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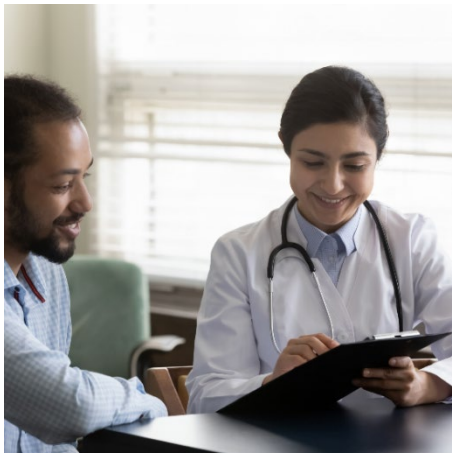
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

FEATURE

INCORPORATING HARM REDUCTION INTO ALCOHOL USE DISORDER TREATMENT AND RECOVERY

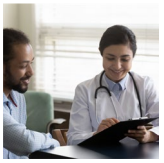


For many years, complete abstinence from alcohol consumption was viewed as the most effective way to recover from alcohol use disorder (AUD) and was a primary outcome of AUD treatment. A large body of evidence, however, suggests that treatment and recovery strategies that reduce heavy alcohol consumption and alcohol-related consequences without complete abstinence can be effective for mitigating the harms associated with alcohol misuse for many individuals. Today, although abstinence is the safest course for certain subgroups, harm reduction strategies that are non-abstinence based have become an important part of the discussion around AUD treatment and the recovery process.

"Indeed, the NIAAA research definition of recovery, released in September 2020, defines recovery as a process through which a person achieves remission from AUD as well as cessation from heavy alcohol consumption, which is a non-abstinent recovery outcome," noted National Institute on Alcohol Abuse and Alcoholism (NIAAA) Director George F. Koob, Ph.D. The definition also emphasizes the importance of biopsychosocial functioning and quality of life in enhancing recovery outcomes. "This definition was developed to help standardize how we view and measure recovery for research studies and, in turn, advance recovery research and the treatment of AUD," said Dr. Koob.

IN THIS ISSUE

FEATURE



1 Incorporating Harm Reduction Into Alcohol Use Disorder Treatment and Recovery

NOTEWORTHY

4 Scientific Diversity Officer Selected for NIAAA

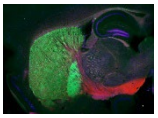
5 Scientific Director for the Division of Intramural Clinical and Biological Research Selected for NIAAA

SPOTLIGHT

6 NIAAA Launches an Educational Virtual Reality Experience for Teens

6 Empowering Health Care Professionals To Provide Evidence-Based Care

A CLOSER LOOK



7 The Beauty of #SciArt

FIVE QUESTIONS WITH …

9 Bin Gao, M.D., Ph.D., Chief, Laboratory of Liver Diseases, NIAAA

Katie Witkiewitz, Ph.D., Distinguished Professor of Psychology and Director of the Center on Alcohol, Substance Use, and Addictions at the University of New Mexico and member of the NIAAA Advisory Council, reviewed the history of harm reduction in alcohol research at the Council's May 2023 meeting. In her presentation, Dr. Witkiewitz argued that expanding the scope of treatment and research to include non-abstinent drinking reductions as a treatment target could substantially lessen the public health burden of AUD.

"An expanding body of research demonstrates that reductions in drinking lead to reductions in risk and has established that individuals can reduce their drinking and/or their experience of harm associated with alcohol use without achieving abstinence," said Dr. Witkiewitz. Dr. Witkiewitz and colleagues recently reviewed this work in NIAAA's Alcohol Research: Current Reviews.[1]

She added that the need to allow for other ways to define "success" for AUD treatment is driven by observations that:

- Few individuals achieve continuous abstinence after undergoing AUD treatment.
- Many who do seek treatment do not want to abstain.
- Many with AUD do not seek treatment because they do not want to abstain.
- Non-abstinent goals for treatment and recovery may encourage more people to seek treatment or reduce drinking on their own.
- Reductions in heavy alcohol use by more people will result in a greater public health benefit.
- Drinking reductions may be more desirable for certain people and may help people seek treatment.

