National Institute on Alcohol Abuse and Alcoholism

NIAAA Director's Report on Institute Activities to the 160th Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism

Tuesday, May 10, 2022
Virtual Meeting

Table of Contents

NIAAA BUDGET

Fiscal Year (FY) 2022

On March 15, 2022, the President signed H.R. 2471 - Consolidated Appropriations Act, 2022. The National Institutes of Health (NIH) received a total of $45.2 billion, $2.3 billion or 5.4 percent above the FY 2021 enacted level. This funding includes allocations for the Helping to End Addiction Long-term (HEAL) Initiative, the 21st Century Cures Act, NIH Brain Research Through Advancing Innovative Neurotechnologies (BRAIN), and the All of Us research program. The bill provides a general increase to NIH Institutes and Centers, and it continues to support for the Gabriella Miller Kids First Act pediatric research initiative.

The FY 2022 appropriation for NIAAA provides $573.7 million. This represents an $18.8 million, or a 3.4 percent increase over the FY 2021 actual budget level. NIAAA estimates it will support a total of 706 research project grants (RPGs) in FY 2022.

FY 2023

The FY 2023 President's Budget (PB) was released on March 28, 2022, requesting $52.0 billion for NIH, a $6.8 billion increase from the FY 2022 enacted budget. The NIAAA PB request is $566.7 million, a $7 million decrease from FY 2022 enacted budget level.

HONORS AND AWARDS

Dr. Vijay Ramchandani, Chief, Laboratory on Human Psychopharmacology, Division of Intramural Clinical and Biological Research (DICBR), received an NIH Bench-to-Bedside Award for a project titled: "Role of Metal Ion Transporter ZIP8 in Alcohol Related Behaviors."

Dr. Research Cinar, Acting Chief, Section on Fibrotic Disorders, DICBR, received an NIH Bench-to-Bedside Award for a project titled: "Endocannabinoid/CB1R system in long-term pulmonary complications of COVID."

Dr. Malliga R. Iyer, Acting Chief, Section on Medicinal Chemistry, DICBR, has been selected for the American Chemical Society (ACS) Med-Chem for Young Investigator Symposium Award. Dr. Iyer will give a talk at the ACS fall meeting in Chicago in August 2022.

Dr. Pinaki Bhattacharjee, Postdoctoral Visiting Fellow, Section on Medicinal Chemistry, DICBR was awarded the NIH Office of Intramural Training and Education Summer Research Mentor Award 2022.

STAFF TRANSITIONS

New Staff

Juan Rivas joined the NIAAA Information Technology Branch (ITB) as an IT Specialist. Prior to this appointment, Juan served as a contractor for 17 years. Juan is well versed in the NIAAA clinic's procedures and has extensive experience supporting the scientific systems and equipment in use throughout the Institute.

Dr. Robin Chholak joined the Clinical Neuroimaging Research Core in the NIAAA Office of the Clinical Director as a Postdoctoral Visiting Fellow and will be studying hyperarousal and negative emotionality using neuropsychophysiologic and imaging methods.

Dr. Fatemeh Shekoohishooli joined the Clinical Neuroimaging Research Core in the NIAAA Office of the Clinical Director and will be studying the effect of hormonal differences in men and women on the development and maintenance of alcohol use disorder using imaging paradigms.

Dr. Jasper Van Oort joined the Clinical Neuroimaging Research Core with the Office of the Clinical Director as a Postdoctoral Visiting Fellow to expand his neuroimaging expertise in functional magnetic resonance imaging, functional near infrared spectroscopy, and other imaging modalities.

Dr. Lenny Pommerolle joined the Section on Fibrotic Disorders as a Postdoctoral Visiting Fellow and will be exploring the role of CB1R and GPR132 receptors in alcohol-induced lung injury and fibrosis.

Dr. Bipul Ray joined the Section on Molecular Pharmacology and Toxicology as a Postdoctoral Visiting Fellow and will be studying the pathologic role of nitrated or phosphorylated proteins in the rodent brain after binge alcohol exposure and/or chronic exposure to Western-style high-fat diets.

Transitions

Dr. Rachel Anderson – Former Health Science Policy Analyst (HSPA) in the NIAAA Office of Science Policy and Communications, transferred to the National Institute of Neurological Disorders and Stroke (NINDS), where she now serves as an HSPA in the Office of Science Policy and Planning.

Dr. Shana Silverstein – Post-Doctoral IRTA, joined NINDS in the laboratory of Dr. Joshua Gordon (Director, National Institute of Mental Health), where she is studying the role of brain circuits in behaviors relevant to schizophrenia.

Departures

Laura Lee – Former Budget Analyst, retired from the Financial Management Branch. Laura worked for the federal government for 20 years, with 17 of those years being with NIAAA. She worked served in many roles in the budget office and often volunteered in the larger NIH finance community.

Yatindra Awasthi – Post-Baccalaureate IRTA, departed NIAAA to assume a data analytics position with a local Maryland company.

