



**NIAAA DIRECTOR’S REPORT
ON INSTITUTE ACTIVITIES TO THE 166TH MEETING
OF THE NATIONAL ADVISORY COUNCIL ON
ALCOHOL ABUSE AND ALCOHOLISM**

Tuesday, May 7, 2024

Hybrid Meeting

TABLE OF CONTENTS

In Memoriam..... 2

NIAAA Budget 2

Honors and Awards 2

Staff Transitions 3

Recently Issued Funding Opportunities 4

Notices Issued by NIAAA..... 5

NIAAA Director’s Activities 6

Notable NIAAA Staff Activities 7

What’s Ahead? 8

NIAAA Research Highlights 8

NIAAA Communications and Public Liaison Activities 13

IN MEMORIAM



Dale Hereld, MD, PhD served as a Health Scientist Administrator in the NIAAA Division of Metabolism and Health Effects from 2008 until his retirement in 2019. In this role, he managed the fetal alcohol spectrum disorders (FASD) research portfolio and was the NIAAA Project Scientist for the Prenatal Alcohol, SIDS, and Stillbirth Research (PASS) Network, the Collaborative Initiative on FASD (CIFASD) research consortium, and the Collaboration on FASD Prevalence (CoFASP) research consortium. Dr. Hereld also represented NIAAA on many NIH-wide committees and projects. Dr. Hereld was a beloved member of the NIAAA family. You counted yourself lucky to have known him, witnessed his charm and kindness, or experienced a touch of his quick-witted humor. He will be deeply missed by his family, friends, and NIAAA colleagues.

NIAAA BUDGET

Fiscal Year (FY) 2024

On March 23rd, 2024, the President signed the H.R. 2882 – Further Consolidated Appropriations Act, 2024. NIH received a total of \$47.2 billion, which is a \$0.4 million (0.8%) decrease below the FY 2023 enacted level.

The FY 2024 appropriation for NIAAA provides \$595.3 million, which is the same enacted level as in FY 2023.

HONORS AND AWARDS

Dr. Michelle Antoine received the 2024 Rising Star – Scientific Investigator Award from the Albert Einstein College of Medicine.

Drs. Tommy Gunawan and Brian Mackowiak received outstanding poster awards at the 2024 Gordon Research Conference on Alcohol and the Nervous System.

Dr. Andrew Holmes won the 2024 Distinguished Investigator Award from the International Behavioral and Neural Genetics Society.

Dr. Paule Joseph was selected as an inductee into the Sigma International Nurse Researcher Hall of Fame and will be honored at Sigma's 35th International Nursing Research Congress this summer. Dr. Joseph also received the Nurse Researcher Award from the Haitian American Association.

The following postdoctoral fellows in the NIAAA Division of Intramural Clinical and Biological Research have been selected as NIH Center on Compulsive Behaviors fellows for 2024:

- **Dr. Kushbu Agarwal**, Section of Sensory Science and Metabolism
- **Dr. Priscila Correa Antonello**, Section on Neural Circuits
- **Dr. Tommy Gunawan**, Laboratory on Human Psychopharmacology
- **Dr. David Haggerty**, Laboratory for Integrative Neuroscience
- **Dr. Lee Peyton**, Laboratory for Integrative Neuroscience

STAFF TRANSITIONS

Senior Staff Appointments



Dr. Philippe Marmillot has been selected as NIAAA's Director of the Office of Extramural Activities (OEA). He served as the Acting Director of NIAAA OEA prior to his new appointment. Dr. Marmillot will provide oversight of NIAAA's grants management, peer review, and committee management activities, including serving as Executive Secretary of the NIAAA Advisory Council. He will also serve as the Referral Officer and Research Integrity Officer for the Institute. Dr. Marmillot joined NIAAA in 2007 as a Scientific Review Officer and previously served as an NIH Guide Liaison.

New Staff



Dr. Mariam Melkumyan joined the Laboratory of Molecular Signaling in the Division of Intramural Clinical and Biological Research as a postdoctoral Intramural Research Training Award fellow. Dr. Melkumyan will conduct research on the mechanisms of docosahexaenoic acid and its metabolites, as well as their effects on neuroinflammatory responses in connection with ethanol consumption using molecular, electrophysiologic, and behavioral approaches.



Dr. Damiya (Miya) Whitaker joined the Treatment, Health Services, and Recovery Branch in the Division of Treatment and Recovery as a Health Scientist Administrator. Before joining NIAAA, Dr. Whitaker was a program director at the NIH Office of Research on Women's Health (ORWH), where she led the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations Administrative Supplement Program. She also organized multiple scientific briefings on the impact of the COVID-19 pandemic on the health of women and represented ORWH on key trans-NIH committees. Dr. Whitaker is a clinical psychologist with postdoctoral training in substance use epidemiology and public health research. She will oversee grants on health services, health equity, and women's health.

Transitions

Dr. Dan Falk was selected as the Chief of the Medications Development Branch in the Division of Treatment and Recovery (DTR). Dr. Falk joined the NIAAA Medications Development team within DTR in 2009 where he facilitated alcohol clinical trials and medications development studies. Dr. Falk is pursuing approval of a new endpoint for pivotal alcohol clinical trials by the U.S. Food and Drug Administration and has also taken the lead in developing the [NIAAA Data Archive](#) and advancing NIAAA's data sharing efforts.

