



WHAT CAN SCIENCE TELL US ABOUT THE DIAGNOSIS, PREVENTION AND TREATMENT OF ALCOHOLISM?

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Acknowledgements



National Institute on Alcohol Abuse and Alcoholism

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University of Maryland, Baltimore County

Dr. Karl Steiner, PhD – *Vice President for Research*

Dr. Don Engel, PhD – *Asst Vice President for Research*

Attendees

Flow of the presentation



- What is addiction?
 - Current understanding of how addiction to alcohol develops
 - How does NIAAA facilitate research on addiction prevention, treatment and recovery?
 - NIAAA budget and allocation of funds across areas
 - Current funding opportunities
 - Looking forward
-

What is addiction?



Alcohol Use Disorder (AUD) — The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) defines AUD as a problematic pattern of alcohol use leading to clinically significant impairment or distress. AUD may be categorized as mild, moderate, or severe depending on the number of diagnostic criteria a patient meets.

Alcohol Addiction — A severe form of AUD, defined as a chronically relapsing disorder that is characterized by a compulsion to seek and drink alcohol, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) in the absence of alcohol.

DSM-5 AUD is common in the US

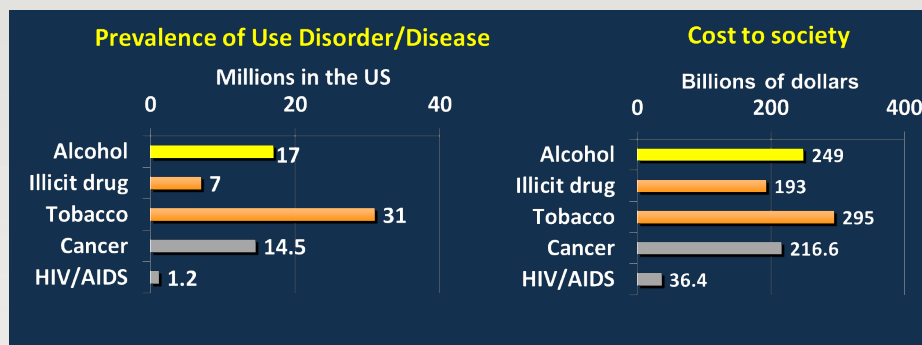


US population 18+	2012-2013 NESARC III
DSM-5 12-month AUDs	13.9%
DSM-5 Lifetime AUDs	29.1%
Past year drinking of at least 5 drinks/ day	39.6%
Past year drinking of at least 8 drinks/ day	20.8%
Past year drinking of at least 10 drinks/ day	15.5%

Few people get help. Only 8 out of 100 (7.7%) who met AUD criteria in the previous year got help during that period and 20 out of 100 (19.8%) got help at some point in their lives.

Source: Grant, BF et al JAMA Psychiatry online June 3, 2015.

Excessive drinking in the US is quite costly



Sources: Prevalence – NSDUH (2014), NCI (2014), CDC (2012); Cost – CDC (2015), National Drug Intelligence Center - National Drug Threat Assessment (2011), 2014 Surgeon General's Report, NHLBI (2012), Hutchinson et. al. 2006.

Alcohol causes considerable harm worldwide

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Global status report on alcohol and health 2014



CHAPTER 3: HEALTH CONSEQUENCES

- In 2012, about 3.3 million deaths, or 5.9% of all global deaths, were attributable to alcohol consumption.
- There are significant sex differences in the proportion of global deaths attributable to alcohol, for example, in 2012 7.6% of deaths among males and 4.0% of deaths among females were attributable to alcohol.
- In 2012 139 million DALYs (disability-adjusted life years), or 5.1% of the global burden of disease and injury, were attributable to alcohol consumption.
- There is also wide geographical variation in the proportion of alcohol-attributable deaths and DALYs, with the highest alcohol-attributable fractions reported in the WHO European Region.

WHO Global Status Report Alcohol and Health, 2014
http://apps.who.int/iris/bitstream/10665/112736/1/9789240692763_eng.pdf

Big questions

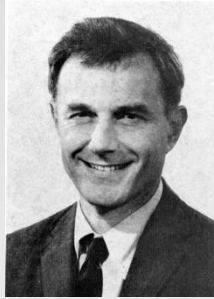
Why does it happen?

How does it happen?

What do we do about it?