Finding the Right Drinking Levels To Measure Harm Reduction

In clinical trials for AUD, abstinence and no heavy-drinking days are currently the only endpoints approved by the U.S. Food and Drug Administration (FDA). However, many individuals who do not achieve these endpoints may still reduce their drinking to less harmful levels during treatment. Dr. Witkiewitz and other investigators have examined associations between reductions in drinking risk levels established by the World Health Organization (WHO) and improvements in physical health and quality of life.

WHO defines four levels of drinking risk: low, medium, high, and very high.

World Health Organization Alcohol Risk Levels (For Males)				
	Low Risk	**Medium Risk**	**High Risk**	**Very High Risk**
Drinks per day (in grams)	1 to 40 g	41 to 60 g	61 to 100 g	101+ g
Drinks per day (in standard drinks)	0 to 2.9 drinks	3.0 to 4.3 drinks	4.4 to 7.1 drinks	7.2+ drinks
World Health Organization Alcohol Risk Levels (For Females)				
	Low Risk	**Medium Risk**	**High Risk**	**Very High Risk**
Drinks per day (in grams)	1 to 20 g	21 to 40 g	41 to 60 g	61+ g
Drinks per day (in standard drinks)	0 to 1.4 drinks	1.5 to 2.8 drinks	2.9 to 4.3 drinks	4.4+ drinks

Witkiewitz K, Kranzler HR, Hallgren KA, O'Malley SS. Drinking risk level reductions associated with improvements in physical health and quality of life among individuals with alcohol use disorder. Alcohol Clin Exp Res. 2018 Dec;42(12):2453-65. PubMed PMID: 30395350

In a variety of AUD treatment studies, researchers have found that reductions of one and two levels of WHO-defined drinking risk (e.g., reducing alcohol consumption from high risk to medium or low risk) were associated with:

- Reduced risk of AUD[1]
- Fewer drinking consequences and better mental health[2]
- Improvements in quality of life, blood pressure, and liver function[3]
- Reduced risk of liver disease, depression, and anxiety disorders[4,5]
- Positive medication treatment effects[6]
- Reductions in health care costs[7]

"These findings suggest a reduction in WHO drinking risk levels could be a meaningful surrogate marker of improvement in how a person feels and functions after AUD treatment and that extending treatment options to target reductions in drinking, rather than complete abstinence, could expand the reach of alcohol treatment and have an important impact on public health," said Dr. Witkiewitz.

Contingency Management as a Means of Harm Reduction?

In a presentation to the NIAAA Advisory Council in early 2022, Council Member H. Westley Clark, M.D., J.D., Dean's Executive Professor at Santa Clara University in Santa Clara, California, provided an overview of contingency management (CM). CM is a behavioral treatment based on the systematic delivery of positive reinforcement, such as incentives, for desired behaviors. Subsequent discussion addressed the possibility that CM could be part of an overall harm reduction treatment strategy. Dr. Clark's presentation focused on the use of CM for treating people with methamphetamine and other stimulant use disorders. Currently, there are no FDA-approved medications for treating individuals with stimulant use disorder, and CM is one of three behavioral treatments with robust empirical evidence of effectiveness.

Dr. Clark explained that, in most CM protocols, the value of the incentive increases as patients demonstrate the target behavior, such as attendance at treatment sessions. If a missed session occurs, for example, then the value of the incentive returns to the original value. He noted that incentives have been used successfully in other fields and could be studied more broadly in AUD treatment. In general, Dr. Clark said that CM incentives should advance goals, as determined by the individual's health care provider. Such goals might include:

- Adherence to a treatment regimen, medication regimen, and/or follow-up care plan
- Management of a disease or condition, improvement in measurable evidence-based health outcomes for the patient or the target patient population
- Ensuring patient safety

Dr. Witkiewitz added that most prior studies of CM have focused on incentivizing abstinence and as a consequence have often focused on abstinence as the benchmark for treatment success. "In the context of AUD treatment, I suspect that contingency management may actually be even more effective than previously tested given that it may be the case that contingency management interventions are also very effective in reducing drinking or harms associated with drinking. It might be especially important

and effective to use incentives that are aligned with the patient's own goals, including harm reduction goals."