Dr. Yaojie Fu transitioned from Postdoctoral Visiting Fellow in the Laboratory of Liver Diseases to a Research Fellow. Dr. Fu will work on the molecular mechanisms underlying alcohol-associated liver disease. Dr. Fu will use a variety of mouse models and advanced cellular and molecular techniques to carry out this work.

Dr. Danielle Sambo transitioned from Postdoctoral Fellow in the Laboratory of Neurogenetics to a Research Fellow. Dr. Sambo will continue to investigate the mechanisms of Fetal Alcohol Effects,

using a mouse model of embryonic alcohol exposure and a variety of techniques including single nucleus and bulk RNA sequencing and spatial transcriptomics. In addition, Dr. Sambo currently serves as editor and publisher of the NIAAA trainee newsletter.

Departures

Dr. Biswait Kundu, a Visiting Fellow in the Section on Medicinal Chemistry departed in March for a position as a postdoctoral fellow at Johns Hopkins University.

Judit O'Connor, Chief of the Office of Financial Management Branch transferred to the National Institute of Allergy and Infectious Diseases (NIAID) as the Director of the Office of Mission Integration and Financial Management.

Robert “Bob” Ward, a Facility Administrative Officer in the Administrative Services Branch, retired after nearly 24 years of federal and military service. Mr. Ward began his NIH career at NIAID in 2005 and joined NIAAA in 2007 where he spent the remaining 17 years of his federal career. During his retirement, Bob plans on traveling, relaxing, and being with those who are closest to him.

Departing Postbaccalaureate Intramural Research Training Award Fellows:

- **Daniel Geda** – Office of the Clinical Director
- **Jessica Laudie** – Office of the Clinical Director
- **Aditi Madhusudan** – Laboratory of Neuroimaging

RECENTLY ISSUED FUNDING OPPORTUNITIES

Notices of Funding Opportunity (NOFOs) issued by NIAAA

Limited Competition: Alcohol-associated Hepatitis Clinical Network - Integrated Treatment Clinical Trials for Clinical Centers - Data Coordinating Center: The purpose of this limited competition NOFO is to leverage both the established clinical infrastructure and the data coordinating center of the previously funded program “Late Phase Clinical Trials and Observational Studies in Alcoholic Hepatitis.” In the next cycle, the program will consist of up to six clinical study sites and one data coordinating center to conduct an integrated treatment clinical trial of alcohol use disorder and alcohol-associated liver disease. [RFA-AA-24-004](#) (Clinical Centers - U01), [RFA-AA-24-005](#) (Data Coordinating Center - U24). *Contacts: Drs. Peter Gao and Joe Wang*

Model Continuums of Care Initiative (MCCI) to Advance Health Equity and End Health Disparities Among Women and Girls in Racial/Ethnic Minority and Other Underserved Communities: The purpose of this NOFO is to support the planning phase of the MCCI initiative, the goal of which is to apply the latest dissemination and implementation science approaches to significantly reduce the prevalence and impact of multi-morbidity among racial/ethnic minority women and girls of reproductive age who are at risk for, and living with, mental health disorders, substance use disorders, chronic stress, cardiopulmonary diseases, common metabolic disorders, cancer, and HIV/AIDS. Special emphasis will be placed on using stakeholder partnerships, provider training, and infrastructure changes to improve access to high quality health care. [RFA-AA-24-006](#) (U34). *Contact: Dr. Deidra Roach*

Notices Issued by NIAAA

Request for Information (RFI): Innovative, Non-invasive Biosensing Technologies with High Accuracy and High Resolution Detection of Blood Alcohol Levels: NIAAA, in collaboration with the National Institute of Biomedical Imaging and Bioengineering, issued an RFI to seek public input on cutting-edge biosensing technologies, such as advanced infrared spectroscopic technology, to accelerate the development of a non-invasive inconspicuous wearable alcohol sensor that continuously detects blood alcohol concentrations with high accuracy in real-time. The RFI was open for comment February 13, 2024 through April 8, 2024. [NOT-AA-24-005](#). *Contacts: Drs. Changhai Cui and Kathy Jung, and Megan Ryan.*

Notices of Intent to Publish Funding Opportunity Announcements for Specialized Alcohol Research Centers (P50), and Comprehensive Alcohol Research Centers (P60 Clinical trial Optional): The overall purpose of the NIAAA Alcohol Research Center program is to provide leadership in conducting and fostering interdisciplinary, collaborative research on a wide variety of topics relevant to the NIAAA mission. Topics include, but are not limited to, the nature, etiology, genetics, diagnosis, treatment, and prevention of AUD, alcohol-related end organ diseases, and their biomedical, psychosocial, and economic consequences, across the lifespan and across racial/ethnic groups and other health disparity populations. The Specialized Research Center (P50) mechanism supports an integrated, broad-based multidisciplinary, multi-investigator, long-term program of research and research support activities planned around a specific major research theme. In addition, for the Comprehensive Alcohol Research Center (P60), an interactive dissemination component is required to accelerate the use of research findings to benefit public health, including among diverse and historically underserved communities, to foster community feedback, and to promote research participation. [NOT-AA-24-007](#) (P50), [NOT-AA-24-008](#) (P60). *Contact: Dr. Philippe Marmillot*

NIH-Wide NOSIs, NOFOs and Notices with NIAAA Participation

NIH Blueprint for Neuroscience Research: Request for Information (RFI) on the NIH Toolbox Assessments Conference, [NOT-AG-23-076](#).