RECENTLY ISSUED FUNDING OPPORTUNITIES

Funding Opportunity Announcements (FOAs) Issued by NIAAA

Specialized Alcohol Research Centers: NIAAA solicits Specialized Center grant applications to foster and conduct interdisciplinary, collaborative research on alcohol use disorder (AUD), alcohol misuse and alcohol related problems, and other health related consequences across the lifespan. 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. Centers are also major contributors to the development of research methods, technologies, and approaches that sustain innovative goal-directed research. (P50 Clinical Trial Optional) RFA-AA-22-001 (Contacts: Dr. M. Katherine Jung, Dr. Mariela Shirley, Dr. Ivana Grakalic, Greg Bloss, Dr. Antonio Noronha).

Comprehensive Alcohol Research Centers: NIAAA solicits Comprehensive Alcohol Research Centers applications. These Centers must include a dissemination core to initiate and expand community education related to the activities of the Center. 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. These topics include, but are not limited to, the nature, etiology, genetics, epigenetics, diagnosis, epidemiology, treatment, and prevention of alcohol misuse, AUD, and alcohol-related end organ diseases, and their biomedical, neurochemical, behavioral, psychosocial, and economic consequences, across the lifespan and across racial/ethnic groups and other health disparity populations. Centers also are regional or national resources that contribute to the development of new research methods, technologies and approaches that sustain innovative goal-directed research. (P60 Clinical Trial Optional) RFA-AA-22-002 (Contacts: Dr. M. Katherine Jung, Dr. Mariela Shirley, Dr. Ivana Grakalic, Greg Bloss, Dr. Antonio Noronha)

Alcohol Health Services Research: NIAAA solicits applications for both the R01 and R34 Clinical Trial Optional mechanisms focusing on alcohol health services. These FOAs will broadly focus on closing the treatment gap for individuals with AUD. Topics include but are not limited to: (1) increasing access to treatment for AUD, (2) making treatment for AUD more appealing, (3) examining cost structures and insurance systems, (4) conducting studies on dissemination and implementation of existing evidence-

based approaches to treating AUD, and (5) reducing health disparities as a means of addressing the treatment gap in AUD for health disparity populations. (R01 Clinical Trial Optional) PAR-22-156; (R34 Clinical Trial Optional) PAR-22-157 (Contact: Dr. Laura Kwako)

Alcohol Treatment and Recovery Research: NIAAA solicits applications for both R01 and R34 Clinical Trial Required mechanisms focusing on alcohol treatment and recovery research. These FOAs will focus broadly on topics relevant for treatment of and recovery from AUD, including medications development, precision medicine, behavioral therapies and mechanisms of behavioral change (MOBC), recovery, translational research, and innovative methods and technologies for AUD treatment and recovery. (R01 Clinical Trial Required) PAR-22-158; (R34 Clinical Trial Required) PAR-22-159. (Contacts: Dr. Brett T. Hagman, Dr. Dan Falk).

Notices Issued by NIAAA

Notice of Special Interest: Research on Alcohol and Coronavirus Disease (COVID-19) within the Mission of NIAAA. This notice solicits grant applications that advance understanding of critical interactions between alcohol use, SARS-CoV-2, and COVID-19. A central focus is research that can improve public health by informing responses to the evolving COVID-19 pandemic and its consequences. Links to the parent announcements (R01, R03, R21 and K99/R00) are listed in NOT-AA-22-012 (Contact: Dr. M. Katherine Jung).

NIH-Wide FOAs with NIAAA Participation

HEAL Initiative: Human Pain-associated Genes and Cells Data Coordination and Integration Center (U24 Clinical Trial Not Allowed) RFA-NS-22-021

HEAL Initiative: Discovery and Functional Evaluation of Human Pain-associated Genes and Cells (U19 Clinical Trial Not Allowed) RFA-NS-22-018

BRAIN Initiative: Targeted BRAIN Circuits Planning Projects TargetedBCPP (R34 Clinical Trials Not Allowed) RFA-NS-22-027

BRAIN Initiative: Targeted BRAIN Circuits Projects- TargetedBCP (R01 Clinical Trial Not Allowed) RFA-NS-22-026

BRAIN Initiative Connectivity across Scales (BRAIN CONNECTS): Comprehensive Centers for Mouse Brain (UM1 Clinical Trial Not Allowed) RFA-NS-22-048

BRAIN Initiative Connectivity across Scales (BRAIN CONNECTS): Comprehensive Centers for Human and Non-Human Primate Brain (UM1 Clinical Trial Not Allowed) RFA-NS-22-047

BRAIN Initiative Connectivity across Scales (BRAIN CONNECTS): Specialized Projects for Scalable Technologies (U01 Clinical Trial Not Allowed) RFA-NS-22-049

BRAIN Initiative: Exploratory Team-Research BRAIN Circuit Programs - eTeamBCP (U01 Clinical Trials Optional) RFA-NS-22-028

BRAIN Initiative: Integration and Analysis of BRAIN Initiative Data (R01 Clinical Trial Not Allowed) RFA-MH-22-220