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NOTEWORTHY

SCIENTIFIC DIVERSITY OFFICER SELECTED FOR THE NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Dawn Wayman, M.H.S., has been selected as the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Scientific Diversity Officer (SDO). The role of SDO represents a new position at NIAAA and emphasizes the institute's commitment to advancing diversity, equity, inclusion, and accessibility (DEIA) both internally and in the broader alcohol research community. In her role as SDO, Ms. Wayman will lead efforts to formulate, plan, execute, and evaluate NIAAA's DEIA initiatives. SDOs are critical to the success of the federal government-wide strategic plan on DEIA, which was developed to facilitate implementation of President Biden's Executive Order 14035: Diversity, Equity, Inclusion, and Accessibility in the Federal Workforce.

Ms. Wayman earned her Master of Health Science in infectious disease epidemiology from the Bloomberg School of Public Health at Johns Hopkins University. She began her National Institutes of Health (NIH) career in 2009

at the National Human Genome Research Institute, where she coordinated research on the use of genomics and race in clinical decision making. Starting in 2015, Ms. Wayman served as a Management Analyst and Human Resources Liaison at the National Institute of Mental Health, and in 2017, she joined the NIH Office of Equity, Diversity, and Inclusion (EDI) as a Diversity and Inclusion Strategist. Ms. Wayman also served as the Director for the Special Emphasis Programs and Strategic Diversity and Inclusion branches during her tenure at NIH EDI.

"I am excited to join the NIAAA family as its first Scientific Diversity Officer," Ms. Wayman said. "After spending many years doing this work at the agency level, I am convinced the way I can have the greatest impact in creating a more welcoming and inclusive work environment is at the institute/center level. NIAAA is the right-sized organization and has a senior leadership team who is fully committed to this important work. That's why I made the decision to join this organization. I look forward to making a difference here for years to come."

NOTEWORTHY

SCIENTIFIC DIRECTOR FOR THE DIVISION OF INTRAMURAL CLINICAL AND BIOLOGICAL RESEARCH SELECTED FOR THE NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

David Lovinger, Ph.D., has been selected as the Scientific Director of the Division of Intramural Clinical and Biological Research at the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

Dr. Lovinger obtained his undergraduate degree from the University of Arizona and his Ph.D. in psychology from Northwestern University. He conducted postdoctoral research at NIAAA before joining the Vanderbilt University School of Medicine in 1991. In 2001, Dr. Lovinger was recruited back to NIAAA and became Chief of the Laboratory for Integrative Neuroscience. He has served as Acting Scientific Director of NIAAA since 2022. Dr. Lovinger's research focuses on the neurobiological bases of behavior, how alcohol affects the connections between neurons, and the neural mechanisms involved in alcohol use and alcohol use disorder.

In his role as Scientific Director, Dr. Lovinger will provide scientific, programmatic, and administrative leadership for the Division of Intramural Clinical and Biological Research. He will also be responsible for promoting an inclusive environment that values diverse perspectives, encouraging collaboration, facilitating mentoring and training, and conducting innovative research. "I am honored to be chosen for this position," Dr. Lovinger said. "I look forward to working with the members of this great institute to build the future of intramural research."

SPOTLIGHT

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM LAUNCHES AN EDUCATIONAL VIRTUAL REALITY EXPERIENCE FOR TEENS

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) recently launched Alcohol and Your Brain, a virtual reality (VR) module to engage and educate young audiences about how alcohol affects the brain. Designed for Oculus Quest, Quest 2, or Meta Quest Pro headsets, this activity takes users on a virtual rollercoaster ride through the brain, with stops to describe alcohol's harmful effects on the prefrontal cortex, nucleus accumbens, amygdala, hippocampus, and cerebellum.

