinking in the United States, NIAAA convened the first meeting of the Working Group on High-Intensity Drinking on October 10, 2018. High-intensity drinking refers to consumption of 2 or more times the gender-specific thresholds for binge drinking, which is to say 10 or more standard drinks (or alcoholic drink-equivalents) for males and 8 or more for females. This pattern

of drinking is significant because it is associated with greater odds for multiple health-risk behaviors and harmful consequences, such as alcohol overdose and vehicle crashes.

The Working Group comprises experts in alcohol and drug policy, neuroscience, digital media, social media analysis, adolescent alcohol intervention research, and global health. Panelists at the kickoff meeting

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BY THE NUMBERS

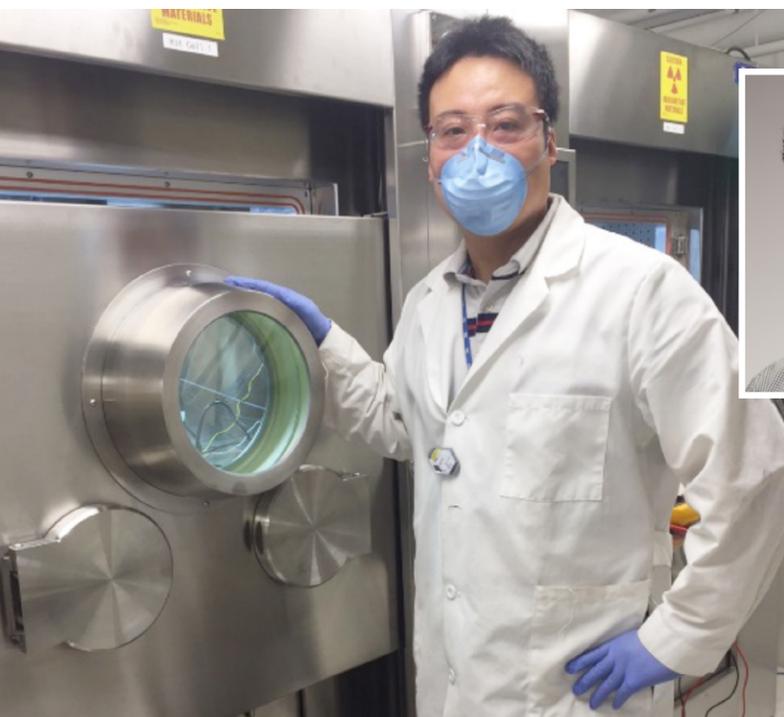


## UNDERAGE DRINKING IN THE UNITED STATES, 1998–2018

The findings of the Monitoring the Future survey, which is funded by the National Institute on Drug Abuse, have demonstrated a decline in underage drinking. From 1998 to 2018, the prevalence of past-month alcohol use decreased 41.9 percent for 12th graders, 52.1 percent for 10th graders, and 64.4 percent for 8th graders.

Source: Miech, R.A.; Schulenberg, J.E.; Johnston, L.D.; et al. National Adolescent Drug Trends in 2018. Table 3—Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12. Ann Arbor, MI: University of Michigan Institute for Social Research, Monitoring the Future, December 17, 2018. <http://www.monitoringthefuture.org/data/18data/18drtbl3.pdf>. Accessed January 11, 2019.

NIAAA@WORK



## LABORATORY OF NEUROIMAGING

Min Guo, Ph.D., Postdoctoral Fellow, works in the radiosynthesis lab at the NIAAA Laboratory of Neuroimaging. Dr. Guo develops novel radioactive agents, called radioligands, for positron-emission tomography (PET) imaging. He is currently working on radioligands for use in brain imaging studies of alcohol and other substance use disorders and Alzheimer’s disease. Dr. Guo is pictured in front of a radiochemistry fume hood, which blocks gamma rays generated during the decay of radioactive materials, protecting the radiochemist during radioligand synthesis.

## 5 QUESTIONS WITH . . .

### SVETLANA RADAeva, PH.D.

*Program Director for Alcohol-Associated Liver Disease—Mechanism and Treatment, Division of Metabolism and Health Effects*



#### 1 What can you tell us about alcohol-associated liver disease (AALD)?

Alcohol-associated liver disease is a serious and potentially fatal health condition. Its development is a common consequence of chronic alcohol misuse and is often associated with alcohol use disorder, or AUD. Almost all people who drink heavily develop fatty liver, which is usually reversible if a person stops drinking. However, for those with fatty liver who continue to engage in heavy alcohol use, a significant number will develop fibrosis [liver scarring], and of those, some will progress to hepatocellular carcinoma [liver cancer]. In addition, approximately 20 percent of people with AUD can suddenly develop alcoholic hepatitis, or AH, which is a form of AALD that can cause death for those most severely affected. Most patients with AALD are not diagnosed until after they have developed jaundice or complications of cirrhosis, which occur when a person's liver disease has progressed. This underscores the need for improved diagnosis of AALD to facilitate earlier intervention and better health outcomes.

#### 2 How would you describe your portfolio of projects in NIAAA's Division of Metabolism and Health Effects?

I oversee the research portfolio on AALD, known previously as alcoholic liver disease. NIAAA-supported studies in this area examine the mechanisms and underlying factors involved in the onset and progression of AALD, as well as develop and test novel interventions for its treatment and prevention. I also serve as Project Scientist for the Alcoholic Hepatitis Clinical and Translational Network, a program established to accelerate research on the underlying pathogenic mechanisms of AH and the development of novel AH treatments.