We have come a long way since the discovery of the reward system

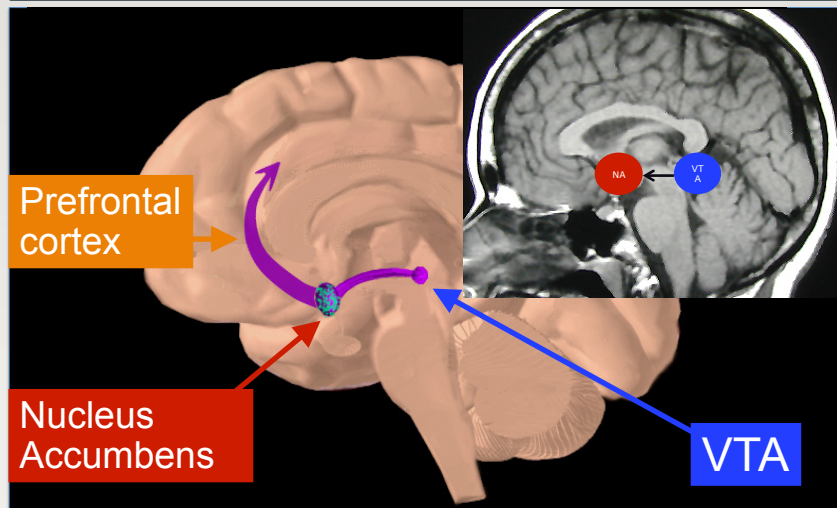


Jim Olds
(1922-1976)

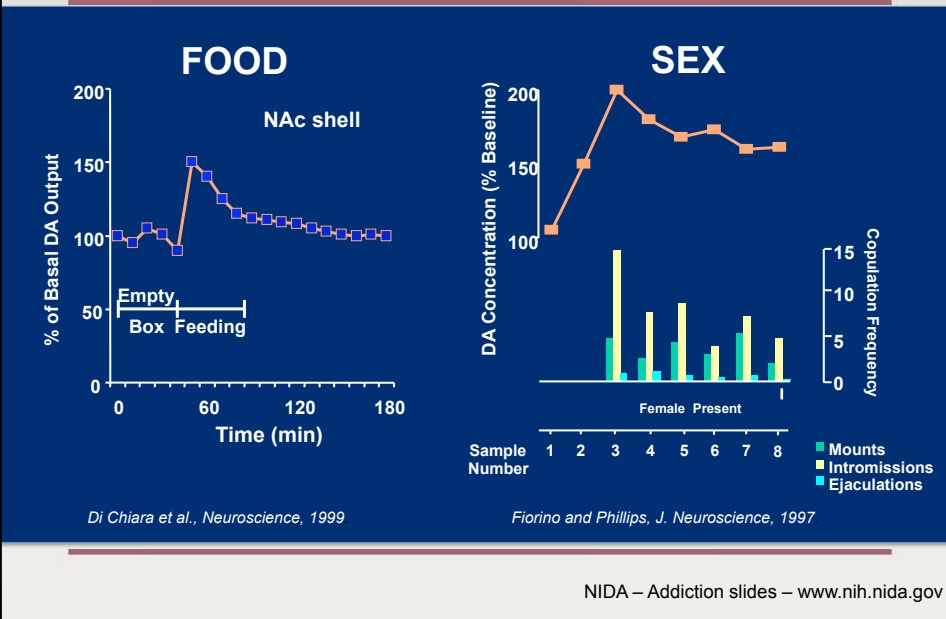


The reward system

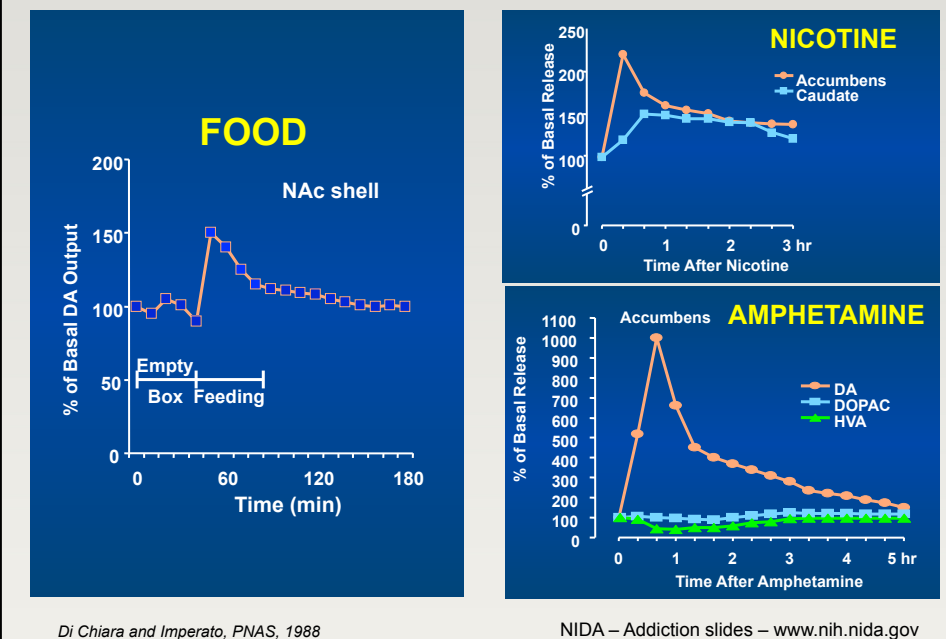
The reward system was discovered to include two main brain areas – the Nucleus Accumbens and the Ventral Tegmental Area (VTA)