NIAAA created a complementary desktop video version of the VR module to make the Alcohol and Your Brain content even more accessible. Parents and educators can share the video with middle schoolers on any computer or mobile device. NIAAA also created a second video version that provides audio descriptions for users with low or no vision. Both videos provide captions for viewers who are deaf or hard of hearing.

NIAAA kicked off the launch of the VR experience during the 2023 National Institutes of Health (NIH) Take Your Child to Work Day event on April 27. The VR experience was well received by participants, and the online, audio-described version earned praise from the NIH Digital Accessibility Program.

NIAAA will showcase the VR experience at upcoming professional association conferences. Students, caregivers, stakeholder groups, news media, and the general public are invited to engage with and share this free resource. You can find more NIAAA educational materials on alcohol and the brain on this webpage.

SPOTLIGHT

EMPOWERING HEALTH CARE PROFESSIONALS TO PROVIDE EVIDENCE-BASED CARE

Since its release just over a year ago, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Healthcare Professional's Core Resource on Alcohol (HPCR) has been the focus of ongoing efforts to empower health care professionals in providing evidence-based alcohol-related care.

Central to these efforts has been partnering with clinical educators, trainees, and state health departments to create awareness and extend the reach of the resource among emerging and established clinicians. These partnering activities have involved NIAAA outreach to hundreds of health care professional school deans, program directors, residency directors, and state health department leaders nationwide. Recent efforts during summer 2023 included outreach to the 30,000 members of the American Medical Student Association.

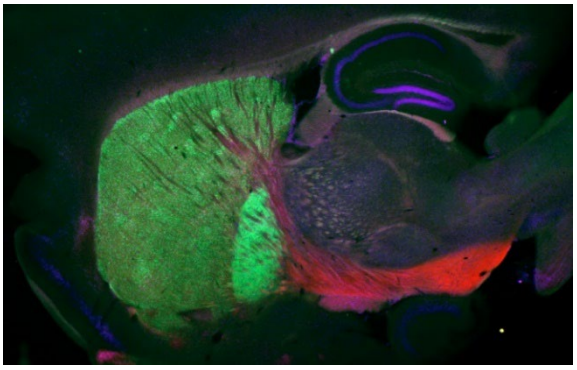
To help health care professionals focus on what's most important to them and their patients, NIAAA added a new Roadmap for Applying the Core Resource to the HPCR in June of this year. The Roadmap sorts HPCR articles broadly into "how-to content" and "context for care" to show how they could be applied in different aspects of clinical practice. It is important to note that all HPCR articles offer free continuing medical education/continuing education (CME/CE) credit for physicians, physician assistants, nurses, psychologists, and pharmacists.

Moving forward, NIAAA will continue partnerships to highlight the HPCR and the importance of delivering evidence-based alcohol-related care by health care providers and health plan organizations. One of these efforts includes a collaboration with the National Committee for Quality Assurance to raise awareness of how the HPCR can help clinicians surmount the challenges they often face in implementing screening practices and follow-up for alcohol use disorder.

For more information about the HPCR, including how to earn up to 10.75 free CME/CE credits, visit niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol.

A CLOSER LOOK

THE BEAUTY OF #SCIART



Sagittal view of a mouse brain showing various components (the cortico-basal ganglia circuitry) that mediate motor action and are implicated in alcohol and other substance use disorders. (Original appeared in Interstellate, Vol. 1; reprinted with permission)

"Things I've seen through a microscope" is the straightforward way Margaret (Meg) Davis, Ph.D., describes her X, formerly known as Twitter, channel, @BrainsRus. Dr. Davis is a retired National Institute on Alcohol Abuse and Alcoholism (NIAAA) neuroscientist and anatomist, who remains dedicated to tweeting about and sharing her fascination with "#SciArt"—the dazzling and colorful scenes visible thanks to innovations in neuroscientific imaging.

