NIAAA Update: Focus on Medications Development Program to Treat Alcohol Use Disorder (AUD)

Dan Falk, Ph.D.
Branch Chief
Medications Development Branch, NIAAA

American Society of Clinical Psychopharmacology
Miami, FL, May 28, 2026

National Institute on Alcohol Abuse and Alcoholism

No conflicts of interest

NIAAA Mission

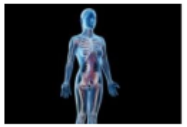
- Mission: To generate and disseminate fundamental knowledge about the adverse effects of alcohol on health and well-being, and apply that knowledge to improve diagnosis, prevention, and treatment of alcohol-related problems, including alcohol use disorder, across the lifespan.

https://grants.nih.gov/funding/find-a-fit-for-your-research/nih-institutes-centers-offices/NIAAA

NIAAA – Strategic Plan (FY 24-28)

Research Goals

The strategic plan's four major research goals cover the depth and breadth of research necessary to improve the understanding of and to address the effects of alcohol misuse on individuals and society.



Goal 1: Elucidate the Biological Mechanisms and Consequences of Alcohol Misuse

NIAAA aims to advance research on the brain cells and circuits that underlie and are altered by alcohol misuse, and the complex relationships between alcohol misuse and physiological effects throughout the body.

Goal 2: Identify Patterns, Trends, and Public Health Impact of Alcohol Misuse

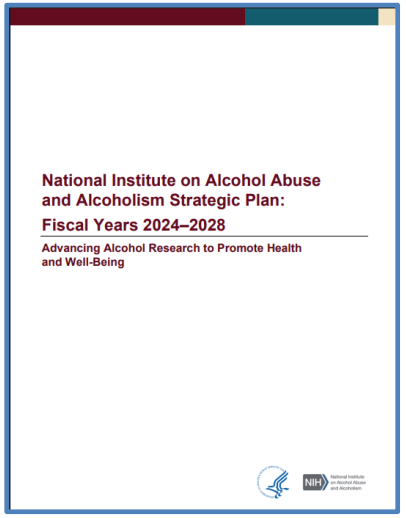
NIAAA will continue to support epidemiological research to identify and track patterns of alcohol use and misuse, drinking-related outcomes and disparities, and individual and environmental variables that confer risk or resilience.

Goal 3: Prevent and Reduce Alcohol Misuse, Alcohol Use Disorder, and Associated Consequences

NIAAA encourages the development, evaluation, and implementation of individual, family, school, community, and policy-based strategies to prevent alcohol misuse, alcohol use disorder, and related consequences.

Goal 4: Improve Diagnosis and Expand Treatment of Alcohol Use Disorder and Alcohol-Related Conditions

NIAAA encourages research to refine diagnosis, enhance treatment, sustain recovery, and ultimately, to reduce the treatment gap for alcohol use disorder and other alcohol-related health conditions.



https://www.niaaa.nih.gov/about-niaaa/strategic-plan-fiscal-years-2024-2028

NIH National Institute on Alcohol Abuse and Alcoholism

NIAAA Extramural Scientific Divisions

Treatment & Recovery (DTR)

- Medications Development
- Behavioral therapies
- Health Services
- Recovery processes
- Innovative tech to improve treatment outcomes & support recovery

Neuroscience & Behavior (DNB)

- How neuronal and behavioral systems are influenced by genetic, developmental, and environmental factors in conjunction with alcohol exposure to engender alcohol use disorder.

Epidemiology & Prevention (DEPR)

Epi & prevention of:

- Hazardous alcohol consumption and related behaviors
- Alcohol use disorder
- Alcohol-related mortality, morbidity, consequences

Metabolism & Health Effects (DMHE)

- Alcohol Metabolism
- Alcohol-Induced Tissue Damage & Disease
- Fetal Alcohol Spectrum Disorders

Cross-Cutting Themes: Improving alcohol health outcomes by utilizing data science and multi-omics techniques, addressing the impact of alcohol use at different life stages and in women, and encouraging a whole-personal health approach.

NIH National Institute on Alcohol Abuse and Alcoholism

Alcohol Use Disorder (AUD)

- 27.9 million Americans, ages 12 and older, suffered from AUD in the past year (9.7%)
- 178,000 annual alcohol-related deaths
- Alcohol misuse costs $249 billion (U.S., 2010)
- AUD is a complex, heterogeneous disorder
- No single treatment intervention works for all
- Advances in developing medications with multiple targets

