

*presentation to the*  
**NIH Scientific Management Review Board**  
*on*

**The National Institute on Alcohol Abuse  
and Alcoholism**

**Kenneth R. Warren, Ph.D.**  
**Acting Director**

**April 27-28, 2009**



# National Institute on Alcohol Abuse and Alcoholism (NIAAA)

**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



"Wedding Toast"  
Erik Henningsen

[https://www.allposters.com/-sp/Wedding-Toast-Posters\\_j2829204\\_.htm](https://www.allposters.com/-sp/Wedding-Toast-Posters_j2829204_.htm)

# Alcohol Consumption: Benefits and Harm



Pierre-Auguste Renoir The Luncheon of the Boating Party (1880)



Nicolae Grigorescu

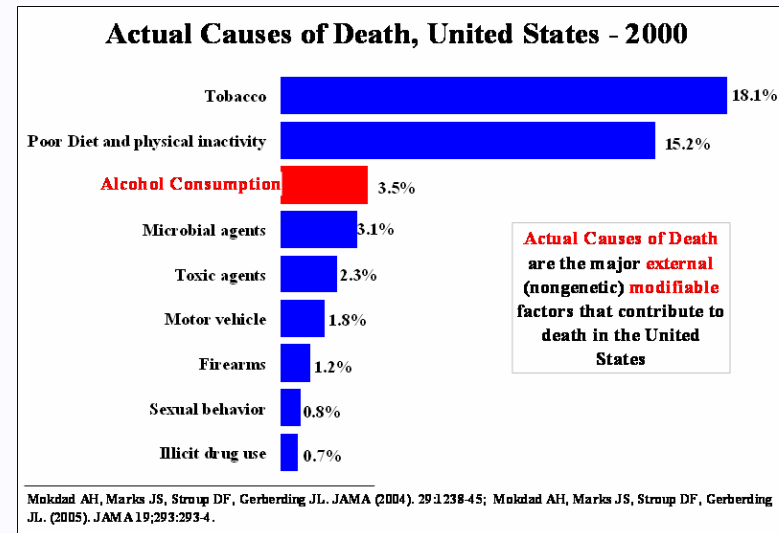
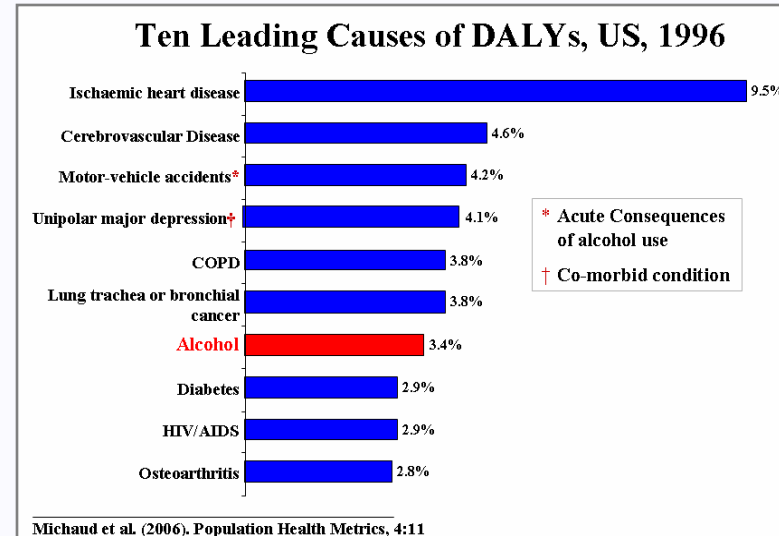
- Alcohol has both **beneficial** and **harmful** health effects, and it is used by most individuals **without causing harm** to themselves or others
- However, alcohol interacts with the **whole body**, and **risk drinking** produces **intoxication** and other impairments to the CNS, and harm to **organs** 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 3<sup>rd</sup> 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



