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

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National Institute on Alcohol Abuse and Alcoholism

No conflicts of interest

Alcohol Use Disorder (AUD)

- 28.9 million Americans, ages 12 and older, suffered from AUD in the past year (10.2%)
- 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

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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

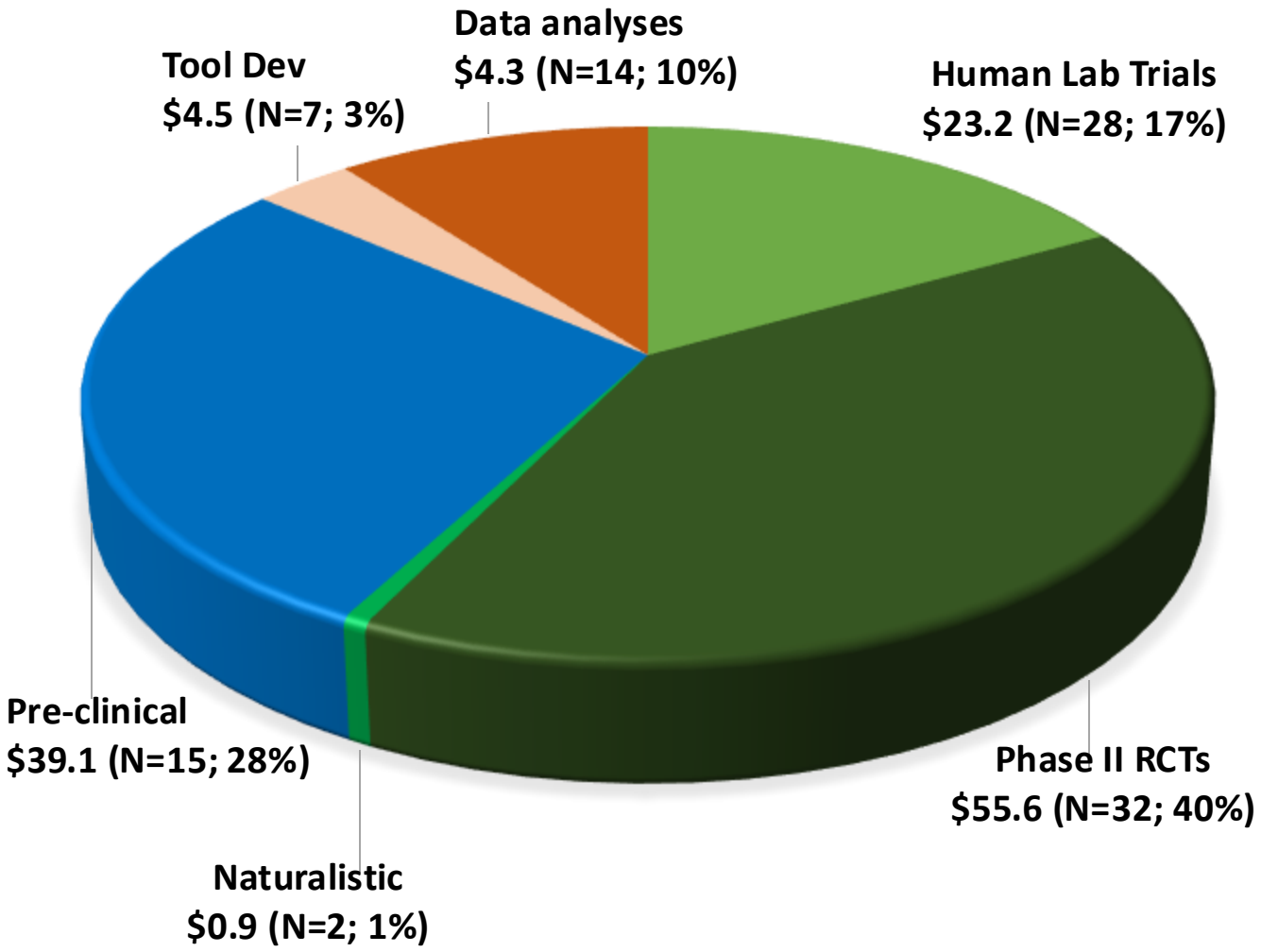
Promising Medications to Treat AUD

Medication	Target
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 (FY 20-24)

Total Cost = $137.5 M, (N=98)



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Note: Costs are in millions for initial and/or outyears; %'s are of total costs; pre-clinical studies include in-vitro, in-vivo and ex-vivo studies.