Notice of Change to Key Dates Listed in PAR-24-092, "Multidisciplinary Studies of HIV/AIDS and Aging. (R21 Clinical Trial Optional)", [NOT-AG-23-079](#), (R01 Clinical Trial Optional)", [NOT-AG-23-081](#).

Notice of Change to Budget Information Listed in PAR-21-357, "Research Enhancement Award Program (REAP) for Health Professional Schools and Graduate Schools (R15 Clinical Trial Required)", [NOT-AG-23-085](#).

Request for Information (RFI): Improving research frameworks to enable rigorous study of the effects of racism on brain and behavioral health across the lifespan, [NOT-MH-24-190](#).

Pre-Application Webinar for RFA-NR-24-004: Transformative Research to Address Health Disparities and Advance Health Equity (U01 Clinical Trial Optional), [NOT-NR-24-006](#).

Notice of Change: Extension of PAR-21-163 Blueprint Neurotherapeutics Network (BPN): Biologic-based Drug Discovery and Development for Disorders of the Nervous System (UG3/UH3), [NOT-NS-24-049](#), U44", [NOT-NS-24-050](#).

Notice of Special Interest (NOSI): Supporting the Exploration of Cloud in NIH-supported Research, [NOT-OD-24-078](#).

Notice of Special Interest (NOSI): Women's Health Research, [NOT-OD-24-079](#).

NIH Support for Conferences and Scientific Meetings (Parent R13 Clinical Trial Not Allowed), [PA-24-141](#).

Support for Research Excellence (SuRE) Award (R16 Clinical Trial Not Allowed), [PAR-24-144](#).

Support for Research Excellence First Independent Research (SuRE-First) Award (R16 - Clinical Trial Not Allowed), [PAR-24-145](#).

BRAIN Initiative: Scaled reagent resources for brain cell type-specific access across vertebrate species (U01 Clinical Trial Not Allowed), [RFA-MH-25-100](#).

BRAIN Initiative: Production and distribution facilities for brain cell type-specific access reagents (U24 Clinical Trial Not Allowed), [RFA-MH-25-105](#).

BRAIN Initiative: Data Archives for the BRAIN Initiative (R24 Clinical Trial Optional), [RFA-MH-25-110](#).

BRAIN Initiative: Research on the Ethical Implications of Advancements in Neurotechnology and Brain Science (R01 Clinical Trial Optional), [RFA-MH-25-170](#), (R21 Clinical Trial Optional), [RFA-MH-25-171](#).

BRAIN Initiative: Next-Generation Devices for Recording and Modulation in the Human Central Nervous System (UG3/UH3 Clinical Trial Optional), [RFA-NS-24-016](#), (UH3 Clinical Trial Optional), [RFA-NS-24-017](#).

NIH Blueprint and BRAIN Initiative Diversity Specialized Predoctoral to Postdoctoral Advancement in Neuroscience (D-SPAN) Award (F99/K00 Clinical Trial Not Allowed), [RFA-NS-24-030](#).

BRAIN Initiative: Preclinical Proof of Concept for Novel Recording and Modulation Technologies in the Human CNS (R18 - Clinical Trial Not Allowed), [RFA-NS-24-031](#).

HEAL Initiative: Studies to Enable Analgesic Discovery (R61/R33 - Clinical Trial Not Allowed), [RFA-NS-25-012](#).

Building Interdisciplinary Research Careers in Women's Health (BIRCWH) (K12 Clinical Trial Optional), [RFA-OD-24-013](#).

NIAAA DIRECTOR'S ACTIVITIES

NIAAA Director **George F. Koob, Ph.D.**, gave the following presentations between January – March 31, 2024:

- “Changing the Conversation Around Alcohol in the United States – Acknowledging the Elephant in the Room” and “NIAAA Updates: Trends, Harms and Solutions for Underage Drinking” at CADCA’s National Leadership Forum, National Harbor, MD on January 30, 2024.

