



National Institute on Alcohol  
Abuse and Alcoholism

# **NIAAA DIRECTOR’S REPORT ON INSTITUTE ACTIVITIES TO THE 163<sup>RD</sup> MEETING OF THE NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND ALCOHOLISM**

Tuesday, May 9, 2023

Hybrid Meeting

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## IN MEMORIAM

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NIAAA and the scientific community mourn the death of **Dr. Enoch Gordis**, who served as the NIAAA director from 1986 to 2001. Dr. Gordis emphasized science as a way of understanding alcohol use disorder. Trained in internal medicine, he conducted research in the laboratory of Dr. Solomon Berson and Nobel laureate Dr. Rosalyn Yalow during his residency at Mount Sinai Hospital in New York City, NY. Subsequently he worked in Dr. Vincent P. Dole's research laboratory at New York's Rockefeller University, where he began his career in the study of addiction. Dr. Gordis would go on to work with psychiatric researcher Dr. Ruth Fox who had helped introduce disulfiram in the United States as a medication to treat alcohol problems. In 1971, Dr. Gordis founded and directed a new alcohol treatment program at Elmhurst Hospital in Queens, NY. He remained there until his appointment as NIAAA Director in 1986. During his tenure as NIAAA Director, Dr. Gordis oversaw the launch of innovative, major initiatives, including the Collaborative Project on the Genetics of Alcoholism, the National Longitudinal Alcohol Epidemiological Survey, the Integrative Neuroscience Initiative on Alcoholism, the Combining Medications and Behavioral Interventions clinical trial, and the NIAAA Task Force on College Drinking. Dr. Gordis's commitment to the next generation of researchers is reflected in the Research Society on Alcohol Enoch Gordis Research Recognition Awards and the symposium that showcases their work at the annual Research Society on Alcohol conference. Dr. Gordis' leadership embodied his love of science, his compassion as a clinician, and his demeanor as a gentleman. He inspired many and left a lasting impact on NIAAA, NIH, and the alcohol research field.



NIAAA and the addiction research community mourn the passing of **Dr. George Fein**, a distinguished investigator in the field of neurobehavioral research. Dr. Fein was renowned as an innovative researcher who applied neurotechnology, neuroimaging, and behavioral assessments to advance our understanding of the impacts of aging, alcohol and other substance use disorders, and psychiatric disorders on brain structure and function. Dr. Fein was a faculty member in the Department of Psychiatry at the University of California San Francisco and the San Francisco VA Medical Center. Following his career in academic medicine, Dr. Fein founded and served as president and Chief Executive Officer of Neurobehavioral Research, Inc. Dr. Fein made many scientific contributions to the alcohol field, including the pivotal finding that treatment for and recovery from alcohol use disorder are associated with compensatory functional network alterations in the brain. Dr. Fein received grants from NIAAA for more than thirty years, as well as funding from NIDA, NIMH, and NIA. Dr. Fein published nearly 200 research articles and mentored over 40 graduates, postgraduates, and junior faculty. In 1989, he received a VA Research Career Scientist Award. In 2014, he was honored by the Research Society on Alcohol with the Henri Begleiter Excellence in Research Award.



With sadness, NIAAA shares the news of the death of **Dr. John M. Littleton**. Dr. Littleton's groundbreaking research contributed to our understanding of the development of functional tolerance to alcohol, the role of L-type Ca<sup>2+</sup> channels in the physiology of alcohol actions, alcohol-nicotine interactions at the behavioral and cellular levels, and the use of mammalian cell culture models to study alcohol effects. His innovative work with high throughput pharmacological screening in plant cell cultures led to the identification of several lead compounds that demonstrated preclinical efficacy in reducing alcohol's effects on the central nervous system. Importantly, Dr. Littleton played a key role in exploring the mechanism of action of acamprostate that led to its approval by the FDA as a treatment for alcohol use disorder. John Littleton began his academic career at Kings College, London University in England then moved to the University of Kentucky, where he spent the rest of his career. Dr. Littleton served on numerous scientific advisory boards and was a generous mentor for undergraduate students, graduate students, postdoctoral fellows, and junior faculty. He will be missed.

## NIAAA BUDGET

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### FY 2023

On December 29, 2022, the President signed H.R. 2617 - Consolidated Appropriations Act, 2023. NIH received a total of \$47.7 billion, representing a \$2.5 billion or a 5.5% increase above the Fiscal Year (FY) 2022 enacted level. The FY 2023 appropriation for NIAAA provides \$596.6 million, including \$1.3 million AIDS transfer. This represents about a \$21.7 million or a 3.8% increase over the FY 2022 budget level.

## HONORS AND AWARDS

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**Rani Richardson** (NIH Graduate Partnership Training Program, Joint NIDA and NIAAA Intramural Laboratory on Clinical Psychoneuroendocrinology and Neuropsychopharmacology) received a 2023 Poster Award from American Society of Addiction Medicine. She is a 2023 Research Society on Alcohol (RSA) Enoch Gordis Research Recognition Award Finalist and a recipient of a 2023 RSA Nadia Chaudhri Rising Scholar Award.

**Dr. Wiramon Rungratanawanich**, Visiting Postdoctoral Fellow in the Section of Molecular Pharmacology, Division of Intramural Clinical and Biological Research, received the 2023 Outstanding Young Investigator Award from the Central Society for Clinical and Translational Research. **Dr. Rungratanawanich** is also a finalist for the 2023 RSA Enoch Gordis Research Recognition Award.