FDA-Approved Medications for Alcohol Dependence

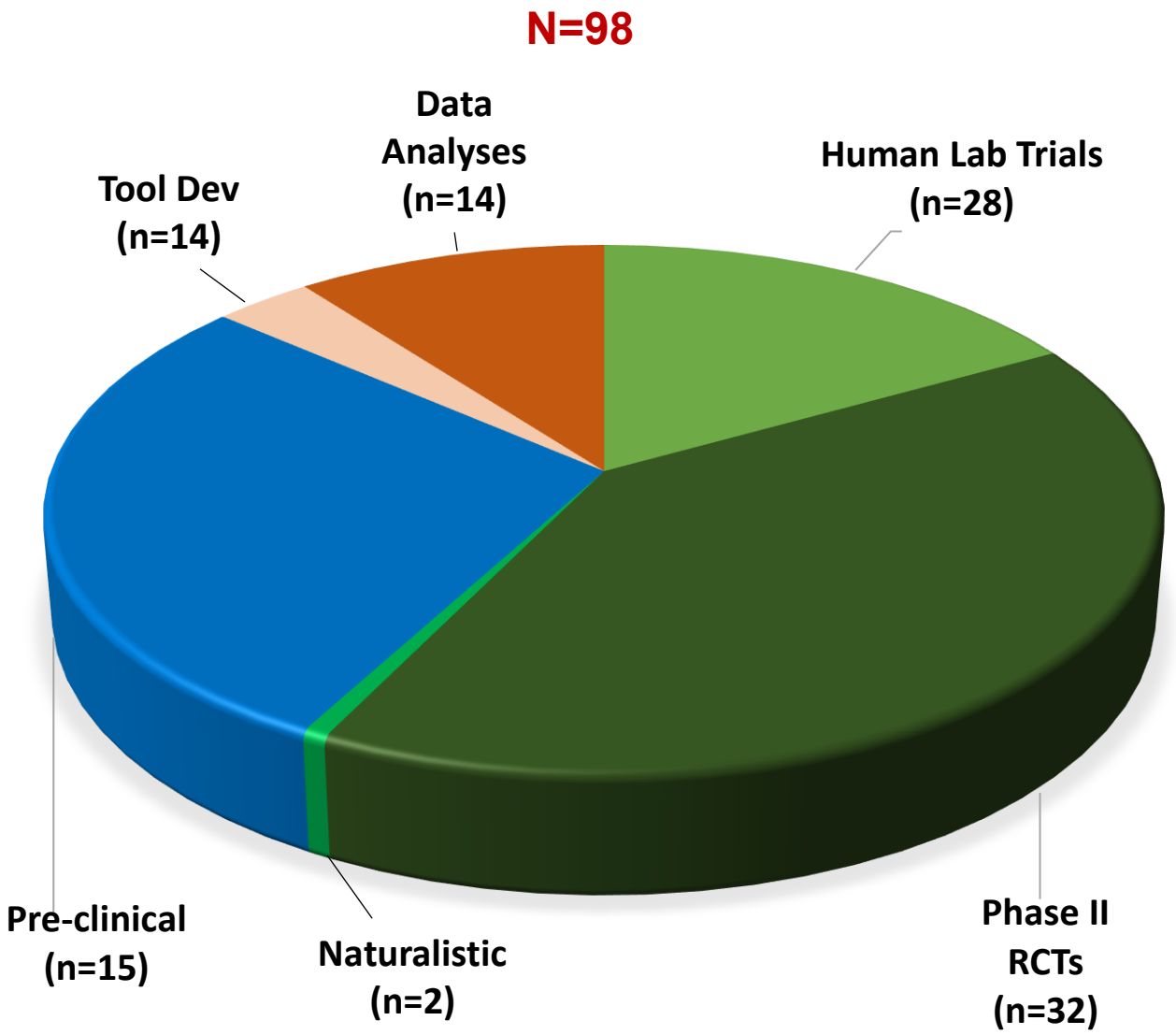
Medication	Target
Disulfiram (Antabuse®)	Aldehyde dehydrogenase 1951
Naltrexone (Revia®, Depade®)	Opioid receptor 1994
Acamprosate (Campral®)	Glutamate modulator 2004
Extended-release naltrexone (Vivitrol®)	Opioid receptor 2006

Promising Medications to Treat AUD

Medication	Target
semaglutide	GLP-1 agonist
nalmefene (approved Europe)	opioid antagonist
baclofen (approved France)	$GABA_B$ agonist
varenicline	Partial nicotinic α4β2 agonist, α7 agonist
topiramate	↑ GABA, ↓AMPA & Kainate, ↓ Ca^{++} & Na^{+} channels
zonisamide	↑ GABA, ↓ Ca^{++} & Na^{+} channels
gabapentin	Ca^{++} channel inhibitor, GABA modulator
ondansetron	$5\text{-}HT_3$ inhibitor
oxytocin	oxytocin receptor agonist
prazosin/doxazosin	α-1 adrenergic antagonist
mifepristone	glucocorticoid antagonist