## acute consequences including:

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

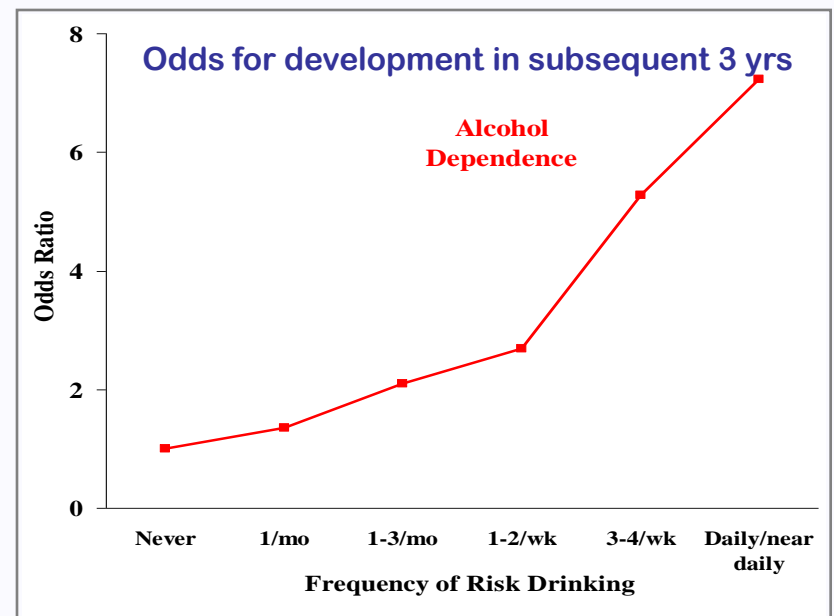
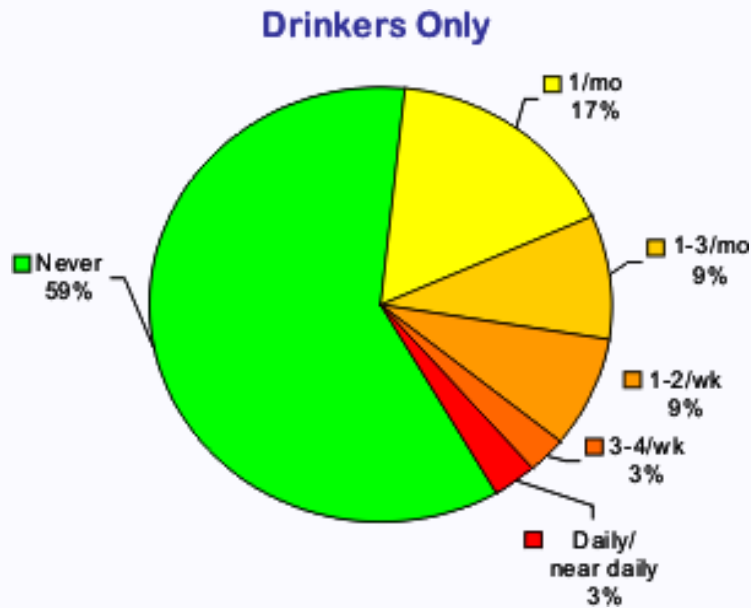
**particularly prevalent among adolescents and young adults**

## chronic consequences including:

- liver cirrhosis
- cardiovascular diseases
- pancreatitis
- dementia
- alcohol dependence

# Frequency of Risk Drinking in U.S. Population

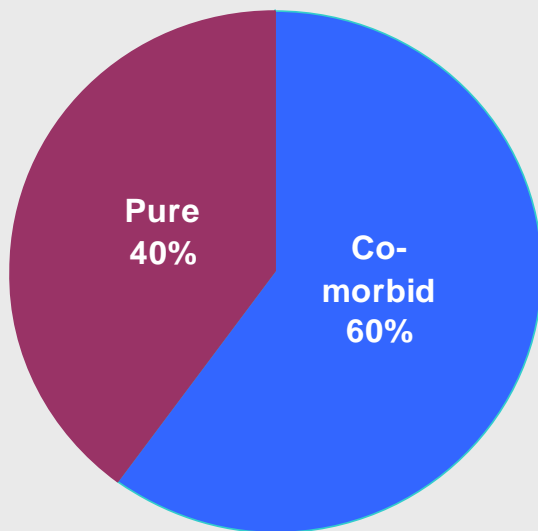
- NIAAA has defined risk drinking as exceeding 5+/4+ per day (14+/7+ per week) based on epidemiologic data from the NESARC and probabilities of an adverse outcome at various drinking levels
- 65% of the U.S. adult population are **current drinkers**
- 59% of **current drinkers** do not report risk drinking



