presentation to the

NIH Scientific Management Review Board

on

The National Institute on Alcohol Abuse and Alcoholism

Kenneth R. Warren, Ph.D.
Acting Director

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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
Why a Special Focus on Problems that Arise from 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

https://www.allposters.com/-sp/Wedding-Toast-Posters_i2629204_.htm
Alcohol has both **beneficial** and **harmful** health effects, and it is used by most individuals **without causing harm** to themselves or others.

However, alcohol interacts with the **whole body**, and risk drinking produces **intoxication** and other impairments to the CNS, and harm to **organs** and **body systems**.

Indeed, alcohol is a **leading risk factor** for **morbidity** and **mortality** in the United States and worldwide.
Harmful Drinking is a Leading Risk Factor for Disease Burden in the U.S.

- 18 million Americans (8.5% of the population age 18 and older) suffer from alcohol abuse or dependence
- Alcohol problems cost U.S. society an estimated $185 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/2 hours

- unintentional death and injury
- homicide and violence
- suicide attempts

particularly prevalent among adolescents and young adults

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

chronic consequences including:
- liver cirrhosis
- cardiovascular diseases
- pancreatitis
- dementia
- alcohol dependence
Frequency of Risk Drinking in U.S. Population

- NIAAA has defined risk drinking as exceeding 5+/4+ per day (14+/7+ per week) based on epidemiologic data from the NESARC and probabilities of an adverse outcome at various drinking levels.

- 65% of the U.S. adult population are current drinkers.

- 59% of current drinkers do not report risk drinking.

### Odds for development in subsequent 3 yrs

<table>
<thead>
<tr>
<th>Frequency of Risk Drinking</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1</td>
</tr>
<tr>
<td>1/mo</td>
<td>1.5</td>
</tr>
<tr>
<td>1-3/mo</td>
<td>3</td>
</tr>
<tr>
<td>1-2/wk</td>
<td>5</td>
</tr>
<tr>
<td>3-4/wk</td>
<td>7</td>
</tr>
<tr>
<td>Daily/near daily</td>
<td>10</td>
</tr>
</tbody>
</table>

### Alcohol Dependence

- Odds for development in subsequent 3 yrs increase with increasing frequency of risk drinking.
Alcohol Use Disorders Can Be Co-morbid With Drug Use and Psychiatric Disorders

- 55% of Individuals with Drug Use Disorders have an Alcohol Use Disorder; **13%** of individuals with Alcohol Use Disorders also have a drug use disorder.

- Research on the pharmacology and treatment of drug and psychiatric disorders co-morbid with AUDs is an important part of our agenda.

### Co-morbidity Rates for 12-month DSM-IV Psychiatric and Drug Disorders Among Individuals with Alcohol Use Disorders in the U.S. Population

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Dependence</td>
<td>33.8%</td>
</tr>
<tr>
<td>Personality Disorders</td>
<td>29%</td>
</tr>
<tr>
<td>Mood Disorders (including major depression)</td>
<td>19%</td>
</tr>
<tr>
<td>Anxiety Disorders</td>
<td>17%</td>
</tr>
<tr>
<td>Drug Use Disorders</td>
<td>13%</td>
</tr>
</tbody>
</table>
NIAAA’s Broad Mandate Requires Research Programs To Address Alcohol Issues Throughout The Lifespan...

- Metabolism
- Genetics
- Epigenetics
- Epidemiology
- AUD Diagnosis
- Neurobiology
- Health Services Research
# Physiological and Pathologic Effects of Alcohol Consumption

<table>
<thead>
<tr>
<th>Brain</th>
<th>Liver</th>
<th>Pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Neurotransmitter System Targets</td>
<td>Hepatic steatosis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Dependence</td>
<td>Fibrosis</td>
<td>Fetus</td>
</tr>
<tr>
<td>Structural Damage</td>
<td>Cirrhosis</td>
<td>FAS/D</td>
</tr>
<tr>
<td>Cognitive Deficits</td>
<td>Hepatocellular carcinoma</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral Neuropathy</strong></td>
<td><strong>Skeletal Muscles</strong></td>
<td><strong>Immune System Deficiency</strong></td>
</tr>
<tr>
<td></td>
<td>Myopathy</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td><strong>Blood Platelet Dysfunction</strong></td>
<td><strong>Endocrine System</strong></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td>HPA/HPG/ HPT Dysfunction</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>Bone</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Blood platelet</td>
<td><strong>Lungs</strong></td>
<td></td>
</tr>
<tr>
<td>dysfunction</td>
<td></td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>Moderate drinking &amp; CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Gastrointestinal Tract</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Esophageal Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Metabolic Syndrome</strong></td>
</tr>
</tbody>
</table>