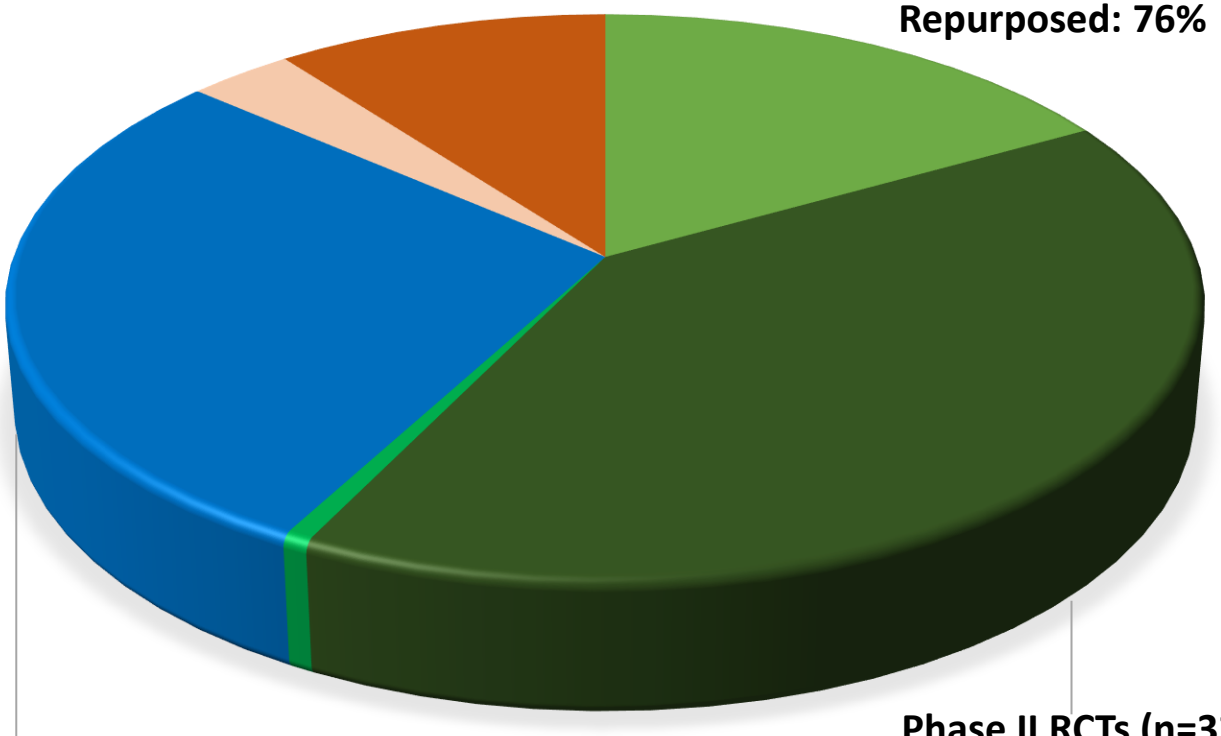
Litten et al., *Substance Abuse* 37:286-298, 2016 and Litten et al. *Handbook of Experimental Pharmacology* online

Grant Portfolio:
NIAAA Medications Development Branch



Note: %'s based on number of grants in category; FY 20-24

Grant Portfolio:
NIAAA Medications Development Branch



Human Lab Trials (n=28)
Novel: 24%
Repurposed: 76%

Pre-clinical (n=15)
Novel: 100%
Repurposed: 0%

Phase II RCTs (n=32)
Novel: 18%
Repurposed: 82%

Note: %'s based on number of grants in category; FY 20-24

NIAAA Medications Development: Six Priority Areas

1. Identify more effective druggable targets
2. Develop screening models that predict high probability of clinical efficacy and safety
3. Engage pharma/biotech companies in medications development for AUD
4. Develop new endpoints for AUD pharmacotherapy trials
5. Advance precision medicine
6. Facilitate the use of alcohol treatment medications in clinical practice

NIAAA Medications Development: Notice of Funding Opportunities (NOFOs)

Alcohol Treatment, Pharmacotherapy, and Recovery Research (Clinical Trial Required) *Expires Sept 8, 2026

- PA-25-163: **R01**
- PAR-25-193: **R34 (Planning grant)**

Medications Development:

- AUD pharmacotherapy trials (efficacy, safety)
- Evaluate predictors of treatment response (precision medicine)
- Develop and evaluate new human laboratory paradigms

Translational Research
Innovative Methods and Technologies
Behavioral Therapies
Recovery from AUD
Special populations (Health Disparities, Psychiatric Comorbidity, Women, Youth)

Medications Development: Highlighted Topic

Novel Targets, Methods, and Pharmacological Approaches to Treat Substance Use Disorder

- Identify novel targets and molecular pathways involved in the etiologies of SUD and the factors that impact trajectories of relapse and recovery.

- Omics, computational/AI approaches

NIAAA's Small Business Program

Small Business Innovation Research (SBIR)
Small Business Technology Transfer Research (STTR)

Don't miss out on this funding opportunity!

NIAAA's SBIR/STTR program provides non-dilutive funding to advance the development and commercialization of innovative products and treatments for the healthcare market. The program supports both grants and contracts, along with technical assistance and entrepreneurial resources, for solutions aimed at preventing, diagnosing, and treating alcohol use disorder (AUD) and related problems.

Fuel innovation, reduce risk, and accelerate your path from idea to impact

- **None-dilutive funding**
- **Early-stage support**
- **Flexible funding path**
- **Access to expertise/technical assistance**
- **Retention of intellectual property**
- **Mission-driven impact**
- **Attracts investors**

Who should apply?

For-profit U.S. small businesses with 500 or fewer employees

Learn more here!