"Scientific images are frequently works of art but languish on computers after their scientific utility has passed. I wanted to share some of these images with a broader audience as art, so I began a Twitter feed," said Dr. Davis. "Although I'm retired, I still answer anatomy and imaging questions from other scientists and trainees, and share interesting research papers on Twitter."

Before she retired, Dr. Davis worked as a Staff Scientist with NIAAA Scientific Director David Lovinger, Ph.D., Chief of the Laboratory for Integrative Neuroscience (LIN), part of NIAAA's Division of Intramural Clinical and Biological Research (DICBR). Dr. Davis' images (shown here) are possible through the excellent resources within LIN and DICBR, including microscopes for widefield and subcellular imaging. Many more images are featured on her X account and publications. "Throughout her career, Meg also mentored a stellar group of trainees who share her enthusiasm for the artistry in neuroanatomy and imaging," commented Dr. Lovinger. "Many are now independent researchers with their own laboratories, generating eye-popping images discovered in a universe—as Dr. Davis might say—'seen through a microscope.'"

Dr. Lovinger said, "Meg is an outstanding neuroanatomist with expertise in fluorescence microscopy and immunohistochemistry, and she has an artist's eye for capturing the stunning beauty of the brain seen through microscopy." Dr. Davis' images have adorned several journal covers, he noted, and she also contributed to a cell science exhibit in Paris. "And I still see some of Meg's artwork displayed in a conference center in Building 1 at the National Institutes of Health," he said.

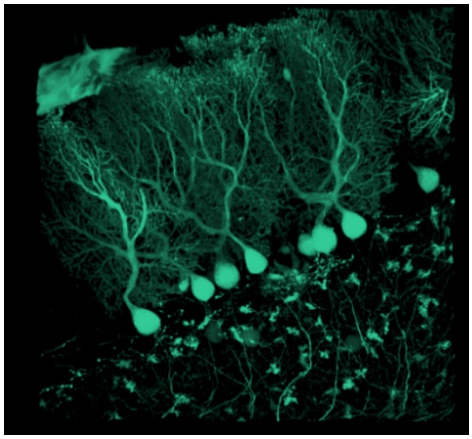
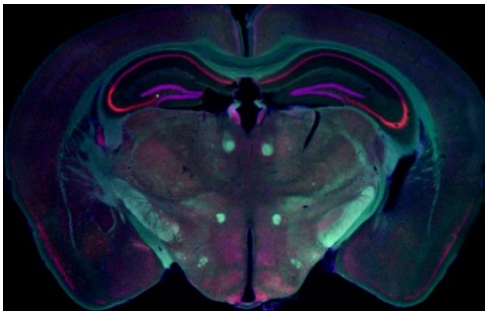
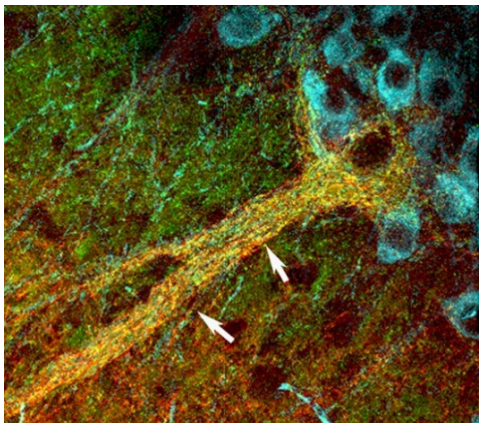


Image of a mouse's cerebellum, the brain region implicated in motor coordination and fine movement control. The Purkinje cells are immunolabeled in turquoise. These neurons are one of the most sensitive cellular targets of both fetal and adult alcohol exposure, contributing to movement and cognitive dysfunction in alcohol use disorder.