Natural rewards increase dopamine levels in the Nucleus Accumbens

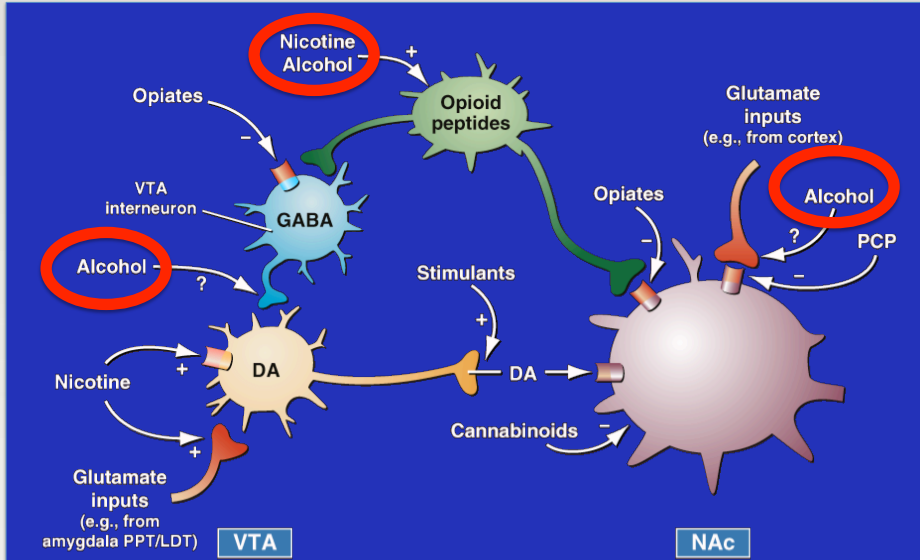


Drugs increase dopamine levels more than natural reinforcers



Reinforcement does not happen through dopamine alone

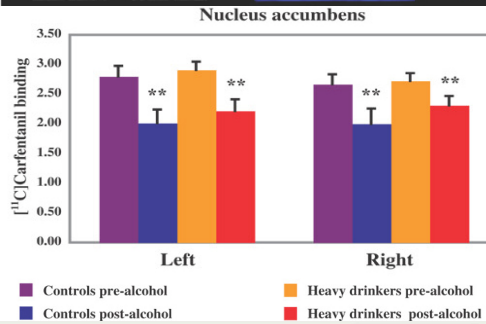
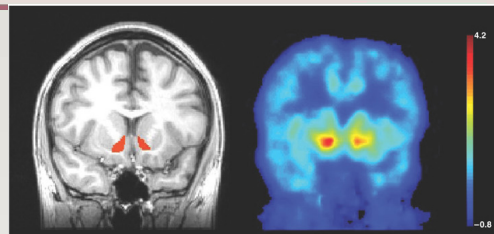
NIH National Institute on Alcohol Abuse and Alcoholism



From: Koob GF. Neurocircuitry of alcohol addiction: synthesis from animal models. In: Sullivan EV, Pfefferbaum A (eds) Alcohol and the Nervous System (series title: Handbook of Clinical Neurology, vol. 125). Elsevier, Amsterdam, 2014, pp. 33-54.

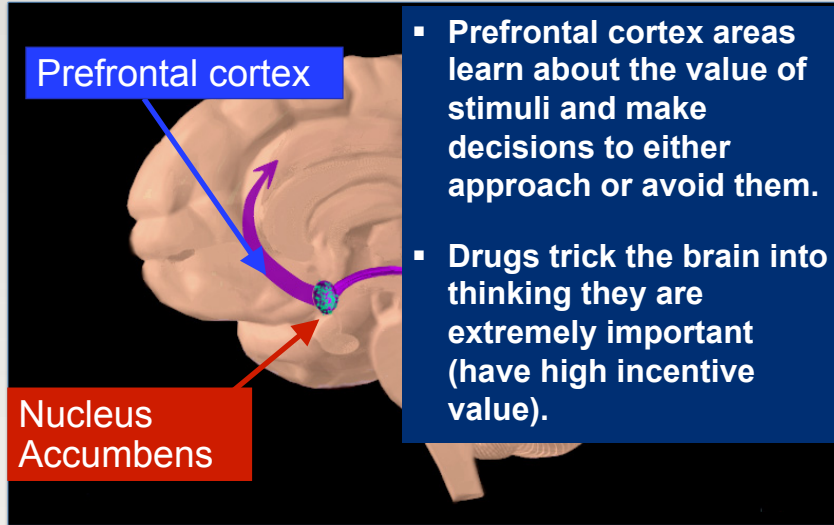
Alcohol increases opioid release in the Nucleus Accumbens