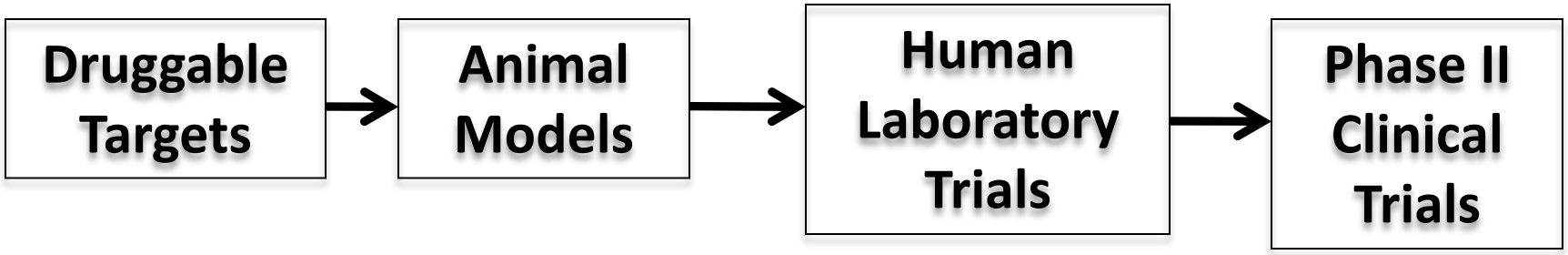
For more information, contact NIAAA SBIR/STTR Team at niaaasbirsttr@mail.nih.gov.

The SBIR and STTR programs were reauthorized on April 13, 2026. Currently, NIH has no active SBIR or STTR Notices of Funding Opportunity (NOFOs). Future NOFOs are forecasted at Grants.gov prior to opening for applications. The next standard receipt date is September 5, 2026.

NIH National Institute on Alcohol Abuse and Alcoholism

Special Initiatives
Focus: Pharma Partnership

Drug Development Pipeline

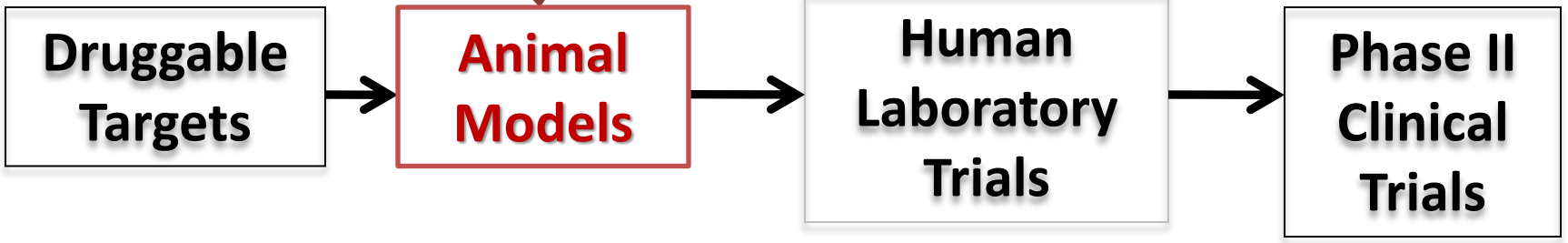


Promising Targets for AUD

- glucagon-like peptide 1 (GLP-1) agonist
- serotonin 2A receptor agonist
- vasopressin 1B receptor antagonist
- hypocretin (orexin) receptor antagonist
- nociception/orphanin FQ (NOP) receptor antagonist
- kappa opioid receptor antagonist
- corticotropin releasing factor (CRF)1 antagonist
- glucocorticoid receptor antagonist
- glutamate NMDA modulator
- cannabinoid receptors
- potassium channel activator
- nicotinic $\alpha 3\beta 4$ partial agonist and $\alpha 7$ positive allosteric modulator
- phosphodiesterase 4b inhibitor
- $GABA_A$ receptor modulator
- $GABA_B$ receptor agonist
- actin cytoskeleton (ACTB) modulator
- histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibitors
- adrenoceptor beta antagonist
- agmatinase inhibitor

NIAAA Preclinical Model Program

Established a *standardized animal model program* to screen promising compounds.



NIAAA Preclinical Compound Evaluation Program

- ***Two-bottle choice paradigms (Becker, PI):***
  - C57BL/6J mice:
  - Binge drinking (Drinking in the Dark)
  - Alcohol dependence (chronic alcohol vapor exposure + forced swim)

Bridge Gap between Preclinical Efficacy & Human Studies:

Blueprint Neurotherapeutics Network (BPN) UG3/UH3 NOFOs

- **Small Molecules:** PAR-25-051
- **Biologics:** PAR-24-293

- **Purpose:** To advance small molecule drug and other biotherapeutic discovery and development projects into the clinic. From lead optimization through first-in-human clinical trials.

- **Phased UG3/UH3**: help from NIH-funded consultants with industry and regulatory experience; can use NIH-funded CROs that specialize in manufacturing, nonclinical studies, and early phase clinical trials.

