Overview of NIAAA Programs

Joint NIAAA – NIDA Council Meeting

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Mission: To understand how alcohol use impacts normal and abnormal biological functions and behavior across the lifespan and at all levels of drinking including:

- Alcohol-associated disease (including alcohol dependence)

- Alcohol-derived organ pathologies

- Public health problems resulting from acute and chronic alcohol use (e.g., alcohol poisoning, accidental injury and death)

Thereby improving the health and well-being of the nation.
What is different about alcohol?

- Alcohol is **legal**, **widely used**, and **easily obtained**.

- It is a part of the **social context** in many countries and cultures and is used in ceremonial occasions such as marriages, and births, and to **enhance the enjoyment of social gatherings**.
In fact, alcohol is used by the majority of adult Americans ......

- 65% of the U.S. adult population drink alcohol at various times during the year = 144 million Americans.
- Of those, 126 million do NOT have an Alcohol Use Disorder.
- 85 million Americans (59% of drinkers) NEVER exceed high risk drinking limits.
- 41 million drinkers (without AUDs) do occasionally exceed high-risk drinking limits, placing them at risk for AUDs.
- 18 million Americans (that is 8.5% of adults or 13% of drinkers) suffer from an Alcohol Use Disorder: Alcohol Dependence; Alcohol Abuse or both.
Harmful Drinking is a Leading Risk Factor for Disease Burden in the U.S.

- This 8.5% of the population >18 yrs with AUDs contribute in a major way to the disease burden in the U.S.

- Alcohol problems cost U.S. society an estimated $235 billion annually.

- Alcohol consumption is among the top ten leading causes of DALYs.*

- Among actual causes of death, alcohol ranks 3rd with an estimated 79,000 deaths annually for 2001-2005.

*Disability-adjusted life years (years of potential life lost due to death plus years of healthy life lost to disability)
Two Distinct Patterns of Drinking Produces the Most Harm

Binge Drinking (too much, too fast)
5+/4+ drinks within 2 hours

Heavy Drinking (too much, too often)
frequent 5+/4+ drinks/day

Acute consequences including:
- unintentional death and injury
- homicide and violence
- suicide attempts

Particularly prevalent among adolescents and young adults

Chronic consequences including:
- liver cirrhosis
- Pancreatitis
- cardiovascular diseases
- dementia
- alcohol dependence
NIAAA’s Broad Mandate Requires Research Programs to Address Alcohol Issues Throughout the Lifespan...

Lifespan Transcending Themes
- Metabolism
- Genetics
- Epigenetics
- Epidemiology
- Neurobiology
- Health Services Research
To cover drinking across the lifespan, NIAAA has a wide-ranging research portfolio ..........
NIAAA Extramural Grant Portfolio, FY 2010

- Prevention (n=112), 11%
- Epidemiology (n=100), 10%
- Health Services (n=31), 3%
- Treatment (n=146), 14%
- Metabolism and Health Effects (n=225), 22%
- Neuroscience and Behavior (n=409), 40%

NIAAA Trans-Divisional Research Emphasis Areas and Resource Development Teams*

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

* These Emphasis Areas Cut across Divisions
NIAAA Division of Neuroscience and Behavior Portfolio

(Active Grants; August 2011)

Total Funding = $165,224,235 (N= 510)

- Neurobiology of Alcohol Dependence (n=176), $55,112,672
- Affect, Learning and Cognition (n=94), $26,686,538
- Training, Centers and Resources (n=101), $25,963,247
- Neurodevelopment including FASD (n=42), $13,801,580
- Animal and Human Genetics (n=66), $34,975,194
- Preclinical and Translational Medication (n=31), $8,685,004
COGA (Collaborative Study on the Genetics of Alcoholism)

- **Primary Goal of COGA:** To find and understand genes that affect the risk for the development of alcoholism and related disorders. This is being accomplished through linkage, GWAS, and whole-exome sequencing studies as well as gene expression and epigenetic studies.

- The COGA family pedigrees are densely affected with alcoholism containing at least 2 alcohol-dependent first-degree relatives in addition to an alcohol dependent proband.