#### 3 How has NIAAA's work building up a research network of collaborators helped bring about new opportunities or milestones in recent years?

In 2012, NIAAA embarked on a large initiative to advance research on AH. This initiative resulted in the funding of four research consortia. It was a huge development for the AALD field because it stimulated greater collaboration among AH researchers and supported the infrastructure to conduct high-quality, high-impact clinical studies in AH. The program quickly became the front line for generating knowledge and innovation in the AH field and has greatly expanded interest in AH among other researchers and clinicians. This highly successful program led to the development of the Alcoholic Hepatitis Clinical and Translational Network.

Building upon this existing momentum, the Network and NIAAA launched a joint effort with the U.S. Food and Drug Administration [FDA], the American Association for the Study of

Liver Diseases [AASLD], and patient advocates from the American Liver Foundation to transform and standardize the drug development process for AH pharmacotherapies. As a result, the AH clinical research field has a new standard definition of AH, clinically meaningful outcome measures for drug development, and novel study designs. This is an enormous achievement.

#### 4 What exciting advances or potential breakthroughs do you see on the horizon for the field?

I believe we have reached the tipping point for a brighter era in AALD research, and that many breakthroughs are just around the corner. In the next few years, we may see the emergence of new biomarkers to diagnose the disease at early stages, shifting the focus from treatment to prevention. Another major step forward will be the recognition of AUD treatment as the most important determinant of long-term survival for individuals with severe AALD. NIAAA envisions AUD treatment as becoming an essential component of AALD clinical trials, with hepatologists ultimately being trained to diagnose and manage AUD in their patients.

#### 5 What made you decide to become a scientist?

I started out wanting to be a chef. However, in high school I read a book that changed my life. It was "Otkrytaya Kniga," or "Open Book," by Veniamin Kaverin, about the team of Oxford University scientists who developed penicillin. The story about the female members of this team was my inspiration in becoming a biologist. Still, I like cooking. After all, science and cooking are a lot alike—both require you to be creative while also following a set of steps. I have never regretted my choice.

**FEATURE: Advancing Alcoholic Hepatitis Research . . . Continued from page 2**

these efforts led NIAAA and the FDA, in partnership with the American Association for the Study of Liver Diseases, to cohost the public workshop “Clinical Trial Design and Endpoints for Alcoholic Hepatitis and Other Alcohol-Associated Liver Diseases.”

To enhance synergies and reduce redundancies in the burgeoning AH clinical research environment, NIAAA Director George F. Koob, Ph.D., recommended that the four AH research consortia be consolidated into a single network. In September 2018, the NIAAA Alcoholic Hepatitis Clinical

and Translational Network was formed by funding eight sites that will conduct a common phase II clinical trial along with studies aimed at increasing our understanding of AH pathogenesis and developing new treatment and management approaches for AH.

“This Network will bring enhanced research coordination across the AH field and has the enormous potential of leading to new effective treatment options for people with alcoholic hepatitis,” says Dr. Koob.

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**NEWS FROM THE FIELD: Prenatal Choline . . . Continued from page 5**

treatment group scored higher than infants in the placebo group on tests of visual recognition memory.

While this study is promising, replicating the results in a larger, and perhaps different, population will help determine if these results can be generalized. According to the study’s authors, future studies should follow the

exposed children beyond 12 months to assess the durability of the benefits and

whether there are additional advantages to choline supplementation.

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Jacobson, S.W.; Carter, R.C.; Molteno, C.D.; Stanton, M.E.; Herbert, J.S.; Lindinger, N.M.; Lewis, C.E.; Dodge, N.C.; Hoyme, H.E.; Zeisel, S.H.; Meintjes, E.M.; Duggan, C.P.; and Jacobson, J.L. Efficacy of maternal choline supplementation during pregnancy in mitigating adverse effects of prenatal alcohol exposure on growth and cognitive function: A randomized, double-blind, placebo-controlled clinical trial. *Alcoholism: Clinical and Experimental Research* 42(7):1327–1341, 2018. PMID: 29750367

**NOTEWORTHY: NIAAA Holds Working Group Meeting . . . Continued from page 5**

were asked to (1) discuss possible causes or drivers of high-intensity drinking, (2) share ideas for how to address the problem, and (3) provide input to identify research gaps and opportunities in this area.

The experts identified numerous factors that may contribute to high-intensity drinking, such as tolerance, social influences, expectations about high-intensity drinking, and maladaptive strategies for coping

with stress. When panelists discussed approaches to address high-intensity drinking, topics centered on the power of social media in shaping one’s perception of harm, the impact of social influencers in promoting desired social norms, the potential role of social media as a platform for prevention and intervention efforts, and the role of alcohol policies.

Ultimately, panelists agreed that a single strategy was unlikely to

produce benefits, given the variety of populations who engage in high-intensity drinking, but that multiple strategies should be brought to bear on the problem. Finally, the panel emphasized the need to conduct research to better understand high-intensity drinking within different social contexts. Information derived from this meeting will help inform NIAAA efforts in moving this research forward.

**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.

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