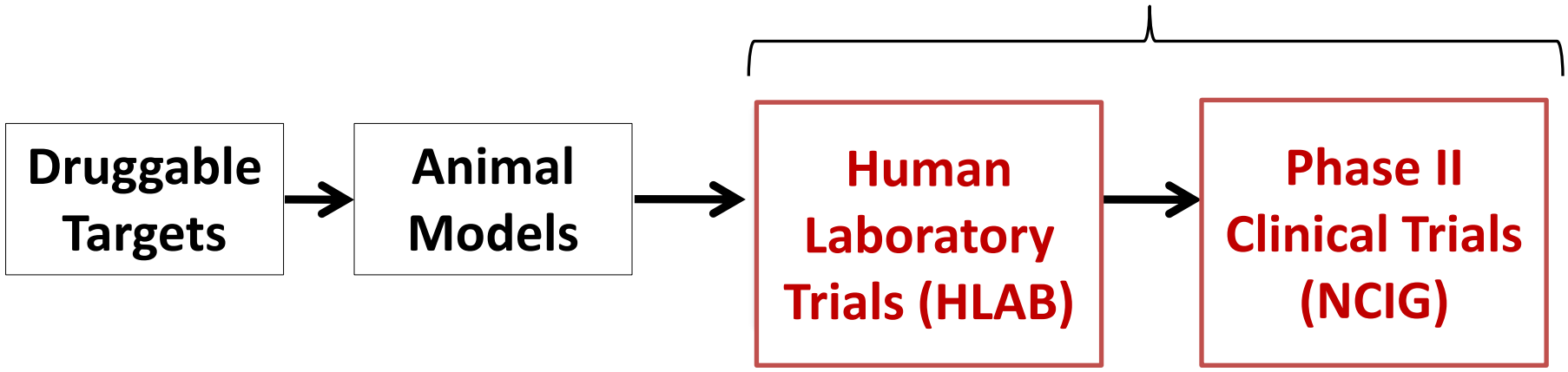
- **Project Period:** UG3 = 2 yrs, UH3 = 4 yrs; budget reflects needs of project*

*talk to NIAAA Project Officer

NIAAA Clinical Trial Program

Established a *standardized clinical trial program* to screen and evaluate candidate compounds.

NIAAA Alcohol Pharmacotherapy Evaluation Program (APEP)



APEP also conducts alcohol interaction studies

NIAAA Alcohol Pharmacotherapy Evaluation Program (APEP)

Contract mechanism to conduct human laboratory and phase II AUD pharmacotherapy clinical trials:

- Novel and Repurposed Medications
- Partnership with Pharma
- Quick turnaround (1½ years)
- Multi-site trials (~4 to 8 high performing academic sites)
- Good Clinical Practice (GCP)

NIAAA Human Lab Program to Screen Candidate Compounds

HLAB contract mechanism (started 2018):

- 1° outcome: alcohol cue-induced craving
- 2° outcomes (during 1-month follow-up):
  naturalistic drinking, mood, sleep, alcohol related consequences; safety

HLAB studies:

1. Varenicline (Chantix®):
   No effect on cue-induced alcohol craving; but craving predicted subsequent alcohol use[1]

2. ANS-6637 (novel ALDH2 inhibitor):
   Early termination due to unexpected liver tox. Gave important safety data.
   Suggestion of efficacy (reduced drinking, consequences, craving).[2]

3. ASP-8062 (novel GABA B positive allosteric modulator):
   No effect on cue-induced alcohol craving or secondary outcomes[3]

4. Apremilast (PDE4b inhibitor):
   Recruitment underway

1 Miranda et al. (2020) Alcohol Clin Exp Res. 2020; 2 O'Malley et al. (2020) Alcohol Alcohol. 2025; 3 Schacht et al. (2020) Alcohol Clin Exp Res. 202

NCIG Multisite Trials (Started Jan 2008)

Study	Medication	Results	Publication
NCIG 001 (n = 224)	quetiapine (Seroquel)	No effect	Litten et al. *Alcohol Clin ExpRes* 36:406-14, 2012
NCIG 002 (n = 130)	levetiracetam (Keppra)	No effect	Fertig et al. *Alcohol Clin Exp Res* 36:1421-30, 2012
NCIG 003 (n = 200)	varenicline (Chantix)	↓heavy drinking days, drinks/day, drinks/drinking day, craving	Litten et al. *J Clin Med* 7:277-86, 2013
NCIG 004 (n = 150)	ABT-436 (V1b antagonist)	↑ % days abstinent, ↓ drinking in subjects with higher baseline stress	Ryan et al. *Neuropsychopharmacology* 42:1012-1023, 2017
NCIG 006 (n = 348)	gabapentin enacarbil (Horizant)	No main effect. But responder subgroup identified.	Falk et al. *Alcohol Clin Exp Res* 43:158-169, 2019
NCIG 007 (n = 100)	oxytocin	Analysis completed	Manuscript accepted *Alcohol Clin Exp Res*

Novel Endpoint

NIH National Institute on Alcohol Abuse and Alcoholism

Endpoints for Pivotal AUD Pharmacotherapy Trials

- **FDA issued: "Alcoholism: Developing Drugs for Treatment: Guidance for Industry" (February 2015)**
  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm433618.pdf

- **FDA's endpoints for pivotal trials**
  - **Total abstinence (original)**
  - **No heavy drinking days (newer)**

- **FDA's new endpoint: 2-level reduction in drinking risk levels**
  - **Alcohol Clinical Trials Initiative (ACTIVE)**
  - **Sponsor: ASCP**