Data Management and Coordinating Center (DMCC) for the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Collaborative Research Centers (CRC) (U24 Basic Experimental Studies with Humans Required) RFA-NS-22-020

Emergency Award: RADx-UP Community-Engaged Research on Rapid SARS-CoV-2 Testing among Underserved and Vulnerable Populations (U01 Clinical Trial Optional) RFA-OD-22-006

Emergency Awards: RADx-UP - Social, Ethical, and Behavioral Implications (SEBI) Research on Disparities in COVID-19 Testing among Underserved and Vulnerable Populations (U01 Clinical Trial Optional) RFA-OD-22-005

Coordinating Center to Support Research on Community Level Interventions for Firearm and Related Violence, Injury and Mortality Prevention (CLIF-VP) (U24 Clinical Trial Not Allowed) PAR-22-120

Research on Community Level Interventions for Firearm and Related Violence, Injury and Mortality Prevention (CLIF-VP) (UG3/UH3 Clinical Trial Optional) PAR-22-115

Chronic, Non-Communicable Diseases and Disorders Across the Lifespan: Fogarty International Research Training Award (NCD-LIFESPAN) (D43 Clinical Trial Optional) PAR-22-104

Accelerating the Pace of Child Health Research Using Existing Data from the Adolescent Brain Cognitive Development (ABCD) Study (R01 Clinical Trial Not Allowed) PAR-22-137

Accelerating the Pace of Child Health Research Using Existing Data from the Adolescent Brain Cognitive Development (ABCD) Study (R21 Clinical Trial Not Allowed) PAR-22-138

NIH Science Education Partnership Award (SEPA) (R25 Clinical Trial Not Allowed) PAR-20-153

NIH-Wide NOSIs with NIAAA Participation

Notice of Special Interest (NOSI): Administrative Supplements to Support Enhancement of Software Tools for Open Science NOT-OD-22-068

HEAL Initiative: Notice of Special Interest (NOSI) regarding the Availability of Administrative Supplements to Support Strategies to Increase Participant Diversity, Inclusion and Engagement in Clinical Studies NOT-NS-22-066

Notice of Special Interest (NOSI) - Administrative Supplements for Research of Emerging and Existing Issues of COVID-19 Related to the Health and Well-Being of Women, Children and Individuals with Physical and/or Intellectual Disabilities NOT-HD-22-003

NIAAA Director's Activities

NIAAA Director **George F. Koob, Ph.D.,** gave the following virtual presentations between January 1 and March 31, 2022:

NIAAA Power Session at the Community Anti-Drug Coalitions of America 32nd Annual National Leadership Forum, February 3, 2022

"The Dark Side of Opioids: The Neurobiological Cycle of Pain, Opioids, Tapering, Hyperkatifeia and Despair" for the American Academy of Hospice and Palliative Medicine (AAHPM), February 11, 2022

"Neurocircuitry of Alcohol Addiction with a subtitle of Heuristic Framework for Etiology, Diagnosis, Prevention and Treatment of Alcohol Use Disorder" for the State University of New York at Buffalo, Research Training on Alcohol Etiology and Treatment T32-wide symposium, February 23, 2022

"Neurobiology of Addiction: Hyperkatifeia, Deaths of Despair, and COVID-19" at the Conférence du Centre de recherche CERVO, Universite Laval, Quebec City, Canada, February 25, 2022

"Alcohol Use Disorder: A Neurobiological Framework for Diagnosis Treatment and Prevention" for the Addiction Medicine Grand Rounds at Howard University Hospital, March 2, 2022

"Alcohol Misuse in the Era of COVID-19: Learning from the Pandemic and Looking Ahead to the Future" at the North American Summit on the COVID-19 Pandemic and Addiction, March 11, 2022

"The Role and Priorities of Alcohol Research in Addiction" for the French Alcohol Society, March 25, 2022

Alcohol, Pain, Hyperalgesia, and Hyperkatifeia, Tackling Pain at the National Institutes of Health: Updates from the Bench, the Clinic, and the New NIH Pain Research Center, Bethesda, MD, March 31, 2022

NOTABLE NIAAA STAFF ACTIVITIES

Dr. Laura Kwako presented "Telehealth Priorities at NIAAA" for FedTel, a trans-HHS meeting from agencies such as NIH and the Health Resources and Services Administration on January 6, 2022.

Dr. Trish Powell and Dr. Tatiana Balachova organized and led the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD) 2022 Public Meeting on April 1, 2022. **Dr. Bill Dunty** provided an NIAAA update during the meeting. This year's public meeting included an invited Special Panel titled "A FASD Changemakers' Lay of the Land Survey: Equality vs Equity – What 468 Adults with FASD Want You to Know" by the Adult Leadership Committee (ALC) of FASD Changemakers. ALC is a renowned group of citizen researchers and experts who have FASD.

Dr. Ralph Hingson gave a presentation titled "Overview of Evidence-Based Policies Programs, Practices and Development of State Performance Measures" at the Interagency Coordinating Committee on the Prevention of Underage Drinking (ICCPUD) Principals meeting on April 6, 2022.