# STAFF TRANSITIONS

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## New Staff



**Dr. Amari Carter** joined the Office of the Clinical Director (OCD) as a Post-Doctoral Intramural Research Training Award (IRTA). Dr. Carter is analyzing AUD data collected at the Clinical Center to study the prevalence of alcohol use in NIH patients. Dr. Carter will also study chemo-sensation in AUD patients and will shadow clinical care of AUD patients and NIAAA consults.



**Dr. Priscila Correa Antonello** joined the Section on Neural Circuits (SNC) as a Post-Doctoral Visiting Fellow to conduct studies to uncover the neurophysiological mechanisms underpinning a phenomenon in which a proportion of children and adolescents with autism spectrum disorder (ASD) exhibit a dramatic improvement in cognitive and motor symptoms during a fever. Because fetal alcohol syndrome (FAS) and ASD share neurodevelopmental symptoms, Dr. Antonello will also develop a mouse model to replicate the overlap between FAS and ASD.



**Dr. Chao Quan** joined the Laboratory of Cardiovascular Physiology and Tissue Injury (LCPT) as a Post-Doctoral Visiting Fellow and will focus on the understanding of interorgan interactions during cardiovascular injury, including alcohol-induced injury. Dr. Quan will also be involved in the development of mouse and rat models of alcohol-associated cardiomyopathies as well as the identification and testing of potential new targets to improve these pathologies.



**Bennett Thilagar** joined the Office of the Clinical Director (OCD) as a Protocol Monitoring Specialist to conduct routine monitoring through the life of a clinical research study and ensure compliance with Good Clinical Practice guidelines, Food and Drug Administration regulations, NIH policies, and the investigational plan.

## New Post-Baccalaureate Intramural Research Training Award (IRTA) Fellows:

**Rishika Shah** – Laboratory of Human Psychopharmacology (HP)

## Departing Staff

**Dr. Pamela Alonso** – Visiting Fellow in the Laboratory for Integrative Neuroscience (LIN) departed for a position as a postdoctoral fellow at the Louisiana State University Health Sciences Center in New Orleans.

**Dr. Michael Authement** –Post-Doctoral IRTA in the Laboratory on the Neurobiology of Compulsive Behaviors (LNCB) has moved to the National Center for Complementary and Integrative Health as a Scientific Review Officer.

**Dr. Daniel Da Silva E Silva** - Research Fellow in the Laboratory on the Neurobiology of Compulsive Behaviors (LNCB) has accepted a position as an Assistant Professor with the Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai.

**Dr. Andras Orosz** – After 14 years as a Health Scientist Administrator with the NIAAA Division of Metabolism and Health Effects, Dr. Orosz has transferred to the National Institute on Aging as a Health Scientist Administrator in the Division of Aging Biology.

### **Transitioning Staff**

**Dr. Robert Freeman** – Has been named as Deputy Director of the NIAAA Division of Epidemiology and Prevention Research (DEPR). Dr. Freeman most recently served in this position in an acting capacity, and prior to that role, served as a Program Official in DEPR for 20 years.

## **RECENTLY ISSUED NOTICES AND NOTICES OF FUNDING OPPORTUNITY**

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### **Notice of Special Interest (NOSI) Issued by NIAAA**

**Advancing mHealth Interventions for Understanding and Preventing Alcohol-Related Domestic Violence.** The purpose of this NOSI is to announce NIAAA’s interest in addressing the critical need for research related to developing, testing, and intervening proximal to drinking occasions, when risk of domestic violence (DV) is elevated, to decrease the likelihood of alcohol consumption at levels sufficient to trigger DV and to provide skills shown to reduce risk of DV perpetration and victimization. This solicitation seeks to advance the development, feasibility, acceptability, pilot testing, potential efficacy, and implementation of scalable, low resource, and remotely delivered interventions via mobile devices (mHealth) that rely on communication technologies for reducing and preventing alcohol consumption and DV. For this NOSI, the term “domestic violence” will extend to child maltreatment (abuse and neglect) and elder abuse, in addition to intimate partner violence (IPV). [NOT-AA-23-003](#) (Contact: Dr. Robert Freeman)

### **Notices Issued by NIAAA**

**Notice of Intent to Publish a Notice of Funding Opportunity for HIV Prevention and Alcohol.** NIAAA intends to promote a new initiative by publishing a Notice of Funding Opportunity to solicit applications to expand the HIV/AIDS prevention toolkit among alcohol impacted populations with a range of patterns of episodic and long-term use and associated behavioral and biological risks for HIV acquisition. This includes integration of effective prevention and treatment interventions with an understanding of the overarching framework for reducing the incidence of new infections by facilitating cross-cutting informative research. This research activity includes the development and testing of new interventions and expansion of existing effective interventions as well as the implementation of these integrative preventive activities in diverse settings and populations. Six areas of research are of primary interest related to

alcohol use and related mental health and substance use comorbidities. These include but are not limited to 1) PrEP Utilization, 2) Treatment as Prevention (TasP), 3) Integration of Preventive Intervention Strategies, 4) Prevention-related Cross-cutting Research, 5) Syndemic Approaches and, 6) Implementation and Operations Research. [NOT-AA-23-005](#) (R01 Clinical Trials Optional), [NOT-AA-23-006](#) (R34 Clinical Trials Optional) (Contact: Dr. Kendall Bryant)