2-Level Reduction Endpoint

% of subjects who reduce by at least 2 levels

- **Very High** to Medium/Low/Abst

Risk Level	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

- **High** to Low/Abst

Risk Level	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

- **Medium** to Abst

Risk Level	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

National Institute on Alcohol Abuse and Alcoholism

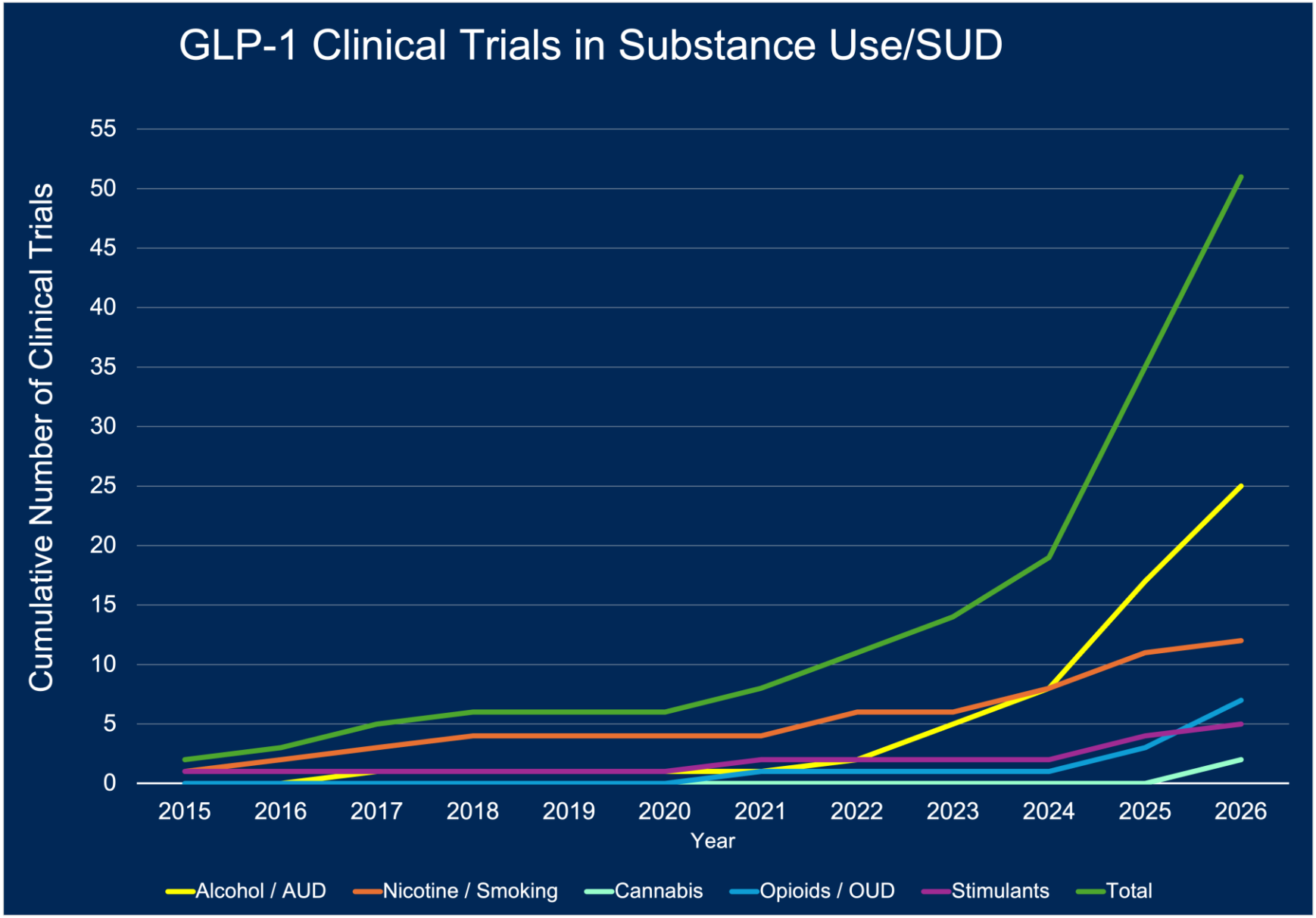
FDA Qualified Endpoint: 2-level Reduction in Drinking

- 30+ peer-reviewed publications
- **Validated**: in 3 AUD pharmacotherapy RCTs, a 2-level reduction in drinking improves feeling and functioning:
  - Reduced AUD risk & severity
  - Reduced alcohol-related consequences
  - Reduced systolic blood pressure
  - Improved mental health & quality of life
  - Improved liver function
- **Pros**:
  - Aligned with patients' treatment goals
  - More achievable than the other FDA-approved endpoints
  - Effect sizes ≥ than the other FDA-approved endpoints
- Qualified for use as a surrogate primary efficacy endpoint for development of pharmacotherapies to treat adults with moderate to severe AUD in Phase 3 trials[1]
- "Incorporation of this DDT has the potential to advance the development of therapies for AUD treatment." [1]

[1] FDA Drug Development Tool Clinical Outcome Assessment (DDT COA #110) Qualification Statement, Jan 14, 2025