- Cardiomyopathy
- Hypertension
- Stroke
- Arrhythmias
- Blood platelet dysfunction
- Moderate drinking & CAD
- Hepatic steatosis
- Fibrosis
- Cirrhosis
- Hepatocellular carcinoma
- Myopathy
- Blood Platelet Dysfunction
- Acute Respiratory Distress Syndrome
- Esophageal Cancer
- Gastritis
- Pancreatitis
- Fetus
- FAS/D
- Immune System Deficiency
- HPA/HPG/ HPT Dysfunction
- Osteoporosis
- Metabolic Syndrome
Beneficial Effects of Moderate Alcohol Use

- Decreased Risk of **Coronary Artery Disease**
  - HDL↑; LDL↓
  - Decreased platelet aggregation
  - Increased fibrinolysis
  - Ischemic/reperfusion
- Decreased risk of **Ischemic Stroke**
- **Metabolic Syndrome and Type 2 Diabetes**
- Decreased **Osteoporosis**
- Decreased risk of **dementia**
- **Improved cognitive function in women**
Alcohol Research: Systems Approach

The wide range of **physiologic** and **pathologic** effects of alcohol on many organs requires that alcohol research be conducted from a broad **systems approach**, where the effects of alcohol on one organ elicits metabolic changes that affect other organs, for example:

- Increased permeability on intestinal mucosa resulting in an increase in LPS which affects liver and brain pathology
- Alcohol’s metabolic effects on liver lipid metabolism affecting vascular system, CHD risk (- and +), dementia risk (- and +)
- Hormones from gut, pancreas, adipose tissue affecting drinking behavior: e.g., CCK, ghrelin (?); PYY (?)
Metabolic Consequences of Alcohol Consumption

- Another key factor that may contribute to alcohol’s broad effects is that it is consumed at levels more typical of a food than a pharmacologic agent.

- A standard alcoholic beverage (12 oz beer, 5 oz wine, 1 ½ oz distilled spirits) has 14 grams of ethanol.

- An individual consuming 6 drinks is ingesting 84 grams of ethanol; 588 calories from ethanol.

- Consequently, alcohol can have profound metabolic effects.
Alcohol Metabolism, ROS Production, and Tissue Damage

Alcohol also inhibits methionine synthase impairing biosynthesis of SAMe and potentially leading to hypomethylation in epigenetics (DNA, histones)

Metabolic Consequences of Alcohol Metabolism

Oxidative Pathways of Alcohol Metabolism

Tissue Damage (apoptosis)

Increase Inflammatory Cytokines (e.g., TNFα, IL-1, IL-6)

Increase Transcription Factors (e.g., NFκB, AP-1)

ROS Production

Lipid peroxidation (+ Acetaldehyde)

DNA Damage

ROS GSH

• NAD+ regeneration via mitochondrial electron transport chain
• microsomal CYP2E1*

Alcohol Metabolism, ROS Production, and Tissue Damage

Alcohol also inhibits methionine synthase impairing biosynthesis of SAMe and potentially leading to hypomethylation in epigenetics (DNA, histones)
NIAAA’s Prevention Portfolio

- NIAAA has a Major Public Health Focus on Underage Drinking
  - Goal: Delaying the Onset of Drinking to reduce risks for development of AUDs later in life (4x greater risk to develop dependence with drinking onset <15 years).
  - NIAAA provided the research base for the Surgeon General’s Call to Action on Underage Drinking.
  - Research on the impact of Enforcement of Underage Drinking Laws (EUDL)
- College Drinking Initiative included translating research to campus and community prevention initiatives
- Community research on price, zoning, outlet density, hours of operation, merchant and server intervention
- NIAAA research on the effect of 21 drinking age, 0.08% BAC limit, and zero tolerance for <21 drinking/driving led to implementation of these laws
Behavioral Treatments

- NIAAA research established that several Behavioral Treatments are effective in the treatment of alcohol dependence:
  - Cognitive Behavioral Therapy
  - 12-Step Facilitation
  - Motivational Enhancement
  - Community Reinforcement
  - Marital Behavioral Therapy

- Screening and Brief Intervention for Alcohol Problems has been established as both effective and economical in:
  - Trauma Centers
  - Prenatal Practice
  - Primary Care (Now a recommendation from the U.S. Preventive Services Task Force)

- In 2006, NIAAA launched a major initiative to understand the mechanisms of behavior change
  - Precursor to NIH Roadmap developmental initiative on Science of Behavior Change
# NIAAA Research – Science in Support of Practice