**NIH-Wide Notices of Funding Opportunity (NOFOs) with NIAAA Participation**

Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grant (Parent T32). [PA-23-048](#)

Ruth L. Kirschstein National Research Service Award (NRSA) Short-Term Institutional Research Training Grant (Parent T35). [PA-23-080](#)

Jointly Sponsored Ruth L. Kirschstein National Research Service Award Institutional Predoctoral Training Program in the Neurosciences (T32 Clinical Trial Not Allowed). [PAR-22-265](#)

Research With Activities Related to Diversity (ReWARD) (R01 Clinical Trial Optional). [PAR-23-122](#)

NIH Science Education Partnership Award (SEPA) (R25 - Clinical Trial Not Allowed). [PAR-23-137](#)

Instrumentation Grant Program for Resource-Limited Institutions (S10 - Clinical Trial Not Allowed). [PAR-23-138](#)

BRAIN Initiative: Exploratory Research Opportunities Using Invasive Neural Recording and Stimulating Technologies in the Human Brain (R61 Basic Experimental Studies with Humans Required). [RFA-DC-24-001](#)

BRAIN Initiative: Transformative Brain Non-invasive Imaging Technology Development (UG3/UH3 Clinical Trial Not Allowed). [RFA-EB-22-003](#)

Innovations for Healthy Living - Improving Minority Health and Eliminating Health Disparities (R43/R44 - Clinical Trial Optional). [RFA-MD-23-003](#)

BRAIN Initiative Fellows: Ruth L. Kirschstein National Research Service Award (NRSA) Individual Postdoctoral Fellowship (F32). [RFA-MH-23-110](#)

BRAIN Initiative: Brain Behavior Quantification and Synchronization Data Coordination and Artificial Intelligence Center (U24 Clinical Trial Optional). [RFA-MH-23-130](#)

BRAIN Initiative: New Technologies and Novel Approaches for Recording and Modulation in the Nervous System (R01 Clinical Trial Not Allowed). [RFA-NS-24-004](#)

BRAIN Initiative: Optimization of Instrumentation and Device Technologies for Recording and Modulation in the Nervous System (U01 Clinical Trials Not Allowed). [RFA-NS-24-005](#)

HEAL Initiative: Discovery of Biomarkers and Biomarker Signatures to Facilitate Clinical Trials for Pain Therapeutics (UG3/UH3 Clinical Trial Optional). [RFA-NS-24-018](#)

### **NIH-Wide NOSIs with NIAAA Participation**

Notice of Special Interest (NOSI): Addressing the Etiology of Health Disparities and Health Advantages Among Immigrant Populations. [NOT-MD-23-002](#)

Notice of Special Interest (NOSI): Addressing Health Disparities Among Immigrant Populations Through Effective Interventions. [NOT-MD-23-003](#)

Notice of Special Interest (NOSI) for Administrative Supplements: Harmonization and Joint Analysis of Human Brain Single-Cell Datasets. [NOT-NS-23-042](#)

Notice of Special Interest (NOSI): Administrative Supplements to Support the Exploration of Cloud in NIH-supported Research. [NOT-OD-23-070](#)

Notice of Special Interest (NOSI): Administrative Supplements to Enhance Software Tools for Open Science. [NOT-OD-23-073](#)

### **NIH-Wide Notices with NIAAA Participation**

Request for Information (RFI): Inviting input on use of a term like preaddiction for identifying and intervening in substance misuse and mild/early-stage substance use disorder. [NOT-DA-23-019](#)

Notice of Intent to Publish a Funding Opportunity Announcement for BRAIN Initiative: New Technologies and Novel Approaches for Recording and Modulation in the Nervous System (R01 Clinical Trial Not Allowed). [NOT-NS-23-035](#)

Notice of Intent to Publish a Funding Opportunity Announcement for BRAIN Initiative: Optimization of Instrumentation and Device Technologies for Recording and Modulation in the Nervous System (U01 Clinical Trials Not Allowed). [NOT-NS-23-036](#)

Notice of Early Expiration of NINDS BRAIN Initiative Funding Opportunity Announcements (FOA) RFA-NS-21-026 and RFA-NS-21-027. [NOT-NS-23-037](#)

## **NIAAA DIRECTOR'S ACTIVITIES**

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NIAAA Director **George F. Koob, Ph.D.**, gave the following presentations between January 1 – March 30:

- “Alcohol and Drug Addiction: The Gain in the Brain is in the Emotional Pain” at Mount Sinai's Department of Psychiatry Grand Rounds (virtual) on January 10, 2023
- “What is addiction: a heuristic neurobiological perspective” at Georgetown University Medical Center (virtual) on January 17, 2023
- “The Neurobiology of Alcohol Use Disorder” at the Western Doctors in Recovery on February 24, 2023
- “Opening Remarks: Scope of the Problem and Closing the Treatment Gap” at the Friends of NIAAA webinar on March 8, 2023

## NOTABLE NIAAA STAFF ACTIVITIES

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**Dr. Ralph Hingson, Dr. Laura Kwako, and Dr. Trish Powell** gave presentations at the 33<sup>rd</sup> Annual National Leadership Forum for the Community Anti-Drug Coalitions of America (CADCA) on January 31-February 1, 2023. Dr. Hingson presented “Trends in and Interventions that Work to Prevent Underage Drinking,” Dr. Kwako presented on the Healthcare Professional Core Resource on Alcohol, and Dr. Powell presented “NIAAA Update: Changing the Conversation Around Alcohol.”