Dr. Andras Orosz was the discussion leader of the "Cancer Stem Cells and Alcohol-Associated Cancer" session at the Gordon Research Conference on Alcohol-Induced End Organ Diseases on April 27. **Dr. Li Lin** was the discussion leader of the "Discovery of Mechanism-Based Biomarkers" session at the conference on April 28

WHAT'S AHEAD?

Neurocognitive Mechanisms of Structural Racism, a virtual meeting sponsored by the National Institute on Drug Abuse, will be held May 17–19, 2022. The event will convene interdisciplinary researchers to discuss the effects of structural racism on neurocognition as it relates to substance use and mental health, and to discuss how to consider and contextualize structural racism in developing research studies.

Precision Probiotic Therapies: Challenges and Opportunities, a virtual workshop sponsored by the National Center for Complementary and Integrative Health, will be held April 26–27, 2022. The goals of this workshop are to identify gaps in our current understanding of the biology of the gut microbiota and of probiotics and to identify research questions and methodological challenges posed by those gaps.

The 17th Annual NIH Pain Consortium Symposium will be held virtually June 1–2, 2022. This year's symposium is titled "Pain Management through the Lens of Whole Person Health" and will feature keynote addresses by Dr. Tracy Gaudet of the Whole Health Institute and Dr. Ruth Wolever of Vanderbilt University.

The 8th Annual NIH BRAIN Initiative Meeting will be held as a hybrid event June 21–22, 2022, on the NIH main campus in Bethesda, Maryland, and online. The meeting is open to all investigators who are interested in learning the most recent conceptual and technological advances made by the BRAIN Initiative

The 45th Annual Research Society on Alcoholism Scientific Meeting will be held June 25–29, 2022, in Orlando, Florida.

NIAAA RESEARCH HIGHLIGHTS

ALCOHOL-RELATED DEATHS DURING THE COVID-19 PANDEMIC

Significance: A recent analysis of mortality data from the National Center for Health Statistics assessed whether alcohol-related deaths increased during the COVID-19 pandemic. The results showed that the number and rate of alcohol-related deaths increased approximately 25 percent between 2019 and 2020, the first year of the COVID-19 pandemic. Rates increased for all age groups, with the largest increases occurring for people ages 35 to 44 and 25 to 34. The rate increase for alcohol-related deaths in 2020 outpaced the increase in all-cause mortality, which was 16.6 percent. Increased drinking to cope with pandemic-related stressors, shifting alcohol policies, and disrupted treatment access are all possible contributing factors. (White AM, Castle IP, Powell PA, Hingson RW, Koob GF., Alcohol-Related Deaths During the COVID-19 Pandemic. *JAMA*. 2022 Mar 18;e224308. doi: 10.1001/jama.2022.4308. Online ahead of print. PMID: 35302593)

SITE OF ALCOHOL FIRST-PASS METABOLISM AMONG WOMEN

Significance: When alcohol is ingested, it enters the digestive tract where some of the alcohol is metabolized by the stomach and liver in a process called first-pass metabolism. The remainder of the alcohol enters the systemic bloodstream and is metabolized when it circulates back to the liver. Previous research has associated bariatric surgery with higher blood alcohol concentrations (BACs), higher bioavailability of alcohol, and, thus, higher risk of alcohol-related consequences. To better understand how the stomach contributes to first-pass metabolism, researchers examined alcohol pharmacokinetics after oral and intravenous alcohol administration among 12 women who had undergone sleeve gastrectomy, a surgical procedure that removes about 80 percent of the stomach. Compared to women without a sleeve gastrectomy, women with the surgical procedure had an approximately 40 percent higher peak BAC after oral alcohol administration. No differences in alcohol elimination rates were observed between the two groups following intravenous alcohol administration. The higher BACs seen among women with the sleeve gastrectomy indicate that the stomach contributes significantly to the first-pass metabolism of alcohol in this population. The results of this study help explain why having bariatric surgery is associated with an elevated risk of alcohol use disorder and other alcohol-related consequences. (Seyedsadjadi N, Acevedo MB, Alfaro R, Ramchandani VA, Plawecki MH, Rowitz B, Pepino MY. Site of Alcohol First-Pass Metabolism Among Women. *JAMA Netw Open*. 2022 Mar 1;5(3):e223711. doi: 10.1001/jamanetworkopen.2022.3711. PMID: 35315921)

SERUM METABOLOMIC ANALYSIS REVEALS SEVERAL NOVEL METABOLITES IN ASSOCIATION WITH EXCESSIVE ALCOHOL USE - AN EXPLORATORY STUDY

Significance: Identifying biomarkers for screening of excessive alcohol use could yield a clinically important tool for healthcare providers to use for early intervention and prevention of adverse alcohol-related health outcomes in their patients. To identify a unique metabolic signature of excessive alcohol use, NIAAA-supported researchers profiled metabolites in the serum of research participants with a history of excessive alcohol use, compared to healthy participants. The researchers identified metabolites that were differentially expressed in participants with excessive alcohol use and tested the diagnostic performance of the top ten metabolites, many of which were in the sphingolipid pathway. Sphingolipids are fatty acid derivatives of sphingosine that occur chiefly in the cell membranes of the brain and nervous tissue. The ten metabolites tested had better diagnostic performance for excessive alcohol consumption than commonly used laboratory tests. Additional research is needed to validate and further characterize the metabolites as potential novel biomarkers of excessive alcohol use.