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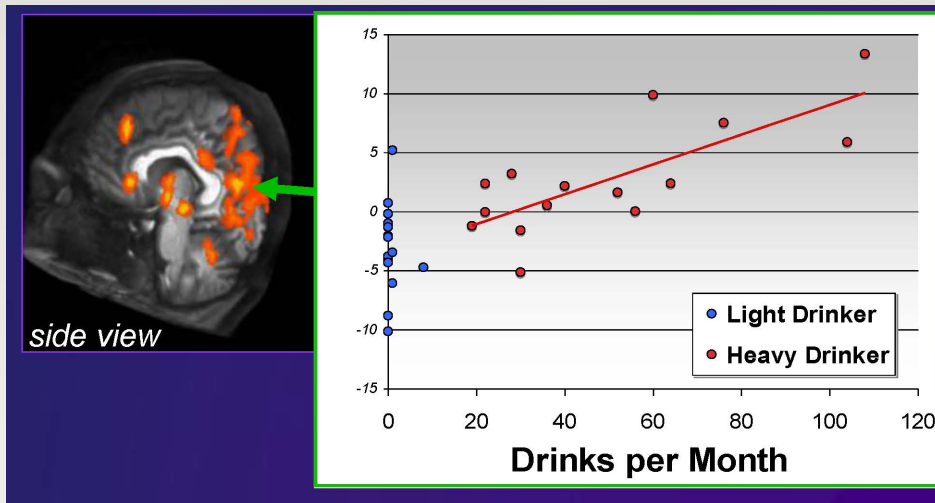


From: Mitchell JM, O'Neil JP, Janabi M, Marks SM, Jagust WJ, Fields HL. *Sci Transl Med*. 2012, 4:116ra6.

Dopamine – Less about pleasure more about attaching high incentive value to drug cues



Heavy drinking teenagers show strong response to alcohol cues



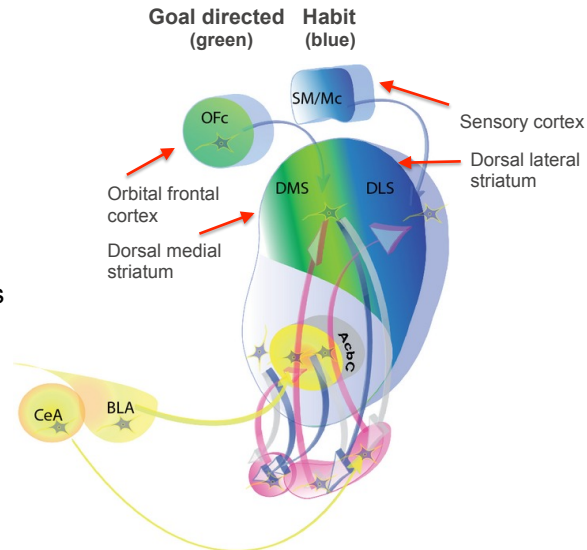
Tapert et al, 2003, Archives of General Psychiatry.

Shift from goal directed drug use to habitual drug use and loss of control

Transition in brain from goal directed to habit circuits facilitates the emergence of compulsivity.

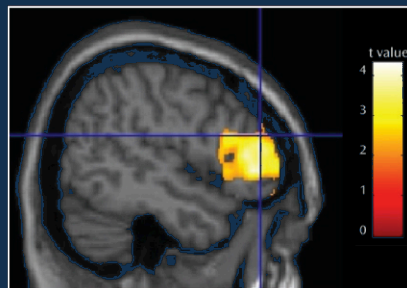
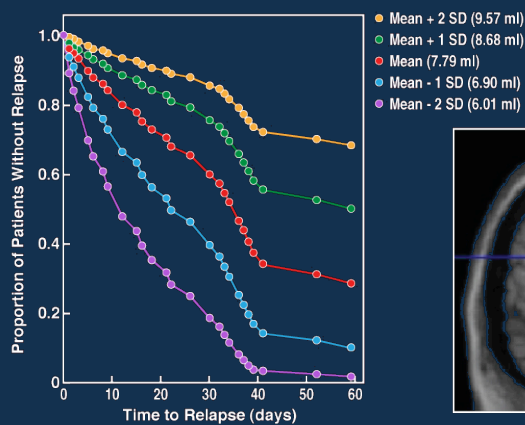
Progressive decrease in inhibitory control by prefrontal cortical areas over drug seeking behavior.