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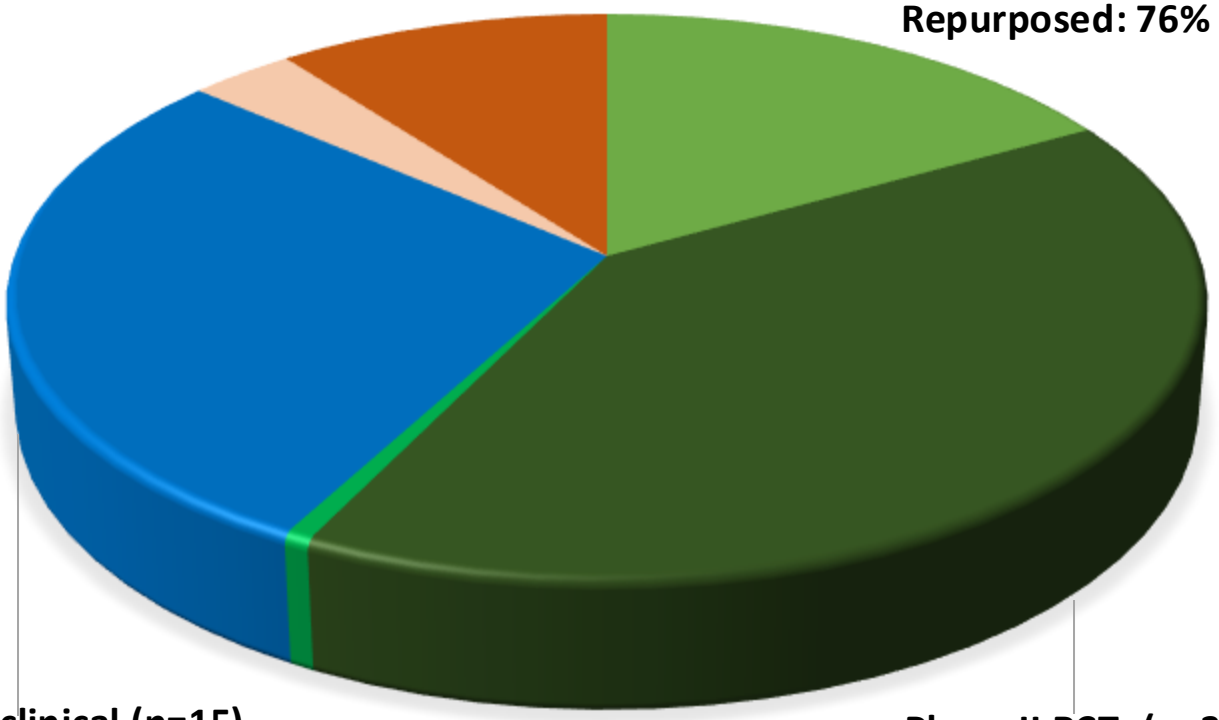


Note: %'s based on number of grants in category

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)

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

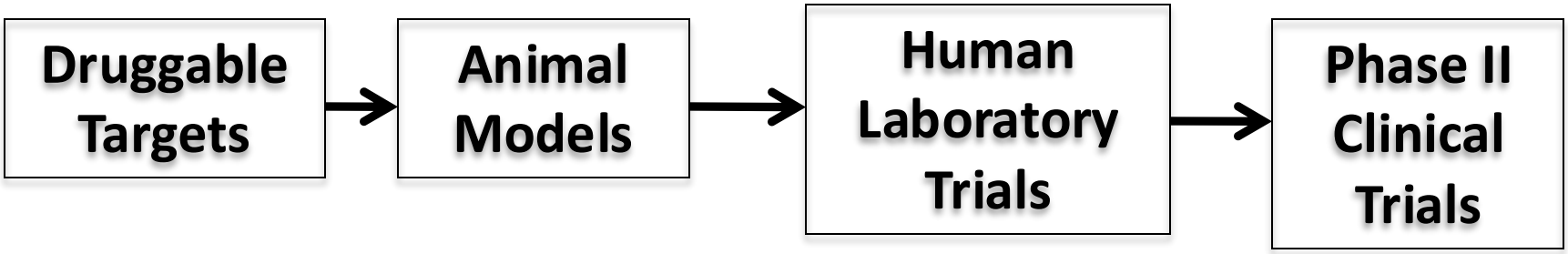
Medications Development:

- 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)