# 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

Pure and Comorbid Past-Year Alcohol Use Disorders in the U.S. Population



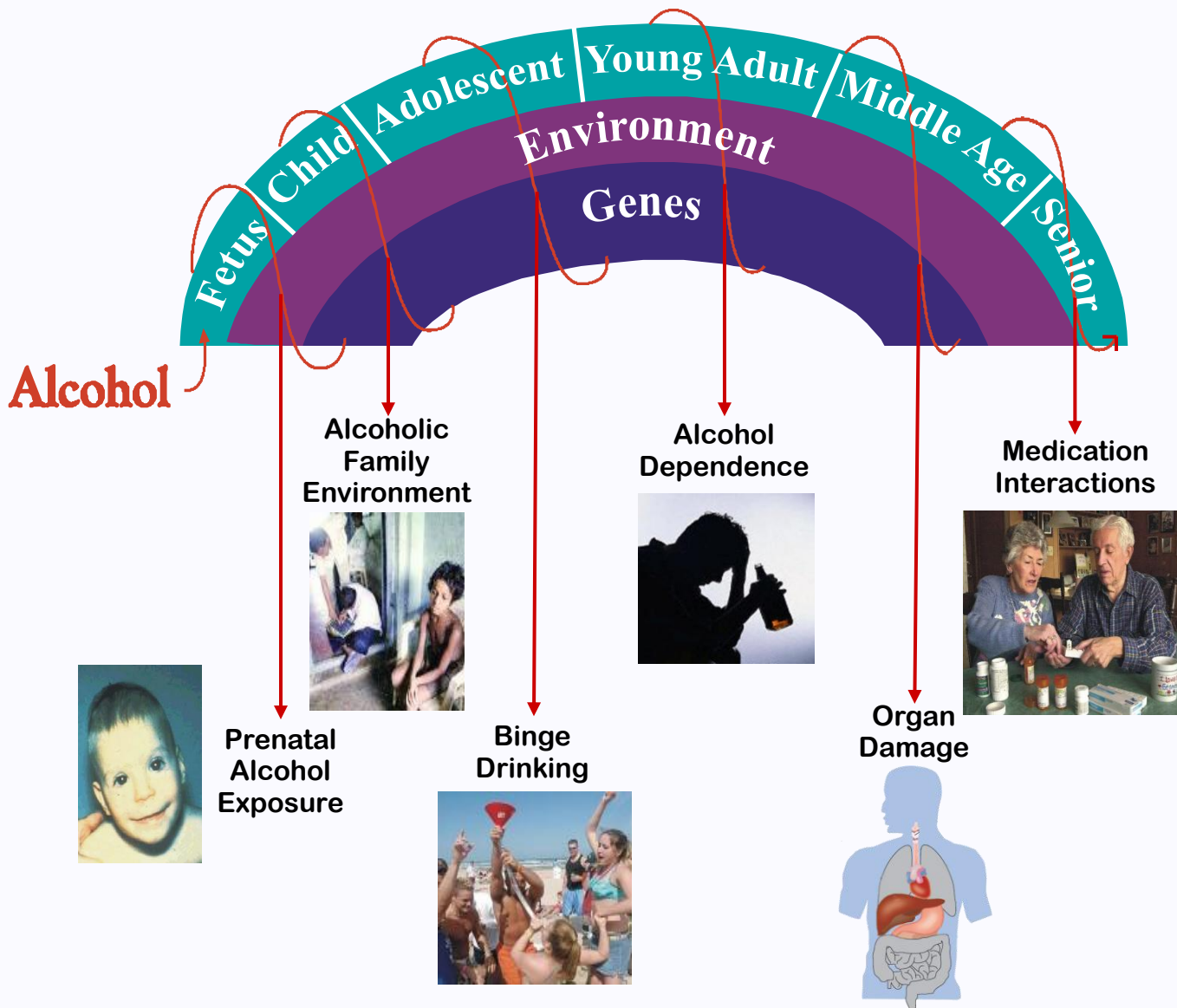
NIAAA NESARC. NIAAA Laboratory of Epidemiology and Biometry

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

Disorder	Rate
Nicotine Dependence	33.8%
Personality Disorders	29%
Mood Disorders (including major depression)	19%
Anxiety Disorders	17%
Drug Use Disorders	13%



# NIAAA's Broad Mandate Requires Research Programs To Address Alcohol Issues Throughout The Lifespan...



- ### Lifespan Transcending Themes
- Metabolism
  - Genetics
  - Epigenetics
  - Epidemiology
  - AUD Diagnosis
  - Neurobiology
  - Health Services Research