- “The Alcohol Use Disorder 3 Stage Cycle, 3 Domain, 3 Neurocircuit Framework: A Catalyst for Translational Research” at the Gordon Research Conference on Alcohol and the Nervous System 2024 Session: Integration of Basic and Clinical Research in Translational Neuroscience, in Galveston, TX, on February 11, 2024.
- “What is Addiction? A Heuristic Neurobiological Perspective” for the Neurobiology Drug Addiction Lecture at Georgetown University Medical Center Department of Neuroscience in Washington, DC on February 27, 2024.
- “What is Addiction? A Heuristic Neurobiological Perspective” for the Student Research Week Keynote at Texas Tech University Health Science Center Campuses: Lubbock, Amarillo, and Abilene (virtual) February 28, 2024.
- “Changing the Conversation Around Alcohol in the United States – Acknowledging the Elephant in the Room,” the Robert Taylor Memorial Lecture at Howard University College of Medicine in Washington, DC on February 28, 2024.
- “Changing the Conversation Around Alcohol in the United States – Acknowledging the Elephant in the Room” at the Albert Einstein College of Medicine-Montefiore Medical Center Grand Rounds (virtual) on March 7, 2024.
- “Preventing Alcohol Misuse: An Overview” for the Friends of NIAAA Congressional Briefing in Washington, DC on March 21, 2024.

NOTABLE NIAAA STAFF ACTIVITIES

Activities between **January 1, 2024- March 31, 2024:**

Joan Romaine gave a presentation at the annual Women’s Weekend Retreat on January 20, 2024 at the Claggett Center in Adamstown, Maryland about the work of the NIH Religion, Spirituality, and Health Scientific Interest Group and the role of faith communities in keeping their communities healthy.

Dr. Ralph Hingson presented “Trends and Interventions That Work to Prevent Underage Drinking” at CADCA’s 34th Annual National Leadership Forum and the Substance Abuse and Mental Health Services Administration’s 20th Annual Prevention Day on January 29-30, 2024.

Dr. Changhai Cui served as a co-discussion leader at the Alcohol and the Nervous System Gordon Research Conference on February 11 - 16, 2024 in Galveston, Texas for a session titled “Alcohol and Gut-Brain Interactions.”

Drs. Trish Powell and Tatiana Balachova organized and led the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders Fall 2023 Executive Meeting on February 28, 2024 in Bethesda, Maryland.

Dr. John Matochik participated in the Program Officer Panel and the Mentoring Sessions for Young Investigators at the ABCD Insights and Innovations Meeting held March 4-5, 2024 in Bethesda, Maryland.

Dr. Robert Freeman participated in a panel discussion titled “Addressing Social and Structural Drives of Health Inequities Among SGM Communities Through Funding Priorities” at the Society of Behavioral Medicine 45th Annual Meeting and Scientific Sessions, on March 14, 2024 in Philadelphia, Pennsylvania.

Dr. Ralph Hingson presented “Interventions that Work to Prevent Underage Drinking and Driving after Drinking” at the Joint Meeting on Youth Prevention, Treatment, and Recovery, held by the National Center on Youth Prevention, Treatment, and Recovery on March 19, 2024 in Baltimore, Maryland.

Dr. Tatiana Balachova moderated the prevention session at the NIH HIV & Women Scientific Workshop: Centering the Health of Women in HIV Research, held virtually on March 22, 2024.

WHAT’S AHEAD?

The Annual [Public Meeting of the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders](#) will be held on May 9, 2024 (Hybrid).

The [32nd Society on Prevention Research Annual Meeting](#), “Advancing Partnerships and Collaborative Approaches in Prevention Science,” will be held May 28-31, 2024, in Washington DC.

The [47th Annual Research Society on Alcohol Scientific Meeting](#) will be held June 22-26, 2024, in Minneapolis, Minnesota.

[CADCA’s 23rd Annual Mid-Year Training Institute](#) will be held July 14-18, 2024 in Chicago, IL.

NIAAA RESEARCH HIGHLIGHTS

[Randomized Controlled Trial of Anakinra plus Zinc vs. Prednisone for Severe Alcohol-associated Hepatitis](#)

Significance: Severe alcohol-associated hepatitis (SAH) is a serious health condition with a high 90-day mortality for which there are no treatments approved by the U.S. Food and Drug Administration. Although 28-day glucocorticoid therapy is often recommended as the standard of care for SAH, this treatment strategy has not been shown to improve patient survival beyond 30 days. Also, prolonged treatment with glucocorticoids increases the risk of bacterial and opportunistic fungal infections which may contribute to mortality. Researchers conducted a double-blind randomized clinical trial to compare the effectiveness of anakinra (an interleukin-1 antagonist) plus zinc to the glucocorticoid prednisone in mediating 90-day survival in patients with SAH. In the prednisone group, the Lille score (a predictor of 6-month survival) was assessed at day 7 and used to guide whether or not prednisone treatment should continue. The researchers found that patients treated with prednisone had a higher 90-day overall and transplant-free survival and a lower incidence of acute kidney injury compared to patients treated with anakinra plus zinc. Infection rates of the two treatment approaches were similar. The findings suggest that tailoring the duration of glucocorticoid therapy using the Day-7 Lille score may be an effective strategy for promoting 90-day survival in individuals with SAH.