**Dr. Deidra Roach** participated in a webinar, “A Community Conversation on Women and Alcohol,” which was sponsored by the Greater Mt. Lebanon Baptist Church, Baltimore, Maryland on February 22, 2023. Topics included an overview of NIAAA-sponsored collaborative activities to improve access to high quality mental health and addiction treatment services for women and girls.

**Drs. Ivana Grakalic and Deidra Roach** presented a webinar “NIAAA Science Spotlight: Update on Activities Centering Women and Girls” that was sponsored by the Interagency Work Group on Drinking and Drug Use in Women and Girls on March 10, 2023.

**Dr. Shailesh Kumar** spoke about NIAAA's mission and priority areas in sleep and alcohol use disorder during NIH Sleep Awareness Week at a Linked Live event on March 16, 2023.

**Dr. Peter Gao** presented “Closing the Treatment Gap: NIAAA Priorities” at the Gordon Research Conference, “Alcohol-Induced End Organ Diseases: Multisystemic Pathophysiological Mechanisms”, which took place on March 26 – 31. **Dr. Joe Wang** was the discussion leader of the Alcohol and Severe Injury section.

## WHAT'S AHEAD?

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The **Alcoholism and Stress: A Framework for Future Treatment Strategies** meeting will be held May 16 - 19, 2023 in Volterra, Italy.

**The Society for Prevention Research 31<sup>st</sup> Annual Meeting**, “The Role of Prevention Science in Achieving Social Justice and Health Equity for All,” will be held May 30-June 2, 2023, in Washington DC.

**The 46<sup>th</sup> Annual Research Society on Alcohol Scientific Conference** will be held June 24-28, 2023, in Bellevue, Washington. The Fetal Alcohol Spectrum Disorders Study Group Meeting will be held on June 24.

**National Institute on Aging-NIAAA workshop on the role of alcohol misuse in the onset and progression of Alzheimer’s disease and its related dementias** will be held as a hybrid meeting on July 26 - 27, 2023, at the Natcher Conference Center, NIH. The workshop aims to facilitate the identification of research gaps and challenges to advance our understanding of the relationship between alcohol misuse and dementias.

# NIAAA RESEARCH HIGHLIGHTS

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## INITIATION OF AND ESCALATION TO HIGH-INTENSITY DRINKING IN YOUNG ADULTS

*Significance:* High-intensity drinking (HID) (defined here as  $\geq 10$  drinks in a row) is a particularly dangerous drinking behavior. This study used a sample of 451 young adults who reported past 30-day drinking while in 12th grade and initiated HID by age 20. Initiating HID by grade 11 (vs later) was associated with higher average weekly alcohol consumption, HID frequency and AUDIT score at age 20 years. Delaying HID initiation may reduce the likelihood of acute and long-term negative alcohol use.

### *Abstract*

**Importance:** HID is associated with acute negative outcomes. Identifying factors associated with HID initiation in adolescence and how it is associated with young adulthood outcomes can inform screening and prevention. **Objective:** To identify when individuals initiate HID and speed of escalation from first drink and first binge to first HID; characteristics associated with initiation and escalation; and whether these characteristics are associated with weekly alcohol consumption, HID frequency, and symptoms of alcohol use disorder at age 20 years. **Design, Setting, and Participants:** This cohort study analyzed web-based survey data from respondents in the US who reported alcohol use in the past 30 days recruited from the 2018 12th grade Monitoring the Future study and surveyed again from February 14 through April 17, 2020, at modal age 20 years in the Young Adult Daily Life Study. Only respondents who reported HID by modal age 20 years were included in the analyses. **Exposures:** Retrospective alcohol use initiation and self-reported alcohol use measures. **Main Outcomes and Measures:** Key retrospective measures included year of initiation for alcohol, first binge ( $\geq 5$  drinks), and HID ( $\geq 10$  drinks). Measures at age 20 years included weekly alcohol consumption, HID frequency, and Alcohol Use Disorders Identification Test (AUDIT) scores. Covariates included biologic sex, race and ethnicity, parental college education, family history of alcohol problems, and college status. Descriptive statistics and multivariable regression models were used, and all analyses were weighted. **Results:** Of the 451 participants with data eligible for analysis, 62.0% were male (38.0% female). On average, alcohol, binge, and HID were initiated during high school. Mean time of escalation from first drink to first HID was 1.9 (95% CI, 1.8-2.1) years and between first binge and first HID, 0.7 (95% CI, 0.6-0.8) years. Initiating HID by grade 11 (vs later) was associated with higher average weekly alcohol consumption (adjusted incidence rate ratio [aIRR], 1.40; 95% CI, 1.10-1.79]), HID frequency (aIRR, 2.01; 95% CI, 1.25-3.22]), and AUDIT score (adjusted odds ratio, 1.17; 95% CI, 1.02-1.34]) at age 20 years. Escalation from first binge to first HID in the same year (vs  $\geq 1$  year) was associated with higher HID frequency at age 20 years (aIRR, 1.66; 95% CI, 1.06-2.61). **Conclusions and Relevance:** These findings suggest that understanding ages and patterns of HID initiation and escalation associated with particular risk may facilitate screening for adolescents and young adults. (Patrick ME, Evans-Polce RJ, Arterberry BJ, Terry-McElrath Y. Initiation of and Escalation to High-Intensity Drinking in Young Adults. *JAMA Pediatr.* 2023 Mar 1;177(3):286-293. doi: 10.1001/jamapediatrics.2022.5642. PMID: 36716022; PMCID: PMC9887533.)