Furthered by damage to frontal lobe circuits following prolonged alcohol use.

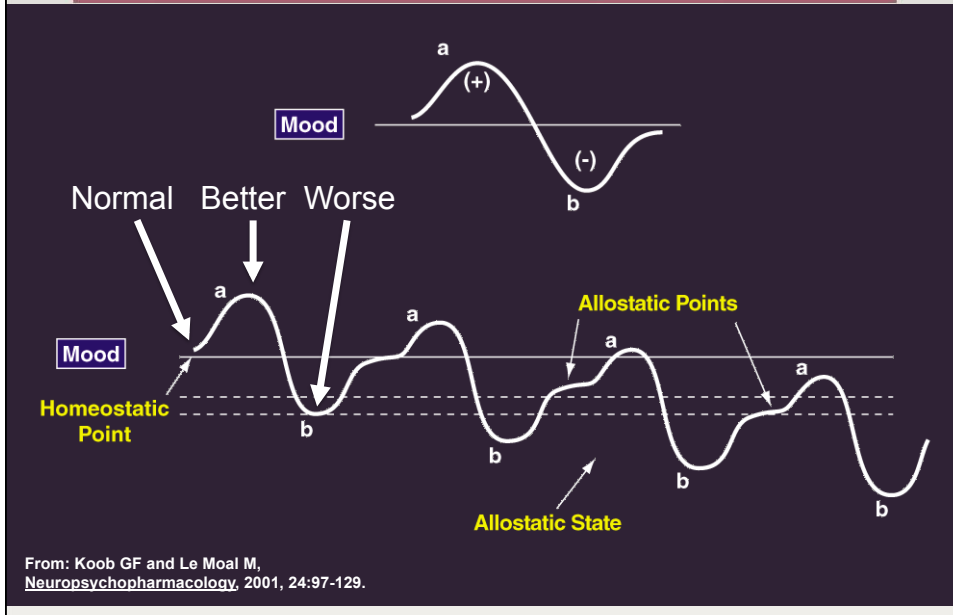


From: George O. Koob GF. Proc Natl Acad Sci USA, 2013, 110:4165-4166; Barry J Everitt. Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories – indications for novel treatments of addiction. Eur J Neurosci. 2014, 40(1): 2163–2182.

Gray matter reduction in the frontal lobes of alcohol dependent patients predicts time to relapse

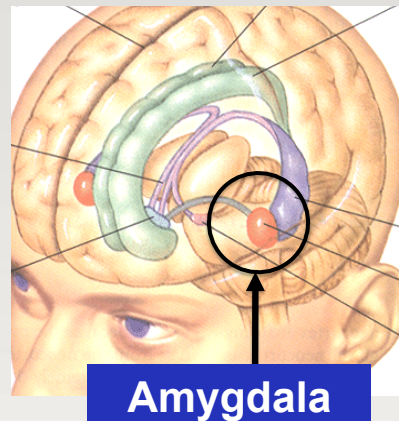


The dark side -- Shift from producing pleasure to reducing discomfort as addiction develops



The amygdala – Headquarters of the dark side!

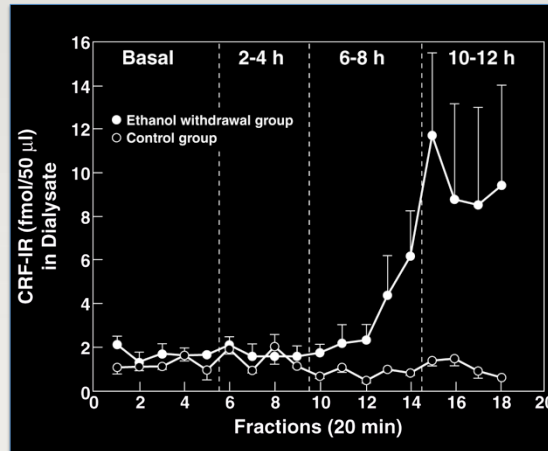
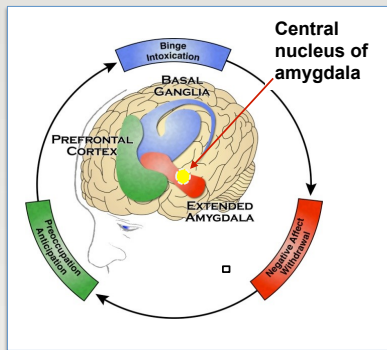
- Activation of some areas of amygdala causes fear and anxiety.
- Alcohol initially decreases activity in amygdala.
- Because of tolerance the amygdala becomes overactive during withdrawal
- Leads to negative affect and drive to use again.
- Key player in the dark side of addiction.