Abstract: *Background:* Severe alcohol-associated hepatitis (SAH) is associated with high 90-day mortality. Glucocorticoid therapy for 28 days improves 30- but not 90-day survival. We assessed the efficacy and safety of a combination of anakinra, an IL-1 antagonist, plus zinc (A+Z) compared to prednisone using the Day-7 Lille score as a stopping rule in patients with SAH. *Methods:* In this phase IIb double-blind randomized trial in adults with SAH and MELD scores of 20-35, participants

were randomized to receive either daily anakinra 100 mg subcutaneously for 14 days plus daily zinc sulfate 220 mg orally for 90 days, or daily prednisone 40 mg orally for 30 days. Prednisone or prednisone placebo was stopped if Day-7 Lille score was >0.45. All study drugs were stopped for uncontrolled infection or ≥ 5 point increase in MELD score. The primary endpoint was overall survival at 90 days. *Results:* Seventy-three participants were randomized to prednisone and 74 to A+Z. The trial was stopped early after a prespecified interim analysis showed prednisone was associated with higher 90-day overall survival (90% vs. 70%; hazard ratio for death = 0.34, 95% CI 0.14-0.83, $p = 0.018$) and transplant-free survival (88% vs. 64%; hazard ratio for transplant or death = 0.30, 95% CI 0.13-0.69, $p = 0.004$) than A+Z. Acute kidney injury was more frequent with A+Z (45%) than prednisone (22%) ($p = 0.001$), but rates of infection were similar (31% in A+Z vs. 27% in prednisone, $p = 0.389$). *Conclusions:* Participants with SAH treated with prednisone using the Day-7 Lille score as a stopping rule had significantly higher overall and transplant-free 90-day survival and lower incidence of acute kidney injury than those treated with A+Z.

Gawrieh S, Dasarathy S, Tu W, Kamath PS, Chalasani NP, McClain CJ, Bataller R, Szabo G, Tang Q, Radaeva S, Barton B, Nagy LE, Shah VH, Sanyal AJ, Mitchell MC; AlcHepNet Investigators. Randomized trial of anakinra plus zinc vs. prednisone for severe alcohol-associated hepatitis. *J Hepatol.* 2024 Feb 10:S0168-8278(24)00109-0.

[Steroid Responsiveness in Alcohol-associated Hepatitis is Linked to Glucocorticoid Metabolism, Mitochondrial Repair, and Heat Shock Proteins](#)

Significance: This study investigated the mechanisms underlying response to corticosteroids and mortality in patients with alcohol-associated hepatitis (AH). Researchers assessed the proteomic profiles of hepatocytes from biopsy samples of patients with AH and controls. They found that responsiveness to steroid treatment is linked to glucocorticoid metabolism and heat shock protein expression levels in hepatocytes, and mitochondrial DNA repair enzymes in the plasma. In addition, analysis of treatment non-responders who survived 24 weeks compared to non-responders who did not survive, revealed several protein expression changes, including increased levels of acute phase proteins, elevated coagulation factors, and reduced mast cell markers. Despite the limitations (small sample size and age difference between treatment responders and non-responders), the work suggests potential prognostic indicators of AH.

Abstract: Background: Alcohol-associated hepatitis (AH) is one of the clinical presentations of alcohol-associated liver disease. AH has poor prognosis, and corticosteroids remain the mainstay of drug therapy. However, ~40% of patients do not respond to this treatment, and the mechanisms underlying the altered response to corticosteroids are not understood. The current study aimed to identify changes in hepatic protein expression associated with responsiveness to corticosteroids and prognosis in patients with AH. *Methods:* Patients with AH were enrolled based on the National Institute on Alcohol Abuse and Alcoholism inclusion criteria for acute AH and further confirmed by a diagnostic liver biopsy. Proteomic analysis was conducted on liver samples acquired from patients with AH grouped as nonresponders (AH-NR, $n = 7$) and responders (AH-R, $n = 14$) to corticosteroids, and nonalcohol-associated liver disease controls ($n = 10$). The definition of responders was based on the clinical prognostic model, the Lille Score, where a score < 0.45 classified patients as AH-R and a score > 0.45 as AH-NR. Primary outcomes used to assess steroid response were Lille Score (eg, improved liver function) and survival at 24 weeks. *Results:* Reduced levels of the glucocorticoid receptor and its transcriptional co-activator, glucocorticoid modulatory element-binding protein 2, were observed in the hepatic proteome of AH-NR versus AH-R. The corticosteroid metabolizing enzyme, 11-beta-hydroxysteroid dehydrogenase 1, was increased in AH-NR versus AH-R along with elevated mitochondrial DNA repair enzymes, while several proteins of the heat shock pathway were reduced. Analysis of differentially expressed

proteins in AH-NR who survived 24 weeks relative to AH-NR nonsurvivors revealed several protein expression changes, including increased levels of acute phase proteins, elevated coagulation factors, and reduced mast cell markers. *Conclusions:* This study identified hepatic proteomic changes that may predict responsiveness to corticosteroids and mortality in patients with AH.

Hardesty J, Hawthorne M, Day L, Warner J, Warner D, Gritsenko M, Asghar A, Stolz A, Morgan T, McClain C, Jacobs J, Kirpich IA. Steroid responsiveness in alcohol-associated hepatitis is linked to glucocorticoid metabolism, mitochondrial repair, and heat shock proteins. *Hepatol Commun.* 2024 Mar 4;8(3):e0393.