- Participants from 7 US sites
NADIA (Neurobiology of Adolescent Drinking in Adulthood)

NADIA is a multi-investigator effort (primarily an animal model study) which will assess the effects of adolescent ethanol exposure on adult:

- **Brain structure** and neurochemistry
- **Impulsivity, reward** and responses to stress
- **Learning, memory and executive cognitive function**
- **Sleep and arousal**
- **Social reward and anxiety**
- **Epigenetic modifications and neuronal plasticity**
- **Drinking behavior** and withdrawal

Combining the efforts and expertise of the consortium investigators is expected to result in synergies which would not be achievable with single research projects.
Integrative Neuroscience Initiative on Alcoholism (INIA)

Neuroadaptation

• An 11 site multidisciplinary consortium devoted to identifying molecular, cellular, and behavioral neuroadaptations that occur in the brain due to alcohol exposure that contribute to excessive alcohol consumption in some individuals.

• The current objective of INIA is to confirm previously identified gene targets and identify druggable targets that are the most promising for medications development for the treatment of alcoholism.

• This will be achieved using:
  - the extensive INIA genomics data set
  - the INIA mutant mouse and behavioral testing cores
  - INIA electrophysiology expertise
Integrative Neuroscience Initiative on Alcoholism (INIA)

Stress

- A cooperative consortium of 15 Principal Investigators from 9 academic institutions across the US.
- The INIA stress consortium uses a state-of-the-art translational approach (mice, monkeys and humans) to:
  - understand the interaction of genetic variation and stress on the promotion of excessive drinking and
  - identify novel, effective and tailored treatment strategies for alcoholism.
Human Adolescent Brain Initiative

New Initiative: A multi-site longitudinal study using neuroimaging and neuropsychological measures to answer questions about the impact of child and adolescent alcohol use on the developing brain:

• what early brain and cognitive markers may predict alcohol use and/or dependence

• what are the short and long-term consequences of alcohol exposure on brain and cognitive development;

• the effects of timing, dose, and duration of alcohol exposure on brain and cognitive development; and

• to what extent are these effects permanent or reversible
DNB - High Priority Areas

• Alcohol & Stress
• Alcohol-Nicotine Interactions
• Alcohol & Neuroimmune Function
• Pain and Alcohol Dependence
• Systems Biology
• Functional Genomics*

*to determine how genetic variation in disease-related candidate genes impacts function at the molecular, cellular and behavioral levels
NIAAA Division of Epidemiology and Prevention Research Portfolio (Active Epidemiology Grants; August 2011)

Total Epidemiology Grant Funding = $14,100,000 (N= 46)

- Special Populations (n=19), $4,470,000
- Methodology, Modeling and Measurement (n=18), $5,980,000
- Gene by Environment Interactions (n=9), $3,650,000
NIAAA’s Research Prevention Portfolio

NIAAA Division of Epidemiology and Prevention Research Portfolio
(Active Prevention Grants; August 2011)
Total Prevention Grant Funding = $73,580,000 (N= 193)

- Fetal Affects (n=8), $5,330,000.00
- Prevention Adolescents (n=62), $22,460,000.00
- Prevention Consequences (n=22), $6,870,000.00
- Prevention Screening and Intervention (n=11), $4,960,000.00
- HIV/AIDS (n=34), $13,220,000.00
- Psychiatric Comorbidities (n=17), $5,470,000.00
- Violence and Sexual Behavior (n=22), $6,070,000.00
- Other (n=25), $9,200,000.00
- Psychiatric Comorbidities (n=17), $5,470,000.00
NIAAA Prevention Policy Research

• Major component of NIAAA’s prevention research portfolio, includes **impact of various laws and policies** on alcohol related problems and behaviors:

• Effects of legislation and policy measures related to:
  - **Zoning** *(incl. drinking at public venues)*
  - Types of sales outlets
  - Hours of Operation
  - Enforcement of Underage Drinking Age
  - College and Underage Policies
  - Per se laws
  - Cost (both price + ease or difficulty of access to product)
  - Advertising
  - And More…
Alcohol Policy Information System
(http://www.alcoholpolicy.niaaa.nih.gov/)

Gathers information on, and facilitates research on Alcohol-Policies through the collection of State laws and policies addressing:

- Alcohol control systems
- Alcohol beverage taxes
- DWI laws
- BAC limits (adults, youths)
- Health insurance parity
- Insurers’ liability for losses due to intoxication (UPPL)
- Vehicular insurance exclusions
- Open container laws
- Underage drinking policies
- Keg registration
- Beverage server training
- Hours/Days sale
- Alcohol and pregnancy
NIAAA Division of Treatment and Recovery Research Portfolio
(Active Grants; August 2011)

Total Funding = $77,629,900 (N = 191)