## Developing Medications

### Medications with Proven Efficacy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disulfiram</td>
<td>Aldehyde Dehydrogenase (FDA approval 1949)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Mu Opioid Receptor (FDA approval 1994)</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Glutamate and GABA-Related (FDA approval 2004)</td>
</tr>
<tr>
<td>Naltrexone Depot</td>
<td>Mu Opioid Receptor (FDA approval 2006)</td>
</tr>
<tr>
<td>Topiramate (AD)</td>
<td>GABA/Glutamate (off-label)</td>
</tr>
</tbody>
</table>

### Examples of Potential Therapeutics Under Investigation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Target/Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate (AD)</td>
<td>GABA/Glutamate</td>
</tr>
<tr>
<td>Ondansetron (AD)</td>
<td>5-HT\textsubscript{3} Receptor</td>
</tr>
<tr>
<td>Nalmefene (AD)</td>
<td>Mu Opioid Receptor</td>
</tr>
<tr>
<td>Baclofen (AD)</td>
<td>GABA\textsubscript{B} Receptor</td>
</tr>
<tr>
<td>Antalarmin (AD)</td>
<td>CRF1 Receptor</td>
</tr>
<tr>
<td>Rimonabant (AD)</td>
<td>CB1 Receptor</td>
</tr>
<tr>
<td>Refanalin (liver fibrosis)</td>
<td>hepatic-growth-factor-mimetic</td>
</tr>
<tr>
<td>NAPVSIPQ and SALLRSIPA (FAS/D)</td>
<td>neuroprotective peptides/L1 receptor</td>
</tr>
<tr>
<td>Choline (FAS/D)</td>
<td>ACH (?)</td>
</tr>
</tbody>
</table>
Extended Continuum: From Low to High Risk to AUD

None

Never exceeds daily limits

~70%

Mild (“At-risk”)

~21%

Moderate (Harmful use)

~5%

Severe (Dependence)

~3%

Chronic dependence

~1%

Suitable for Primary Care

Specialty Care

- DSM-IV Abuse/Dependence
  - None
  - Mild (“At-risk”)
  - Moderate (Harmful use)
  - Severe (Dependence)
  - Chronic dependence

- Criteria
  - None
  - Mild
  - Moderate
  - Severe
  - Chronic

- Characteristics
  - Never exceeds daily limits
  - Exceeds daily limits episodically
  - Daily or near daily heavy drinking
  - Chronic or relapsing
  - Functional impairment

- DSM-IV Abuse/Dependence
  - None
  - Mild
  - Moderate
  - Severe
  - Chronic

- Criteria
  - None
  - Mild
  - Moderate
  - Severe
  - Chronic

- Characteristics
  - No distress or harm
  - No distress or harm
  - Daily or near daily heavy drinking
  - Daily or near daily heavy drinking

- DSM-IV Abuse/Dependence
  - None
  - Mild
  - Moderate
  - Severe
  - Chronic

- Criteria
  - None
  - Mild
  - Moderate
  - Severe
  - Chronic

- Characteristics
  - No distress or harm
  - No distress or harm
  - Daily or near daily heavy drinking
  - Daily or near daily heavy drinking

- DSM-IV Abuse/Dependence
  - None
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- Criteria
  - None
  - Mild
  - Moderate
  - Severe
  - Chronic

- Characteristics
  - No distress or harm
  - No distress or harm
  - Daily or near daily heavy drinking
  - Daily or near daily heavy drinking
The NIAAA Clinician’s Guide, was developed as the first fully evidence-based guide for primary health care to provide screening for all patients, provide brief intervention for risk drinkers, diagnose DSM-IV alcohol use disorders and provide treatment or referral to specialty treatment services.

The Guide has penetrated primary and mental-health care with the extensive help of the AMA and other professional organizations.

The guide makes it is easier for clinicians to address alcohol use with their patients and de-stigmatizing alcohol treatment.

CME credit available at: www.niaaa.nih.gov/guide
For the Consumer

- Our goal for the Consumer Guide *Re-Thinking Drinking* (as with our Clinician’s Guide) is to help facilitate a healthy relationship with alcohol for those many adults who choose to drink thereby helping them to avoid the adverse health and personal consequences associated with harmful alcohol use.

- For those individuals with Alcohol Use Disorders, our goal is to develop a range of treatment options (behavioral and pharmacologic) that are accessible, acceptable, affordable, and appealing to clients, and thereby close the treatment gap for alcohol use disorders.
Thank you!

Kenneth R. Warren, Ph.D.
Acting Director
National Institute on Alcohol Abuse and Alcoholism