NIAAA Director's Report on Institute Activities to the 156th Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism

February 4, 2021
Virtual Meeting

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Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

https://www.niaaa.nih.gov/about-niaaa/advisory-council

In Memoriam
Kathleen (Kathy) M. Carroll, Ph.D.

Dr. Carroll was a clinical scientist in the Yale Department of Psychiatry who made seminal contributions to improving treatments for addiction. She was the Albert E. Kent Professor of Psychiatry at Yale School of Medicine and the Director of the Psychosocial Research in the Division on Addictions.

Throughout her career, Dr. Carroll promoted broader recognition of the efficacy, safety, and durability of behavioral therapies. She helped establish the Stage Model of Behavioral Therapies Development that facilitated important advances by defining stages of science for behavioral therapies development.

Her work also led to the development of an effective web-based version of cognitive behavioral therapy ("CBT4CBT"), one of the first evidence-based computerized interventions for a range of substance use disorders.

NIAAA extends our deepest sympathies to her family, friends, and colleagues.

In Memoriam
Samuel W. French, M.D.

Dr. French was an exceptional pathologist, educator, and researcher for more than half a century. He most recently held positions as Distinguished Professor of Pathology at the University of California, Los Angeles and researcher at the Lundquist Institute for Biomedical Innovation. His prolific and original research, particularly on alcohol-associated liver disease (ALD), was first funded by NIH in 1960 and has resulted in over 500 publications.

His seminal contributions to the study of hypoxia, nutrition, and Mallory-Denk bodies in ALD were recognized by high honors, including the 2017 Lifetime Achievement Award from the Research Society on Alcoholism and the Gold Headed Cane Award from American Society for Investigative Pathology.

In Memoriam
Linda P. Spear, Ph.D.

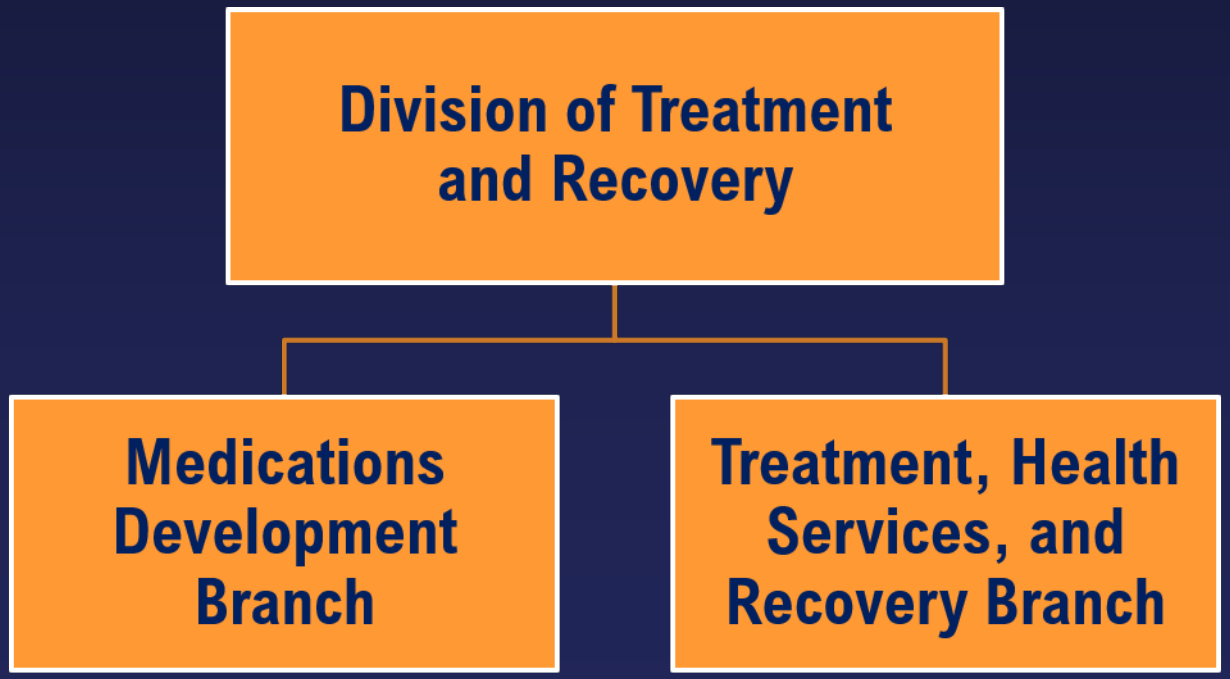
The NIAAA community mourns the passing of our friend and colleague, Dr. Linda Spear, Distinguished Professor Emerita of Psychology at Binghamton University.

Over a long and distinguished career, Dr. Spear amassed an extraordinary record of scientific accomplishment and leadership in alcohol research. Her studies of the behavioral effects of alcohol in adolescents and the effects of alcohol exposure on the developing brain have been foundational to advances in that area and have continued to the present day with her work as one of the founding members and leaders of the ongoing Neurobiology of Adolescent Drinking in Adulthood (NADIA) Consortium.

Dr. Spear served as a member of the NIAAA Advisory Council from 2008 to 2012 and as a member of the NIAAA Extramural Advisory Board from 2004 to 2012. Her excellence in alcohol research was recognized by numerous awards, including the NIAAA Mark Keller Award and the 2018 Lifetime Achievement Award from the Research Society on Alcoholism.

NIAAA Scientific Division Update

NIAAA announces the merging of two Divisions – the Division of Medications Development and the Division of Treatment and Recovery Research – into one Division with two branches.