Koob GF. The dark side of emotion: the addiction perspective. *Eur J Pharmacol*. 2015 Apr 15;753:73-87

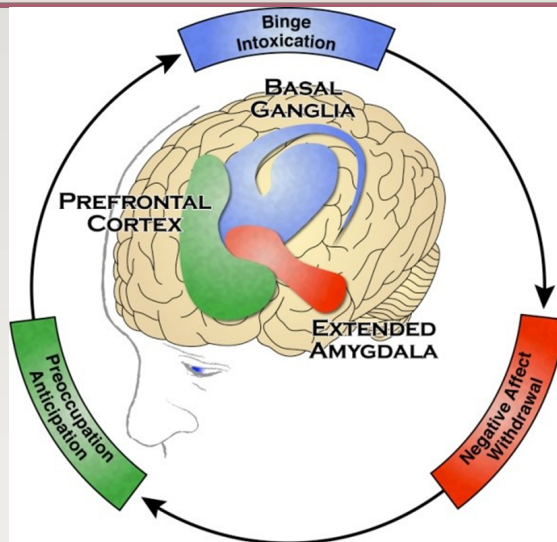
Alcohol withdrawal increases CRF levels in the amygdala and increases sympathetic nervous system activity

Corticotropin releasing factor (CRF) in the amygdala triggers anxiety



From: Merlo-Pich E, Lorang M, Yeganeh M, Rodriguez de Fonseca F, Koob GF and Weiss F, *J Neurosci*, 1995, 15:5439-5447.

Locked in a cycle



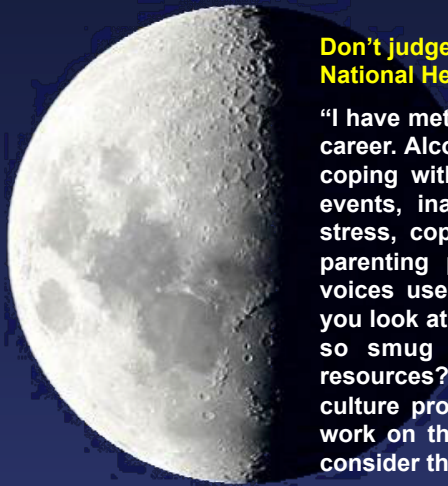
From: Koob GF. Theoretical frameworks and mechanistic aspects of alcohol addiction: alcohol addiction as a reward deficit disorder. In: Spanagel R, Sommer W (eds) *Behavioral Neurobiology of Alcohol Addiction* (series title: *Current Topics in Behavioral Neuroscience*, vol 13), Springer, New York, pp 3-30.

How does understanding the neurobiology help us prevent and treat alcoholism?



- Drug development – Beyond blocking euphoria
- Supports need for prevention efforts to delay the onset of drinking – Rapid learning during adolescence leads to strong incentive salience
- Suggests that simply staying sober might not be enough – Recovery needs to involve learning new strategies for both positive and negative reinforcement
- Supports the use of mindfulness and other stress reduction techniques in treatment and recovery
- Helps explain high comorbidity between AUD and PTSD
- Helps remove the stigma that addicts are only seeking pleasure

The Dark Side of Alcohol Addiction



Don't judge people who drink alcohol and end up in National Health Services (NHS).

"I have met many people from all walks of life in my career. Alcohol is often an emotional prop, a way of coping with pain, harm, sexual assault, traumatic events, inability to find the words to talk about stress, coping with financial pressure, family life, parenting pressure, death. Individuals who hear voices use alcohol to self-medicate. So next time you look at the person getting drunk, should you be so smug as to judge them as wasting NHS resources? Or should you think differently? Our culture promotes drinking for fun and we need to work on that. But let's look a little bit deeper and consider this more."

Sarah Johnson, The impact of alcohol on the NHS: 'We get the drunks in 24/7,' The Guardian, January 22, 2016.

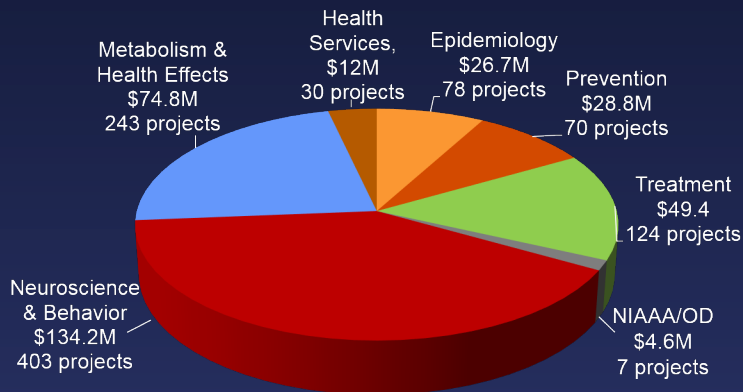


National Institute
on Alcohol Abuse
and Alcoholism

NIH...Turning Discovery Into Health®

What is NIAAA doing to facilitate our understanding of the diagnosis, treatment and prevention of AUD?