# Physiological and Pathologic Effects of Alcohol Consumption

## Brain

Multiple Neurotransmitter System Targets  
 Dependence  
 Structural Damage  
 Cognitive Deficits  
 Dementia

## Peripheral Neuropathy

## Cardiovascular System

Cardiomyopathy  
 Hypertension  
 Stroke  
 Arrhythmias  
 Blood platelet dysfunction

Moderate drinking & CAD

## Liver

Hepatic steatosis  
 Fibrosis  
 Cirrhosis  
 Hepatocellular carcinoma

## Skeletal Muscles

Myopathy

## Blood Platelet Dysfunction

## Lungs

Acute Respiratory Distress Syndrome

## Gastrointestinal Tract

Esophageal Cancer  
 Gastritis

## Pancreas

Pancreatitis

## Fetus

FAS/D

## Immune System Deficiency

## Endocrine System

HPA/HPG/  
 HPT Dysfunction

## Bone

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:

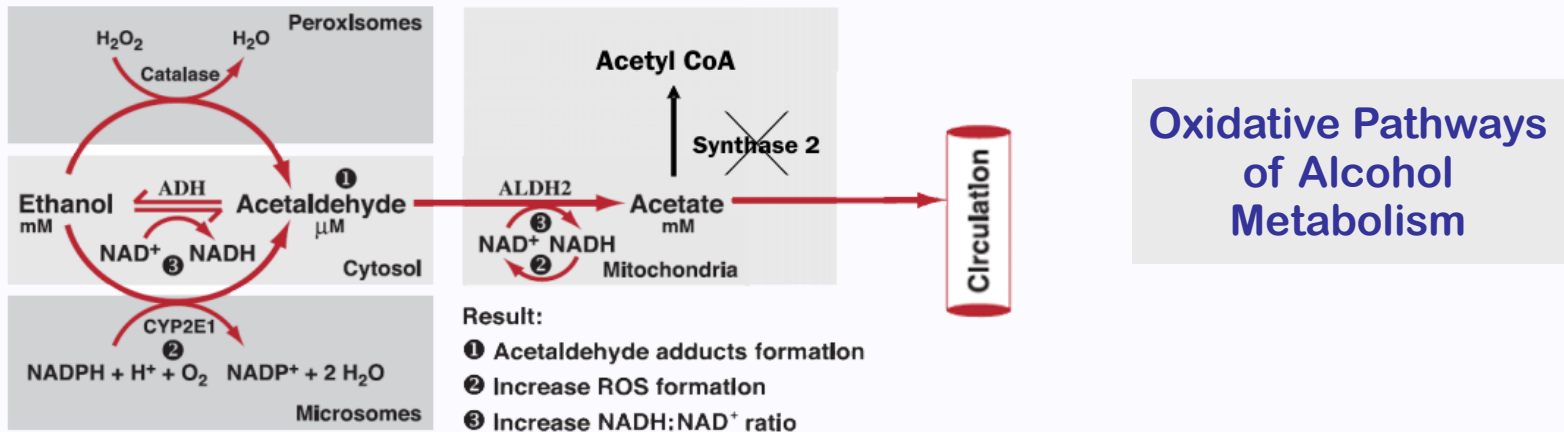
- Increased permeability on intestinal mucosa resulting in an increase in LPS which affects liver and brain pathology
- Alcohol's metabolic effects on liver lipid metabolism affecting vascular system, CHD risk (- and +), dementia risk (- and +)
- Hormones from gut, pancreas, adipose tissue affecting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