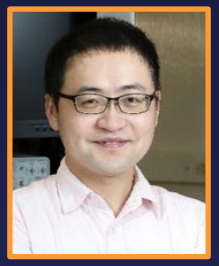
Welcome to New NIAAA Staff

Dr. Sukru Demiral joined the Division of Intramural Clinical and Biological Research Laboratory of Neuroimaging. Dr. Demiral will use brain imaging (PET, MRI and simultaneous PET/MRI) to study the neurocircuitry that underlies the rewarding effects of drugs of abuse and of natural reinforcers and their disruption in substance use disorders and obesity.

Dr. Paule Joseph joined NIAAA as a Tenure Track Investigator and Chief of the Section of Sensory Science and Metabolism with a joint appointment at the National Institute of Nursing Research (NINR). Dr. Joseph was previously a Postdoctoral Fellow and Assistant Clinical Investigator with NINR. She was selected as a Lasker Scholar in 2019 and NIH Distinguished Scholar in 2018. Dr. Joseph's research focuses on the relationship between hedonic pathways, sensory systems, and disease.

Welcome to New NIAAA Staff

Dr. Shailesh Kumar joined the Division of Neuroscience and Behavior (DNB) as a Health Scientist Administrator (Program Officer). Dr. Kumar comes to DNB from the Systems Biology Center (SBC) at the National Heart, Lung, and Blood Institute, where he was a Staff Scientist for the past 6 years. Dr. Kumar's portfolio within DNB will be in the area of animal and human sleep research.



Dr. Yiming Shen joined the Division of Intramural Clinical and Biological Research as a postdoctoral fellow in the Section on Neural Circuits. Dr. Shen obtained his Ph.D. from Seoul National University in 2019. For his thesis project, he examined whether alterations in synaptic plasticity in the hypothalamus helped promote the beneficial effects of exercise training in a rodent model of heart failure.

Internal Transitions

Megan Ryan joined the NIAAA Office of the Director (OD) in September 2020 as a Senior Health Scientific Policy Analyst. She has previously worked in the NIAAA Division of Medications Development (DMD) and Division of Treatment and Recovery Research (DTRR). During this time, she provided leadership as both the NIAAA Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Program Director and the Technology Development Coordinator. She will continue both roles in her new position.

Dr. Mariela Shirley joined the Division of Treatment and Recovery (DTR) after previously serving in the Division of Epidemiology and Prevention Research (DEPR). Dr. Shirley serves as Co-Chair of the NIAAA Centers and Training Working Group. Her research expertise areas include screening and behavioral interventions, underage/college drinking, psychiatric comorbidity, and behavioral medicine. In DTR, she oversees a research portfolio that includes alcohol use disorder in youth and older populations, translational research, innovative technologies, and comorbidity.

Dr. Bethany Stangl joined the Section on Human Psychopharmacology as a Staff Scientist. She has previously worked in this laboratory as a postdoctoral fellow, a research fellow, and most recently as a contract Research Scientist. Since her arrival in the laboratory, Dr. Stangl has led the development and implementation of the IV alcohol self-administration paradigm that has become a standard in the field of human behavioral pharmacology research in alcohol.

Departing Staff

Deilia (Dee) Beard, Information Technology (IT) Specialist, retired in August 2020 after 20 years of service at NIAAA. Ms. Beard provided IT support at Fishers Lane for many years, including management of software, equipment, network and server services, and account administration.

Isabel Ellis, Public Health Analyst, retired in December 2020 after 40 years of federal service. Over the last 20 years at NIAAA, her efforts included serving as project officer for the development of NIAAA's web-based social work curriculum and providing guidance on Certificates of Confidentiality to NIAAA investigators seeking to protect the privacy of research participants.

Thelma Fulton, former Extramural Support Assistant in the Extramural Project Review Branch within the Office of Extramural Activities, has recently taken a position as an Administrative Officer with the Federal Emergency Management Agency (FEMA).

Dr. Klaus Gawrisch, Chief of the Laboratory of Membrane Biochemistry and Biophysics, retired in September 2020. Dr. Gawrisch is an internationally recognized expert in structural biology and the role of lipids in membrane protein function and in the cellular actions of alcohol. His laboratory used nuclear magnetic resonance techniques to examine lipid and protein structures and structural changes, and his work contributed to understanding the effects of omega fatty acids on membrane properties and the structure and function of G-protein coupled receptors.

Dr. Aya Matsui completed her postdoctoral training in the Laboratory of Neurobiology of Compulsive Behaviors and has joined the Gouaux laboratory at Oregon Health & Science University to study the structure and function of synaptic receptors.

FY 2020 Budget

- NIAAA closed out the FY 2020 budget ($545.4 million) This funding supported:
  - 750 research project grants (RPGs)
  - 182 other research grants
  - 21 research centers
  - 323 training positions
- NIAAA funding for Research and Development contracts was $34.1 million.
- NIAAA support for Intramural research totaled $56.5 million.

FY 2021 Budget

- NIH received a total of $42.9 billion for FY 2021, including:
  - General increases to NIH institutes and Centers
  - Coronavirus supplemental appropriations
  - Allocations for the HEAL Initiative, the 21st Century Cures Act, the BRAIN Initiative, and research on influenza
  - Continued support for the Gabriella Miller Kids First Act pediatric research initiative
- NIAAA received a total of $554.9 million for 2021.
  - NIAAA, at this time, estimates supporting a total of 736 RPGs in FY 2021.