NIAAA Extramural Grant Portfolio, FY 2015 Total Funding \$330M, 960 projects



NIAAA Trans-Divisional Research Emphasis Areas

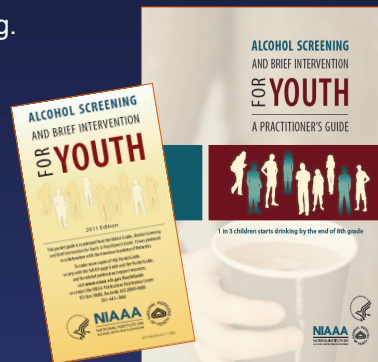
- Biomarkers
- Fetal Alcohol Spectrum Disorders
- Genes and Environment
- Health Disparities
- HIV and AIDS
- Systems Biology
- Medications Development
- International Research
- Mechanisms of Behavior Change
- Underage Drinking



Screening & Brief Intervention for Youth

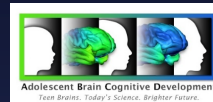
NIAAA Alcohol Screening Guide

- A brief, easy to score, empirically-based screen for risk, alcohol use, and problems that overcomes time constraints and other common barriers to youth alcohol screening.
- It is based on just two questions – one about **friends' drinking** and the other about **personal drinking frequency**. Analysis of data from more than 160,000 youth indicated these questions had the greatest predictive power.
- The Guide is endorsed by the **American Academy of Pediatrics**.
- A **Medscape course** provides training on using the guide – **CME credit** is available – to date over 24,000 clinicians have been Medscape certified.



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Adolescent Brain Cognitive Development (ABCD) Study



- In September 2015, NIH launched the **ABCD Study**.
- ABCD is the **largest long-term study** of cognitive and brain development in children in the U.S. to date.
- ABCD is recruiting **10,000 healthy children ages 9-10 and following them over 10 years into early adulthood**.
- ABCD investigators will **measure brain maturation** in the context of social, emotional, and cognitive development at a level of precision that has only recently become possible. Investigators will look at **multiple health outcomes** including alcohol and drug use, mental health, weight, growth, sleep quality, injury, and other life experiences such as driving a car, academic success, and physical activity.
- Findings from ABCD are expected to increase our ability to distinguish environmental, sociocultural, and genetic factors relevant to brain and cognitive development, in order to inform prevention and treatment intervention and public health strategies.

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College Alcohol Intervention Matrix

COLLEGEAIM

- Binge drinking and high intensity drinking remain significant problems among college students.
- In response to a request from its College Presidents Working Group, NIAAA engaged top researchers in the field to develop an interactive, user-friendly decision tool to help colleges and universities select appropriate strategies to meet their alcohol intervention goals.
- CollegeAIM allows users to search for individually and environmentally-oriented interventions according to their levels of effectiveness, their relative costs, and barriers to implementation, as well as other parameters.



Rethinking Drinking

RETHINKING
DRINKING
Alcohol & your health

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DO YOU KNOW:

**THE SIGNS
THAT ALCOHOL
IS CAUSING
HARM?**



NIAAA Medications Development Program

In 2015 NIAAA established the **Division of Medications Development** to coordinate extramural efforts to identify, screen, and evaluate compounds for treating AUD.



- **Human laboratory screening studies** to bridge the gap between preclinical and clinical trials
- **SBIR/STTR program** to bridge the “valley of death” between basic and clinical research by facilitating studies leading to the development of an IND application to the FDA
- **NIAAA Clinical Investigations Group (NCIG)** to streamline the AUD medications development process by conducting “fast success/fast fail” phase II clinical trials, with a turn-around time of 18 months
 - launched a clinical trial of gabapentin in June 2015

NIAAA’s intramural program also conducts clinical studies on novel compounds with AUD treatment potential.

NIAAA also focuses on **disseminating information about treatment options including medications** to health professionals and the general public.



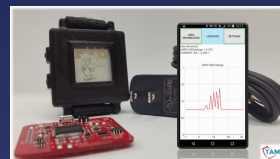
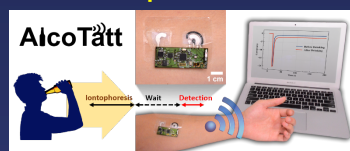
2015 NIAAA Alcohol Biosensor Challenge

- For the design and production of a wearable device to monitor blood alcohol levels in real time.
- Useful in research, clinical, and treatment settings and for individual health monitoring.

