NIAAA Update

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

Research Society on Alcoholism
Annual Meeting
June 17, 2018
Moderate Alcohol and Cardiovascular Health Trial

“I am grateful for the review of the MACH study by the Advisory Committee to the Director, which has brought to light significant concerns about the study and its ultimate credibility.

There is a real concern as to whether the study design can address the possible negative consequences of moderate alcohol intake on diseases other than cardiovascular health and diabetes. Additionally, significant process irregularities in the development of the funding opportunities for MACH would no doubt call into question the study’s findings.

Under these circumstances, NIAAA cannot justify continuing the study. NIAAA will work with the NIH Office of the Director and the grantee institution, Beth Israel Deaconess Medical Center, to conduct an orderly closeout of the study.”
Robert Huebner, Ph.D., Acting Director of the Division of Treatment and Recovery Research, retired Dec. 31, 2017 after 31 years of federal service

- Helped develop NIAAA’s research portfolio on behavioral treatments and health services research
- Actively involved in efforts to promote evidence-based therapies for AUD
- Oversaw the development and implementation of NIAAA’s Alcohol Treatment Navigator
- Recipient of numerous awards
- Produced numerous publications on alcohol treatment

Fair winds and following seas Bob!
In 2016, 6% (14.6 million) of people 18+ reached criteria for alcohol use disorder (AUD)

• ~ 88,000 people die annually from alcohol-related causes

• ~ 50% of all liver disease deaths attributable to alcohol misuse

• Increase in the intensity of binge drinking, ED visits and hospitalizations in last 10 years

• <10% of people with AUD get any treatment and fewer than 4% receive pharmacotherapy

FY 2018 and FY 2019 Budgets

- FY 2018 Omnibus passed March 23, 2018:
  - NIH received $37 billion
  - NIAAA received $509.6 million, $27.1 million above FY 2017 enacted level

- FY 2019 budget not yet finalized—Congressional appropriations bills in development
Progress: Alcohol Policy Research

- NIAAA’s Policy Portfolio:
  - 12 active grants ($7.4 million) in FY 2014 and 18 active grants ($9.5 million) in FY 2017
  - Policy grants = 10% of the budget in Division of Epidemiology and Prevention Research in 2014 and 10% in 2017

- Program Announcement “Public Policy Effects of Alcohol, Marijuana, and Other Substance Related Behaviors and Outcomes” (Issued in 2017; NIDA and NCI also participate) to encourage more applications on policy research

- NIAAA maintains the Alcohol Policy Information System (APIS), a large searchable database of alcohol-related federal and state policies:
  - In 2018 the contract supporting APIS was renewed for 5 years
  - Marijuana policies recently added
Progress: Reducing Underage and College Drinking

- Underage and young adult harmful drinking is a major focus at NIAAA.
- Underage drinking prevention = 27 grants ($8 million) in FY 17.
- College-age drinking prevention = 47 grants ($15 million) in FY 17.
- *Alcohol Screening and Brief Intervention for Youth: A Practitioner’s Guide*
- *CollegeAIM* — Resource for helping colleges address harmful and underage student drinking.
- *National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA)* — Examines impact of alcohol on teen brain development in 831 subjects.
- *Adolescent Brain Cognitive Development (ABCD)* study — Tracks brain development of roughly 10,000 kids aged 9-10 for 10 years.

Note: Active grants include all grants except no cost extensions and supplements. In addition there were 58 grants ($39 million) in FY 17 for research on alcohol and the adolescent brain.
Brain regions where heavy drinking adolescents have steeper reductions in gray matter volume than no/low drinking adolescents

Progress: Adolescent Brain Cognitive Development (ABCD) Study

• **9,000+ participants** enrolled (target: 11,500 children)

• First curated release of ABCD study data occurred in February 2018 through the NIMH Data Archive

• Provides high-quality baseline **data from first 4,500 participants** that includes demographics, physical and mental health, substance use, culture and environment, neurocognition, and brain imaging as well as biological data such as pubertal hormone analyses