NIAAA Funding Opportunities

- **Integrative Neuroscience Initiative on Alcoholism (INIA) Consortia** ***(U01 Research Project; U24 Research Resource; U24 Administrative Resource – Clinical Trial Optional):*** **INIA is a translational, multidisciplinary, collaborative research effort studying brain mechanisms of excessive alcohol drinking associated with alcohol use disorder (AUD). The primary goal of INIA is to identify brain adaptations at multiple levels of analysis that result in excessive alcohol consumption. RFA-AA-20-011; RFA-AA-20-012; RFA-AA-20-013**
- **Improving Health Disparities in Alcohol Health Services** ***(R01 – Clinical Trial Optional):*** **This FOA solicits applications on health disparities and health services-related research focusing on 1) access to treatment; 2) making treatment more appealing; 3) costs; 4) dissemination and implementation. RFA-AA-21-001**
- **NIAAA Resource-Related Research Projects** ***(R24 – Clinical Trial Not Allowed):*** **The R24 resource grant mechanism is a non-hypothesis-driven activity to provide data, materials, tools, or services that are essential to making timely, high quality, and cost-efficient progress in a field. PAR-21-072**

NIAAA Funding Opportunities

- **Prevention and Intervention Approaches for Fetal Alcohol Spectrum Disorders** ***(R34 – Clinical Trial Optional):*** **This FOA for R34 planning grant applications focuses on prevention and intervention strategies for fetal alcohol spectrum disorders (FASD) throughout the lifespan. The intent of this FOA is to support research that advances (1) prevention approaches to reduce prenatal alcohol exposure and incidence of FASD and (2) interventions for FASD. PAR-21-097**
- **Prevention and Intervention Approaches for Fetal Alcohol Spectrum Disorders** ***(R61/R33 – Clinical Trial Optional):*** **The intent of this FOA is to support research that advances (1) prevention approaches to reduce prenatal alcohol exposure and the incidence of FASD and (2) interventions for FASD. These objectives will be accomplished with the Exploratory/Developmental Phased Award (R61/R33) mechanism, clinical trial optional. The R61 phase will support pilot studies or secondary data analysis for hypothesis development and feasibility, and research testing the hypotheses can be expanded in the R33 phase. PAR-21-098**

NIAAA Notices of Special Interest (NOSIs)

- **Advances in Research for the Treatment, Services, and Recovery of Alcohol Use Disorder:** The purpose of this NOSI is to advance research on various topics that fall within NIAAA's Division of Treatment and Recovery, such as health services, behavioral therapies and mechanisms of behavioral change (MOBC), recovery, translational research, and innovative methods and technologies for alcohol use disorder (AUD) treatment and sustaining recovery. Other areas of interest include topics focusing on special-emphasis and underserved populations, including NIH-designated U.S. health disparity populations, as well as those with co-occurring disorders; and fetal alcohol spectrum disorders (FASD). NOT-AA-20-022

- **Alcohol-induced Tissue-specific and Organ System Diseases:** The purpose of this NOSI is to inform potential applicants of NIAAA's special interest in research project applications studying the harmful effects of alcohol on the body's tissues, organs, and systems in diverse populations across the lifespan. NOT-AA-20-024