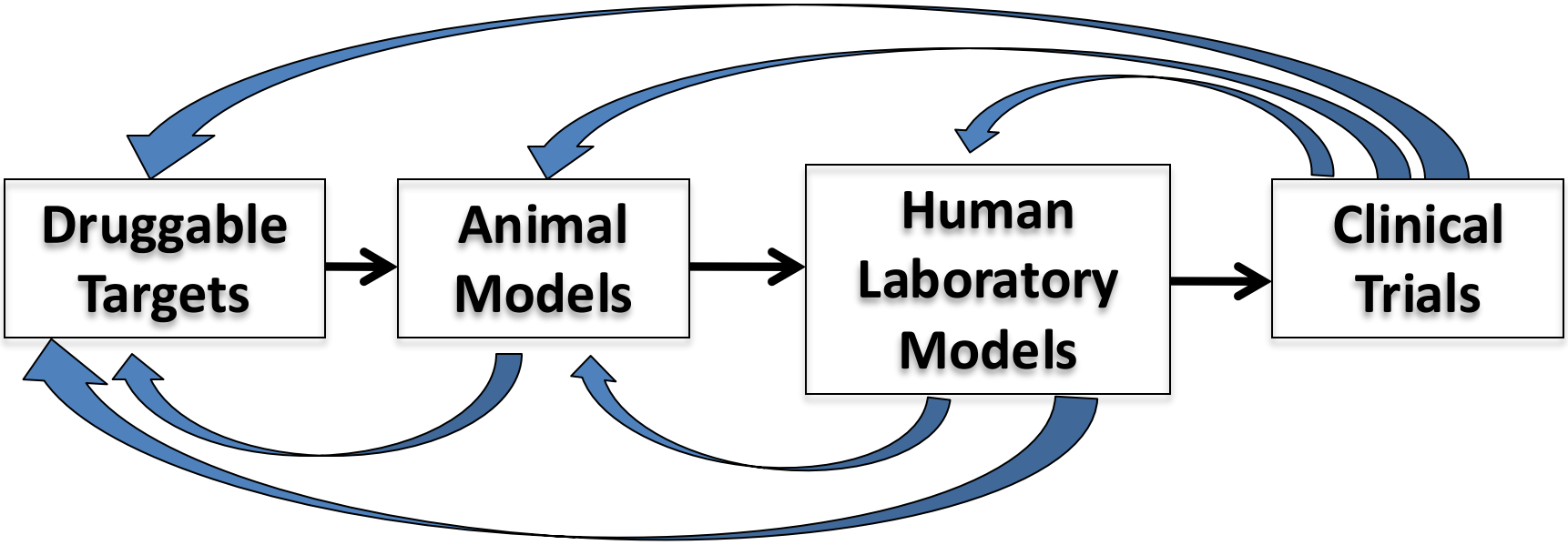
Special Initiatives
Focus: Pharma Partnership

Drug Development Pipeline



NIAAA Medications Development

Validation Process: Bidirectional Integration

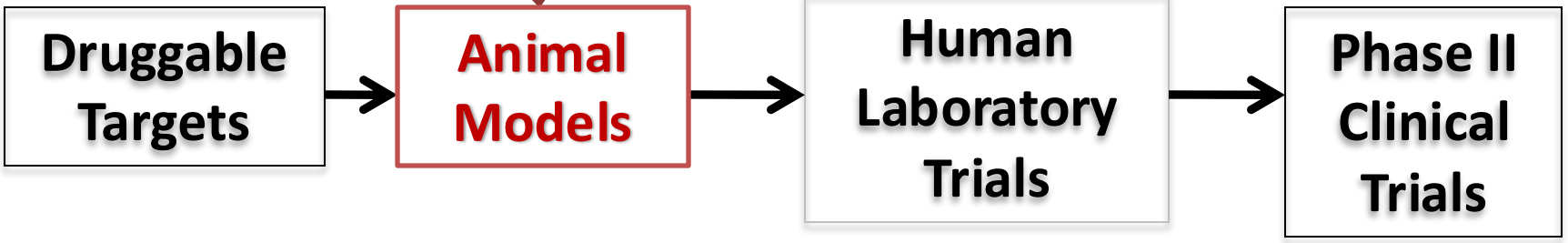


Promising Targets for AUD

- 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 Paradigm

- ***Dependent Mice (Becker, PI):***
  - C57BL/6J mice: nondependent vs dependent (chronic alcohol vapor exposure + forced swim)