Source: Dr. Richard Watts and ABCD/Univ. of VT P.I. Dr. Hugh Garavan

MRI of adolescent brains activated during a memory task in ABCD study

https://data-archive.nimh.nih.gov/abcd
ABCD Study: Early Exposure Data

Data from first 4,500 Participants

Substance Use: Sipping Alcohol

- **Total Sips** – range 1-500 (M=4.7, SD=20)
- **Non-religious** – range 0-158 (M=2.2, SD=6.9)
  - 60% 1-2 sips
  - No Sex Difference
- **Average age of first sip** - 7.5 (range 1-10)
  - No sex difference
- 1.1% finished the drink after the first sip
- More males report either being **offered sip** or **intentionally taking sip in secret**
- More females report **accidentally taking sip**
  - Sex difference: Chi-sq=12.0, p=.002

Courtesy of Mary Heitzeg (University of Michigan)
Progress: New Fetal Alcohol Spectrum Disorders Prevalence Estimates in US Communities

Over 6,600 first grade children examined using comprehensive criteria based on facial features, growth, and neurodevelopmental performance. Prevalence estimates ranged from 1.1-5% and likely more accurate than previously reported estimates, supporting that FASD is a significant public health problem and strategies to expand screening, diagnosis, prevention, and treatment are needed.

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<thead>
<tr>
<th>Site and Sample No.</th>
<th>Sampling Method</th>
<th>Year Initiated</th>
<th>No. of Eligible Children</th>
<th>No. of Cases</th>
<th>Fetal Alcohol Syndrome</th>
<th>Partial Fetal Alcohol Syndrome</th>
<th>Alcohol-Related Neurodevelopmental Disorder</th>
<th>Total Fetal Alcohol Spectrum Disorders</th>
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<td>2010</td>
<td>2033</td>
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Estimates ranged from 11.3 – 50 cases per 1,000 children

Alcoholic Hepatitis Network: NIAAA is establishing a clinical and translational network to streamline the design, initiation, and conduct of clinical trials for alcoholic hepatitis, reduce administrative redundancy, and optimize the use of scientific innovations.

NIAAA, FDA, and the American Association for the Study of Liver Diseases hosted a 2-day workshop in March to develop recommendations for standardized definitions, variable sets, screening and assessment tools, and research and drug development procedures.
Potential AALD Targets and Drugs by Pathogenic Mechanism

IMPARED PROTECTIVE RESPONSES

- Autophagy inhibition
- ER stress and apoptosis
- Severity of steatosis, inflammation and fibrogenesis

FIBROGENESIS & CARCINOGENESIS

- Up-regulation of type I collagen
- Up-regulation of connective tissue growth factor (CCN2)

STEArosis & HEPATOTOXICITY

- Oxidative stress and JNK-MAPK activation
- Fatty acid and bile acid metabolism
- Hepatocellular death
- Metabolic-, oxidative-, and inflammatory-related stress

INFLAMMATION & STEATOHEPATITIS

- Neutrophil infiltration↑
liver-gut crosstalk
- Susceptibility of aged livers to ethanol-induced injury
- Extracellular vesicles
- Kupffer cell activation via TLR4
Progress: COGA Findings
Collaborative Studies on Genetics of Alcoholism

Neurophysiology
Endophenotypes
- GABRA2, CHRM2, GRM8, KCNJ6, CRHR1, chr 3 ~ BCHE, GABRB1, PRKG2, DSE, ZEB2, CTBP2, METTL21C, GPR153, HECTD1, LINC01029, FTO (nearest genes)

Developmental Trajectories
- GABRA2, ADH4, ADH1B, CHRM2, KCNJ6, CREM, CHRNB4

Common variants
AD-related phenotypes
- GABRA2, CHRM2, OPRK1, PDYN, NFkB1, SNCA, TACR3, C15orf53, DRD2/ANKK1, NPY2R, NPY5R, SERPINC1, PLCL1, PPAR, ABCB1, PRMT3, ABCC4, CLDN10, CDKN1A, GCOM1, MYZAP, PKD1L2 (nearest genes)

Uncommon variants
AD-related phenotypes
- CHRNA5-CHRNA3-CHRNB4, ADH1B, CHRNA6-CHRNB3

Genomics of AD & related phenotypes

Informatics, molecular & cellular studies

Neural biomarkers & neurocognitive function

Transitions to & from AUD, GxE

Genes for multiple phenotypes in blue

Informatics/Lab Studies
- iPSC (KCNJ6, CHRNA5, GABRA2)
- Expression studies (brain, LCLs)
Do the Effects of Positive and Negative Reinforcement on Alcohol Consumption Change as Individuals Develop Alcohol Dependence?