- Health Services Research (N=42) $17,603,793
- Behavioral Therapies/ MOBC (N=80) $32,424,538
- Recovery Research (N=9) $3,016,815
- Medications (N=52) $21,219,658
- Personalized Medicine (N=8) $3,365,096

Total: $77,629,900 (N = 191)
NCIG is a medications development program (housed in DTRR) designed to:

- rapidly and efficiently test compounds for efficacy and safety in treating AUDs
- bridge the gap between pre-clinical and large Phase III trials in the drug discovery pipeline
- stimulate Pharma and academic researchers to continue testing on promising compounds to treat AUDs
### Industry Collaborations for Medications Development for Alcohol Dependence

<table>
<thead>
<tr>
<th>Product</th>
<th>Target</th>
<th>Company</th>
<th>Development Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>topiramate (Topamax)*</td>
<td>Anticonvulsant (glutamate/GABA)</td>
<td>Ortho-McNeil</td>
<td>Phase II</td>
</tr>
<tr>
<td>gabapentin (Neurontin)*</td>
<td>Anticonvulsant (glutamate/GABA)</td>
<td>Parke-Davis (Pfizer)</td>
<td>Phase II</td>
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<tr>
<td>levetiracetam (Keppra)*</td>
<td>Anticonvulsant (glutamate/GABA)</td>
<td>UCB</td>
<td>Phase II</td>
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<tr>
<td>zonisamide (Zonegran)*</td>
<td>Anticonvulsant (glutamate/GABA)</td>
<td>Dainippon</td>
<td>Phase II</td>
</tr>
<tr>
<td>pregabalin (Lyrica)</td>
<td>Anticonvulsant (glutamine/GABA)</td>
<td>Pfizer</td>
<td>Phase II</td>
</tr>
<tr>
<td>ondansetron (Zofran)*</td>
<td>Serontonin 5-HT&lt;sub&gt;3&lt;/sub&gt;</td>
<td>GlaxoSmithKline</td>
<td>Phase II</td>
</tr>
<tr>
<td>olanzapine (Zyprexa)*</td>
<td>D&lt;sub&gt;1&lt;/sub&gt;-4, 5-HT&lt;sub&gt;2A&lt;/sub&gt;, 5-HT&lt;sub&gt;2c&lt;/sub&gt;</td>
<td>Eli Lilly</td>
<td>Phase II</td>
</tr>
<tr>
<td>quetiapine (Seroquel)</td>
<td>D&lt;sub&gt;1&lt;/sub&gt;, D&lt;sub&gt;2&lt;/sub&gt;, 5-HT&lt;sub&gt;1A&lt;/sub&gt;, 5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Astra Zeneca</td>
<td>Phase II</td>
</tr>
<tr>
<td>baclofen (Lioresal)*</td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt;</td>
<td>Novartis</td>
<td>Phase II</td>
</tr>
<tr>
<td>prazosin (Minipress)*</td>
<td>α&lt;sub&gt;1&lt;/sub&gt; adrenergic</td>
<td>Pfizer</td>
<td>Phase II</td>
</tr>
<tr>
<td>duloxetine (Cymbalta)</td>
<td>5-HT, NE Transporter</td>
<td>Eli Lilly</td>
<td>Phase II</td>
</tr>
<tr>
<td>Puerarin</td>
<td>Extract of kudzu</td>
<td></td>
<td>Phase II</td>
</tr>
<tr>
<td>varenicline (Chantix)</td>
<td>Nicotinic α4β2</td>
<td>Pfizer</td>
<td>Phase I</td>
</tr>
<tr>
<td>rimonabant (Acomplia)*</td>
<td>Cannabinoid CB&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Sanofi - Aventis</td>
<td>Phase I</td>
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<tr>
<td>LY686017</td>
<td>NK1</td>
<td>Eli Lilly</td>
<td>Phase I</td>
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<tr>
<td>aripiprazole (Abilify)</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;, 5-HT&lt;sub&gt;1A&lt;/sub&gt;, 5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Otsuka/Bristol-Myers Squibb</td>
<td>Phase I</td>
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<tr>
<td>Kudzu</td>
<td>Unknown</td>
<td></td>
<td>Phase I</td>
</tr>
<tr>
<td>mecamylamine (Inversine)</td>
<td>Nicotinic</td>
<td>Merck</td>
<td>Phase I</td>
</tr>
</tbody>
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*Generic version is currently available*
Division of Metabolism and Health Effects Portfolio