## CANDIDA ALBICANS-SPECIFIC TH17 CELL-MEDIATED RESPONSE CONTRIBUTES TO ALCOHOL-ASSOCIATED LIVER DISEASE

*Significance:* Alcohol-associated liver disease (ALD) is accompanied by an imbalance of the intestinal fungal microbiome (mycobiome dysbiosis). Proinflammatory cytokines, such as IL-17, produced mainly by T helper 17 (Th17) lymphocytes, are a contributing factor of autoimmune and inflammatory conditions. This report found that T-helper 17 (Th17) cells reactive to the yeast *Candida albicans* increase in the blood

and liver of patients with ALD. In a mouse model, data shows that molecular activation of T-cells reactive to *Candida* developed more severe ethanol-induced liver disease, and an antifungal agent decreased ethanol-induced liver disease in mice. Results suggests that *Candida albicans*-reactive Th17 cells migrate from the intestine to the liver, where they contribute to the development of ALD.

### Abstract

Alcohol-associated liver disease is accompanied by intestinal mycobiome dysbiosis, yet the impacts on liver disease are unclear. We demonstrate that *Candida albicans*-specific T helper 17 (Th17) cells are increased in circulation and present in the liver of patients with alcohol-associated liver disease. Chronic ethanol administration in mice causes migration of *Candida albicans* (*C. albicans*)-reactive Th17 cells from the intestine to the liver. The antifungal agent nystatin decreased *C. albicans*-specific Th17 cells in the liver and reduced ethanol-induced liver disease in mice. Transgenic mice expressing T cell receptors (TCRs) reactive to *Candida* antigens developed more severe ethanol-induced liver disease than transgene-negative littermates. Adoptively transferring *Candida*-specific TCR transgenic T cells or polyclonal *C. albicans*-primed T cells exacerbated ethanol-induced liver disease in wild-type mice. Interleukin-17 (IL-17) receptor A signaling in Kupffer cells was required for the effects of polyclonal *C. albicans*-primed T cells. Our findings indicate that ethanol increases *C. albicans*-specific Th17 cells, which contribute to alcohol-associated liver disease. (Zeng S, Rosati E, Saggau C, Messner B, Chu H, Duan Y, Hartmann P, Wang Y, Ma S, Huang WJM, Lee J, Lee SM, Carvalho-Gontijo R, Zhang V, Hoffmann JP, Kolls JK, Raz E, Brenner DA, Kisseleva T, LeibundGut-Landmann S, Bacher P, Stärkel P, Schnabl B. *Candida albicans*-specific Th17 cell-mediated response contributes to alcohol-associated liver disease. *Cell Host Microbe*. 2023 Mar 8;31(3):389-404.e7. doi: 10.1016/j.chom.2023.02.001. PMID: 36893735; PMCID: PMC10039706.)

## **PRECLINICAL AND CLINICAL EVIDENCE FOR SUPPRESSION OF ALCOHOL INTAKE BY APREMILAST**

Significance: Phosphodiesterases are a superfamily of enzymes that hydrolyze the cyclic nucleotides cAMP and cGMP. Apremilast is a phosphodiesterase type 4 (PDE4) inhibitor and currently an FDA-approved for the treatment of psoriasis. Via PDE 4 inhibition, apremilast elevates intracellular cAMP levels, which is thought to decrease levels of some pro-inflammatory mediators and increase the production of certain anti-inflammatory mediators. Previous research has demonstrated in animal models that inhibition of phosphodiesterases reduces alcohol intake and may serve as potential therapeutic targets. The current study evaluated the effectiveness of apremilast in reducing alcohol intake in animal models of excessive drinking and in a human phase 2a study of non-treatment seeking individuals with AUD. The researchers found that apremilast reduced excessive alcohol use in multiple animal models, potentially by increasing neural activity in the nucleus accumbens, a key brain region in the regulation of alcohol consumption. In the phase 2a study, apremilast reduced drinks per day and the rate of heavy drinking days.

### Abstract

Treatment options for alcohol use disorders (AUDs) have minimally advanced since 2004, while the annual deaths and economic toll have increased alarmingly. Phosphodiesterase type 4 (PDE4) is associated with alcohol and nicotine dependence. PDE4 inhibitors were identified as a potential AUD treatment using a bioinformatics approach. We prioritized a newer PDE4 inhibitor, apremilast, as ideal for repurposing (i.e., FDA approved for psoriasis, low incidence of adverse events, excellent safety profile) and tested it using multiple animal strains and models, as well as in a human phase IIa study. We found that apremilast reduced binge-like alcohol intake and behavioral measures of alcohol motivation in mouse models of genetic risk for drinking to intoxication. Apremilast also reduced excessive alcohol drinking in models of stress-facilitated drinking and alcohol dependence. Using site-directed drug infusions and

electrophysiology, we uncovered that apremilast may act to lessen drinking in mice by increasing neural activity in the nucleus accumbens, a key brain region in the regulation of alcohol intake. Importantly, apremilast (90 mg/d) reduced excessive drinking in non-treatment-seeking individuals with AUD in a double-blind, placebo-controlled study. These results demonstrate that apremilast suppresses excessive alcohol drinking across the spectrum of AUD severity. (Grigsby KB, Mangieri RA, Roberts AJ, Lopez MF, Firsick EJ, Townsley KG, Beneze A, Bess J, Eisenstein TK, Meissler JJ, Light JM, Miller J, Quello S, Shadan F, Skinner M, Aziz HC, Metten P, Morrisett RA, Crabbe JC, Roberto M, Becker HC, Mason BJ, Ozburn AR. Preclinical and clinical evidence for suppression of alcohol intake by apremilast. *J Clin Invest.* 2023 Mar 15;133(6):e159103. doi: 10.1172/JCI159103. PMID: 36656645; PMCID: PMC10014105.)