- ***Dependent Rats (Edwards, PI)***
  - Wistar rats
  - Alcohol vapored exposed
  - Operant self-administration
  - Pain avoidance measurement

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High-Throughput/Faster Screening Tools

- RFA-AA-24-001: Develop HTS models to quickly screen multiple candidate compounds, drug combinations, or targets to increase the efficiency of the drug development process

- *in vitro* and *ex-vivo* tools
  - 3D cell cultures (brain organoids derived from human iPSCs)
  - Phenotypical screening using cell painting approach (multiple fluorescent markers)

- Whole organisms (*in vivo*)
  - zebrafish
  - nematode C. elegans (roundworms)
  - fruit flies

Must validate new screening models for predictive clinical efficacy and safety

Bridge Gap between Preclinical Efficacy & Human Studies:

NIAAA SBIR/STTR "Notice of Intent to Publish" NOFOs

- Small business (SBIR R43/R44): NOT-AA-24-015
- Small business & academic partner (STTR R41/R42): NOT-AA-24-014

- **Purpose**: Translate research discoveries into new treatments for AUD (or alcohol related diseases) by supporting efforts to achieve an IND and conduct early-stage clinical trials. From lead optimization to Phase 2 RCTs.

- **Budget**: Up to $1M total costs/yr for 2 yrs (SBIR Phase I)
  Up to $2M total costs/yr for 3 yrs (SBIR Phase II)

Bridge Gap between Preclinical Efficacy & Human Studies:

Blueprint Neurotherapeutics Network (BPN) SBIR (U44) NOFOs

- **Small Molecules:** PAR-24-063
- **Biologics:** PAR-24-294

- **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.

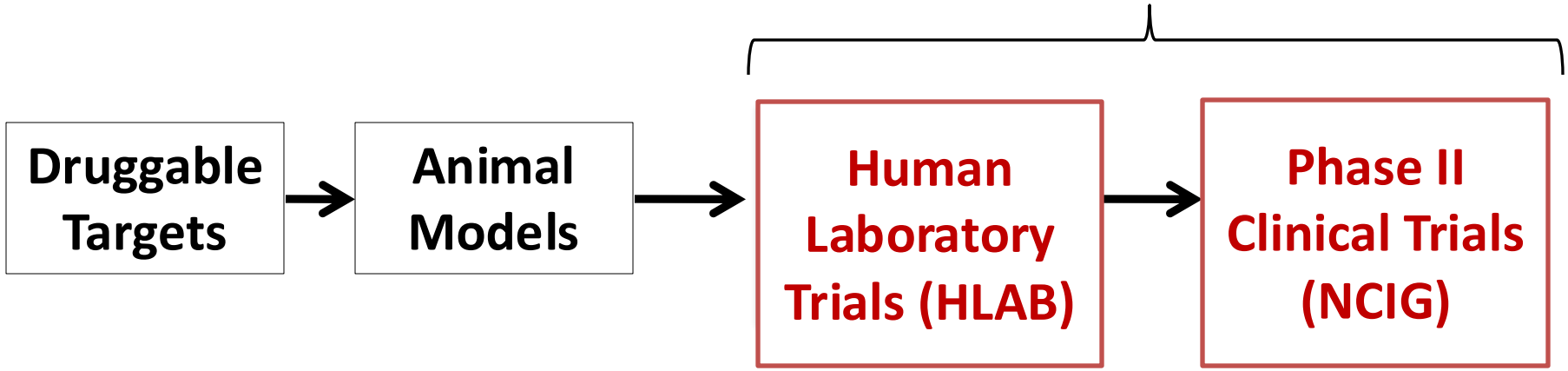
- **Co-operative mechanism (U)**: help from NIH-funded consultants with industry and regulatory experience; can use NIH-funded CROs that specialize in manufacturing, nonclinical studies, and early phase clinical trials.

- **Budget:** **Up to $0.5M total costs/yr for 2 yrs (SBIR Phase I)**
  Up to $1.5M total costs/yr for 3 yrs (SBIR Phase II)

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]

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. 2024

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 in progress

Novel Endpoint

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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

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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
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FDA Qualified Endpoint: 2-level Reduction in Drinking

- So far, over 30 publications in peer-reviewed journals on this endpoint
- **Validation**: in 3 AUD pharmacotherapy RCTs, individuals with at least 2-level reduction in drinking have improvements in 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**:
  - May be better 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

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

Thank You!

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