Imaging a Putative Marker of Brain Cortisol Regulation in Alcohol Use Disorder

Significance: Chronic alcohol misuse is associated with a dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) response that may reduce the body's ability to respond to stress appropriately. The current study used positron emission tomography to measure 11 β -HSD1 (an enzyme that converts cortisone to cortisol) in the human brain. Compared to patients without alcohol use disorder (AUD), there was higher availability of 11 β -HSD1 in individuals with moderate to severe AUD in prefrontal and limbic brain regions associated with stress pathophysiology and the addiction cycle. The higher availability of 11 β -HSD1 was also correlated with drinking frequency measures and AUD severity in the ventral medial prefrontal cortex (vmPFC). The results suggest that central nervous system glucocorticoid activity is increased in individuals with AUD in addition to peripheral glucocorticoid dysregulation and provide an additional insight into the neural mechanisms of stress regulation dysfunction associated with AUD.

Abstract: Background: Stress is a potent activator of the hypothalamic-pituitary-adrenal (HPA) axis, initiating the release of glucocorticoid hormones, such as cortisol. Alcohol consumption can lead to HPA axis dysfunction, including altered cortisol levels. Until recently, research has only been able to examine peripheral cortisol associated with alcohol use disorder (AUD) in humans. We used positron emission tomography (PET) brain imaging with the radiotracer [18 F]AS2471907 to measure 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), a cortisol-regenerating enzyme, in people with AUD compared to healthy controls. **Methods:** We imaged 9 individuals with moderate to severe AUD (5 men, 4 women; mean age = 38 years) and 12 healthy controls (8 men, 4 women; mean age = 29 years). Participants received 93.5 ± 15.6 MBq of the 11 β -HSD1 inhibitor radiotracer [18 F]AS2471907 as a bolus injection and were imaged for 150-180 min on the High-Resolution Research Tomograph. 11 β -HSD1 availability was quantified by [18 F]AS2471907 volume of distribution (V_T ; mL/cm 3). *A priori* regions of interest included amygdala, anterior cingulate cortex (ACC), hippocampus, ventromedial PFC (vmPFC) and caudate. **Results:** Individuals with AUD consumed 52.4 drinks/week with 5.8 drinking days/week. Healthy controls consumed 2.8 drinks/week with 1.3 drinking days/week. Preliminary findings suggest that [18 F]AS2471907 V_T was higher in amygdala, ACC, hippocampus, vmPFC, and caudate of those with AUD compared to healthy controls ($p < 0.05$). In AUD, vmPFC [18 F]AS2471907 V_T was associated with drinks per week ($r = 0.81$, $p = 0.01$) and quantity per drinking episode ($r = 0.75$, $p = 0.02$). **Conclusions:** This is the first *in vivo* examination of 11 β -HSD1 availability in individuals with AUD. Our data suggest higher brain availability of the cortisol-regenerating enzyme 11 β -HSD1 in people with AUD (vs. controls), and that higher vmPFC 11 β -HSD1 availability is related to greater alcohol consumption. Thus, in addition to the literature suggesting that people with AUD have elevated peripheral cortisol, our findings suggest there may also be heightened central HPA activity. These findings set the foundation for future hypotheses on mechanisms related to HPA axis function in this population.

Verplaetse TL, Hillmer AT, Bhatt S, Rusowicz A, Li S, Nabulsi N, Matuskey D, Huang Y, McKee SA, Cosgrove KP. Imaging a putative marker of brain cortisol regulation in alcohol use disorder. *Neurobiol Stress*. 2024 Jan 21;29:100609.

[Molecular Mechanisms Involved in Alcohol Craving, IRF3, and Endoplasmic Reticulum Stress: A Multi-omics Study](#)

Significance: This study investigated the molecular mechanisms underlying alcohol craving and the actions of anti-craving AUD medications (acamprosate and naltrexone). A series of genes enriched in immune-related pathways were associated with elevated baseline craving intensity in peripheral blood mononuclear cells from patients with AUD. The study also utilized a patient-derived induced pluripotent stem cell (iPSC)-based model system to study IRF3, a transcription factor that plays a role in mediating endoplasmic reticulum (ER) stress. In human iPSC-derived astrocytes, alcohol increased IRF3 levels, while acamprosate and naltrexone attenuated IRF3, leading to a decrease in ER stress. These data suggest possible relationships among craving, ER stress, IRF3, and the actions of anti-craving drugs that may be useful for identifying novel anti-craving treatments.

