NIAAA’s Medications Development Program to Treat Alcohol Use Disorder: Advances, Goals, and Initiatives

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Alcohol Use Disorder (AUD)

- Over 15.7 million Americans suffer from AUD
- Complex, heterogeneous disorder
- No single treatment intervention works for all
- Advances in developing medications for multiple targets
## FDA-Approved Medications for Alcohol Dependence

<table>
<thead>
<tr>
<th>Medication</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disulfiram (Antabuse®)</td>
<td>Aldehyde dehydrogenase 1949</td>
</tr>
<tr>
<td>Naltrexone (Revia®, Depade®)</td>
<td>Opioid receptor 1994</td>
</tr>
<tr>
<td>Acamprosate (Campral®)</td>
<td>Glutamate receptor 2004</td>
</tr>
<tr>
<td>Extended-release naltrexone (Vivitrol®)</td>
<td>Opioid receptor 2006</td>
</tr>
</tbody>
</table>
Potential Medications to Treat AUD

Medications with Promising Results from Human Studies

• nalmefene
• varenicline
• topiramate
• zonisamide
• gabapentin
• baclofen
• ondansetron
• oxytocin
• mifepristone

Litten et al., *Substance Abuse* 37:286-298, 2016
NIAAA’s Strategic Plan for Medications Development: Goals

• Increase treatment effect of candidate medications

• Find efficiencies in the drug development process:
  – speed
  – predictability
  – expense

• Facilitate the use of alcohol medications in real-world clinical practice
New Initiatives & Strategies

Topics

• Identify domains and targets of AUD
• Bridge gaps in drug development pipeline
• Validate screening models
• Interactions with FDA
• Facilitate medication use in real world settings
Addictions Neuroclinical Assessment (ANA) Program

Purpose

• Assess and classify individual differences (heterogeneity) in AUD

• Develop constructs and measures (genetic, molecular, cellular pathways, circuit-level, behavioral) of different domains of AUD
  – Incentive salience/reward
  – Negative emotionality
  – Cognitive control

Currently over 40 + targets have been identified……..

Research questions:
• How to organize/prioritize targets?
• Do they directly or indirectly cause and/or maintain AUD?
• Are targets related or independent of each other?
• How do they fit within AUD domains to produce the heterogeneity?
Determine How Targets Inter-Relate in Domains, Circuits, Functional Pathways

One Approach:

Develop, integrate, and data mine biomolecular and cellular networks to discover druggable targets for AUD.

- **Biomolecular networks types:** gene-gene interactive, gene-protein, protein-protein interactions, metabolic, regulatory
- NIAAA issued NIH Guide for researchers
Bridge the Gaps in the Drug Development Process
Phases of Drug Development

Preclinical Testing
- Drug Discovery:
  - Target ID
  - HTS
  - Lead Optimization
- Efficacy:
  - Animal Models
- IND
  - Requisites:
    - GMP
    - Synthesis
    - Formulation
    - pK
    - Animal Toxicology

Clinical Testing
- Phase 1:
  - Safety
  - pK
  - Dose
  - Alcohol Interaction
- POC:
  - Human Lab Early Phase 2:
    - Efficacy
    - Dose
    - Safety
- Confirmation:
  - Late Phase 2
  - Phase 3:
    - Verify
    - Efficacy & Safety
- Phase 4:
  - Monitor Safety Implementation
  - Adoption

IND — Investigational New Drug
HTS — High-throughput screening
POC — Proof of Concept
pK — Pharmacokinetics
NDA — New Drug Application

NIH — National Institute on Alcohol Abuse and Alcoholism
Valley of Death
Bridge Gap Between Preclinical Efficacy And Human Phase 2 studies

- Small Business Innovation Research (SBIR)/ Small Business Technology Transfer (STTR) program announcement “IND-Enabling Medications Development to Treat AUD”

- Includes support for IND-enabling development and early human phase 1 activities
## SBIR/STTR IND-Enabling Funded Studies

<table>
<thead>
<tr>
<th>Company</th>
<th>Novel Compound</th>
<th>Site of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lohocla Research Corporation</td>
<td>Nezavist</td>
<td>positive allosteric modulator of $\text{GABA}_A$ receptor</td>
</tr>
<tr>
<td>Cerecor</td>
<td>CERC-501</td>
<td>kappa opioid receptor antagonist</td>
</tr>
</tbody>
</table>
Predictive Validation of Models to Screen Candidate Compounds
SCREENING MODELS

Molecular Targets → Animal Models → Human Laboratory Models → Clinical Trials
SCREENING MODELS