Appropriate screening tool for excessive alcohol use (EAU) is clinically important as it may help providers encourage early intervention and prevent adverse outcomes. We hypothesized that patients with excessive alcohol use will have distinct serum metabolites when compared to healthy controls. Serum metabolic profiling of 22 healthy controls and 147 patients with a history of EAU was performed. We employed seemingly unrelated regression to identify the unique metabolites and found 67 metabolites (out of 556), which were differentially expressed in patients with EAU. Sixteen metabolites belong to the sphingolipid metabolism, 13 belong to phospholipid metabolism, and the remaining 38 were metabolites of 25 different pathways. We also found 93 serum metabolites that were significantly associated with the total quantity of alcohol consumption in the last 30 days. A total of 15 metabolites belong to the sphingolipid metabolism, 11 belong to phospholipid metabolism, and 7 metabolites belong to lysolipid. Using a Venn diagram approach, we found the top 10 metabolites with differentially expressed in EAU and significantly associated with the quantity of alcohol consumption, sphingomyelin (d18:2/18:1), sphingomyelin (d18:2/21:0,d16:2/23:0), guanosine, S-methylmethionine, 10-undecenoate (11:1n1), sphingomyelin

(d18:1/20:1, d18:2/20:0), sphingomyelin (d18:1/17:0, d17:1/18:0, d19:1/16:0), N-acetylasparagine, sphingomyelin (d18:1/19:0, d19:1/18:0), and 1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1). The diagnostic performance of the top 10 metabolites, using the area under the ROC curve, was significantly higher than that of commonly used markers. We have identified a unique metaboloic signature among patients with EAU. Future studies to validate and determine the kinetics of these markers as a function of alcohol consumption are needed. (Liu D, Yang Z, Chandler K, Oshodi A, Zhang T, Ma J, Kusumanchi P, Huda N, Heathers L, Perez K, Tyler K, Ross RA, Jiang Y, Zhang D, Zhang M, Liangpunsakul S. Serum metabolomic analysis reveals several novel metabolites in association with excessive alcohol use - an exploratory study. *Transl Res*. 2022 Feb;240:87-98. doi: 10.1016/j.trsl.2021.10.008. Epub 2021 Nov 3.PMID: 34743014).

The study was supported in part by the NIAAA career development award K01AA026385.

HIGH-RISK DRINKERS ENGAGE DISTINCT STRESS-PREDICTIVE BRAIN NETWORKS

Significance: Coping with emotional stress is an important driver of alcohol misuse. The goal of this study was to examine whether changes in brain networks that underlie the response to stress can serve as an early marker of alcohol misuse. The investigators recruited people ages 18 to 53 who regularly engaged in binge drinking (defined as more than 5 drinks for men, and more than 4 drinks for women, per occasion) and compared them to people who engaged in "light drinking" (defined as less than 14 drinks for men, and less than 7 drinks for women, per week). Functional brain imaging and predictive modeling were conducted to identify unique brain connectivity patterns as predictors of stress. For the people who engaged in binge drinking, emotional stress was associated with visual and motor networks, whereas for people who engaged in light drinking, emotional stress was associated with the default mode and frontoparietal networks. The stress-predictive brain networks identified for the binge drinking group distinctly predicted future real-world stress and loss of control over drinking. These findings suggest that changes in brain/stress relationships may be an important early marker of maladaptive drinking behavior.

BACKGROUND: Excessive alcohol intake is a major public health problem and can be triggered by stress. Heavy drinking in patients with alcohol use disorder also alters neural, physiological, and emotional stress responses. However, it is unclear whether adaptations in stress-predictive brain networks can be an early marker of risky drinking behavior. METHODS: Risky social drinkers (regular bingers; N = 53) and light drinker controls (N = 51), aged 18-53 completed an fMRI-based sustained stress protocol with repeated measures of subjective stress state, during which whole-brain functional connectivity was computed. This was followed by prospective daily ecological momentary assessment for 30 days. We used brain computational predictive modeling with cross-validation to identify unique brain connectivity predictors of stress in risky drinkers, and determine the prospective utility of stress-brain networks for subsequent loss of control over drinking. RESULTS: Risky drinkers had anatomically and functionally distinct stress-predictive brain networks (showing stronger predictions from visual and motor networks) compared to light drinkers (default mode and frontoparietal networks). Stress-predictive brain networks defined for risky drinkers selectively predicted future real-world stress levels for risky drinkers, and successfully predicted prospective future real-world loss of control over drinking across all participants. CONCLUSIONS: These results indicate adaptations in computationally derived stress-related brain circuitry among high-risk drinkers, suggesting potential targets for early preventive intervention and revealing the malleability of the neural processes that govern stress responses. (Goldfarb EV, Scheinost D, Fogelman N, Seo D, Sinha R. High-risk drinkers engage distinct stress-predictive brain networks. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2022 Mar 7:S2451-9022(22)00049-0. doi: 10.1016/j.bpsc.2022.02.010. Online ahead of print. PMID: 35272096).