Abstract: Alcohol use disorder (AUD) is the most prevalent substance use disorder worldwide. Acamprosate and naltrexone are anti-craving drugs used in AUD pharmacotherapy. However, molecular mechanisms underlying their anti-craving effect remain unclear. This study utilized a patient-derived induced pluripotent stem cell (iPSC)-based model system and anti-craving drugs that are used to treat AUD as "molecular probes" to identify possible mechanisms associated with alcohol craving. We examined the pathophysiology of craving and anti-craving drugs by performing functional genomics studies using iPSC-derived astrocytes and next-generation sequencing. Specifically, RNA sequencing performed using peripheral blood mononuclear cells from AUD patients with extreme values for alcohol craving intensity prior to treatment showed that inflammation-related pathways were highly associated with alcohol cravings. We then performed a genome-wide assessment of chromatin accessibility and gene expression profiles of induced iPSC-derived astrocytes in response to ethanol or anti-craving drugs. Those experiments identified drug-dependent epigenomic signatures, with IRF3 as the most significantly enriched motif in chromatin accessible regions. Furthermore, the activation of IRF3 was associated with ethanol-induced endoplasmic reticulum (ER) stress which could be attenuated by anti-craving drugs, suggesting that ER stress attenuation might be a target for anti-craving agents. In conclusion, we found that craving intensity was associated with alcohol consumption and treatment outcomes. Our functional genomic studies suggest possible relationships among craving, ER stress, IRF3 and the actions of anti-craving drugs.

Ho MF, Zhang C, Moon I, Tuncturk M, Coombes BJ, Biernacka J, Skime M, Oesterle TS, Karpyak VM, Li H, Weinshilboum R. Molecular mechanisms involved in alcohol craving, IRF3, and endoplasmic reticulum stress: a multi-omics study. *Transl Psychiatry*. 2024 Mar 26; 14(1): 165.

Sober Curiosity and Participation in Temporary Alcohol Abstinence Challenges in a Cohort of U.S. Emerging Adults

Significance: This study assessed awareness of and engagement in Sober Curious and alcohol abstinence challenges (such as Dry January) and the characteristics of young adults who participate. Participation was relatively uncommon among a sample of 18–29-year-olds with a recent history of alcohol use. However, half of alcohol abstinence challenge participants reported drinking less after the challenge ended, and 15% remained abstinent. Sober Curious familiarity and abstinence challenge participation were both associated with past-month heavy drinking, cannabis use, higher Alcohol Use Disorders Identification Test (AUDIT) scores, more past-year alcohol and cannabis consequences, past-year substance use treatment, and greater readiness to quit alcohol. These findings suggest that alcohol abstinence challenges have potential promise for reducing alcohol use by emerging adults at higher risk for alcohol misuse but who show greater readiness to change.

Abstract: Background: Thus far, behavioral health research in the United States has not explored the prevalence or correlates of sober curiosity (SC; exploratory or experimental abstinence or moderation) or temporary alcohol abstinence challenges (TAACs; e.g., "Dry January"), despite significant attention in media and popular discourse. We explored these activities in a sample of U.S. emerging adults (e.g., ages 18-29), a population with higher risk drinking behavior yet some of the lowest rates of treatment engagement for alcohol use problems. **Method:** Survey data were collected in 2021-2022 among participants ($n = 1,659$; M age = 24.7 years). We assessed SC awareness/engagement and past-year TAAC participation, and differences across demographics and behavioral characteristics. **Results:** Overall, 9% of emerging adults were familiar with SC and 7% had participated in a TAAC in the past year. Half of TAAC participants reported drinking less after the TAAC, and 15% remained abstinent after the TAAC ended. SC familiarity and TAAC were both associated with past-month heavy drinking, cannabis use, higher Alcohol Use Disorders Identification Test (AUDIT) scores, more past-year alcohol and cannabis consequences, past-year substance use treatment, and greater readiness to quit alcohol. **Conclusions:** Both SC and TAACs may have potential to engage young people with a desire to moderate or eliminate their alcohol consumption. This may occur directly through use of these strategies or by helping them connect to additional services. Future research can help the field understand the uptake of SC and TAACs, gauge efficacy, and identify avenues to link young people to resources and interventions.

Siconolfi D, Tucker JS, Pedersen ER, Perez LG, Dunbar MS, Davis JP, Rodriguez A, Seelam R, D'Amico EJ. Sober Curiosity and Participation in Temporary Alcohol Abstinence Challenges in a Cohort of U.S. Emerging Adults. *J Stud Alcohol Drugs*. 2024 Mar;85(2):201-209.

NIAAA COMMUNICATIONS AND PUBLIC LIAISON ACTIVITIES

News Media

News releases, announcements, and blogs

Dr. Koob, along with Dr. Aaron White and other NIAAA scientists completed 48 media interviews, including a Satellite Media Tour, from January 2024 through March 2024. Noteworthy stories include:

Highlights

- 'Dry January' Satellite Media Tour – Dr. Koob highlighted NIAAA's messages, reaching 17 local and national radio and television outlets across the country.
- New York Times, 3/30/24: [Why Are Older Americans Drinking So Much?](#) – Dr. Koob discussed new data on alcohol-related deaths among older people in the U.S.
- New York Times, 1/30/24: [How Does Alcohol Affect the Gut Microbiome?](#) – Dr. Lorenzo Leggio discussed the effects of heavy drinking on the balance of “good” and “bad” bacteria in the intestine, and related health problems.
- Washington Post, 1/5/24: [Can giving up alcohol improve your sleep?](#) – Dr. Aaron White discussed how even small amounts of alcohol can disrupt sleep patterns.
- Pittsburgh Tribune-Review, 1/4/24: [Dry January, Damp January or sober curious? What you need to know about reducing alcohol intake.](#) Dr. Koob discussed the health benefits of reducing drinking during Dry January, and from other “sober curious” practices.