#SciArt of a mouse brain created with a tricolor stain, showing nuclei (blue), myelin (turquoise), and somatic RNA (red). This image shows a coronal section of a mouse brain containing several alcohol-sensitive brain regions. This type of staining can be used to look for gross abnormalities produced by alcohol or other neurotoxic agents.



Immunolabeling of a "dendron bouquet" of axons (yellow) shown surrounding a dopamine neuron (blue) in the mouse midbrain. Arrows indicate where the neurons from the striatum make synaptic contact with the dendritic parts of neurons in the substantia nigra. Dopamine release from these neurons is stimulated by substance misuse, including alcohol misuse. These beautiful structures, reminiscent of flower arrangements, help to control dopamine release. (Original appeared in PLOS ONE article)

FIVE QUESTIONS WITH ...

BIN GAO, M.D., PH.D., CHIEF, LABORATORY OF LIVER DISEASES, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

1 *You are Chief of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Laboratory of Liver Diseases. How would you describe your research to the general public?*

The primary goal of our lab is to study the pathogenesis of, and explore therapeutic targets for, alcohol-associated liver disease (ALD). ALD is a major cause of chronic liver disease and can lead to cirrhosis, liver cancer, and death. Of the 100,530 liver disease deaths among people ages 12 and older in 2021, 47.4% involved alcohol. Although clinical trials are underway, no medications have been approved by the U.S. Food and Drug Administration to treat ALD.

2 *How did you get involved in your current research?*

I received my medical training at Wannan Medical College in China, my graduate training in immunology at Norman Bethune Medical University of Medical Sciences (now Jilin University) in China, and my postdoctoral training in liver biology at NIAAA and the Medical College of Virginia (now Virginia Commonwealth University School of Medicine). During this time, I developed my interest in studying liver immunology and identifying the molecular mechanisms underlying liver inflammation in severe ALD.

3 *What do you consider your lab's most significant research accomplishments in the last 20 years?*

In 2004, we discovered that interleukin-22, a protein produced by immune cells, is a key cytokine for liver cell survival and proliferation. Over the last 10 years, we have extensively studied interleukin-22 biology in the liver and found that interleukin-22 protects against ALD. Our studies led to the ongoing clinical trials evaluating interleukin-22 for the treatment of acute liver failure involved in conditions such as severe alcohol-associated hepatitis (AH), a form of liver disease with a high short-term mortality rate. In addition, a phase IIb clinical trial, which studies the safety and effectiveness of an intervention, has generated promising results for using interleukin-22 for the treatment of severe AH.

We have also established several preclinical mouse models for studying the adverse effects of alcohol on the liver, including the chronic-plus-binge ethanol feeding model, known as the *NIAAA model*. We also established the high-fat diet-plus-binge ethanol feeding model and several new models mimicking acute-on-chronic liver failure and acute liver failure in patients. The NIAAA model is now a well-accepted preclinical model to study the pathogenesis of AH and to test potential compounds for the treatment of the disease.

More recently, we characterized liver inflammation in severe AH. We identified two distinct cell profiles of severe AH by examining the immune cell populations observed in patients with the disease. Our data suggest a separate mechanism driving liver injury and/or failure in these patients.

4 *What is the most exciting project you are working on now?*

We are currently working on two exciting projects. The first one is to investigate the contribution of organ systems other than the liver—such as gut and fat tissue—to alcohol metabolism and drinking behavior. The second one is to characterize liver inflammation in AH, which will identify the molecular mechanisms that trigger inflammation in severe AH and discover novel therapeutic targets for the treatment of AH.

5 *What do you like to do outside of the office?*

I enjoy hiking and traveling. I hike every weekend in Maryland and West Virginia, and often hike Sugarloaf Mountain, the Appalachian Trail, and the Harpers Ferry area, to name a few. I have traveled many times to Europe and Asia, but many traveling destinations are still on the list, including several northern European countries, South American countries, Australia, and New Zealand, among others. I also like to watch soccer games and play the sport.

ABOUT US

NIAAA Spectrum is NIAAA's 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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