- Liver and Metabolism (n=214), $65,584,745
- FASD (n=62), $17,565,962
- Cardiovascular/Lung (n=40), $10,928,535
- Muscle/Bone (n=7), $1,644,087
- Immune System (n=15), $3,375,589
- Cancer (n=9), $2,027,131
- Biomarker/Biosensor, etc. (n=16), $4,577,859

Note that the common element is actions of alcohol on a diverse organ systems
Beneficial Effects of Moderate Drinking

Consumption = < 30 g/d

- Decreased risk of CAD
  - HDL ↑; LDL ↓
  - Decreased platelet aggregation
  - Increased fibrinolysis
  - Decreased Ischemic/reperfusion injury

- Protection against Congestive Heart Failure
- Decreased risk of Ischemic Stroke
- Protection against T2D and Metabolic Syndrome
- Decreased risk of Osteoporosis
- Decreased risk of Dementia
As a result of alcohol research….

Alda1, an ALDH-2 activator, was developed as a preventative agent for MI

(ALDH 2 deficiency highly prevalent in Asian populations)
Fetal Alcohol Spectrum Disorder Portfolio

• Portfolio crosses all NIAAA Divisions
• Funding Level – FY 2010 $25,624,279
• Number of Projects: 122
• FAS and FASD are the leading preventable birth defects associated with cognitive impairments in the U.S.
• The prevalence of FAS and FASD are similar to that of autism and autism spectrum disorders, respectively.

* Photo courtesy of Teresa Kellerman
FASD have a High Prevalence in the U.S. and Worldwide
Data from School-Based Active Case Ascertainment

<table>
<thead>
<tr>
<th>Country (Location, Reference Year)</th>
<th>FAS+pFAS Percent (/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States (Midwestern City, 2008)</td>
<td>1.4 – 2.5</td>
</tr>
<tr>
<td>Italy (Lazio Provence, 2007)</td>
<td>2.7 – 5.5</td>
</tr>
<tr>
<td>South Africa (Western Cape, 2007)</td>
<td>6.8 – 9.0</td>
</tr>
<tr>
<td>South Africa (Northern Cape, 2008)</td>
<td>14 – 25</td>
</tr>
</tbody>
</table>

* Above includes FAS and pFAS only – ARND was not measured in above studies.
Why FASD is a Substance Use Issue

• Given this prevalence coupled to the long-term nature of FASD disabilities -- reducing or eliminating alcohol exposure in pregnancy, or by those at risk for pregnancy, emerges as a central issue – a clear substance (alcohol) use research issue.

• Much of our FASD portfolio centers on the identification of high-risk mothers by improved in utero (ultrasound) and infant case recognition (3-D facial recognition, early recognition of behavior patterns in infants and children).
NIAAA’s Research Portfolio Encompasses Fetal Alcohol Spectrum Disorders

Priority Research areas include:

- **Case Recognition** (improved dysmorphology)
- **Defining the full neurodevelopmental phenotype**
- **Development of neurodevelopmental interventions for affected individuals**
- **Integration of screening for risk drinking and case recognition into primary care**
- **Changing social norms on drinking in pregnancy**
- **Further elucidation of underlying etiologic mechanism(s)**
- **Development of interventions to target teratogenic action of alcohol**
- **Exploration of alcohol in SIDS (jointly with NICHD)**
FASD Major Initiatives in NIAAA

- **CoFASD**: Epidemiologic Active Ascertainment in multi-communities across the U.S.

- **CIFASD**: Collaborative Initiative on FASD

- **PASS**: Prenatal Alcohol SIDS and Stillbirth Network (joint with NICHD)
What is the Fate of the Diverse NIAAA Portfolio in the New Substance Use and Addiction Disorders Institute?

At their September 2010 meeting – the SMRB voted (12-3) to accept Option 1 verbatim as presented in the SUAA Working Group Report, which states:

- “This new institute would integrate all relevant addiction research portfolios from NIAAA, NIDA, and other institutes at NIH.”

- It then continues: “Non-addiction research portfolios currently held by NIAAA and NIDA would be transferred to other institutes as deemed appropriate. For example, research on alcohol liver disease could be reassigned to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) or research on Fetal Alcohol Spectrum Disorders could be reassigned to the National Institute of Child Health and Human Development.” *(color emphasis added)*

- Some questions: When is alcohol research not substance use research?
  - When alcohol is consumed in pregnancy?
  - When it involves alcohol metabolites?
  - How will common mechanisms of action for alcohol (e.g., peripheral organ and brain) be addressed within the NIH if dispersed across multiple ICs each with differing priorities?
Thank you

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