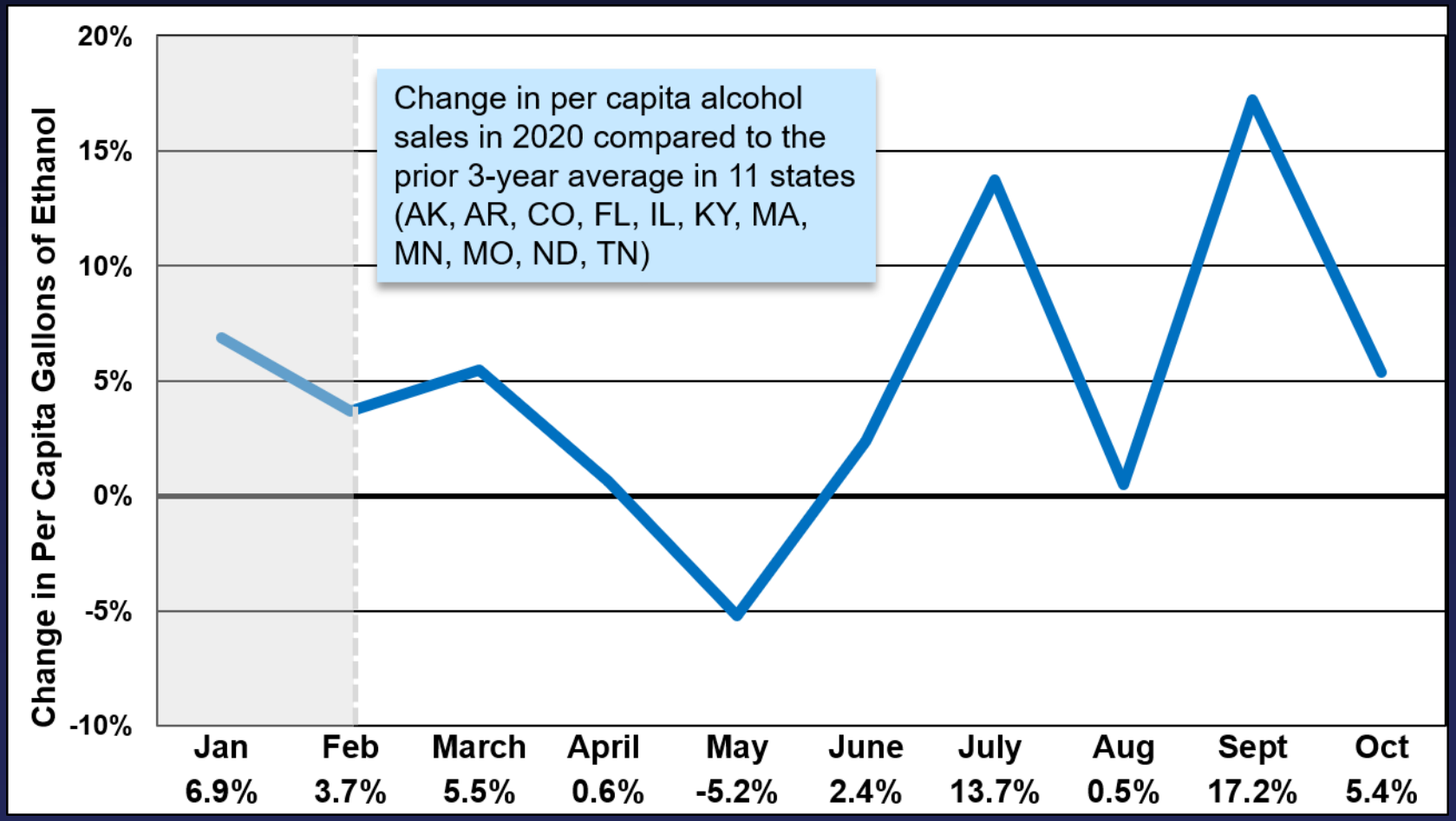
NIAAA Participation in NIH-wide FOAs

- Providing Research Education Experiences to Enhance Diversity in the Next Generation of Substance Use and Addiction Scientists PAR-20-236
- Health Services Research on Minority Health and Health Disparities PAR-20-310
- BRAIN Initiative
  - Pilot Resources for Brain Cell Type-Specific Access and Manipulation Across Vertebrate Species RFA-MH-20-556
  - BRAIN Initiative Cell Census Network (BICCN) Scalable Technologies and Tools for Brain Cell Census RFA-MH-21-140
  - New Concepts and Early-Stage Research for Recording and Modulation in the Nervous System RFA-EY-21-001
- HEAL Initiative
  - Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain RFA-NS-21-010
  - HEALthy Brain and Child Development Study RFA-DA-21-020; RFA-DA-21-021; RFA-DA-21-023; RFA-DA-21-022
  - Integrative Management of Chronic Pain and OUD for Whole Recovery (IMPOWR) RFA-DA-21-029; RFA-DA-21-030

See Director's Report for full listing.

Tracking Alcohol Sales During the COVID-19 Pandemic

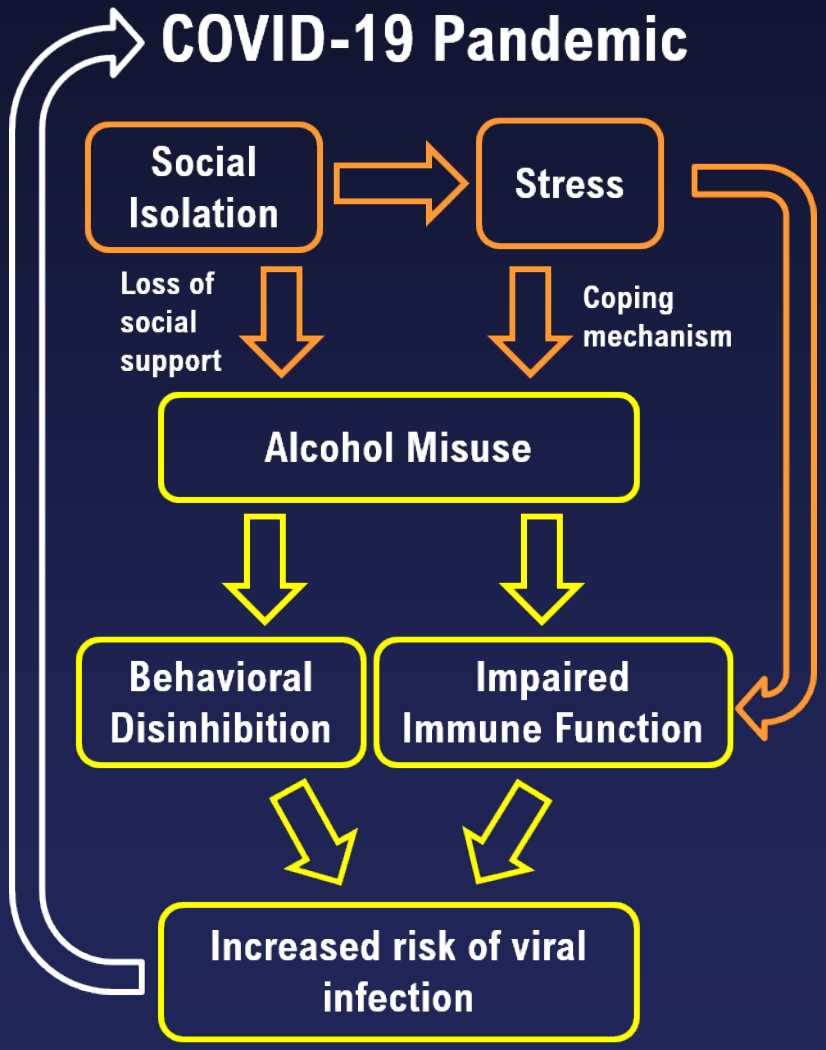
Combined On-Premise And Off-Premise Sales: Small Declines Followed By Increases



Source: NIAAA Alcohol Epidemiologic Data System

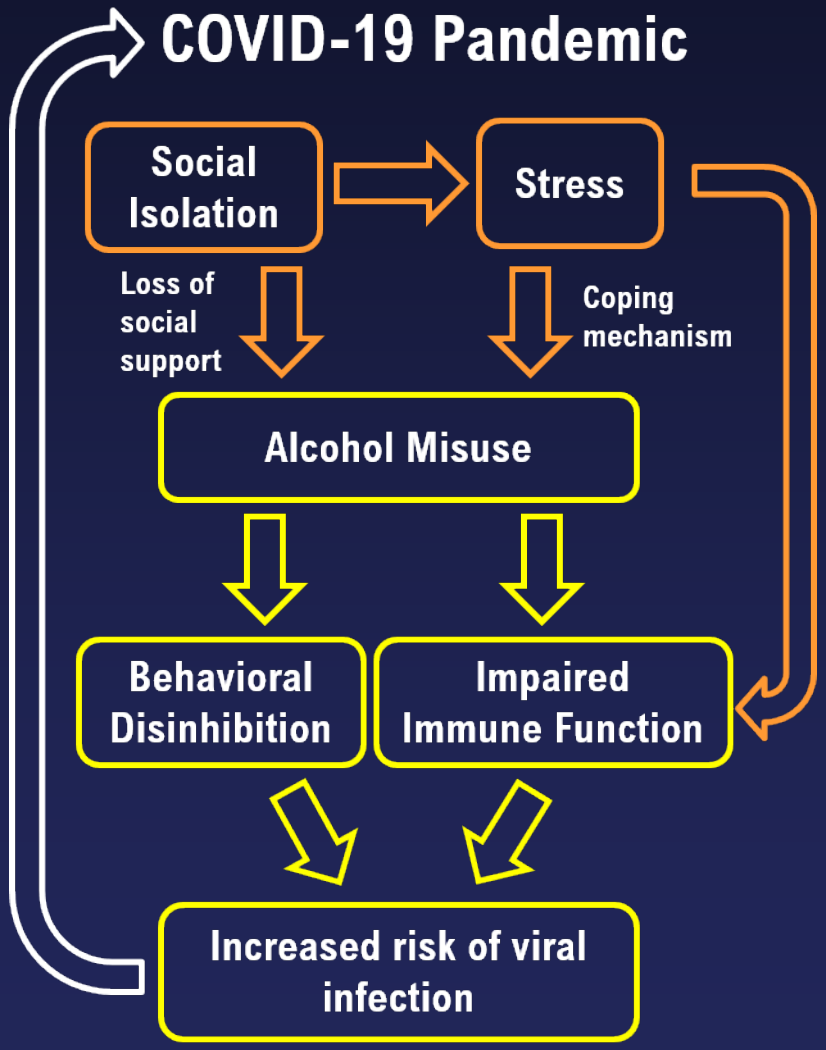
Alcohol and the COVID-19 Pandemic: A Bidirectional Relationship

- **Isolation and stress associated with the pandemic could lead to increased alcohol misuse:**
  - Physical distancing can lead to social isolation or loss of social support, which can lead to stress or precipitate relapse for those in recovery.
  - Physical distancing also poses challenges for treatment and recovery. Telehealth and virtual meetings can be helpful options for individuals seeking treatment or in recovery from AUD.



Alcohol and the COVID-19 Pandemic: A Bidirectional Relationship

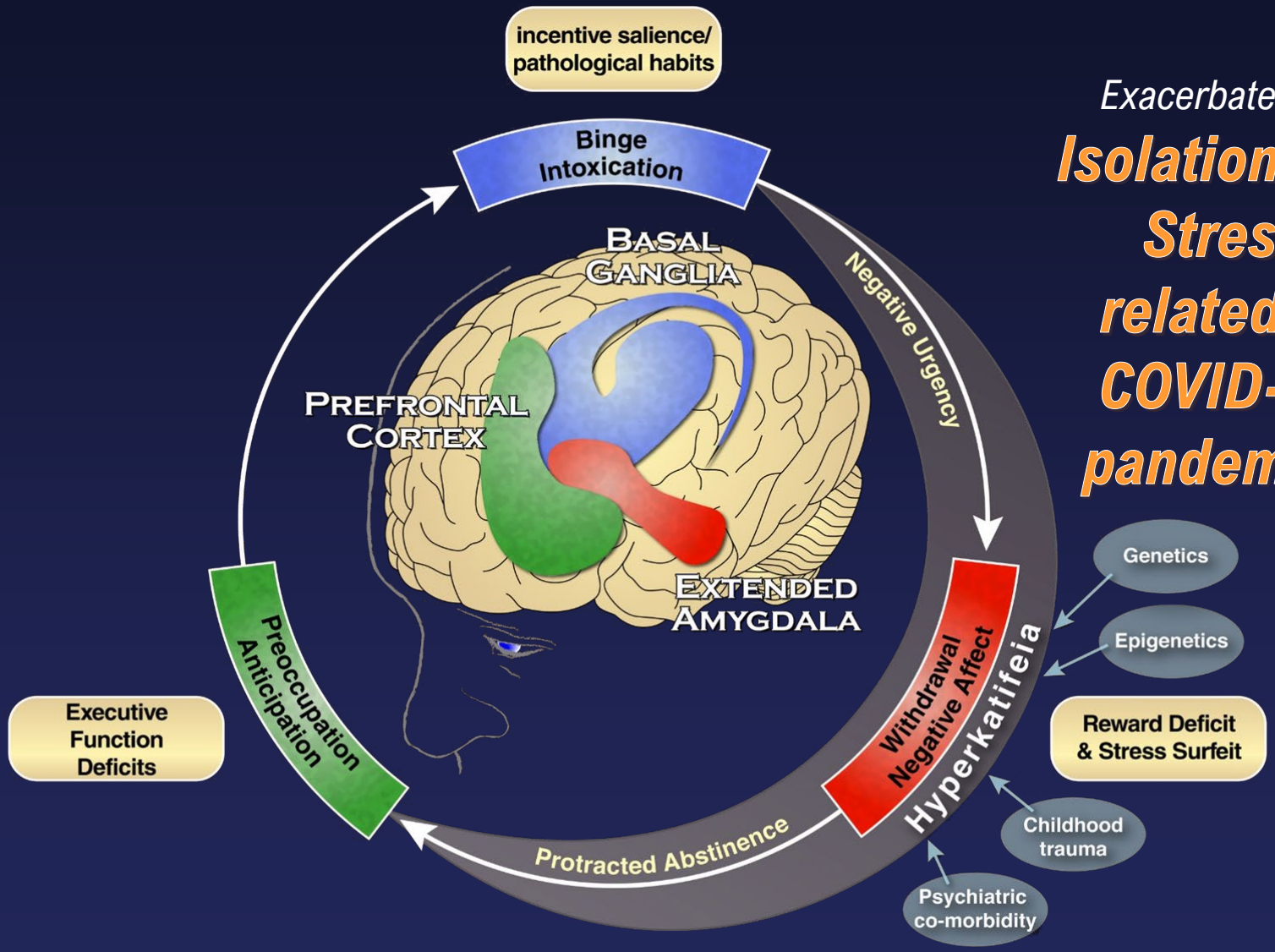
- **Biological and behavioral effects of alcohol misuse could also exacerbate the pandemic:**
  - Alcohol produces behavioral disinhibition that may promote risky behavior and less compliance with guidelines to reduce the spread of the virus.
  - Alcohol compromises immune function, increasing the risk and severity of lung infections.



Drinking to Cope During the COVID-19 Pandemic

- Surveys of consumers in the US and elsewhere suggest that some people are drinking more while others are drinking less
- For those who are consuming more alcohol, limited data suggest that stress is a contributing factor. For instance:
  - Alcohol use increased among college students in March particularly among those reporting higher levels of stress and anxiety *(Lechner et. al. 2020)*
  - People who said their psychological well-being was impacted negatively by the pandemic also reported more drinking days and more drinks per occasion *(Rodriguez et. al. 2020; Grossman et al., 2020)*
  - An Australian survey found that 20% of people reported drinking more during the pandemic and about half endorsed stress, anxiety, boredom, or worry about COVID-19 as reasons for drinking more *(Biddle et. al. 2020)*
- Such findings are concerning given that drinking to cope places a person on a slippery slope to AUD
- In addition, increases in consumption can increase the risk of injuries at a time when many hospitals are inundated with sick patients

Addiction as a Coping Response: Hyperkatifeia, Deaths of Despair, and COVID 19



Exacerbated by

Isolation and Stress related to COVID-19 pandemic?

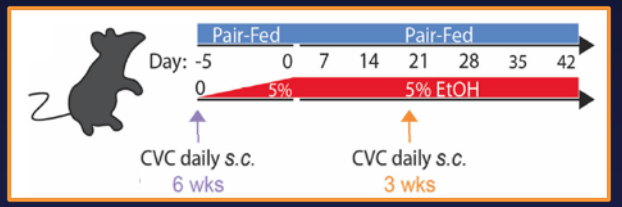
From: Koob, GF, Powell, P., and White, A. Addiction as a Coping Response: Hyperkatifeia, Deaths of Despair, and COVID-19 American Journal Psychiatry, 177 (2020) 1031-1037

Research Highlights

Chronic Alcohol-Induced Neuroinflammation Involves CCR2/5-Dependent Peripheral Macrophage Infiltration and Microglia Alterations

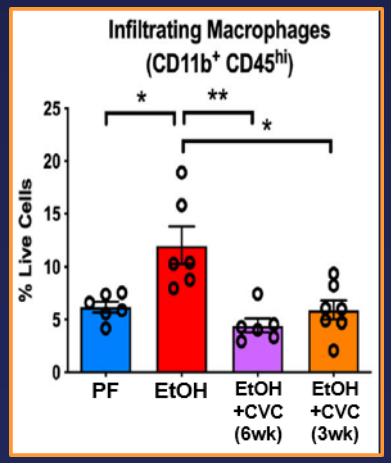
This report provides evidence that chronic alcohol can induce peripheral macrophage infiltration to the central nervous system (CNS). Further, blockade of CCR2/5 signaling with cenicriviroc (CVC) successfully limited the alcohol-induced infiltration of peripheral macrophages into the CNS. CVC treatment also reduced alcohol-induced markers of inflammation in the hippocampus and reversed some alcohol-induced alterations in CCR2/5 axis gene expression.

Mice on 5% EtOH or pair-fed diet were treated with vehicle or CVC (to block CCR2/5 signaling)

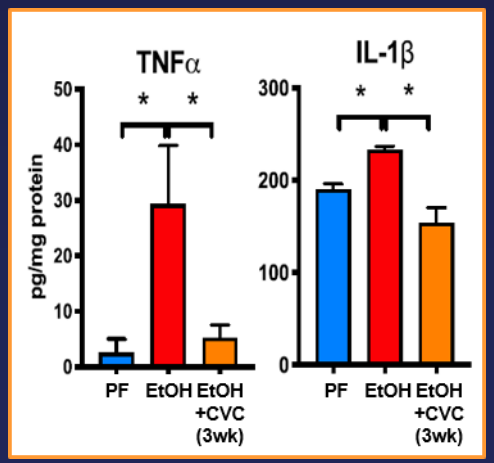


CVC reversed effects induced by chronic alcohol diet, including:

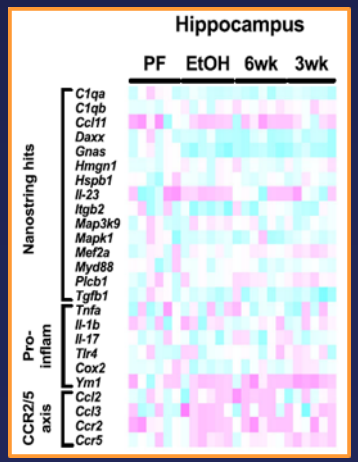
1) macrophage infiltration



2) inflammatory markers in the hippocampus



3) alterations in CCR2/5 axis gene expression



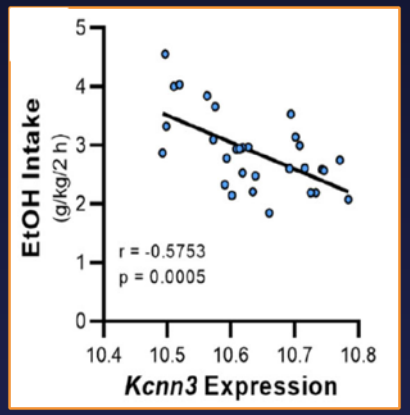
These data establish that chronic alcohol promotes the recruitment of peripheral macrophages into the CNS through the CCR2/5 axis and support further exploration of the CCR2/5 axis as a therapeutic target for the treatment of alcohol-associated neuro-inflammation.

Citation: Lowe PP, Morel C, Ambade A, Iracheta-Vellve A, Kwiatkowski E, Satishchandran A, Furi I, Cho Y, Gyongyosi B, Catalano D, Lefebvre E, Fischer L, Seyedkazemi S, Schafer DP, Szabo G. J Neuroinflammation. 2020 Oct 9;17(1):296.

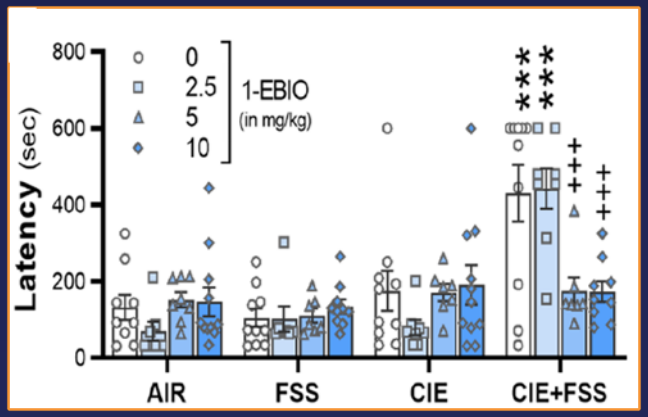
Bioinformatics Identification and Pharmacological Validation of Kcnn3/K Ca 2 Channels as a Mediator of Negative Affective Behaviors and Excessive Alcohol Drinking in Mice

Investigators used a bioinformatics discovery tool to identify K+ channel genes in the amygdala that correlated with both anxiety-like and high alcohol drinking phenotypes in genetically diverse mice. The top candidate gene, *Kcnn3* (which encodes a small-conductance calcium-activated potassium channel, KCa2.3), was then pharmacologically validated in behavioral testing.

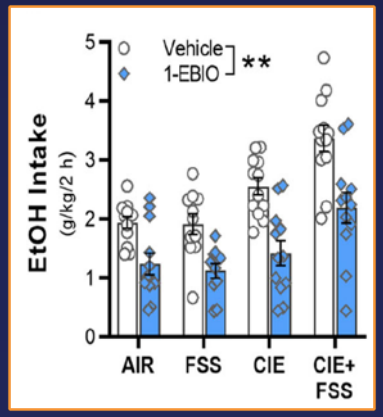
Correlation of Kcnn3 and alcohol intake after chronic mild stress in 31 BXD strains



Positive modulation of KCa2 channels (with 1-EBIO) reversed a measure of negative affect in stressed, alcohol-dependent mice (latency to eat in a novelty –suppressed feeding task).



1-EBIO reduced drinking in all mice.



By identifying a role for *Kcnn3* in regulating excessive drinking and negative affective behaviors in stressed, alcohol-dependent mice, these results demonstrate that KCa2 channels may be a potential pharmacogenetic target for the therapeutic treatment of alcohol use disorder and comorbid mood disorders.

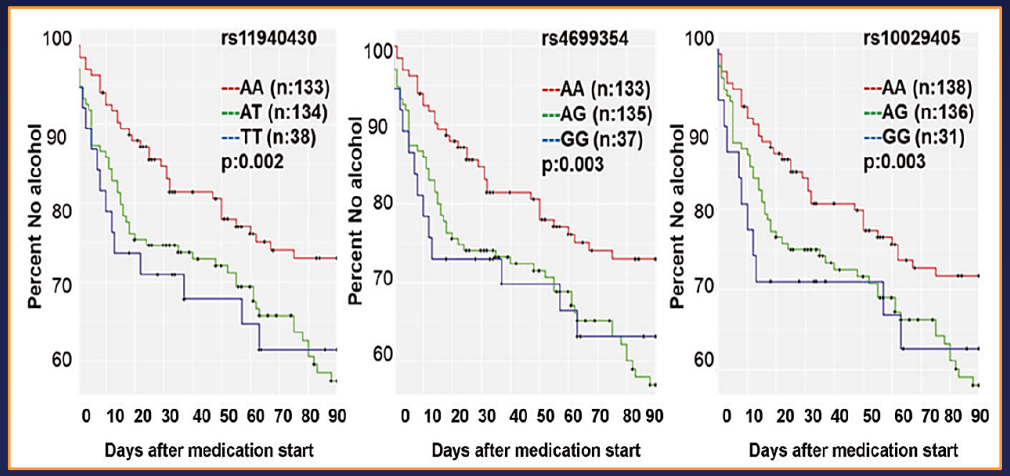
Citation: Padula AE, Rinker JA, Lopez, MF, Mulligan MK, Williams RW, Becker, HC, Mulholland, PJ. Transl Psychiatry. 2020 Nov 27;10(1):414.

TSPAN5 Influences Serotonin and Kynurenine: Pharmacogenomic Mechanisms Related to Alcohol Use Disorder and Acamprosate Treatment Response

Previous studies have shown that genetic variants near the *TSPAN5* gene were associated with both plasma serotonin concentration and risk for alcohol use disorder (AUD). As part of a study designed to explore the biological function of TSPAN5, investigators assessed the relationship between genetic variants near *TSPAN5* and the length of abstinence during three months of acamprosate treatment in patients with AUD.

Results demonstrated that several *TSPAN5* genetic variants might be biomarkers for abstinence length in patients with AUD treated with acamprosate, suggesting that TSPAN5 might contribute to individualized acamprosate treatment outcomes through a novel pharmacogenomic mechanism.

Genetic variants near TSPAN5 were associated with length of abstinence during 3 months of acamprosate treatment



	Abstinence to first drink	Abstinence to heavy drinking	Complete abstinence
rs11940430	**p: 0.0019 HR:1.56 (1.17-2.07)**	**p: 0.0035 HR:1.59 (1.16-2.17)**	p: 0.053 OR:1.56 (0.995-2.45)
rs4699354	**p: 0.0027 HR:1.54 (1.16-2.05)**	**p: 0.0053 HR:1.56 (1.14-2.15)**	p: 0.068 OR:1.53 (0.97-2.42)
rs10029405	**p: 0.0031 HR:1.59 (1.17-2.17)**	**p: 0.0096 HR:1.56 (1.11-2.19)**	**p: 0.045 OR:1.63 (1.01-2.64)**

Citation: Ho MF, Zhang C, Zhang L, Wei L, Zhou Y, Moon I, Geske JR, Choi DS, Biernacka J, Frye M, Wen Z, Karpyak VM, Li H, Weinshilboum R. Mol Psychiatry. 2020 Aug 4. doi: 10.1038/s41380-020-0855-9.

A Multimodal, Longitudinal Investigation of Alcohol's Emotional Rewards and Drinking Over Time in Young Adults

Researchers assessed real-time emotional responses to alcohol in a laboratory study of 60 young adult heavy social drinkers. A subset also participated in an ambulatory (real-world) assessment. A follow-up was conducted 18 months later to determine the impact of alcohol's emotional rewards at baseline on drinking behavior and problems over time.

Results from the laboratory study indicated that alcohol-related positive mood enhancement at baseline predicted drinking problems and binge drinking status at 18-month follow-up. Similarly, alcohol-related reduction in negative mood in the lab predicted drinking problems at follow-up. In the ambulatory study, use of alcohol to reduce negative mood measured in everyday contexts significantly predicted drinking problems at follow-up. Results suggest that emotional rewards may be a factor contributing to problematic drinking.

Variable	Laboratory positive mood effects		Laboratory negative mood effects		Ambulatory positive mood effects		Ambulatory negative mood effects	
	B	*p*	*B*	*p*	*B*	*p*	*B*	*p*
1. Models Predicting Drinking at 18-Month Follow-Up Controlling for Baseline Drinking								
Drinking days	.020	.974	1.293	.174	−1.795	.583	−2.700	.794
Drinking quantity	.074	.318	−.003	.979	−.401	.386	.491	.729
Drinking problems	.159	.026	−.238	.024	−.420	.311	−3.140	.010
Binge drinking status	3.221	.019	.282	.735	−4.525	.200	2.505	.762

Citation: Venerable WJ, Fairbairn CE. Psychol Addict Behav. 2020 Aug;34(5):601-612.

Prescription Opioid Use and Risk for Major Depressive Disorder and Anxiety and Stress-Related Disorders: A Multivariable Mendelian Randomization Analysis

To investigate the potential relationship between genetic liability for prescription opioid and other non-opioid pain medication use and both major depressive disorder and anxiety and stress-related disorders, investigators performed 2-sample mendelian randomization using summary statistics from genome-wide association studies (GWAS).

Analysis indicated that the genetic liability for prescription opioid use, but not other non-opioid pain analgesics, may increase the risk for major depression and anxiety disorders – even after accounting for chronic pain conditions.

These results suggest a link between prescription opioid use and mood disorders, which may inform future intervention and prevention strategies.

		Major depressive disorder			Anxiety and stress disorders		
MV exposures	Methods	No. of SNVs	OR (95% CI)	*P* value	No. of SNVs	OR (95% CI)	*P* value
Opioid use	MV IVW	92	1.14 (1.04-1.25)	.005	86	1.30 (1.08-1.56)	.006
	MV Egger	92	1.13 (1.02-1.26)	.02	86	1.18 (0.95-1.46)	.13
NSAID use	MV IVW	92	0.98 (0.84-1.15)	.81	86	1.37 (0.99-1.90)	.06
	MV Egger	92	0.97 (0.82-1.15)	.72	86	1.23 (0.87-1.73)	.24
Salicylic acid use	MV IVW	92	0.99 (0.89-1.11)	.88	86	0.96 (0.76-1.21)	.70
	MV Egger	92	0.98 (0.87-1.11)	.76	86	0.84 (0.64-1.10)	.21

Citation: Rosoff DB, Smith GD, Lohoff FW. JAMA Psychiatry. 2020 Nov 11:e203554.

THANK YOU!

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