News stories and NIAAA Director's blogs

- January 2024 – [Alcohol Research Current Reviews Celebrates Its 50th Anniversary](#)
- February 2024 – [Researchers identify brain hub with key role in learned response to direct and indirect threats](#)
- February 2024 – [National Institute on Alcohol Abuse and Alcoholism announces content on Kahoot!](#)
- February 2024 – Director's Blog: [Support your team and your guests: Tips for hosting a party including guests who may not be drinking](#)
- March 2024 – [New NIAAA web resources for middles and high school](#)
- March 2024 – [April is Alcohol Awareness Month](#)
- March 2024 – Director's Blog: [Alcohol Awareness Month: Raising Awareness about the Dangers of Alcohol Use Among Teens](#)



Major Activities, Events, and Products

- NIAAA launched the new website, [NIAAA Facts About Teen Drinking](#).
- Alcohol Awareness Month: NIAAA shared paid, organic, and video messages on social media and posted a [Director's Blog](#) and [web announcement](#). [Alcohol Awareness Month was featured on the](#) NIH website home page. Dr. Koob was interviewed for ASAM's podcast, [The Treat Addiction Save Lives Podcast, in recognition of Alcohol Awareness Month](#).
- New [Short Takes with NIAAA](#) videos – A new set of concise videos are available on the topics of older adults and alcohol, underage drinking, and how alcohol affects the adolescent brain.
- [Engagement in the Black Community - NAADAC Virtual Summit](#) – NIAAA was a sponsor of this virtual event which discussed critical issues in the Black community relevant to treatment and recovery.

Social Media

NIAAA's X account ([@NIAAAnews](#)) currently has 29,475 followers (0.2% increase since December 31), NIAAA's Instagram account ([@NIAAAnews](#)) has 4,414 followers (9.5% increase), and NIAAA's Facebook ([@NIAAAgov](#)) has 3,676 followers (11% increase).



Highlights from social media:

- NIAAA engaged in social media campaigns for major health observances, including Dry January (garnering over 43,000 impressions) and Brain Awareness Week (5,932 impressions).
- Dry January ads garnered 423,305 impressions and 27,651 total engagements. Additionally, NIAAA's Dry January influencers delivered 235 social media posts resulting in 13,332,432 total impressions.
- The launch for [NIAAA Facts About Teen Drinking](#) generated 18,245 impressions.

Educational Resources

Top NIAAA resources:

- Publications ordered: [Rethinking Drinking](#), [Harmful Interactions](#), [Treatment for Alcohol Problems](#)
- Publications online: [Underage Drinking](#), [Alcohol Overdose](#), [Wernicke-Korsacoff Syndrome](#)
- Webpages: [Alcohol's Effects on the Body](#), [Underage Drinking fact sheet](#), [Drinking Levels Defined](#)

New and updated resources:

- Several NIAAA fact sheets were updated with new Alcohol-Related Disease Impact data from the Centers for Disease Control and Prevention (CDC) and National Survey of Drug Use and Health data from the Substance Abuse and Mental Health Services Administration (SAMHSA). The infographics for [Alcohol: Facts and Statistics](#) were also revised.

Notable Pickup of NIAAA Content

- NIH Research Matters featured NIAAA-supported research in [Anti-diabetes drugs may reduce the risk of colorectal cancer](#).
- NIH News in Health highlighted [Interrupted Memories: Alcohol-Induced Blackouts](#) in an article. The Spanish-language version also included links to NIAAA's other resources in Spanish: [¿Qué es una bebida alcohólica estándar?](#), [Tratamiento del alcoholismo: cómo buscar y obtener ayuda](#), [Recursos en español sobre el alcohol](#).
- NIH Newsletter (February) featured [NIAAA for Middle School](#) and (April) featured Dr. Koob's blog for AAM.
- The National Institute on Drug Abuse highlighted the new teen website, [NIAAA Facts About Teen Drinking](#), in their National Drug & Alcohol Facts Week newsletter.
- NIH homepage rotator and X account featured NIAAA messages on Dry January, [NIAAA Facts About Teen Drinking](#), and [NIAAA for Middle School](#) and AAM.
- HHS Assistant Secretary for Health [mentioned on X](#) NIAAA Facts About Teen Drinking
- The National Association of Therapeutic Schools and Programs and Yale University posted on X about [NIAAA Facts About Teen Drinking](#)
- SAMHSA and Partnership to End Addiction X account and CADCA Coalitions Online highlighted [NIAAA's Kahoot! quiz on underage drinking](#).





-
- HHS X account and newsletter highlighted NIAAA's messages about [alcohol's adverse effects on heart health](#), NIAAA Facts About Teen Drinking, and parenting resources.
- HHS Office of Disease Prevention and Health Promotion [post on X](#) about NIAAA's VR experience, Alcohol and Your Brain, in the context of AAM.
- The National Center on Safe Supportive Learning Environments highlighted [Harmful and Underage College Drinking](#) and [CollegeAIM](#).
- Positive Choices, an Australian non-profit, posted on X about the VR experience.