The study was supported in part by the NIAAA career development award K01AA027832.

THE AMYGDALA NORADRENERGIC SYSTEM IS COMPROMISED WITH ALCOHOL USE DISORDER

Significance: The central amygdala (CeA) of the brain plays crucial roles in the brain's stress response and AUD. The CeA interacts with the noradrenaline/norepinephrine (NA) system that also regulates the brain's response to stress and alcohol. To better understand the relationship between the NA system and the CeA in AUD, the investigators examined CeA and NA activity in rodent models of AUD. They found that receptors involved in the NA system (i.e., α_1 and β receptors) potentiated CeA GABAergic (gamma-aminobutyric acidergic) transmission and drove alcohol intake. In a rodent model of alcohol dependence, β receptors disinhibited a subpopulation of CeA neurons, contributing to elevated alcohol intake. In protracted alcohol withdrawal in rodents, functional recovery in the CeA was observed with no change in local NA tissue concentrations, although long-lasting differences in the cellular patterns of adrenergic receptor mRNA expression were seen. Postmortem analyses of human brain tissue revealed increased α_{1B} receptor mRNA expression in the amygdala of humans with AUD. These basic and translational research findings provide novel targets for AUD medications development.

BACKGROUND: Alcohol use disorder (AUD) is a leading preventable cause of death. The central amygdala (CeA) is a hub for stress and AUD, while dysfunction of the noradrenaline stress system is implicated in AUD relapse. METHODS: Here, we investigated whether alcohol (ethanol) dependence and protracted withdrawal alter noradrenergic regulation of the amygdala in rodents and humans. Male adult rats were housed under control conditions, subjected to chronic intermittent ethanol vapor exposure to induce dependence, or withdrawn from chronic intermittent ethanol vapor exposure for 2 weeks, and ex vivo electrophysiology, biochemistry (catecholamine quantification by high-performance liquid chromatography), in situ hybridization, and behavioral brain-site specific pharmacology studies were performed. We also used real-time quantitative polymerase chain reaction to assess gene expression of α_{1B}, β_1, and β_2 adrenergic receptors in human postmortem brain tissue from men diagnosed with AUD and matched control subjects. RESULTS: We found that α_1 receptors potentiate CeA GABAergic (gamma-aminobutyric acidergic) transmission and drive moderate alcohol intake in control rats. In dependent rats, β receptors disinhibit a subpopulation of CeA neurons, contributing to their excessive drinking. Withdrawal produces CeA functional recovery with no change in local noradrenaline tissue concentrations, although there are some long-lasting differences in the cellular patterns of adrenergic receptor messenger RNA expression. In addition, postmortem brain analyses reveal increased α_{1B} receptor messenger RNA in the amygdala of humans with AUD. CONCLUSIONS: CeA adrenergic receptors are key neural substrates of AUD. Identification of these novel mechanisms that drive alcohol drinking, particularly during the alcohol-dependent state, supports ongoing new medication development for AUD. (Varodayan FP, Patel RR, Matzeu A, Wolfe SA, Curley DE, Khom S, Gandhi PJ, Rodriguez L, Bajo M, D'Ambrosio S, Sun H, Kerr TM, Gonzales RA, Leggio L, Natividad LA, Haass-Koffler CL, Martin-Fardon R, Roberto M. The amygdala noradrenergic system is compromised with Alcohol Use Disorder. *Biol Psychiatry*. 2022 Apr 5:S0006-3223(22)00090-7. doi: 10.1016/j.biopsych.2022.02.006. Online ahead of print. PMID: 35430085).

The study was supported in part by the NIAAA training award T32AA007456.

GENETIC VARIANTS ASSOCIATED WITH ACAMPROSATE TREATMENT RESPONSE IN ALCOHOL USE DISORDER PATIENTS: A MULTIPLE OMICS STUDY

Significance: Acamprosate is one of the three medications approved by the U.S. Food and Drug Administration for the treatment of alcohol use disorder (AUD). Acamprosate is thought to reduce the alcohol craving observed after individuals with AUD abstain from drinking. Patients vary in their treatment response to acamprosate, e.g., some achieve abstinence and some may experience relapse. Pharmacogenomic variations could partially explain differences in treatment response. Researchers conducted a metabolomics-informed genome-wide association study (GWAS) to identify genetic variants that contribute to variations in plasma metabolomic profiles that are associated with craving and/or acamprosate treatment outcomes. A series of genes were found to be alcohol responsive and regulated by acamprosate, and in particular, a series of single nucleotide polymorphisms that were associated with acamprosate treatment outcomes.. These results serve as important step towards a precision medicine approach to AUD pharmacotherapy