## **CHEMOSENSORY ALTERATIONS AND IMPACT ON QUALITY OF LIFE IN PERSISTENT ALCOHOL DRINKERS**

*Significance:* To better understand chemosensory dysfunction associated with heavy alcohol consumption, investigators examined chemosensation in individuals with different alcohol drinking behaviors and the association with changes in quality of life (QOL) domains. Participants were divided into three groups (non-drinking, moderate drinking, and heavy drinking) based on their Alcohol Use Disorders Identification Test consumption scores at four different time points (at enrollment, week 4, week 8, and week 12). The researchers observed significant impairment in smell ability of heavy drinking individuals compared to the non-drinking group, and this impairment was associated with a deterioration in their physical, psychological, social, and environmental QOL. Early assessment of smell function in individuals with AUD could potentially help predict disease-associated comorbidities, especially those related to QOL.

### **Abstract**

**Background:** Heavy alcohol consumption-associated chemosensory dysfunction is understudied, and early detection can help predict disease-associated comorbidities, especially those related to four quality of life (QOL) domains (physical, psychological, social and environment). We examined self-reports of chemosensory ability of individuals with different alcohol drinking behaviors and their association with changes in QOL domains. **Methods:** Participants (n = 466) were recruited between June 2020 and September 2021 into the NIAAA COVID-19 Pandemic Impact on Alcohol study. Group-based trajectory modeling was used to categorize participants without any known COVID-19 infection into three groups (non-drinkers, moderate drinkers and heavy drinkers) based on their Alcohol Use Disorders Identification Test consumption scores at four different time points (at enrollment, week 4, week 8 and week 12). Linear mixed models were used to examine chemosensory differences between these groups. The associations between chemosensory abilities and QOL were determined in each group. **Results:** We observed significant impairment in self-reported smell ability of heavy drinking individuals compared to non-drinkers. In contrast, taste ability showed marginal impairment between these groups. There were no significant differences in smell and taste abilities between the moderate and non-drinking groups. Heavy drinkers' impairment in smell and taste abilities was significantly associated with deterioration in their physical, psychological, social, and environmental QOL. **Conclusion:** Persistent heavy drinking was associated with lower chemosensory ability. Heavy drinkers' reduced smell and taste function and association with poorer QOL indicate that early assessment of chemosensory changes may be crucial in identifying poorer well-being outcomes in heavy drinkers at risk for alcohol use disorder. (Agarwal K, Luk JW, Manza P, McDuffie C, To L, Jaime-Lara RB, Stangl BL, Schwandt ML, Momenan R, Goldman D, Diazgranados N, Ramchandani VA, Joseph PV. Chemosensory Alterations and Impact on Quality of Life in

Persistent Alcohol Drinkers. *Alcohol Alcohol*. 2023 Jan 9;58(1):84-92. doi: 10.1093/alcalc/agac047. PMID: 36208183; PMCID: PMC9619625.)

## ADDITIVE EFFECTS OF STRESS AND ALCOHOL EXPOSURE ON ACCELERATED EPIGENETIC AGING IN ALCOHOL USE DISORDER

*Significance:* Stress contributes to premature aging and susceptibility to alcohol use disorder (AUD), and AUD itself is a factor in premature aging. To better understand the interrelationships between stress, AUD, and premature aging, this study used high density methylome arrays and telomere length assays in a deeply phenotyped sample of patients from the NIAAA intramural program. The present study showed that combination of stress and heavy alcohol use additively accelerated epigenetic cellular age by about 4.5 years, and the finding was replicated in external samples from the Grady Trauma project and Generation Scotland. Epigenetic age correlates highly with chronological age but accelerated epigenetic age due to factors such as combined stress and AUD likely increases the risks of morbidity and mortality.

### Abstract

**Background:** Stress contributes to premature aging and susceptibility to alcohol use disorder (AUD), and AUD itself is a factor in premature aging; however, the interrelationships of stress, AUD, and premature aging are poorly understood. **Methods:** We constructed a composite score of stress from 13 stress-related outcomes in a discovery cohort of 317 individuals with AUD and control subjects. We then developed a novel methylation score of stress (MS stress) as a proxy of composite score of stress comprising 211 CpGs selected using a penalized regression model. The effects of MS stress on health outcomes and epigenetic aging were assessed in a sample of 615 patients with AUD and control subjects using epigenetic clocks and DNA methylation-based telomere length. Statistical analysis with an additive model using MS stress and a MS for alcohol consumption (MS alcohol) was conducted. Results were replicated in 2 independent cohorts (Generation Scotland, N = 7028 and the Grady Trauma Project, N = 795). **Results:** Composite score of stress and MS stress were strongly associated with heavy alcohol consumption, trauma experience, epigenetic age acceleration (EAA), and shortened DNA methylation-based telomere length in AUD. Together, MS stress and MS alcohol additively showed strong stepwise increases in EAA. Replication analyses showed robust association between MS stress and EAA in the Generation Scotland and Grady Trauma Project cohorts. **Conclusions:** A methylation-derived score tracking stress exposure is associated with various stress-related phenotypes and EAA. Stress and alcohol have additive effects on aging, offering new insights into the pathophysiology of premature aging in AUD and, potentially, other aspects of gene dysregulation in this disorder. (Jung J, McCartney DL, Wagner J, Yoo J, Bell AS, Mavromatis LA, Rosoff DB, Hodgkinson CA, Sun H, Schwandt M, Diazgranados N, Smith AK, Michopoulos V, Powers A, Stevens J, Bradley B, Fani N, Walker RM, Campbell A, Porteous DJ, McIntosh AM, Horvath S, Marioni RE, Evans KL, Goldman D, Lohoff FW. Additive Effects of Stress and Alcohol Exposure on Accelerated Epigenetic Aging in Alcohol Use Disorder. *Biol Psychiatry*. 2023 Feb 15;93(4):331-341. doi: 10.1016/j.biopsych.2022.06.036. Epub 2022 Jul 16. PMID: 36182531.)