With the onset of alcohol dependence, the association between positive reinforcement and alcohol consumption became weaker, whereas the association between negative reinforcement and alcohol consumption became stronger.

Effect of positive and negative reinforcement on drinking frequency before and after onset of alcohol dependence

Positive/Negative Reinforcement: Concurrently measured using Alcohol Expectancy Questionnaire (Brown et al., 1987)

Positive: Physical and Social Pleasure subscale

Negative: Tension Reduction and Relaxation subscale

6884 observations from 2556 participants (51.6% females) of COGA Prospective Study

To assist people in finding AUD treatment, NIAAA has developed the NIAAA Alcohol Treatment Navigator℠. It is a one-of-a-kind resource that:

- Outlines the features of evidence-based AUD treatment
- Describes the varied routes to recovery
- Provides a strategy for locating qualified treatment specialists

Launched October 3, 2017

NIAAA is exploring a similar resource as well as a “core curriculum” of alcohol information for health care providers.
Progress: AUD Medications Development

- **Varenicline**: FDA approved smoking cessation drug
  - Reduced craving and drinking in study participants with AUD who had moderate to high levels of depression (Roberts et al 2017)

- **ABT-436**: Novel vasopressin receptor (V1b) antagonist
  - Increased percent of days abstinent in participants with AUD
  - Those reporting high stress responded better: decreased drinking frequency and heavy drinking days (Ryan et al 2017)

- **Oxytocin**: hormone that regulates stress and social affiliation
  - Reduced alcohol self administration in animal models (MacFayden et al 2016; King et al 2017)
  - Blocked alcohol withdrawal in human pilot study (Pedersen et al 2013)
  - Reduced alcohol craving in pilot study of anxious individuals with AUD (Mitchell et al 2016)

- **Ghrelin**: appetite-stimulating hormone
  - Increased alcohol craving and self administration in human lab paradigms (Leggio et al 2014; Farokhnia et al 2017)
  - Ghrelin receptor inverse agonist (PF-5190457) reduced alcohol craving in a preliminary human lab study (Lee et al 2018)
  - Ghrelin receptor knockout rat in development (Zallar et al 2018)
Progress: Wearable Alcohol Biosensor Challenge

• Winning prototype: **BACtrack Skyn™** submitted by **BACtrack**
  – Worn on the wrist
  – Detects alcohol in sweat
  – Continuous BAC monitoring
  – Stores data to a smartphone via Bluetooth
  – Expected to be marketed later this year

• Second place winner, **Milo**, launched Kickstarter campaign marketing their alcohol biosensor **PROOF™**; research package in development (Milo exhibiting at RSA on June 19)

• NIAAA remains very interested in biosensor technology and innovation and is continuing to support biosensor development through SBIR program
Opportunities: Investigational New Drug (IND)-enabling Development of Medications to Treat AUD and Alcohol-related Disorders (SBIR/STTR)

- Small business (SBIR) or small business and academic partner (STTR) opportunity
- **Purpose:** Translating research discoveries into new treatments for AUD or alcohol related diseases by supporting efforts to achieve an IND
- **Mechanism:** Cooperative agreement (U44/UT2) work closely with NIAAA Medication’s Development staff
- **Budget:** Up to $1.0M total costs per year for Phase I and up to $1.5M total costs per year for Phase II may be requested.