GLP-1 Agonists: NIAAA Research Highlights

NIH National Institute on Alcohol Abuse and Alcoholism



Hendershot (unpublished) reproduced with permission

USC

USC Institute for Addiction Science

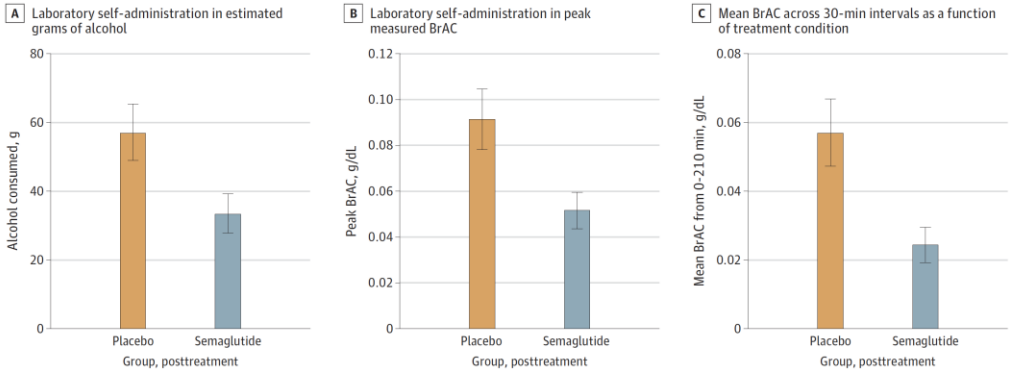
NIAAA-funded study #1: PI: Christian Hendershot (Feb 2025)

Laboratory Alcohol Self Administration

JAMA Psychiatry | Original Investigation

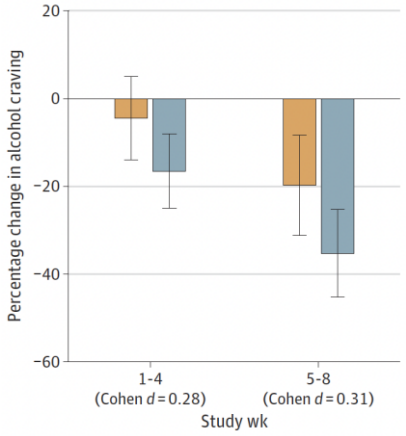
Once-Weekly Semaglutide in Adults With Alcohol Use Disorder
A Randomized Clinical Trial

Christian S. Hendershot, PhD; Michael P. Bremmer, MA; Michael B. Paladino, BS; Georgios Kostantinis, BA; Thomas A. Gilmore, BA; Neil R. Sullivan, BA; Amanda C. Tow, MD, PhD; Sarah S. Dermody, PhD, CPsych; Mark A. Prince, PhD; Robyn Jordan, MD, PhD; Sherry A. McKee, PhD; Paul J. Fletcher, PhD; Eric D. Claus, PhD; Klara R. Klein, MD, PhD

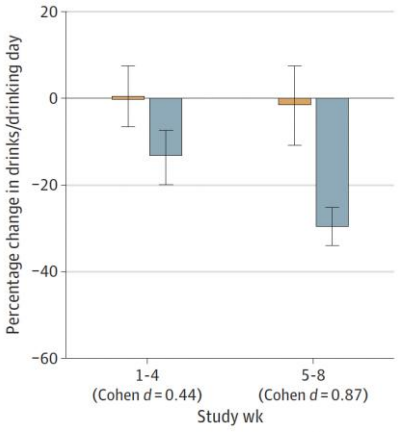


Placebo
Semaglutide

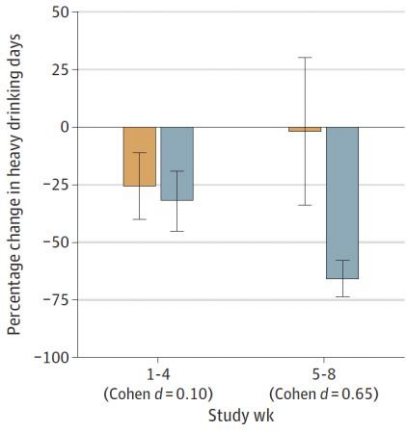
Alcohol Craving (PACS)



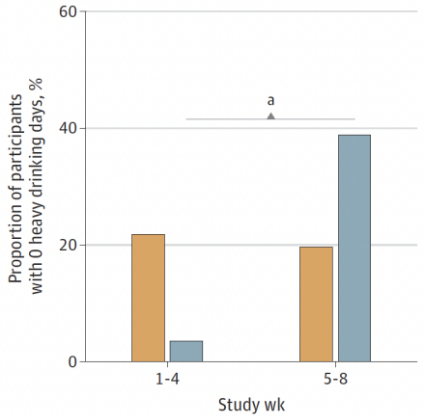
Drinks Per Drinking Day



Heavy Drinking Days



% Participants with Zero HDD



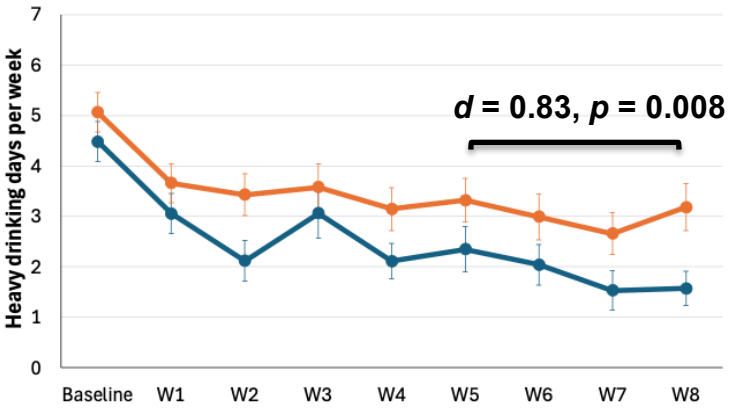
NIAAA-funded study #2: PI: Joseph Schacht (in press, Am J Psychiatry)