# Metabolic Consequences of Alcohol Consumption

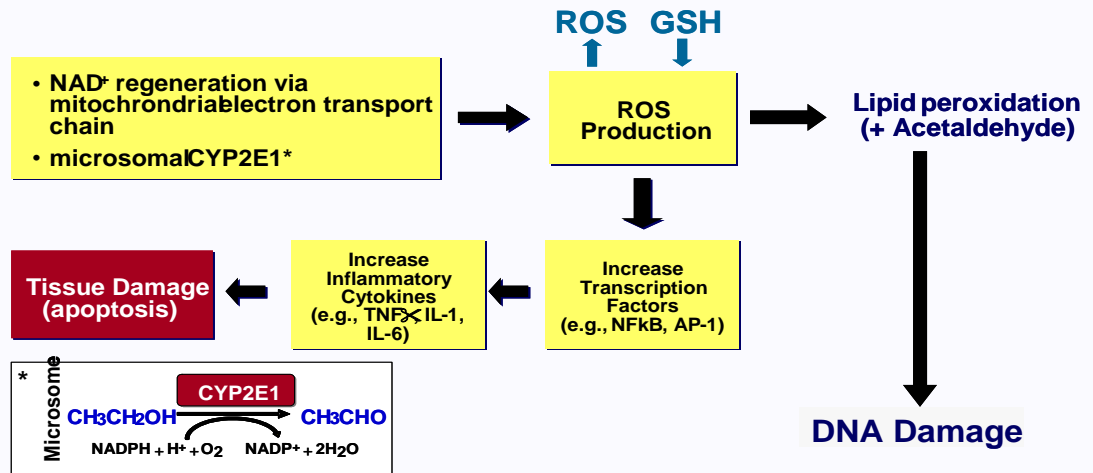
- Another key factor that may contribute to alcohol's broad effects is that it is consumed at levels more typical of a food than a pharmacologic agent
- A standard alcoholic beverage (12 oz beer, 5 oz wine, 1 ½ oz distilled spirits) has 14 grams of ethanol
- An individual consuming 6 drinks is ingesting 84 grams of ethanol; 588 calories from ethanol
- Consequently, alcohol can have profound metabolic effects



# Metabolic Consequences of Alcohol Metabolism



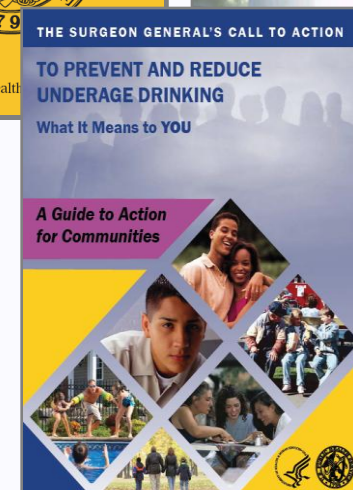
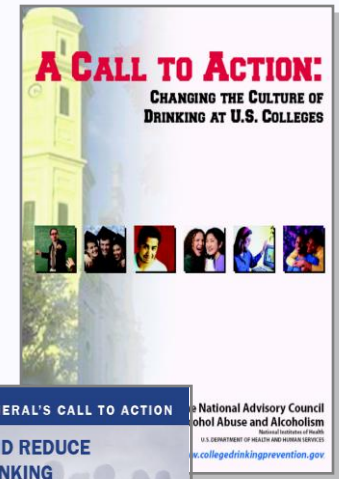
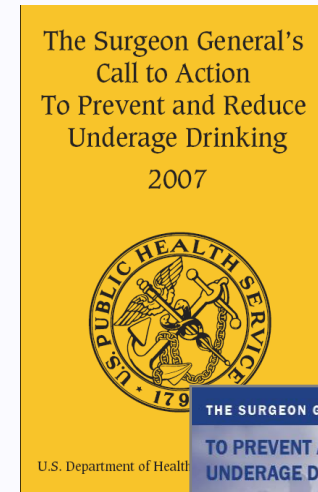
## Alcohol Metabolism, ROS Production, and Tissue Damage