BACKGROUND AND PURPOSE: Acamprosate is an anti-craving drug used for the pharmacotherapy of alcohol use disorder (AUD). However, only some patients achieve optimal therapeutic outcomes. This study was designed to explore differences in metabolomic profiles between patients who maintained sobriety and those who relapsed, to determine whether those differences provide insight into variation in acamprosate treatment response phenotypes. EXPERIMENTAL APPROACH: We previously conducted an acamprosate trial involving 442 AUD patients, and 267 of these subjects presented themselves for a 3-month follow-up. The primary outcome was abstinence. Clinical information, genomic data and metabolomics data were collected. Baseline plasma samples were assayed using targeted metabolomics. KEY RESULTS: Baseline plasma arginine, threonine, α-aminoadipic acid and ethanolamine concentrations were associated with acamprosate treatment outcomes and baseline craving intensity, a measure that has been associated with acamprosate treatment response. We next applied a pharmacometabolomics-informed genome-wide association study (GWAS) strategy to identify genetic variants that might contribute to variations in plasma metabolomic profiles that were associated with craving and/or acamprosate treatment outcome. Gene expression data for induced pluripotent stem cell-derived forebrain astrocytes showed that a series of genes identified during the metabolomics-informed GWAS were ethanol responsive. Furthermore, a large number of those genes could be regulated by acamprosate. Finally, we identified a series of single nucleotide polymorphisms that were associated with acamprosate treatment outcomes. CONCLUSION AND IMPLICATIONS: These results serve as an important step towards advancing our understanding of disease pathophysiology and drug action responsible for variation in acamprosate response and alcohol craving in AUD patients. (Ho MF, Zhang C, Wei L, Zhang L, Moon I, Geske JR, Skime MK, Choi DS, Biernacka JM, Oesterle TS, Frye MA, Seppala MD, Karpyak VM, Li H, Weinshilboum RM. Genetic variants associated with acamprosate treatment response in alcohol use disorder patients: A multiple omics study. *Br J Pharmacol*. 2022 Jan 11. doi: 10.1111/bph.15795. Online ahead of print. PMID: 35016259)

AGE 18-30 TRAJECTORIES OF BINGE DRINKING FREQUENCY AND PREVALENCE ACROSS THE PAST 30 YEARS FOR MEN AND WOMEN: DELINEATING WHEN AND WHY HISTORICAL TRENDS REVERSED ACROSS AGE

Significance: Available research indicates that in recent cohorts binge drinking at age 18 has been decreasing historically, but by the mid to late 20s, the reverse is true as reflected in increased binge drinking. The current study examined U.S. national, longitudinal data from the Monitoring the Future study to examine this reversal. The researchers found that, with respect to developmental time or age, the reversal manifested primarily between the ages of 18 and 24 for men and ages 18 and 22 for women. They also found that the reversal generally emerged gradually and steadily across the cohorts, suggesting

the reversal is the result of a broad and durable historical shift. Historical variation in social roles and the minimum legal drinking age collectively accounted for only a modest amount of the reversal, and marriage was found to be the most influential factor examined. The historical narrowing in the gap in binge drinking between men and women was more pronounced at the beginning than at end of the transition to adulthood, suggesting that the convergence is developmentally limited. These results suggest that early in the transition to adulthood is a crucial point of intervention for binge drinking among young adults.

Historical analyses based on US data indicate that recent cohorts engage in lower binge drinking at age 18 relative to past cohorts, but by the mid- to late-20s the reverse is true: recent cohorts engage in higher binge drinking relative to past cohorts. We pinpoint when - both developmentally and historically - this reversal manifested, examine possible reasons for this reversal, and examine sex convergence in these developmental and historical patterns. As part of the US national Monitoring the Future Study, over 75,000 youths from the high school classes of 1976-2006 were surveyed biennially between ages 18 and 30. We found that the reversal primarily manifested between ages 18 and 24 for men and 18 and 22 for women. We also found that the reversal emerged gradually across the last three decades, suggesting it is the result of a broad and durable historical shift. Our findings indicated that historical variation in social roles and minimum legal drinking age collectively accounted for only a modest amount of the reversal, although marriage was the most influential among the factors examined here. Finally, we found evidence that sex convergence in binge drinking was developmentally limited and far more pronounced at the beginning of the transition to adulthood. (Jager J, Keyes KM, Son D, Patrick ME, Platt J, Schulenberg JE. Age 18-30 trajectories of binge drinking frequency and prevalence across the past 30 years for men and women: Delineating when and why historical trends reversed across age. *Dev Psychopathol*. 2022 Jan 24:1-15. doi: 10.1017/S0954579421001218. Online ahead of print. PMID: 35068407)

NIAAA Communications and Public Liaison Activities

Media Interviews

Dr. Koob and other NIAAA scientists completed 58 total interviews from January 1 to March 31, 2021. **Noteworthy media outlets:** The New York Times, CNN, BBC News, The Washington Post, Associated Press, Harper's Magazine, Bloomberg News, Axios, and NBC.