Colorado oral semaglutide trial

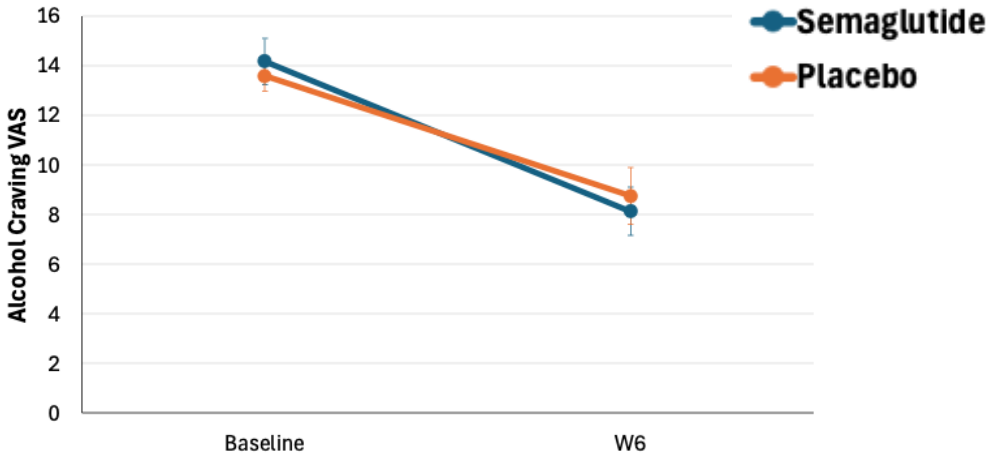
- **8-week RCT, *N*=50 treatment-seeking patients (AUD)**
- **Dose:** 3 mg x 4 weeks, then 7 mg x 4 weeks
- **Effect sizes** (drinking outcomes) similar to injectable semaglutide among non-tx-seekers (Hendershot et al., 2025)

Anschutz

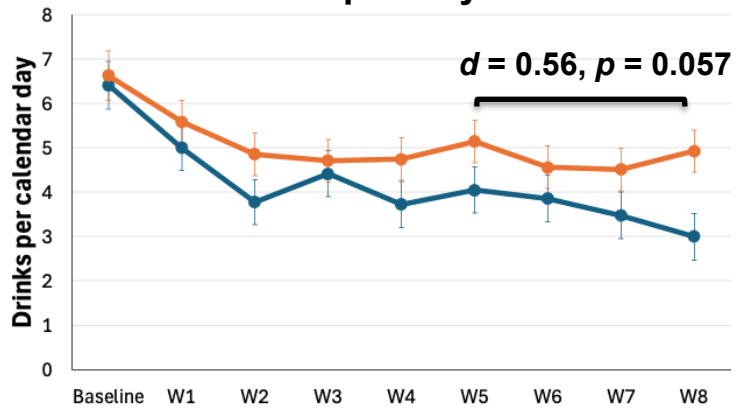
Heavy Drinking Days



Alcohol Craving (VAS) – primary outcome



Drinks per Day



NIAAA-funded study #3: PI Christian Hendershot

Phase 2 Trial of Tirzepatide in Adults with AUD and Overweight or Obesity

- Investigator-initiated Phase 2 trial of tirzepatide in treatment-seeking adults with AUD (NCT06994338)
- Aims to characterize safety and efficacy of short-term tirzepatide treatment
  - 2.5mg/week for 4 weeks; 5mg/week for 4 weeks
- BMI 27+ (M = 34.6, SD = 5.87)
- Targeting moderate-to-severe alcohol use disorder (4+ symptoms out of 11)
  - WHO drinking risk level: High or Very High Risk
    - High risk: 60-100g/day for men; 40-60g/day for women
    - Very high risk: >100g/day for men; >60 g/day for women

NIAAA (R21AA031892)

Conclusions

- **Many exciting possibilities to advance AUD treatment:**
  - **Develop more effective medications**
  - **Partner with pharma**
  - **Make drug development process more efficient**
  - **Novel, validated endpoints**
  - **Advance personalized medicine**
  - **Facilitate adoption of treatments into clinical practice**

- **Work together as a team:**
  - **Stakeholders: NIAAA, other NIH Institutes, FDA, DoD, Academia, Pharma, Biotech, third-party payers, health-care organizations**
  - **Scientists: geneticists, chemists, data analysts, basic, clinical, and health service scientists**

Parting-Thought Suggestion

Consider an AUD indication

- Given high rates of alcohol consumption/AUD comorbid with other psychiatric disorders + overlapping mechanistic targets of medications….
- Collect alcohol use pilot data in your existing pharmacotherapy RCTs for non-AUD indications
- Consider at least AUDIT-C: 3 questions on alcohol consumption (30 seconds) as an outcome
- Submit RCT grant application to NIAAA!

Thank You!

To learn more about
NIAAA Medications Development Program
& opportunities for research,
please contact:

Dan Falk
falkde@mail.nih.gov

Google:
NIAAA Division of Treatment and Recovery (DTR)

NIH National Institute on Alcohol Abuse and Alcoholism