Opportunities: Understanding Processes of Recovery in the Treatment of Alcohol Use Disorder

- **Defining Recovery:** Develop comprehensive measures of recovery that reflect the multiple domains and dynamic nature of recovery

- **New and Innovative Methods to Examine Precipitants of Relapse:** Examine new and innovative methods to identify novel relapse biomarkers

- **Mutual Help and Recovery:** Evaluate the effectiveness of understudied mutual help groups (e.g., LifeRing, Women for Sobriety)

- **Extended Treatment/Interventions for AUD:** Explore the optimal timing and dose of extended AUD interventions (e.g., intensive telephone-monitoring, recovery check-ups) needed to maximize and sustain recovery

- **Recovery Systems of Care:** Evaluate the linkage of clients and families to recovery mutual aid groups and other local recovery support institutions


Opportunities: Research at Intersection of Mechanisms of Behavior Change and Recovery

• During recovery, determine specific behavioral variables and/or neurobiological factors associated with alcohol seeking and drinking behavior

• Evaluate the nature and timing of relapse episodes using advanced data collection methods (e.g., Ecological Momentary Assessment) and data analytic techniques (e.g., Dynamic Systems Modeling)

• Conduct studies that seek to identify and evaluate specific mechanisms that underlie how mutual help groups and/or continuing care/extended AUD treatments aid in recovery

• Identify and evaluate moderators of recovery (e.g., cognitive functioning; AUD symptom severity) and sustained behavior change mechanisms; evaluate moderated-mediated pathways as well as mediated pathways
Emerging Issue: Alcohol and Women’s Health

- Gaps between women and men narrowing on prevalence, frequency, and intensity of drinking, early onset drinking, AUD, drunk driving, and self-reported consequences (Slade et al., 2016; White et al, 2017)

- Women more likely to experience blackouts, liver inflammation, brain atrophy, cognitive deficits, certain cancers, and negative affect during withdrawal and stress or anxiety-induced relapse (Becker and Koob, 2016)

- Only 26% of 230 structural neuroimaging studies on substance use over 23 years evaluated sex differences (Lind et al., 2017)

- National Conference on Alcohol and Opioid Use in Women and Girls hosted by NIAAA and the Women, Drinking, and Pregnancy Work Group of the Interagency Coordinating Committee on FASD in October 2017

- Portfolio review underway to guide future research
Emerging Issue:
Adolescent Alcohol and Marijuana Use

- More drinks per drinking day predicted poorer performance on attention and executive function composites
- More frequent use of marijuana associated with poorer memory performance
- Adolescents in the substance use disorder group had lower scores on attention, memory, and processing speed composites
- Family history positive adolescents had poorer visuospatial ability
Emerging Issue: More People Aged 60+ Are Drinking and Binge Drinking

**Lifetime Abstinence**

Men: AAPC=-0.9 (p=0.41)
Women: AAPC=-1.3^ (p=0.006)

**Current Drinking**

Men: AAPC=-0.7^ (p=0.02)
Women: AAPC=-1.6^ (p=0.0001)

**Binge Drinking†**

Men: AAPC=0.9 (p=0.30)
Women: AAPC=3.7^ (p<0.0001)

AAPC = average annual percentage change; ^p<0.025; †among current drinkers.

Breslow RA, Castle IP, Chen CM, Graubard BI. Alcohol Clin Exp Res. 2017 May;41(5):976-986
AUD Facilitates Decreases in Frontal Cortex Volumes with Aging

Changes in regional brain volumes among alcohol-dependent individuals and age-matched controls, ages 25-75, were examined over a 14-year period. Alcohol-dependent individuals had significant age-related decreases in brain volumes, most prominently in the frontal cortex. Drug dependence or HCV compounded the effects.

Regional brain volumes showing decreases in 222 alcohol-dependent subjects

Age-associated declines in top-down control may interact with impairments in top-down control caused by chronic high-dose alcohol use

Emerging Issue: Sleep and Alcohol Use

- Long-term effects of low, moderate, and heavy alcohol use on sleep quality and mechanisms of alcohol-related sleep disorders

- Mechanisms of persistent sleep problems in abstinence from chronic alcohol use and as a risk factor for relapse

- Effects of prenatal and adolescent alcohol exposure on sleep patterns in later life and role in developing AUD

- Factors that may predispose people to sleep disorders and alcohol dependence and relapse, including stress, genetic variability and epigenetic modifications

- Sleep and alcohol use across the lifespan, including in adolescent and aging populations and potential reversibility of alcohol-induced sleep problems
Emerging Issue: Increase in Alcohol-Related Emergency Department Visits

- Rate of ED visits due to acute and chronic alcohol misuse up 47%, 2006-2014
- Per capita alcohol consumption increased <2%
- Alcohol-related ED visits increased from 3,080,214 to 4,976,136
- Increases were larger for women and older drinkers

Emerging Issue: Extreme Binge Drinking

Binge drinking – 4+ drinks for women, 5+ drinks for men, on an occasion

Extreme binge drinking – consuming 2 or more times these thresholds
• Nearly 32 million adults engaged in extreme binge drinking

NIAAA is forming a working group of external experts to better understand the social and cultural determinants of extreme binge drinking to inform the development of improved interventions.