The contest:

- 8 entries from existing businesses, academic teams, and individual entrepreneurs
- Different approaches, e.g. wristbands, temporary tattoos, accessories
- Winner -- **BACtrack Skyn**. Worn on the wrist and uses fuel cell technology to detect alcohol.

Examples of entries:



Additional NIAAA Research Priorities

- **Recovery from AUD** – What are the individual and environmental factors that facilitate recovery? What happens in the brain during recovery? What about long term recovery?
- **Alcohol Addiction Research Domain Criteria (AARDoC)** – Framework for classifying individual differences in AUD based on phenotypes corresponding to an individual's disorder.
- **Sex differences** – Understanding sex differences in the development, progression and treatment of AUD.
- **Aging** – More research is needed to understand how alcohol differentially affects older individuals, e.g. increased sensitivity to alcohol, medication interactions.
- **Integrate addiction medicine training in primary care and preventive care and develop an addiction core curriculum for medical student training** through collaborations with professional organizations and other stakeholders.



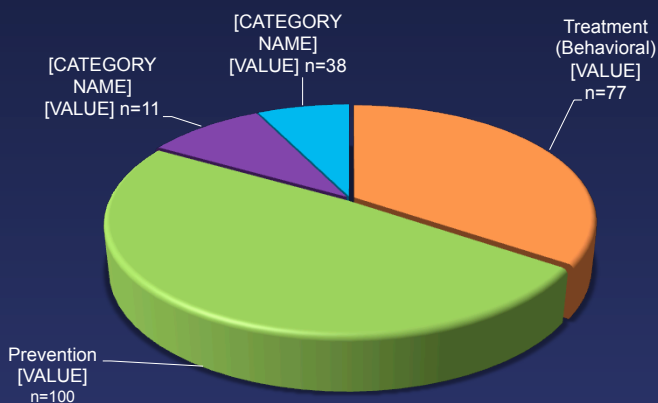
Additional NIAAA Research Priorities

- **Comorbidities** – NIAAA is seeking to better understand the relationship between AUD and PTSD, and to develop interventions to prevent and treat these disorders including
- **Liver disease** – NIAAA supports basic and translational research on the pathogenesis of alcoholic liver disease and is exploring novel therapeutic targets for treatment.
- **Health services research** – Research on implementing Screening and Brief Intervention (SBI) in primary care, emergency departments and hospitals, increasing use of meds in primary and specialty care.
- **Effective prevention** – Drinking during pregnancy, alcohol and HIV, adolescent and young adult drinking



Behavioral Intervention Grants at NIAAA

Funding Level = \$88,049,087, N=226



Note: FY 2015; funding level includes HIV/AIDS funds. Health Services grants not included.

NIAAA Funding Opportunities



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Grant Funding



How to apply for grants funded by NIAAA and manage existing grants

NIAAA funds wide-ranging extramural grants for research and training projects on alcohol abuse, alcohol dependence, and other health effects of alcohol. The vast majority of NIAAA's budget is devoted to supporting extramural research.

Funding Opportunities

NIAAA's requests for applications (RFAs), program announcements (PAs), and other funding opportunity announcements

Application Process

Applying for extramural grants and understanding how applications are reviewed and selected for funding

Management & Reporting

Grants management information for grantees and administrators

NIAAA-funded grants

A complete list of NIAAA-funded extramural grants is available from the NIH RePORTER database. Going back to 1988, the database includes research summaries and other information about each grant.

<http://www.niaaa.nih.gov/grant-funding>

Current funding opportunities



Grant Mechanisms

http://grants.nih.gov/grants/funding/funding_program.htm

PA – Program Announcement

http://grants.nih.gov/grants/guide/search_guide_results.htm?Text_Curr=&PrimaryIC=NIAAA&ParticipatingIC=&Status=Active&DocType=PA&List%20Order1%20=DocNum&ListOrder2=None

RFA – Research Funding Announcement

http://grants.nih.gov/grants/guide/search_guide_results.htm?Text_Curr=&PrimaryIC=NIAAA&ParticipatingIC=&Status=Active&DocType=RFA&List%20Order1%20=DocNum&ListOrder2=None

Two things to consider regarding grant proposals

“What do you know once you know that?” (from Floyd E. Bloom, Professor Emeritus, The Scripps Research Institute, Editor Emeritus Science Magazine)

“Before submitting any grant application to NIAAA, please call your program officer” (from George F. Koob, Director NIAAA)

NIAAA: The Source for Credible Research Information on Alcohol Across the Lifespan



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Thank you!