## NEUROIMAGING-DERIVED PREDICTED BRAIN AGE AND ALCOHOL USE AMONG COMMUNITY-DWELLING OLDER ADULTS

*Significance:* A growing body of evidence indicates that alcohol misuse among older adults contributes to accelerated aging in certain brain regions and impaired cognitive function, learning, memory, and motor function. The current study showed that heavier drinkers showed older brain predicted age differences (brain-PAD) than light drinkers (by about 6 years). Brain-PAD is the difference between the brain-predicted age and chronological age based on neuroimaging data. The brain-predicted age difference among light and moderate drinking older adults did not differ from their nondrinking counterparts, suggesting no protective benefit of alcohol on brain aging.

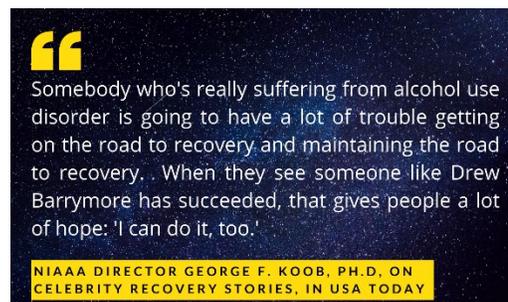
### *Abstract*

**Objectives:** Observational studies have suggested that moderate alcohol use is associated with reduced risk of dementia. However, the nature of this association is not understood. We investigated whether light to moderate alcohol use may be associated with slower brain aging, among a cohort of older community-dwelling adults using a biomarker of brain age based on structural neuroimaging measures. **Design:** Cross-sectional observational study. **Participants:** Well-characterized members of a longitudinal cohort study who underwent neuroimaging. We categorized the 163 participants (mean age 76.7  $\pm$  7.7, 60% women) into current nondrinkers, light drinkers (1–7 drinks/week) moderate drinkers (>7–14 drinks/week), or heavier drinkers (>14 drinks/week). **Measurements:** We calculated brain-predicted age using structural MRIs processed with the BrainAgeR program and calculated the difference between brain-predicted age and chronological age (brain-predicted age difference, or brain-PAD). We used analysis of variance to determine if brain-PAD differed across alcohol groups, controlling for potential confounders. **Results:** Brain-PAD differed across alcohol groups ( $F[3, 150] = 4.02$ ;  $p = 0.009$ ) with heavier drinkers showing older brain-PAD than light drinkers (by about 6 years). Brain-PAD did not differ across light, moderate, and nondrinkers. Similar results were obtained after adjusting for potentially mediating health-related measures, and after excluding individuals with a history of heavier drinking. **Discussion:** Among this sample of healthy older adults, consumption of more than 14 drinks/week was associated with a biomarker of advanced brain aging. Light and moderate drinking was not associated with slower brain aging relative to non-drinking. (Funk-White M, Wing D, Eyer LT, Moore AA, Reas ET, McEvoy L. Neuroimaging-Derived Predicted Brain Age and Alcohol Use Among Community-Dwelling Older Adults. *Am J Geriatr Psychiatry*. 2023 Feb 20:S1064-7481(23)00217-8. doi: 10.1016/j.jagp.2023.02.043. Epub ahead of print. PMID: 36925380.)

## NIAAA COMMUNICATIONS AND PUBLIC LIAISON ACTIVITIES

### News Media

Dr. Koob, Dr. Aaron White, and other NIAAA scientists completed 45 media interviews from January through March 2023. Noteworthy stories include those from the [New York Times](#), [Good Morning America](#), [USA Today](#), [The Hill](#), and the [Washington Post](#).



## Highlights:

- [NPR 1A podcast](#) – Dr. White discussed alcohol consumption patterns in the U.S. and the growing popularity of **Dry January** and other “sober curious” movements.
- [CBS News](#) – Dr. Koob discussed the dangers of “**blackout rage gallons,**” or **BORGs**, a new drinking trend among college students fueled by challenges on social media.
- [This is Getting Old podcast](#) – Dr. Koob discussed the risks of **alcohol use among older adults** in this Alliance for Aging Research podcast.
- [Chef AJ Live](#) – Dr. Paule Joseph discussed how **COVID-19 affects taste and smell** on a live YouTube presentation on Chef AJ Live, as well as participating in Chef AJs Summit in February on the topic of **taste and smell on nutrition**.