Emerging Issue: Alcohol and Opioids: A Dangerous Combination for Overdose Deaths

Alcohol involved in ~15% of cases

Source: CDC-WONDER, Multiple Cause of Death Data
Alcohol Reduces Pain Sensitivity at Doses that Exceed Low-Risk Drinking

Meta-analysis of 18 controlled experiments comparing pain in people given alcohol versus no-alcohol

- Findings support the pain reducing effects of alcohol
- A mean BAC of ~0.08% (legal driving limit) produced a small elevation in pain threshold and a significant reduction in pain intensity
- Higher BAC is associated with greater pain insensitivity
- These effects could explain alcohol misuse in those with persistent pain despite its potential consequences for long-term health

Increased Pain Sensitivity in Alcohol Withdrawal

Emerging Issue: NIAAA Data Sharing Policy

Federal Guide Notice:
Notice of Data-Sharing Policy for Human Subjects Grants Research Funded by NIAAA (NOT-AA-18-010)

- **New policy:** NIAAA will expect prospective grant applicants (PIs/Institutions) to provide basic plans for submitting grant-related human subjects data to a NIAAA-sponsored data repository.

- **Exempt from policy:** Fellowship (F), Training (T), Small Business (SBIR/STTR), Education (R25) grants.

- **Effective implementation date:** All NIAAA applicable applications submitted after January 25, 2019.

- **NIAAA Point of Contact:** Dr. Daniel Falk (falkde@mail.nih.gov).

- **RSA info/training session:** Tuesday, 11am-1pm, Harbor I
- **RSA booth:** Sun-Wed, “NIMH Data Archive”
- **Training webinars:** Summer 2018 (ongoing)
Thank You!

Special thanks to:

Lori Ducharme
Brett Hagman
Jennifer A. Hobin
Dan Falk
Patricia Powell
Soundar Regunathan
Megan Ryan
Aaron White
Bridget Williams-Simmons
Percentile to Which Early Stage Investigator (ESI) Applications Were Funded
**Training in Advanced Data Analytics for Behavioral and Social Sciences**

- Notice of Intent to Publish a Funding Opportunity Announcement: *Predoctoral Training in Advanced Data Analytics for Behavioral and Social Sciences Research (BSSR) - Institutional Research Training Program (T32) program*

- NIAAA will support training in advanced data analysis and computational modeling to improve our understanding of risky and hazardous drinking and related behaviors and interventions

- Estimated FOA Publication Date: **October 16, 2018**

- Estimated Application Due Date: **May 25, 2019**

- Federal Guide Notice: **NOT-OD-18-174**

- NIAAA Point of Contact: Dr. Daniel Falk ([falkde@mail.nih.gov](mailto:falkde@mail.nih.gov))
Mary Jeanne Kreek: Scientist, Scholar, Clinical Researcher, Pioneer, Role Model, and Friend

Scientist: identified the role of the endogenous opioid system in drug addiction at the molecular, genetic and neurocircuitry levels of function

Scholar: Early on hypothesized allostatic changes in the pituitary and brain stress systems that drive and perpetuate addiction.

Clinical researcher: one of the first to indentify parenteral drug users as the second risk group for acquiring HIV-1/AIDS infection

Pioneer: performed the initial studies of the use of a long-acting opioid agonist, methadone, in chronic management of heroin addiction.

Role Model: won an Assistant Professorship at Rockefeller University in 1967 and a Full Professorship in 1994 providing a role model for women neuroscientists everywhere.

MJK and GFK with Eric Simon at the 5th Anniversary of the Irene and Eric Simon Brain Research Foundation meeting November 4, 2009