VALIDATION PROCESS: BIDIRECTIONAL INTEGRATION

Molecular Targets → Animal Models → Human Laboratory Models → Clinical Trials

Molecular Targets
Animal Models
Human Laboratory Models
Clinical Trials
Initiate Screening Model Program

Goals

• **Increase the efficiency of drug development by establishing screening models that predict clinical success (Go/No-Go Decision)**

• **Standardize screening models by using same paradigms at the same site to test candidate compounds**

• **Funding through Contracts**

• **Make the screening models attractive to pharma and encourage participation**
Established standardized animal model program to screen promising compounds.
NIAAA Started with Genetic and Alcohol Dependent Animals using Two-Bottle Choice Paradigm

• **Genetic Model (Bell, PI):**
  – Indiana alcohol-preferring (P) rats
  – Indiana high alcohol-drinking (HAD)-1 rats

• **Dependent Models (Becker, PI):**
  – C57BL/6J mice: nondependent vs dependent (chronic alcohol vapor exposure)
# Medications Tested in Animal Models: Reference Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>P</th>
<th>HAD1</th>
<th>Dep. Mice</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>naltrexone</td>
<td>Reduction</td>
<td>Reduction</td>
<td>Reduction</td>
<td>Small effect</td>
</tr>
<tr>
<td>topiramate</td>
<td>Reduction</td>
<td>Reduction</td>
<td>Reduction</td>
<td>Small effect</td>
</tr>
<tr>
<td>acamprosate</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Small effect</td>
</tr>
<tr>
<td>levetiracetam</td>
<td>No effect</td>
<td>Increase</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>Reduction</td>
<td>No effect</td>
<td>Reduction</td>
<td>No effect</td>
</tr>
<tr>
<td>quetiapine</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
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Establishing a standardized human laboratory program to screen candidate compounds.
Human Laboratory Model for Screening

Why use human laboratory paradigms as a screening model for medications development?

- Human laboratory studies are faster and less expensive than clinical trials
Launched this program last month:

- Selected a limited number of paradigms (e.g., cue-induced craving) and associated dependent measures that are most sensitive in predicting clinical success

- Clinical Sites - Brown University (Miranda, PI) and Yale University (O’Malley, PI) for a quick turnaround

- Medication - varenicline (Chantix)
NIAAA Medications Development

Developed network of sites to conduct clinical trials.

- Molecular Targets
- Animal Models
- Human Laboratory Models
- Clinical Trials
Network of Sites to Conduct Alcohol Clinical Trials

- Partnership with pharmaceutical companies
- Quick turnaround (1½ years)
- Good Clinical Practice (GCP)
# Multisite Trials (Started Jan 2008)

<table>
<thead>
<tr>
<th>Study</th>
<th>Medication</th>
<th>Publication</th>
</tr>
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<tbody>
<tr>
<td>NCIG 001</td>
<td>Quetiapine (Seroquel)</td>
<td>Litten et al. <em>ACER</em> 36:406-14, 2012</td>
</tr>
<tr>
<td>NCIG 004</td>
<td>ABT-436 (V1b antagonist)</td>
<td>Ryan et al. <em>Neuropsychopharmacology</em> 42:1012-1023, 2017</td>
</tr>
<tr>
<td>NCIG 005</td>
<td>gabapentin enacarbil (Horizant)</td>
<td>Completed study (N=348), Analysis in Progress</td>
</tr>
</tbody>
</table>
Interaction with Food and Drug Administration (FDA)
Alcohol Clinical Trials Initiative (ACTIVE) Group

- **Purpose:** to advance the methodology of alcohol treatment clinical trials

- **Members:** pharma, academic researchers, NIAAA, NIDA, FDA, European Medications Agency (EMA)

- **Sponsor:** ASCP

FDA issued guidance for development of medications to treat AUD

Alcohol Clinical Trials Initiative (ACTIVE) Group

FDA’s endpoints for Phase III trials
• Total abstinence
• Percent subjects with no heavy drinking days

ACTIVE and NIAAA provided analysis to validate a new endpoint: Reduction in drinking based on World Health Organization (WHO) drinking risk levels

– Hasin et al. Lancet Psychiatry online
Medications for Alcohol Treatment in Real-World Settings

NIAAA-Issued Funding Opportunity Announcement

• “Increasing the Use of Medications for the Treatment of Alcohol Use Disorders (R01)”

Screening/Interventions

• Clinician’s Guide

• Alcohol Screening and Brief Intervention for Youth

• Medications to Treat Alcohol Use Disorder: A Brief Guide
Conclusions

- Across two decades, **solid advances** in medications development

- Many **exciting possibilities** as NIAAA develops a solid infrastructure to accelerate promising medications through the drug development pipeline

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