## News releases, announcements, and NIAAA Director’s blogs:

- January 2023 – [Vacancy announcement: NIAAA Scientific Diversity Officer](#)
- January 2023 – [American Heart Month: An opportunity to examine your relationship with alcohol](#)
- February 2023 – NIAAA Director’s Blog: [Science-Based Resources about Alcohol and Health](#)
- March 2023 – [New NIH study reveals shared genetic markers underlying substance use disorders](#)
- March 2023 – [In Memoriam: George Fein, Ph.D.](#)
- April 2023 – [In Memoriam: Enoch Gordis, M.D.](#)
- May 2023 – [In Memoriam: John Littleton, M.D., Ph.D.](#)
- April 2023 – [Alcohol-related deaths, which increased during the first year of the COVID-19 pandemic, continued to rise in 2021](#)

## Major Activities, Events, and Products

- **Alcohol Awareness Month:** In recognition of Alcohol Awareness Month in April, NIAAA shared messages on social media and engaged in a Twitter chat with the American Society of Addiction Medicine on alcohol myth busting and treatment.
- **Dry January:** NIAAA engaged in a promotional campaign for Dry January, an event where individuals choose to not drink alcohol for the month. NIAAA posted an [NIAAA Director’s blog post](#), and developed a social media campaign which reached approximately 27,000 people. Dr. Koob also engaged in a satellite media tour with an audience of approximately 1.8 million people through interviews with 17 local and national radio and television media outlets.
- **NAADAC Engagement in the Black Community Summit:** As part of Black History Month, NAADAC—The Association for Addiction Professionals, organized this event to discuss critical issues in the Black community relevant to treatment and recovery. NIAAA sponsored the event and shared NIAAA web resources with participants.



From NIAAA social media posts



From NIAAA social media posts

## Publications and Web Activities

### Top NIAAA topics – publications and webpages

- (publications viewed online) [Alcohol Flush Reaction](#), [Alcohol Use Disorder](#), [Alcohol Overdose](#)
- (publications ordered/printed) [Rethinking Drinking](#), [Treatment for Alcohol Problems: Finding and Getting Help](#), [Making a Difference: Talk to Your Child About Alcohol](#)
- (webpages) [Alcohol's Effects on the Body](#), [Drinking Levels Defined](#), [Alcohol Flush Reaction](#)

### New and updated resources

- New [Alcohol Facts and Statistics](#) webpages: NIAAA launched a major update to [Alcohol Facts and Statistics](#), a popular online resource which consistently ranks among the most viewed NIAAA webpages. It has been updated with recent alcohol statistics and expanded with demographic information. The material is now presented on separate topic pages for improved readability and navigability. Topics include prevalence and trends in alcohol consumption, the scope of alcohol misuse-related health and societal consequences, and drinking during pregnancy.
- The [NIAAA Director's Blog webpages](#) were visually and functionally refreshed to optimize the ease of navigation between current and past blog posts.
- A new [Mouse Lung Fibrosis Atlas](#) provides an interactive tool to explore and visualize multi-omics data generated by the NIAAA Intramural [Section on Fibrotic Disorders](#).

### Advances in translations

- New Spanish translation of [Alcohol and the Brain: An Overview](#)
- NIAAA [news releases](#) are now translated to Spanish

## Social Media Highlights

NIAAA's Twitter account ([@NIAAAnews](#)) currently has almost 30,000 followers (a 1.4 percent increase since January 1, 2023), NIAAA's Instagram account ([@NIAAAnews](#)) has more than 3,000 followers (a 7 percent increase), and NIAAA's Facebook ([@NIAAAgov](#)) has almost 2,000 followers (a 9 percent increase). Highlights from social media:

#### Instagram @NIAAAnews

#DYK alcohol use can affect nearly every organ in your body? ...



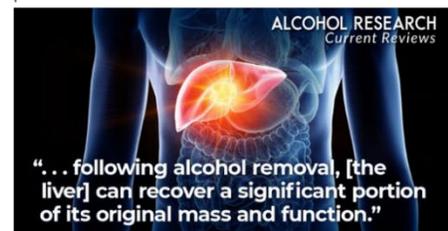
#### Facebook @NIAAAgov

Long-term, drinking less alcohol could help to reduce your risk of serious heart problems. As an added benefit, you may also notice improvements in the overall health of your mind and body. ...



#### Twitter @NIAAAnews

This [#ARCRJournal](#) review by researchers at [@unmc](#) and VA Nebraska-Western Iowa discusses the negative effects of [#alcoholmisuse](#) on the body's organs, and how recovery is possible ...



*Notable pickup of NIAAA content:*

- NIH
  - The NIH Catalyst featured Dr. Lorenzo Leggio: “[Bugs, the Brain, and Behavior.](#)”
  - MedlinePlus Magazine featured Dr. Koob: “[Meet the Director Series](#)”
  - The NIH Record featured Dr. Paule Joseph: “[Getting to Know Inspiring Women Leaders at NIH.](#)”
  - NIH homepage rotator slides featured NIAAA messages on alcohol and heart health, alcohol-associated blackouts, and Alcohol Awareness Month.
- AAAP Newsletter: NIAAA research on predicting treatment outcomes
- CADCA Coalitions Online: Interview with Dr. Koob on Dry January and other topics
- American politician and health advocate Patrick J. Kennedy: Retweeted about the NIAAA Healthcare Professional’s Core Resource on Alcohol
- Minnesota Public radio: Story and tweet featuring [Rethinking Drinking](#)