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

Intake

Withdrawal

Anxiety

Stress

Relapse

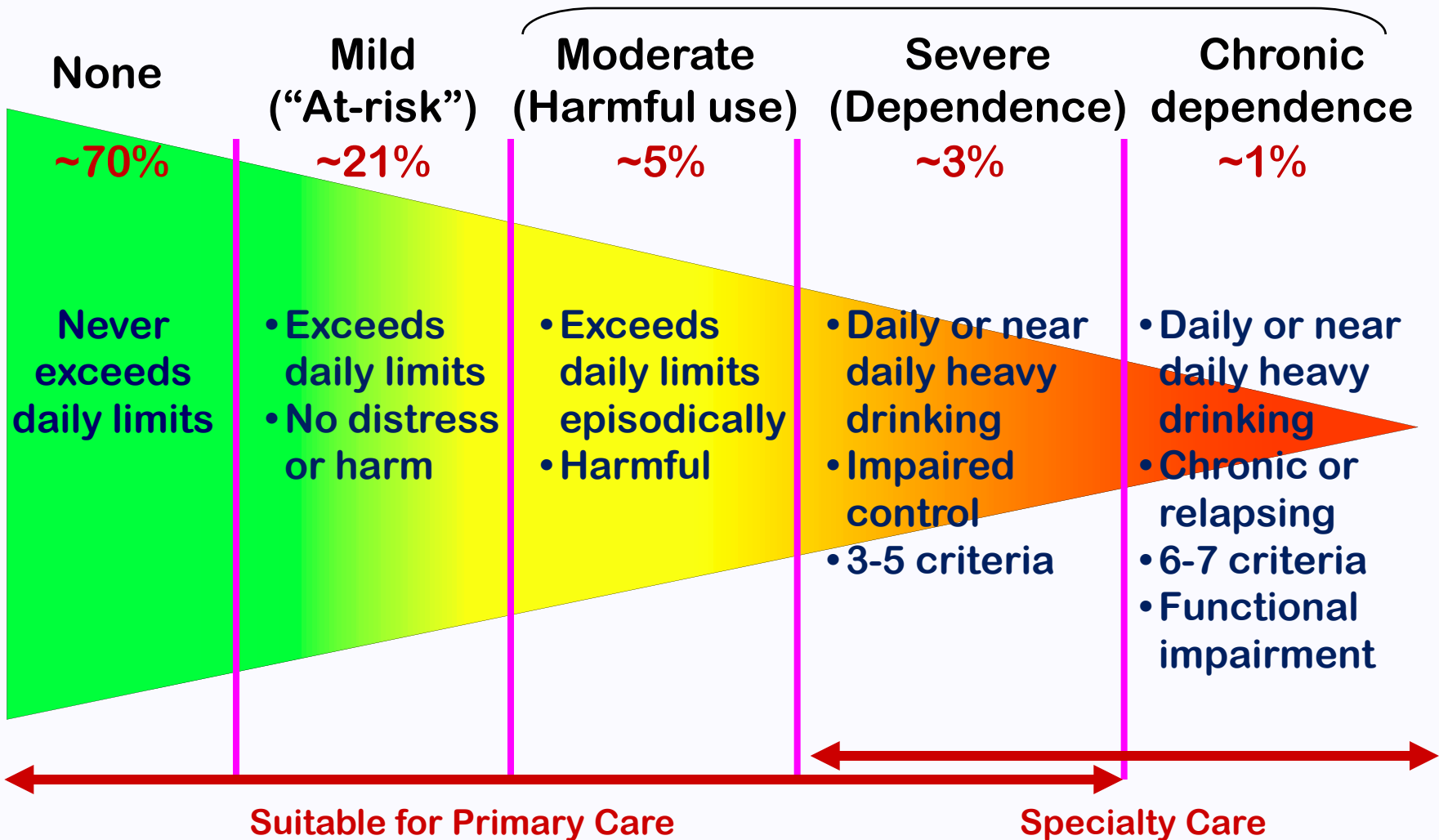
Liver Fibrosis

FAS/D

Medications with Proven Efficacy	
Medication	Target
Disulfiram	Aldehyde Dehydrogenase (FDA approval 1949)
Naltrexone	Mu Opioid Receptor (FDA approval 1994)
Acamprosate	Glutamate and GABA-Related (FDA approval 2004)
Naltrexone Depot	Mu Opioid Receptor (FDA approval 2006)
Topiramate (AD)	GABA/Glutamate (off-label)
Examples of Potential Therapeutics Under Investigation	
Medication	Target/Type
Valproate (AD)	GABA/Glutamate
Ondansetron (AD)	5-HT <sub>3</sub> Receptor
Nalmefene (AD)	Mu Opioid Receptor
Baclofen (AD)	GABA <sub>B</sub> Receptor
Antalarmin (AD)	CRF1 Receptor
Rimonabant (AD)	CB1 Receptor
Refanalin (liver fibrosis)	heptic-growth-factor-mimetic
NAPVSIPQ and SALLRSIPA (FAS/D)	neuroprotective peptides/L1 receptor
Choline (FAS/D)	ACH (?)

# Extended Continuum: From Low to High Risk to AUD

## DSM-IV Abuse/Dependence





# NIAAA Research – Science in Support of Practice

## Developing Evidence-Based Guidelines for Primary Care Clinicians...

- 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](http://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

[RethinkingDrinking.niaaa.nih.gov](http://RethinkingDrinking.niaaa.nih.gov)



- 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**



NATIONAL INSTITUTE ON  
ALCOHOL ABUSE AND ALCOHOLISM

*of the NATIONAL INSTITUTES OF HEALTH*

<http://www.niaaa.nih.gov>