To bolster these efforts, in January NIAAA held a satellite media tour on the topic "*Looking Back at the Holidays: Taking a Break from Alcohol During Dry January and Recognizing Signs of an Alcohol Problem*." During this media tour, Dr. Koob did 17 interviews with a mix of radio, TV, and internet outlets, with an estimated total audience of 23 million.

Also, a March 18 *JAMA* Research Letter written by NIAAA researchers, "Alcohol-Related Deaths During the COVID-19 Pandemic," garnered 23 national and international interviews with first author Dr. Aaron White.

Other media engagements:

- Dr. Koob recorded a radio interview for iHeart Radio's WONK-FM and for shorter segments that aired on HOT 97 FM from January 2 to 22.

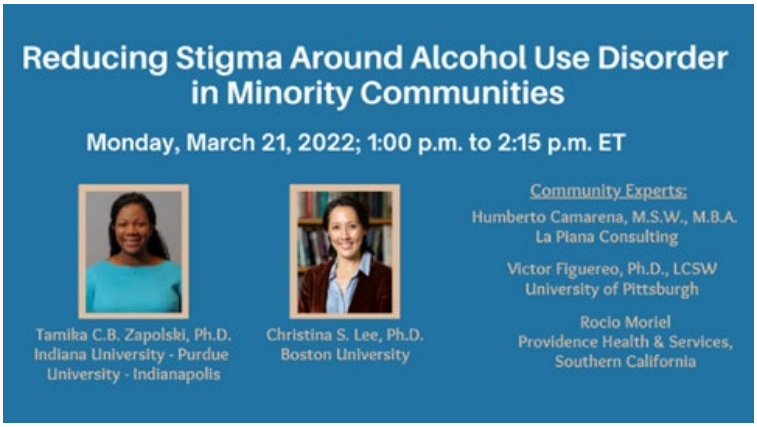
- NIAAA worked with several radio networks serving primarily Black and minority audiences to share information about stigma around alcohol-related problems and finding help for alcohol-related problems. Spots aired between January 15 to 31 on radio networks including:
    - Urban One: WERQ-FM/Baltimore and WKYS-FM/Washington, D.C.
    - Gen Media Partners: A network of 11 rural stations with coverage spanning Baltimore and Salisbury, Maryland; Raleigh, North Carolina; and Norfolk, Richmond, and Roanoke, Virginia.
    - Power News Radio Network: A Black-owned information network with 17 rural affiliate stations in multiple states.

NIAAA Director's Blog Posts

- April 2022 – A Better Way to Talk About Problems with Alcohol Misuse. This piece about stigma was originally published as a guest post on the NIH Director's Blog.
- March 2022 – Celebrate St Patrick's Day Safely. This piece originally appeared on March 16, on the National Library of Medicine's NLM Musings from the Mezzanine.

Major Activities and Events

Webinar – Reducing Stigma Around Alcohol Use Disorder in Minority Communities, featuring researchers and community experts, held on March 21, 2022.



Presentations at CADCA National Meeting – Dr. George F. Koob, Dr. Ralph Hingson, and Dr. Aaron White gave virtual presentations at the Community Anti-Drug Coalitions of America (CADCA) National Leadership Forum, held January 31–February 3, 2022

Event sponsorship – During Black History Month, NIAAA was among the sponsors for an Association for Addiction Professionals (NAADAC) virtual summit, Engagement in the Black Community, held February 24 – 25, 2022.

Update on college sexual assaults statistic – NIAAA collaborated with experts in college drinking research to update information about sexual assaults among college students for its College Drinking Prevention website. Estimating the number of alcohol-related sexual assaults is exceptionally challenging and the updated statement, based on current research, on this important topic can be found on the college prevention website under "Consequences of Alcohol Use."

Publications and web activities

NIAAA publications elicited about 741,000 pageviews, 16,000 downloads, and almost 42,000 print copies ordered. The most viewed NIAAA publications were Alcohol Facts and Statistics, the Understanding

Alcohol Use Disorder factsheet, and the Understanding the Dangers of Alcohol Overdose factsheet. The most frequently downloaded publication was the Understanding Alcohol Use Disorder factsheet. The most frequently ordered NIAAA publications were the Rethinking Drinking: Alcohol and Your Health, Harmful Interactions: Mixing Alcohol with Medications, and Treatment for Alcohol Problems: Finding and Getting Help booklets.

NIAAA developed and launched three new online fact sheets:

- The Cycle of Alcohol Addiction
- NIAAA Resources on Alcohol and the Brain (a compilation of NIAAA factsheets that include information about the effects of alcohol misuse on the brain)
- Alcohol Flush Reaction: Does Drinking Make Your Face Red?

After a two-year hiatus due to pandemic-related restrictions, in-person exhibits promoting NIAAA resources resumed in March.

Social Media Highlights

NIAAA's Twitter account (@NIAAAnews) currently has more than 28,000 followers (a 1.5 percent increase since January 1), NIAAA's Instagram account (@NIAAAnews) has over 2,300 followers (a 9 percent increase since January 1), and NIAAA's Facebook (@NIAAAgov) has almost 1,000 followers (a 16 percent increase since January 1). Highlights include: