NIAAA Director's Report on Institute Activities to the 152nd Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism

September 12, 2019
Bethesda, MD

George F. Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

NIH National Institute on Alcohol Abuse and Alcoholism

In Memoriam
R. Thomas (Tom) Gentry, Ph.D.

Tom worked at NIAAA from 1996 until his retirement in 2012. As a program officer for the Division of Metabolism and Health Effects, he advanced efforts to develop a wearable alcohol biosensor, an interest he actively maintained into retirement. He was motivated by the hope for potential tools to help those battling addiction to re-connect with their families and maintain employment.

During his research career prior to joining NIAAA, Tom made important contributions to the field of alcohol pharmacokinetics at Rockefeller University and the Alcohol Research Center at the Bronx VA Medical Center.

In Memoriam
Robert E. Taylor, M.D., Ph.D.

Dr. Taylor had a distinguished career as the Dean of the College of Medicine, Chair of the Department of Pharmacology, and Director of the NIAAA-funded Collaborative Alcohol Research Center at Howard University. He also served as an NIAAA Council member from 2002-2006 and more recently as an ad hoc member of the Council's Working Group on Diversity and Health Disparities in the Biomedical Workforce.

Dr. Taylor will be remembered for his dedication to multidisciplinary research to address alcohol-related health disparities and his passion for mentoring and increasing diversity in the biomedical research workforce.

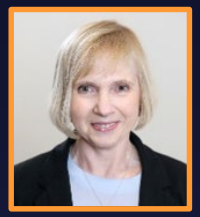
Welcome to New NIAAA Staff

Gabriela Coello joined the Administrative Services Branch as an Administrative Officer supporting the intramural laboratories of Drs. Goldman, Kim, Pacher, and Veech. She previously worked at the National Cancer Institute.

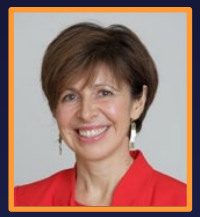
Dr. Yong He joined the Laboratory of Liver Diseases (LLD) as a Research Fellow in the Visiting Program. He previously served in the NIH Graduate Partnership Program in LLD. Dr. He received his Ph.D. in Pharmacology from Anhui Medical University in Hefei, China.

Cassie Williams joined the Administrative Services Branch as an Administrative Officer supporting the intramural laboratories of Drs. Lovinger, Vogel, and Gawrisch. She previously worked at the National Institute of Allergy and Infectious Diseases.

NIAAA Internal Staff Transitions



Dr. Tatiana Balachova joined the Division of Epidemiology and Prevention Research as Senior Scientific Administrator after previously serving at NIAAA through the Intergovernmental Personnel Act Mobility Program.



Dr. Svetlana Radaeva has been selected as the Deputy Director of NIAAA's Division of Metabolism and Health Effects (DMHE). She previously served as a Staff Scientist in NIAAA's Section on Liver Biology and has served as Program Officer within DMHE since 2006.

Dr. Mehdi Farokhnia was promoted to Research Fellow in the Section on Clinical Psychoneuroendocrinology and Neuropsycho-pharmacology (CPN) after previously serving as a post-doc IRTA Fellow in CPN.

Dr. Laura Kwako transitioned from her role as Clinical Research Psychologist in the Office of the Clinical Director to Program Officer in the Division of Treatment and Recovery Research.

Dr. Rachel Anderson transitioned from her role as an AAAS Science and Technology Policy Fellow to Health Science Policy Analyst in the Science Policy Branch.

Departing Staff

Erin Bryant, Science Writer and Social Media Strategist in the Communications and Public Liaison Branch, has moved to the NIH Office of the Director where she now works as a technical writer for NIH Research Matters and NIH News in Health.

Yolanda Carter, Administrative Laboratory Manager with Laboratory of Integrative Neuroscience, moved to NIH Office of Research Facilities.

Dr. Abhishek Desai completed his fellowship in the Laboratory of Molecular Signaling and is currently spending time with his family.

Dr. Lori Ducharme, former Program Director in the Division of Treatment and Recovery Research, transferred to the National Institute on Drug Abuse where she now serves as Health Scientist Administrator in the Services Research Branch.

Lynn Morin, former Chair of the Centers and Training Working Group and Diversity Supplement Program Coordinator for the NIAAA Office of Extramural Activities, transferred to the NIH Office of Research on Women's Health after eight years of service at NIAAA.

Monte Philips, Biologist in the Section on Clinical Genomics and Experimental Therapeutics, has retired after working in the NIAAA intramural research program for 29 years.

Dr. Richard Rippe, Scientific Review Officer, Extramural Project Review Branch, Office of Extramural Activities, retired after 10 years of federal service.

Kamilah Smith, Administrative Assistant with the Division of Neuroscience and Behavior, accepted a position as Program Specialist with the Center for Drug Evaluation and Research within the U.S. Food and Drug Administration (FDA).

FY 2019 NIAAA Budget Closeout

	FY 2019 Enacted Budget
NIH	$39.3 billion
NIAAA	$525.6 million
Research Project Grants	782
Competing Awards	192
Other Research Grants	194
Research Centers	21
Training Positions	295
Research and Development Contracts	$34 million

The FY 2020 budget is under development.

Funding Opportunity Announcements (FOAs)

FOAs recently issued by NIAAA:

- Mechanisms of Tolerance (R21/R33 Clinical Trial Required)
- Specialized Alcohol Research Centers (P50 Clinical Trial Optional)
- Comprehensive Alcohol Research Centers (P60 Clinical Trial Optional)

NIAAA participation in NIH-wide FOAs:

- Secondary Analyses of Existing Datasets of Tobacco Use and Health (R21 Clinical Trial Not Allowed)
- Maximizing the Scientific Value of Existing Biospecimen Collections: Scientific Opportunities for Exploratory Research (R21 Clinical Trial Not Allowed)
- Methods to Improve Reproducibility of Human iPSC Derivation, Growth and Differentiation (SBIR) (R44 Clinical Trial Not Allowed)
- Dissemination and Implementation Research in Health (R01 Clinical Trial Optional; R21 Clinical Trial Optional; R03 Clinical Trial Not Allowed)

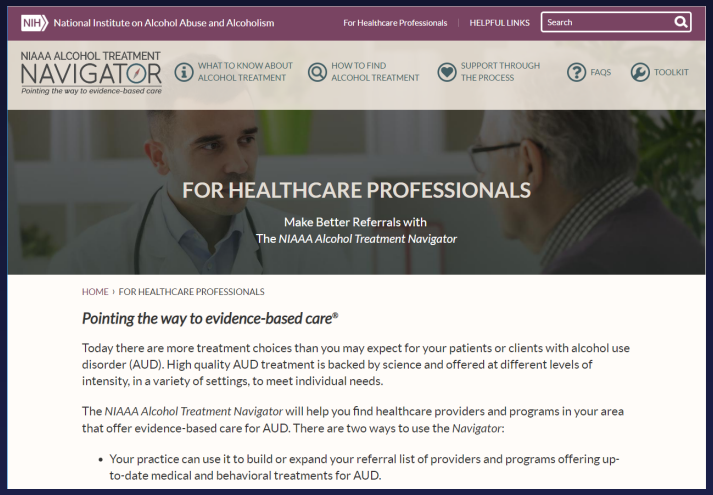
NIAAA participation in BRAIN Initiative FOAs

Recently issued BRAIN Initiative FOAs include:

- Non-Invasive Neuromodulation - New Tools and Techniques for Spatiotemporal Precision (R01 Clinical Trial Optional)
- Proof of Concept Development of Early Stage Next Generation Human Brain Imaging (R01 Clinical Trial Not Allowed)
- Development of Next Generation Human Brain Imaging Tools and Technologies (U01 Clinical Trial not allowed)
- Marmoset Coordination Center (U24 Clinical Trials Not Allowed)
- Marmoset Colonies for Neuroscience Research (U24 Clinical Trials Not Allowed)
- Research to Develop and Validate Advanced Human Cell-Based Assays To Model Brain Structure and Function (R01 Clinical Trial Not Allowed)

Updates to the NIAAA Alcohol Treatment Navigator

The NIAAA Alcohol Treatment Navigator now includes a portal for healthcare professionals. This portal will help clinicians build or expand their referral lists to include providers offering up-to-date, science-backed AUD treatments that meet the varied needs of their patients. It also provides tips for sharing the *Navigator* directly with patients who wish to search on their own.



Other content update include:

- Expansion of types of treatment content to promote better awareness of the full range of options
- Addition of a new filter to the *Navigator*'s simple program research tool to make it easier for clinicians and the public to locate telehealth services for AUD

What's Ahead

- ***Alcoholic and Nonalcoholic Steatohepatitis: Pathogenesis and Mechanisms of Liver Injury Workshop*** **will be held September 16-17, 2019, in Bethesda, Maryland. Jointly sponsored by NIAAA and NIDDK, the workshop will bring together investigators in these two fields to summarize the current state of the science of various pathophysiological mechanisms that lead to fatty liver injury.** ***Drs. Svetlana Radaeva and Joe Wang are the program contacts.***

- **NIAAA and NIDA, along with NIMHD, will again sponsor the** ***National Hispanic Science Network*** **annual meeting on October 9-11, 2019, in New Orleans, Louisiana. In addition to scientific sessions on basic and clinical addiction research, the program includes two invited symposia on alcohol-related research.** ***Dr. Judith Arroyo is the program contact.***

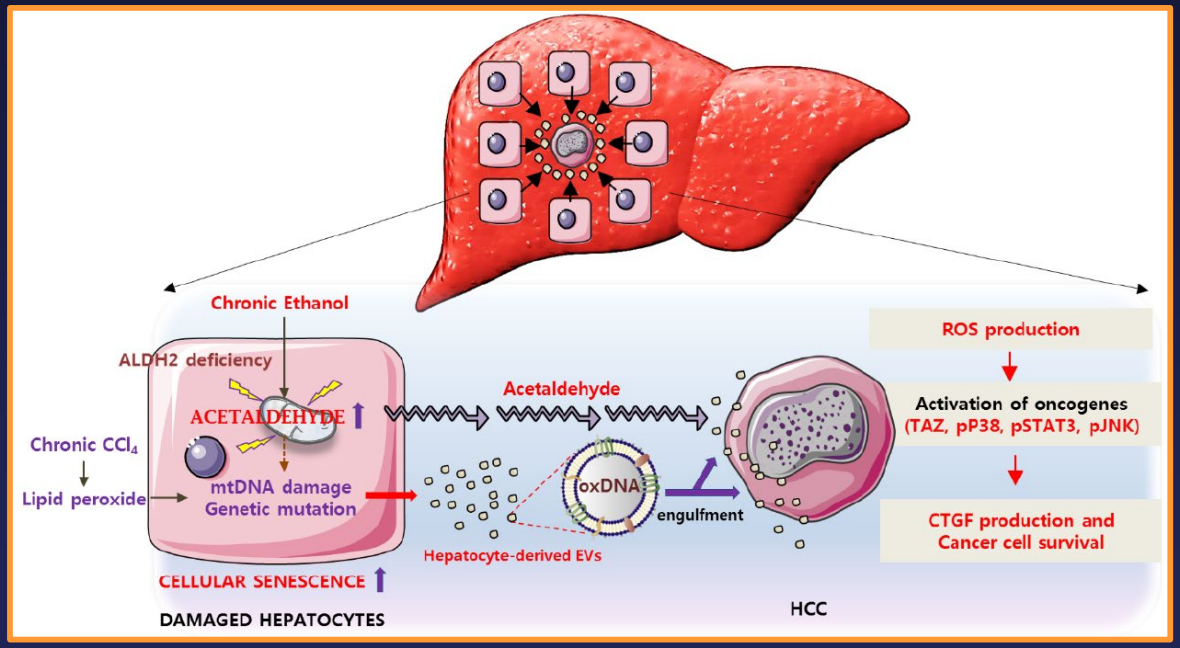
- ***The Cancer Moonshot Collaborative Meeting (CMCM)*** **will be held November 18-20, 2019, at the Bethesda North Marriott Hotel & Conference Center in Rockville, Maryland.** ***Dr. Gary Murray is the NIAAA representative for the meeting.***

Research Highlights

ALDH2 Deficiency Promotes Alcohol-Associated Liver Cancer by Activating Oncogenic Pathways via Oxidized DNA Enriched Extracellular Vesicles

This study demonstrated that **ALDH2-deficient mice or humans with chronic liver disease and alcohol consumption are more susceptible to liver cancer**, due to increased production of oxidized mitochondrial DNA-enriched extracellular vesicles that activate multiple oncogenic pathways.

After chronic alcohol exposure, Aldh2-deficient liver cells produce damaged DNA in vesicles that can be delivered to nearby hepatocellular carcinoma cells and activate oncogenic pathways.



Inhibition of oxidized mitochondrial DNA-enriched extracellular vesicle production could be a novel therapeutic strategy for ameliorating alcohol-associated liver cancer in ALDH2-deficient individuals.

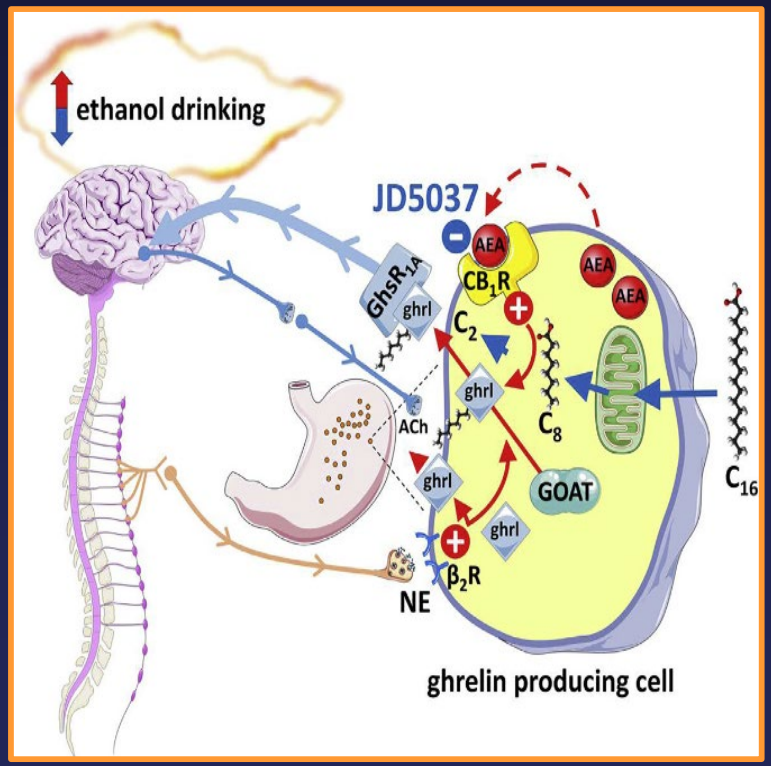
Citation: Seo W, Gao Y, He Y, Sun J, Xu H, Feng D, Hee Park S, Cho YE, Guillot A, Ren T, Wu R, Wang J, Kim SJ, Hwang S, Liangpunsakul S, Yang Y, Niu J, and Gao B. J Hepatol. 2019 Jul 4.

Targeting Peripheral CB1 Receptors Reduces Ethanol Intake via a Gut-Brain Axis

This study demonstrated that cannabinoid-1 receptor (CB1R) signaling in ghrelin-producing stomach cells modulates the formation of biologically active ghrelin, which then activates a gut-brain signaling pathway that leads to increased alcohol consumption.

Peripherally-restricted pharmacological inhibition of CB1R, which avoids the psychiatric side effects of blocking CB1R in the central nervous system, reduced ethanol drinking in mice. Thus, peripheral CB1 receptor blockade may have therapeutic potential in the treatment of alcoholism.

In stomach cells, blockade of CB1R with JD5037 inhibits the formation of biologically active ghrelin, preventing activation of a gut-brain signaling pathway that promotes elevated alcohol intake.



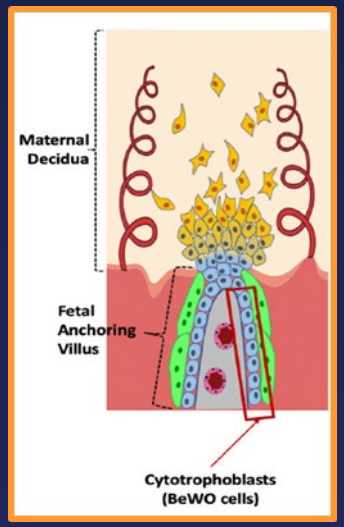
Citation: Godlewski G, Cinar R, Coffey NJ, Liu J, Jourdan T, Mukhopadhyay B, Chedester L, Liu Z, Osei-Hyiaman D, Iyer MR, Park JK, Smith RG, Iwakura H, and Kunos G. Cell Metab. 2019 Jun 4;29(6):1320-1333.e8

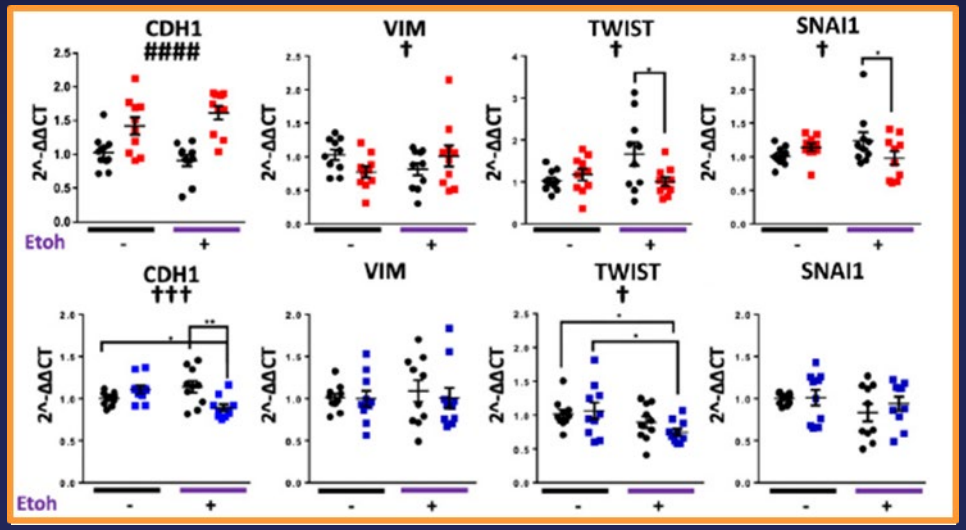
Maternal Circulating miRNAs that Predict Infant FASD Outcomes Influence Placental Maturation

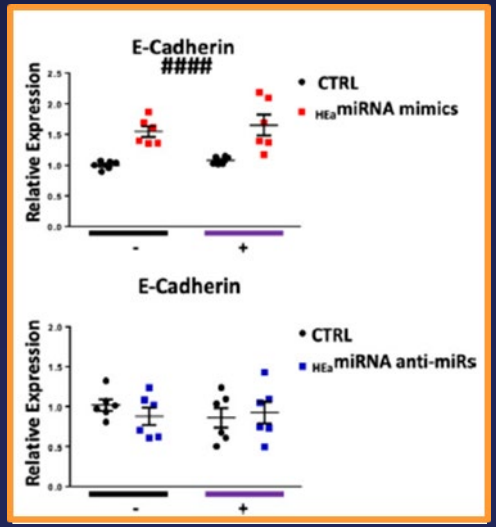
Previous research identified 11 miRNAs in the plasma of pregnant women that predict infant FASD outcomes following prenatal alcohol exposure. In the current report, the same team demonstrated that these **miRNAs restrict placental maturation by inhibiting trophoblast epithelial-mesenchymal transition (EMT)**, a key process for development of the placenta. In vitro cell data also supported the potential of targeting these miRNAs for therapeutic intervention. Collectively, these findings suggest that prenatal alcohol results in fetal growth restriction in part by impairing placental function via specific miRNAs.

Cytotrophoblasts undergo EMT to mature into cells forming the placenta.

Effects of the 11 miRNAs (shown in red) on expression of four markers used to assess trophoblast EMT were consistent with impairment of the EMT process. Antagomirs that silence these 11 miRNAs (shown in blue) prevented these effects.







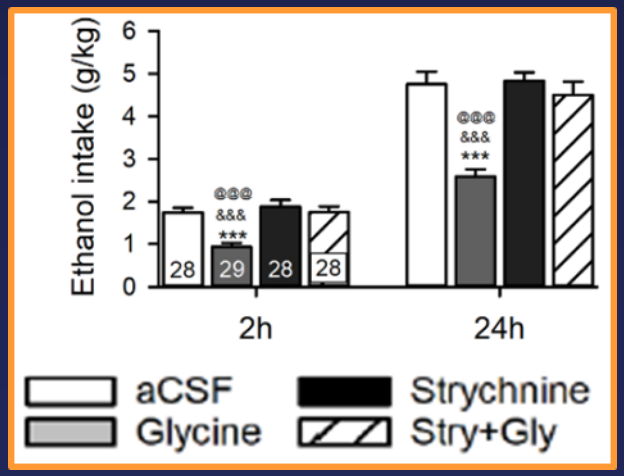
Citation: Tseng AM, Mahnke AH, Wells AB, Salem NA, Allan AM, Roberts VH, Newman N, Walter NA, Kroenke CD, Grant KA, Akison LK, Moritz KM, Chambers CD, and Miranda RC; Collaborative Initiative on Fetal Alcohol Spectrum Disorders. Life Sci Alliance. 2019 Mar 4;2(2).

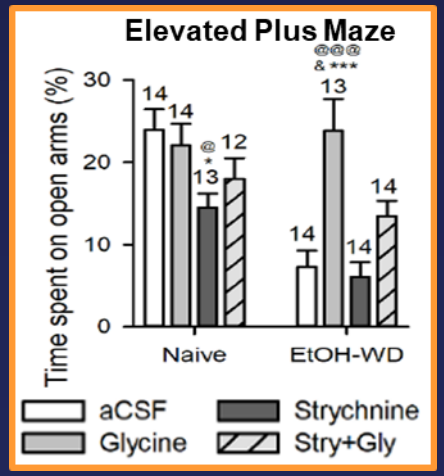
Activation of Glycine Receptors in the Lateral Habenula Rescues Anxiety- and Depression-like Behaviors Associated with Alcohol Withdrawal and Reduces Alcohol Intake in Rats

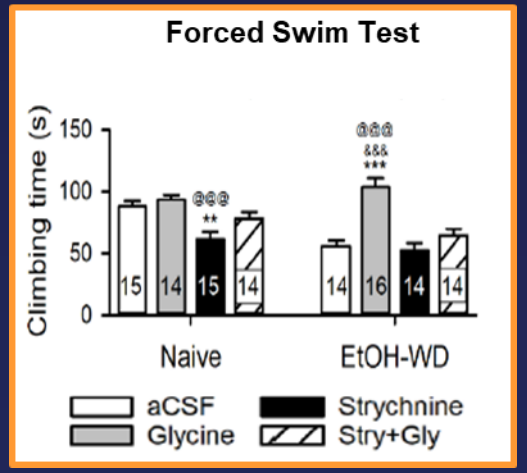
The negative emotional state associated with alcohol withdrawal is a driving force for alcohol relapse; however, the underlying neurobiological mechanisms are not fully understood. This study demonstrates a role for glycine signaling in the lateral habenula in negative affective states associated with alcohol withdrawal, offering a potential therapeutic target for alcohol use disorder.

Glycine administration in the lateral habenula reduced drinking in alcohol-withdrawn rats, an effect blocked by the glycine receptor antagonist strychnine.

In alcohol-withdrawn rats, glycine administration in the lateral habenula reduced anxiety-like behavior (elevated plus maze) and depression-like behavior (forced swim test). This effect was blocked by strychnine.







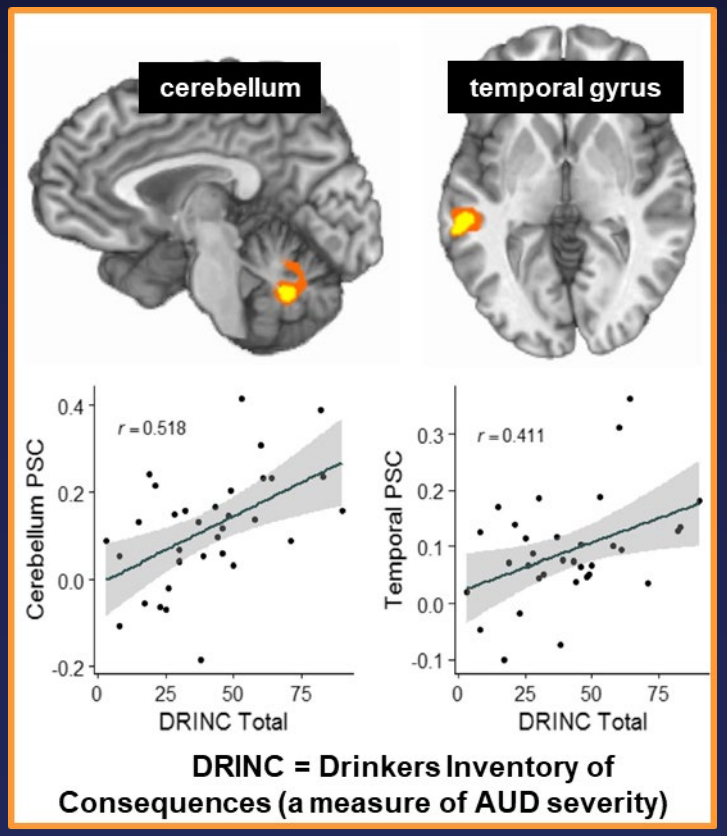
Citation: Li W, Zuo W, Wu W, Zuo QK, Fu R, Wu L, Zhang H, Ndukwe M, and Ye JH. Neuropharmacology. 2019 Oct; 157:107688

Stroop-related Cerebellar and Temporal Activation is Correlated with Negative Affect and Alcohol Use Disorder Severity

This study used functional brain imaging to study the relationships between cognitive control, the severity of an alcohol use disorder (AUD), and measures of negative affect such as anxiety, depression, and affective lability.

There was greater activation in the cerebellum and temporal cortex during a cognitive interference task that was correlated with a greater degree of AUD severity and increased negative affect. **Activation in the cerebellum was still associated with negative affect after controlling for the effects of drinking history and AUD severity.** These results suggest that the cerebellum may play a more prominent role in negative affect and AUD than previously realized and provides a potential target for intervention.

Greater activation of the cerebellum and temporal cortex during a cognitive interference task was correlated with a greater degree of AUD severity.



Citation: Wilcox CE, Clifford J, Ling J, Mayer AR, Bigelow R, Bogenschutz MP, and Tonigan JS. Brain Imaging and Behavior 2019 May 22.

Sex Differences in Trait Anxiety's Association with Alcohol Problems in Emerging Adults: The Influence of Symptoms of Depression and Borderline Personality

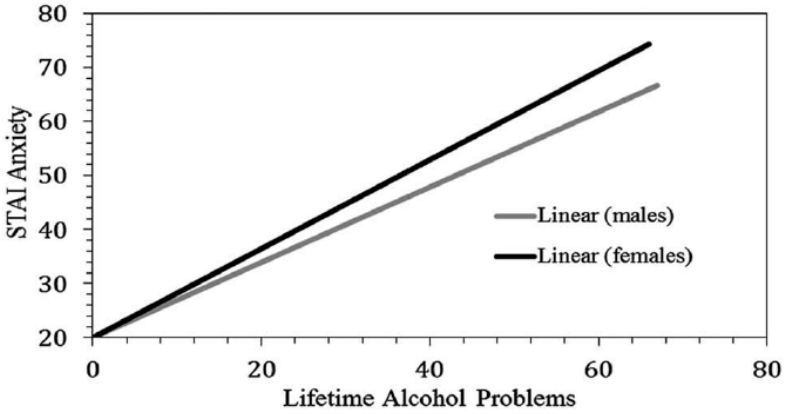
Lifetime alcohol drinking is often associated with anxiety, depression, and other mental health conditions such as borderline personality disorder (BPD). However, the extent to which sex differences contribute to these conditions in relation to drinking problems is not well understood.

This study assessed trait anxiety, depression, and symptoms of BPD in a large sample of young adults (age 18-30) with varying lifetime alcohol-related problems. The results showed that the **correlation between trait anxiety and alcohol problems was significantly stronger in men than women**, regardless of depression and BPD symptoms. These findings suggest sex-specific mechanisms underlying the relationship between trait anxiety and alcohol problems.

Anxiety, BPD symptoms, and depression were each correlated with alcohol problems in both males and females. The correlation between anxiety and alcohol problems was significantly higher in males.

	Males	Females	
	Alcohol Problems	Alcohol Problems	z-score
STAI Anxiety	0.379**	0.249**	2.04*
BPD Symptoms	0.398**	0.340**	0.097
BDI Depression	0.397**	0.407**	−0.15

*= p < .05;**= p < .0001



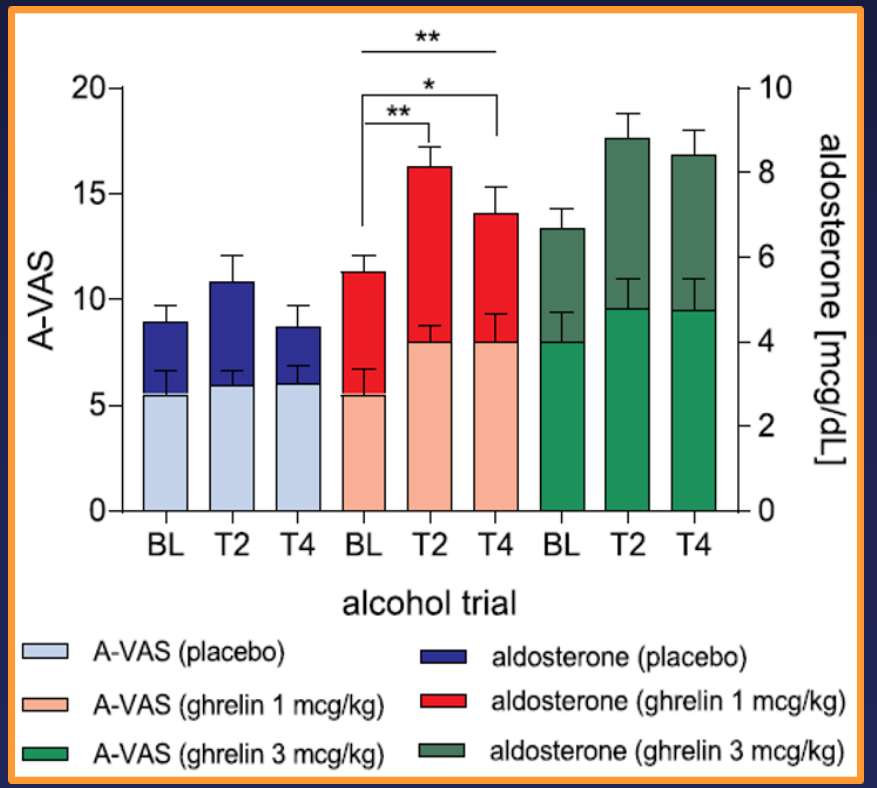
Citation: Atkinson EA and Finn PR. Journal of Substance Use. 2019. 24:3, 323-328.

IV Administration of Ghrelin Increases Serum Cortisol and Aldosterone Concentrations in Heavy-Drinking Alcohol-Dependent Individuals: Results from a Double-Blind, Placebo-Controlled Human Laboratory Study

In this study, serum concentrations of cortisol and aldosterone were used to develop a model to predict the effect of exogenous ghrelin administration on alcohol craving in individuals with AUD. **Ghrelin-induced changes in aldosterone (but not cortisol) predicted craving.**

These findings provide initial evidence of a link between ghrelin and glucocorticoids/mineralocorticoids in the context of AUD, thereby providing additional information on how the ghrelin system may play a role in alcohol-related behaviors.

Intravenous ghrelin administration increased endogenous levels of aldosterone (darker shade bars). Ghrelin-induced elevation of aldosterone corresponded with increased craving (assessed via alcohol visual analog scale, A-VAS; lighter shade bars).



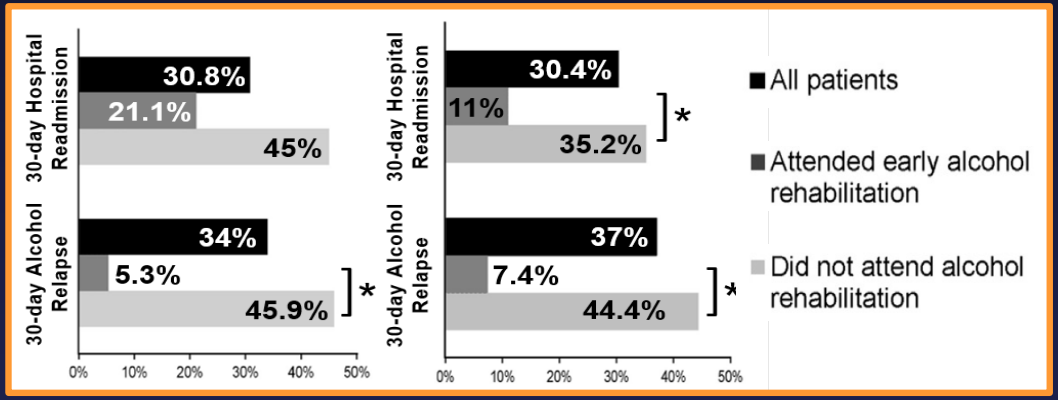
Citation: Haass-Koffler CL, Long VM, Farokhnia M, Magill M, Kenna GA, Swift RM, and Leggio L. Neuropharmacology. 2019 Jul 13:107711.

Alcohol Rehabilitation Within 30 Days of Hospital Discharge Is Associated With Reduced Readmission, Relapse, and Death in Patients With Alcoholic Hepatitis

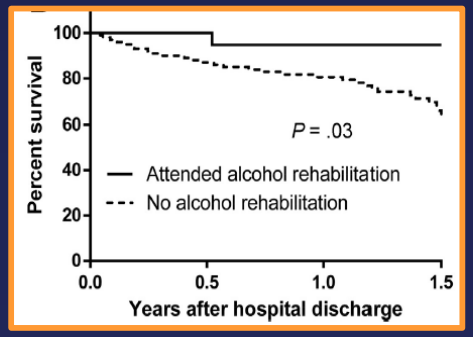
Patients who have recovered from alcoholic hepatitis (AH) remain at risk of hospital readmission and death, outcomes generally attributed to alcohol relapse. This analysis of two patient cohorts evaluated rates of hospital readmission, alcohol relapse, and mortality in AH patients.

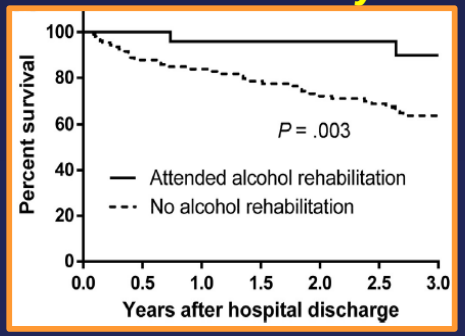
These results suggest that all patients with AH should be formally evaluated by addiction specialists during their hospital stay and referred for treatment within 30 days of hospital discharge.

Participation in early alcohol rehabilitation (within 30 days of discharge) was associated with decreased 30-day readmission and alcohol relapse in both cohorts.



Participation in early alcohol rehabilitation was also associated with reduced mortality.





Citation: Peeraphatdit TB, Kamath PS, Karpyak VM, Davis B, Desai V, Liangpunsakul S, Sanyal A, Chalasani N, Shah VH, and Simonetto DA. Clin Gastroenterol Hepatol. 2019 Apr 28.

Health Care Use Over 3 Years After Adolescent SBIRT

This study used electronic health data to examine subsequent health care use among adolescents from a randomized clinical trial comparing usual care to two modalities of delivering SBIRT in pediatric primary care (either pediatrician- or behavioral clinician-delivered).

Adolescents in the SBIRT group were likely to have had more substance use treatment visits and fewer psychiatry department visits and total outpatient visits over a 3-year period compared with those in usual care.

Covariates	Emergency			Primary Care			Substance Use Treatment			Psychiatry			All Outpatient		
	iRR	95% CI	*P*	iRR	95% CI	*P*	iRR	95% CI	*P*	iRR	95% CI	*P*	iRR	95% CI	*P*
SBIRT group (reference = usual care)	0.99	0.83–1.17	—	0.99	0.90–1.09	—	2.04	1.28–3.27	***	0.65	0.51–0.83	***	0.85	0.76–0.96	***
Sex (reference = male)	1.27	1.08–1.49	***	1.56	1.42–1.71	***	0.84	0.60–1.17	—	1.27	1.00–1.61	***	1.35	1.21–1.50	***
Age	0.95	0.90–1.00	***	0.91	0.89–0.94	***	1.06	0.91–1.24	—	0.60	0.55–0.66	***	0.87	0.84–0.90	***
Race and/or ethnicity (reference = white)															
Asian American	0.69	0.50–0.97	***	0.89	0.75–1.04	—	0.12	0.06–0.24	***	0.68	0.45–1.03	**	0.78	0.65–0.95	***
African American	2.06	1.67–2.55	***	1.04	0.92–1.17	—	0.09	0.05–0.16	***	0.78	0.58–1.05	—	0.92	0.79–1.06	—
Hispanic	1.84	1.46–2.31	***	0.94	0.83–1.07	—	0.64	0.36–1.12	—	0.70	0.51–0.97	***	0.98	0.84–1.15	—
Missing or unknown	1.15	0.79–1.68	—	1.05	0.86–1.28	—	0.20	0.08–0.46	***	0.95	0.57–1.59	—	0.90	0.70–1.15	—
Previous use of similar service	2.29	1.90–2.75	***	1.30	1.17–1.43	—	7.27	1.96–26.98	***	4.48	3.28–6.14	***	1.56	1.37–1.77	***

—, not significant.
*** $P < .05$; ** $P < .10$.

iRR = incidence rate ratio

These findings suggest that providing SBIRT in primary care may reduce health care use and improve adolescent health.

Citation: Sterling S, Kline-Simon AH, Jones A, Hartman L, Saba K, Weisner C, and Parthasarathy S. Pediatrics. 2019 May;143(5).

The Relationship Between the U.S. State Alcohol Policy Environment and Individuals' Experience of Secondhand Effects: Alcohol Harms Due to Others' Drinking

This study examined the prevalence of alcohol's secondhand effects and whether the prevalence of these effects differed based on the strength of a state's policies.

Researchers then modeled the effects of a 10% increase in alcohol policy restrictiveness, which was linked with lower levels of aggression-related harms and drunk driving-related harms for individuals under age 40. These findings suggest that state policies known to reduce binge drinking and impaired driving might also reduce the secondhand harms of alcohol, particularly among individuals under 40.

Secondhand harms in three categories (aggression-related, family- or financial-related, and driving-related) were experienced by 16.8% of people under 40 and 7.8% of people over 40.

Type of harms	Overall Harms (%)	Overall *n*	Under age 40 Harms (%)	Age 40 and over Harms (%)
Aggression-related harms	4.9	26,731	8.0	3.1
Pushed, hit or assaulted	3.5	25,470	6.0	2.1
House, car or property vandalized	2.4	25,113	3.8	1.6
Family-related or financial harms	4.4	26,734	6.0	3.5
Family problems/ marriage difficulties	4.0	25,472	5.4	3.1
Financial trouble	1.5	25,476	2.0	1.3
Driving-related harms	5.3	25,568	9.0	3.1
Passenger with drunk driver	5.1	25,443	8.6	2.9
Traffic accident due to another drinker	0.5	25,512	0.8	0.3
Any of 3 harm areas[a]	11.2	26,744	16.8	7.8

[a]Any harm exposure indicated in each of the paired items composing the 3 harm areas.

Citation: Greenfield TK, Cook WK, Karriker-Jaffe KJ, Patterson D, Kerr WC, Xuan Z, and Naimi TS. Alcohol Clin Exp Res. 2019 Jun;43(6):1234-1243

THANK YOU!

Special thanks to:

Rachel Anderson

Cara Breeden

Judit O'Connor

Patricia Powell

Aaron White

Bridget Williams-Simmons